U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of HHS

Draft Report of the Secretary's Advisory Committee on Genetics, Health, and Society

Available for Public Comment
November 5 – December 21, 2007

A Note to the Public

The mandate of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) is to advise the Secretary of Health and Human Services (HHS) on policy issues raised by the development and use of genetic technologies and their integration into clinical and public health practice. Given the expanded use of genetic testing in clinical practice and public health and the pace and extent of technological change in the ways testing is performed, SACGHS identified the oversight of genetic testing as a high priority issue. In addition, its predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT), issued a report in 2000 that identified a number of gaps in oversight and made recommendations to address them.

After several years of monitoring the issue, SACGHS began a concentrated effort in 2006 to assess the various systems of oversight that play a role in genetic testing. Like SACGT, the Committee's overarching concern was the adequacy of the oversight system and whether there were gaps in it that could lead to harms in public health. In March 2007, HHS launched the Personalized Health care (PHC) Initiative to advance the integration of genomic technologies that are capable of tailoring treatment and prevention strategies to each patient's unique genetic characteristics and individual needs into general health care. The Initiative recognizes that the accuracy, clinical validity, and clinical utility of genetic tests are central to the realization of personalized health care. Because this effort dovetailed with the work underway by SACGHS, the Secretary gave SACGHS a specific charge: to develop a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests and to consider questions about the regulatory policies related to genetic testing, the scientific information and oversight structures needed to ensure that tests are properly developed and used, and the transparency of the oversight system.

SACGHS formed a task force to address the Secretary's charge. It was composed of SACGHS members, *ex officios* and *ad hoc* experts from the public and private sectors. This draft report is a product of the work of the task force. This draft report is the product of the task force and is now being disseminated to the public for comment. SACGHS would appreciate input on whether the draft report fully responds to the Secretary's charge, proposes appropriate remedies to close gaps in the current system, and adequately anticipates future developments in the field of genetics and genomics. Comments received by **December 21, 2007** will be considered by SACGHS in the preparation of the final report that will be presented to the Secretary of HHS.

To submit comments to SACGHS, please email them to Cathy Fomous, Ph.D. at cfomous@od.nih.gov. Alternatively, comments can be mailed to Dr. Fomous at the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 700, Bethesda, MD, 20892 (20817 for non-US Postal Service mail) or faxed to 301-496-9839.

About SACGHS

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was first chartered in 2002 by the Secretary of Health and Human Services (HHS) as a public forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues. Its mandate includes the following areas of study:

- Integration of genetic and genomic technologies into health care and public health;
- Clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications;
- Opportunities and gaps in research and data collection and analysis efforts;
- Impact of current patent policy and licensing practices on access to genetic and genomic technologies; and
- Uses of genetic information in education, employment, insurance, and law.

SACGHS consists of up to 17 individuals from around the Nation who have expertise in disciplines relevant to genetics and genetic technologies. These disciplines include biomedical sciences, human genetics, healthcare delivery, evidence-based practice, public health, behavioral sciences, social sciences, health services research, health policy, health disparities, ethics, economics, law, healthcare financing, consumer issues, and other relevant fields. At least two of the members are specifically selected for their knowledge of consumer issues and concerns and the views and perspectives of the general public.

Representatives of at least 19 Federal department or agencies also sit on SACGHS in an *ex officio* (nonvoting) capacity. The departments and agencies are the Department of Commerce, Department of Defense, Department of Education, Department of Energy, Administration for Children and Families (HHS), Agency for Health care Research and Quality (HHS), Centers for Disease Control and Prevention (HHS), Centers for Medicare & Medicaid Services (HHS), Food and Drug Administration (HHS), Health Resources and Services Administration (HHS), National Institutes of Health (HHS), Office for Civil Rights (HHS), Office for Human Research Protections (HHS), Office of Public Health and Science (HHS), Department of Justice, Department of Labor, Department of Veterans Affairs, Equal Employment Opportunity Commission, and Federal Trade Commission.

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Executive Summary

Since the launch of the Human Genome Project, genetic testing has been adopted increasingly into standard practice for diagnosing and managing disease, expanding on its roles in predicting the risk of future disease and informing decisions about life planning and behavior change. Today, genetic tests use combinations of biochemical, cytogenetic, and molecular methods to analyze deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, proteins, and selected metabolites. Advances in genetics research are enabling improved prevention, treatment and disease management for common chronic conditions such as cancer, heart disease, and diabetes.

As genetic testing technology is integrated into health care, increasingly detailed information about individual and population genetic variations becomes available to patients and providers. More and more, health professionals are turning to genetic testing to assess the risk of disease in individuals, families, and populations and using this information to guide healthcare decisions. Yet availability of this information requires significant support for efforts to understand its validity, interpretation, and utility in clinical and personal decisionmaking. Scientific and technological advances in genetic testing present certain challenges to existing frameworks for regulation and oversight. It is critical to anticipate and adapt to the impacts of these advances on individual health care and public health.

The significance of the information that can result from genetic tests, their expanded use of genetic testing in clinical practice and public health, and the pace and extent of technological change in the ways testing is performed, have prompted efforts to examine the current systems of oversight and regulation of genetic tests and test results. The Secretary's Advisory Committee for Genetics, Health, and Society (SACGHS) first identified oversight of genetic tests as a priority area in 2004. After several years of monitoring the issue, SACGHS began a concentrated effort in 2006 to assess the various systems of oversight that play a role in genetic testing. Like SACGT, the Committee's overarching concern was the adequacy of the oversight system and whether there were gaps in it that could lead to harms in public health. In March 2007, HHS launched the Personalized Health Care (PHC) Initiative to advance the integration of genomic technologies that are capable of tailoring treatment and prevention strategies to each patient's unique genetic characteristics and individual needs into general health care. [1] The Initiative recognizes that the accuracy, clinical validity, and clinical utility of genetic tests are central to the realization of personalized health care. Because this effort dovetailed with the work underway by SACGHS, the Secretary charged the Committee with investigating specific issues related to the adequacy and transparency of current oversight systems for genetic testing. The charge complements related efforts underway at the Federal level and encompasses all sectors of the healthcare system concerning oversight, including the Federal Government, State Governments, and the private sector. Refined during Committee discussion, the charge is to:

> Undertake the development of a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. Consider and address the following questions:
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> - What evidence of harm exists regarding genetic tests? Is that harm attributable to analytic validity, clinical validity, or clinical utility of the tests? If evidence does not exist, what threats are not currently being addressed? What public health benefits are not accruing as quickly as they might?

[1] Personalized Health Care: Goals. Washington, DC: The Department of Health and Human Services. http://www.dhhs.gov/myhealth care/goals/index.html#Goal3 Accessed August 14, 2007.

- What distinguishes genetic tests from other laboratory tests for oversight purposes?
- What are the existing pathways that examine the analytic validity, clinical validity, and clinical utility of genetic tests? Consider the use of case studies.
- What organizations are currently involved with each of these aspects, and what are they doing to address these issues? Who should be responsible for each of these aspects?
- What resources (e.g., standards reagents/materials) are needed to develop proficiency testing kits or protocols for genetic tests? What is currently available in terms of proficiency testing kits or protocols for genetic tests? What information is provided by proficiency testing? Is the current level of proficiency testing for genetic tests adequate and are the results of such laboratory performance assessments sufficiently transparent?
- What are the potential pathways to communicate clear information to guide test and treatment selection by the provider?
- What new approaches or models should be considered for private and public-private sector engagement in demonstrating clinical validity and clinical utility for developing effectiveness measures of genetic tests in clinical practice?
- Would additional or revised Government oversight add value for patients, and if so, how and where?

This report focuses on the oversight of genetic testing and the application of genetic information in patient care and management. To help frame recommendations for the Secretary and other policymakers and stakeholders, the SACGHS Oversight Task Force has explored a range of specific issues relevant to genetic testing. These include the discussion of analytical validity, clinical validity, and clinical utility of genetic testing, possible gaps in testing oversight that may lead to harms, evidence development for oversight of genetic and genomic tests, and new approaches to demonstrate the clinical validity and clinical utility of genetic testing in clinical practice.

Current Trends in the Oversight of Genetic Testing

Advances in the technology and application of genetic testing have confirmed and widened some gaps and ambiguities that exist in current systems of oversight. The prevalence of genetic testing in health care today has highlighted the need to examine the regulatory framework governing a variety of test uses and testing procedures. The responsibilities for the oversight of genetic testing are shared by multiple Governmental and nonGovernmental bodies. Systems of oversight address activities related to genetic tests that range from the research and development of tests, to the delivery of tests, and to the interpretation and use of tests results to guide health and lifestyle decisions. Depending on the aspect of testing, oversight is provided by Government agencies, healthcare payers, professional associations, or other groups; voluntarily by certain sectors; or not at all. Some aspects of oversight are quite specific to genetic testing while others are of broader scope, applying to medical devices or other products or professional activities in general.

At the Federal level, oversight of genetic tests includes activities carried out by the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS). Currently, there are two main pathways for bringing genetic tests into clinical practice. Some genetic tests are developed by in vitro diagnostic (IVD) test manufacturers for distribution in interstate commerce to multiple laboratories. Other tests, known as laboratory developed tests (LDTs), are developed for use solely in the test developer's laboratory.

FDA regulates genetic tests that qualify as medical and IVD devices, which includes test kits and analyte specific reagents (ASRs). ASRs can be antibodies, receptor proteins, nucleic acid sequences, and other biological or chemical reagents used to identify or quantify substances in biological specimens.[2] Until recently, FDA has not exercised its regulatory authority over LDTs; the regulation of those tests have been left, for the most part, to regulations governing the laboratories that develop LDTs, the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[3]

CLIA, which is overseen by CMS, requires all clinical laboratories, including genetic testing laboratories, to undergo inspections to assess their compliance with established standards. This process includes inspections for personnel qualification and responsibilities, quality control standards, proficiency testing (PT), quality assurance, and record keeping. Before new tests can be offered, CLIA requires laboratories to verify and establish the test's analytical performance characteristics. While CMS provides guidance and resources to help laboratories achieve compliance, current regulations do not specify particular procedures or protocols. Rather, they require laboratories to assure that their test results are accurate, reliable, timely, and confidential, and do not present the risk of harm to patients. Many have called for a closer examination and coordination of the dual regulations of FDA and CLIA. In addition, bills were introduced in the 110th Congress that addressed the oversight of genetic testing.[4,5]

At the State level, many agencies use CLIA requirements to regulate genetic testing laboratories. New York and Washington, however, independently operate State laboratory certification programs, both of which are exempt from CLIA because CMS has deemed them equal to or more stringent than CLIA requirements. The New York State Department of Health has one of the most stringent State-level oversight systems, requiring pre-approval prior to offering a genetic test in a clinical setting. All laboratories that solicit and receive specimens from New York are subject to these clinical laboratory requirements.[6] An estimated 75 percent of all cytogenetic and genetic specimens tested in the United States are subject to New York State oversight.[7]

Assuring the analytical and clinical validity of genetic testing is paramount. Analytical validity refers to a test's ability to measure the genotype of interest accurately and reliably; clinical validity refers to a test's ability to detect or predict the associated disorder (phenotype). Only analytical validity is has been fully enforced under CLIA.[8] Moreover, prospective data of a test's clinical validity is often unavailable or incomplete for years after a test is developed, especially for predictive or presymptomatic tests. As such, numerous challenges remain for the demonstration of clinical validity, such as the collection of postmarket data and sharing of information between laboratories. FDA plays a role in assessing the clinical validity of genetic tests insofar as it is charged with assessing "safety and effectiveness." Its evaluation of clinical performance depends on the nature of the test, its intended use, and the amount of existing information about the associations of genetic markers and clinical diagnosis.

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[2] Gutman SI. FDA's role in the regulation of in vitro diagnostic. Presentation May 10, 2003. Rockville, MD: United States Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Device Evaluation and Safety, 2003. Accessed September 1, 2007. http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html.

[3] Clinical Laboratory Improvement Amendments (CLIA). Baltimore, MD: Centers for Medicare and Medicaid Services, 2007. Accessed September 14, 2007. http://www.cms.hhs.gov/clia.

[4] S.976: Genomics and Personalized Medicine Act of 2007. See http://www.govtrack.us/congress/billtext.xpd?bill=s110-976. Accessed Sept. 1, 2007.

[5] Senator Kennedy introduced the Laboratory Test Improvement Act. Genetics and Public Policy Center. Accessed September 5, 2007. http://www.dnapolicy.org/news.enews.article.nocategory.php?action=detail&newsletter_id=20&article_id=78

[6] New York State Department of Health. Clinical Laboratory Evaluation Program. Accessed October 19, 2007. http://www.wadsworth.org/labcert/clep/clep.html

[7] Willey AW. New York State Laboratory Specific Assay Validation Review and Approval as Applied to Genetic Testing. New York State Department of Health. Presentation to SACGHS meeting, March 26, 2007. Accessed October 18, 2007. http://www4.od.nih.gov/oba/sacghs/meetings/Mar2007/Mon%20pm%20-%20Willey.pdf.

[8] CLIA, 2007.

There are also questions about the sufficiency of CLIA's requirements for assessing the performance of genetic testing laboratories. While CLIA requires laboratories to have quality assurance programs in place, most genetic testing laboratories are not required by CLIA to perform the type of assessment called proficiency testing (PT) unless they are testing a small subset of established analytes regulated under CLIA,[9] none of which are genetic tests per se. PT serves as an assessment of laboratory competence by comparing a laboratory's test performance and results to an established external standard,[10] and it is considered to be the most rigorous form of performance assessment currently available. In principle, genetic tests and all genetic tests and other high-complexity tests should be required to undergo PT. Thus, gaps in oversight still exist regarding the regulation, breadth, costs, and availability of testing materials for existing PT programs.

Clinical utility, which refers to the net balance of risks and benefits associated with using a test in routine practice, is another critical element for translating genetic testing into clinical practice. With the establishment of analytical and clinical validity as prerequisites, information and data illustrating the potential health benefits and harms of a genetic test are necessary for the effective management of patients, the development of professional guidelines, and coverage decisions. The current evidence base for the clinical utility of genetic testing is limited, and healthcare payers are increasingly calling for such evidence in order to make coverage decisions. Although Federal initiatives by the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH) have made great strides in evidence development for genetic testing, a more coordinated approach for effectively translating genomic applications into clinical practice and health policy is needed.

Technical advances in genetic testing must be accompanied by accurate interpretation and communication of genetic test results. Professional recommendations, including those from such groups as the American College of Medical Genetics, U.S. Preventive Services Task Force and others, provide information to practitioners about the ordering of genetic tests and reporting of results.[11] Organizations such as the National Coalition for Health Professional Education in Genetics have engaged in efforts to enhance clinician understanding genetic testing and its appropriate use.[12] Yet, there is insufficient data about how well practitioners order, conduct, and interpret genetic tests and the extent to which genetic test results are used appropriately to support clinical decisionmaking. Most practitioners are unfamiliar with guidelines for the appropriate use of genetic tests, and few processes have been implemented, evaluated, or enforced to support practitioners in this regard.

Along with efforts to guide healthcare professionals, it is necessary to improve the education of patients and other consumers. The increasing prevalence of genetic testing has led to a rise in direct-to-consumer (DTC) advertising of genetic tests. In 2006, the Federal Trade Commission (FTC), in conjunction with FDA and CDC, issued a consumer alert warning consumers to be wary of claims made by at-home

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[9] Clinical Laboratory Improvement Amendments (CLIA), Subpart I – Proficiency testing program for non-waived testing. Atlanta, GA: Centers for Disease and Control Prevention. Accessed August 9, 2007. http://wwwn.cdc.gov/clia/regs/subpart_i.aspx.

[10] Tholen DW, Berte LM, Boone DJ et al. Using proficiency testing to improve the clinical laboratory; Approved guideline – 2nd Edition. GP27-A2, Vol. 27(8). Wayne, PA: Clinical and Laboratory Standards Institute. Accessed October 19, 2007. http://www.clsi.org/source/orders/free/gp27-a2.pdf

[11] American College of Medical Genetics – Practice Guidelines. Bethesda, MD: American College of Medical Genetics. Accessed October 19, 2007. http://www.acmg.net/AM/Template.cfm?Section=Practice_Guidelines&Template=/CM/HTMLDisplay.cfm&ContentID=2257

[12] Contracts and Grants. Lutherville, MD: National Coalition for Health Professional Education in Genetics (NCHPEG). Accessed October 19, 2007. http://www.nchpeg.org/content.asp?dbsection=contracts#1

genetic tests.[13] There also appears to be a lack of patient guidance for interpreting information from all forms of genetic testing, not just DTC tests. With the exception of State-based newborn screening programs, few patients have access to genetics expertise, as there are only a small number of formally trained genetic service providers in the country. There have thus been calls for more genetics professionals and counselors to help patients understand the health impact of their genetic information.

Challenges and Key Considerations

There are many challenges to effective oversight of genetic testing. Analytical and clinical validity must be established for the increasing number of new technologies to be of practical use to clinicians and patients, highlighting the need for information exchange, premarket and postmarket data, and reference materials to verify newly developed assays. Clarification and better coordination of FDA, CLIA, and State-based regulations over quality assurance and PT will be necessary to reduce ambiguity and increase consistency over standards for laboratory compliance. The small body of existing research on clinical utility of genetic testing highlights a critical lack of information on how genetic test information is used to influence clinical decisionmaking and affects health outcomes. A related shortcoming is the dearth of educational programs for clinicians, practitioners, and healthcare professionals on how to deliver and interpret genetic information for patients. The translation of genetic tests into clinical practice will rely heavily on pre- and post-analytic clinical decision support and research into the impact of genetic information on healthcare delivery, outcomes, and costs.

Key considerations for the oversight of genetic testing include the following:

- **Analytical and clinical validity** must be established for emerging genetic testing technologies, including through the development of assay validation tools, improved data sharing among researchers, and establishment of evidentiary standards. This effort requires clear provisions for authority and resources for oversight.

- **Proficiency testing and quality assurance** are essential for the continuous quality management and maintenance of process standards for laboratories performing genetic testing. Emerging technologies continue to pose a significant challenge for the availability of materials for PT and quality assurance.

- **Demonstration of clinical utility**, using data from a variety of prospective and retrospective studies, can help to establish how genetic testing affects health outcomes. The development of evidentiary standards, data sources, and evidence-based methods applicable to genetic testing can help to establish clinical utility and guide the effective translation of genetic research into practice.

- **Education and guidance** for physicians, clinicians, laboratory personnel, and other healthcare professionals are essential to ensure the accurate use and interpretation of genetic tests. Training on the effective use of electronic health records and clinical decision support in the pre- and post-analytic phases of genetic testing is also needed.

- **Coordination of public and private sector activities** has the potential to strengthen oversight of genetic testing through complementary and consistent State and Federal requirements for

[13] At-home genetic tests: a healthy dose of skepticism may be the best prescription. Washington, DC: Federal Trade Commission, 2006. Accessed June 25, 2007. http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm.

establishing analytical validity, quality assurance, clinical validity, clinical utility, and education and guidance.

Recommendations

The Committee makes the following recommendations with the hope that they will be useful to the Secretary in leading HHS efforts to maximize the benefits of genetic testing in the United States and the important role they play and will continue to play in achieving personalized health care.

Overarching Recommendation

SACGHS' analysis of the U.S. system of oversight of genetic testing found a complex system involving many dedicated, hard-working public and private sector entities at both the national and State levels. Nonetheless, the Committee also found significant gaps in the system that could lead to harms. The Committee formulated a number of recommendations that, if implemented and sufficiently supported, could help close these gaps. A critical theme in many of the recommendations is that new and enhanced collaborations and public partnerships between the Federal Government and the private sector are needed. In the Committee's view, it is also important for the HHS to enhance interagency coordination so that the agencies with regulatory roles (CMS and FDA) are working synergistically with one another, with other regulatory agencies (FTC), and with the knowledge generation agencies (AHRQ, CDC, HRSA, and NIH). Such coordination would help enhance the consistency and complementarity of Federal programs and ensure the most efficient and effective use of the public-private partnerships that will be key to closing gaps in the oversight of genetic testing. To this end, SACGHS recommends that:

> The HHS Secretary take steps to enhance interagency coordination of the activities associated with the oversight of genetic testing, including policy and resource development, education, regulation, and knowledge generation.

Analytical Validity, Proficiency Testing, and Clinical Validity

1) For a number of years, CMS had been planning to address gaps in the oversight of laboratories that conduct genetic tests with the addition of a genetic testing specialty under CLIA. Recently, CMS changed direction and is now addressing these gaps with a multi-faceted action plan. SACGHS considered CMS' rationale and reviewed the agency's action plan. SACGHS carefully considered the recommendations of prior groups as well as the perspectives of stakeholders who support the specialty. In the end, the Committee came to the conclusion that identified gaps can be addressed without the creation of a genetic testing specialty. SACGHS proposes the following recommendations to support and/or augment the CMS action plan:

   A. Currently, CLIA requires all non-waived tests to undergo some form of performance assessment, but only 83 specific analytes, none of which are genetic tests per se, are required to undergo the type of assessment called proficiency testing (PT). PT is currently considered to be the most rigorous form of performance assessment. In principle, genetic tests and all other high-complexity tests should be required to undergo PT. However, such a goal may not be achievable. Consequently, the following actions should be taken:

      1. HHS should fund studies of the effectiveness of other types of performance assessment methods to determine whether they are as robust as PT and support innovations in the way PT is performed such as through methodology-based processes.

2. In the interim, steps need to be taken to increase the use of PT for genetic tests.

    a. CMS should amend the CLIA regulation to expand the list of regulated analytes to include genetic tests for which PT products are available. In addition, CMS should restructure the PT provision of the rule to enable the list to be updated more rapidly and assure an efficient process to review new PT products.

    b. CMS should seek advice from an appropriately constituted group of relevant experts to determine which genetic tests should be added to the list of regulated analytes.

    c. HHS should develop incentives for PT providers to expand PT products for those genetic tests.

B. CMS should consult or contract with experts in the field to train inspectors of genetic testing laboratories. Training by such experts will enhance inspectors' understanding of the technologies, processes, and procedures utilized by genetic testing laboratories and equip them to assess compliance with CLIA requirements. In addition, CMS should identify and evaluate innovative, alternative mechanisms to inspect genetic testing laboratories.

C. As recommended in a 2006 Government Accountability Office report on clinical laboratory quality, CMS should use revenues generated by the CLIA program to hire sufficient staff to fulfill CLIA's statutory responsibilities and the program should be exempted from any hiring constraints imposed by or on the agency.

2) Currently, there are gaps in the extent to which analytical validity and clinical validity data can be generated and evaluated for genetic tests. To address these gaps, SACGHS recommends supporting public resources for genetic testing through the following actions:

A. In consultation with relevant agencies, HHS should assure funding for development and characterization of reference materials, methods, and samples (e.g., positive and negative controls and samples from different ethnic/geographic populations) for assay validation, quality control, and performance assessment.

B. HHS should assure funding for the development of a mechanism to establish and support a laboratory-oriented consortium to provide a forum for sharing information regarding method validation, quality control, and performance issues.

C. HHS agencies, including NIH and CDC, should continue to work with public and private partners to support, develop, and enhance public reference databases to enable more effective and efficient collection of mutation and polymorphism data and expand clinical reference sequence databases, and provide summary data on gene-disease associations to inform clinical validity assessments (e.g., RefSeqGene, HuGENet).

D. HHS should support the development by professional organizations of additional standards and guidelines for applying genetic tests in clinical practice.

3) Today, there continue to be considerable information gaps about the number and identity of laboratories performing genetic tests and the specific genetic tests being performed. In the Committee's view, registration efforts are needed to understand the universe of genetic tests being

offered and to enhance the transparency of this field. SACGHS reviewed a number of proposals of both a voluntary and mandatory nature. SACGHS recommends:

A. The establishment of a voluntary system of genetic test registration through a public-private partnership. Specifically,

    1. HHS should provide additional funding to expand GeneTests to include genomic applications with the potential for broad public health impact, including those related to pharmacogenomics, and somatic genetic disorders and other types of testing methods (e.g., biochemical testing).

    2. HHS should provide incentives to encourage laboratories to register with GeneTests, and this information should be easily accessible to the public.

    3. After five years, HHS should assess the completeness and adequacy of the voluntary system. If the system is found to be inadequate, HHS should consider whether registration should be mandatory.

4) There has been much debate in the past decade regarding FDA's role in regulating laboratory developed tests (LDTs). SACGHS supports FDA regulation of LDTs and the flexible risk-based approach the agency is taking to prioritize genetic LDTs, an approach that should be robust enough to accommodate new genetic testing technologies and methodologies. SACGHS agrees that applying the same regulatory framework to every genetic test is infeasible given the number of tests in use and in development and the costs and resources that would be needed to support such a structure. Moreover, such a policy could unnecessarily delay patient access to important new technologies. FDA has taken an important step forward in defining the type of LDTs that will be subject to premarket review. However, SACGHS suggests that further analysis, deliberation, and consultation are needed to determine whether the appropriate weight has been apportioned to the risks associated with the novelty and complexity of the testing platform and technology. SACGHS recommends that:

A. HHS convene relevant HHS agencies, including FDA, CMS, CDC, AHRQ, and NIH, as well as stakeholders to provide further input into the development of a risk-based framework for the regulation of LDTs.

B. For LDTs that will not be subject to FDA review and clearance processes, SACGHS recommends that:

    1. HHS encourage and support the development of new and transparent models for private sector efforts or public-private partnerships that could assess the analytical and clinical validity of laboratory developed genetic tests.

    2. Laboratory developed tests that have undergone such an assessment would be certified as having been through the process. Such certifications should be made publicly available and could be included as part of the test's listing in GeneTests. For a test whose assessment is negative, i.e., it is found to lack analytical validity and/or clinical validity, HHS should determine the appropriate course of action.

5) SACGHS' fact finding also identified gaps in the enforcement of existing regulations. The following steps should be taken to address them:

A. Further efforts are needed to prevent laboratories from performing genetic tests without appropriate CLIA certification. In addition, although the CLIA program has an array of enforcement actions available, those actions cannot be imposed on uncertified laboratories. Instead, CMS must report the laboratory to the HHS Inspector General for action. HHS should explore mechanisms and seek or develop new authorities and resources to enable CMS to strengthen its enforcement efforts against laboratories that perform genetic tests for clinical purposes without proper CLIA certification. CMS should step up its efforts to make publicly available a list of laboratories that have been cited by CLIA for condition-level deficiencies.

B. Appropriate Federal agencies, including CDC, CMS, FDA, and FTC, should strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about genetic tests.

6) SACGHS is concerned about certain types of health-related genetic tests that are marketed directly to consumers and appear to fall outside the scope of CLIA. Some nutrigenomic tests (e.g., a test for caffeine metabolism) and tests to determine the gender of a fetus are examples of health-related genetic tests that are skirting the boundaries of CLIA's authority. There is insufficient oversight of laboratories offering such tests and their potential impact on the public health is an increasing concern. SACGHS recommends that:

CLIA regulations, or if necessary, CLIA's statutory authority, should be expanded to encompass the full range of health-related genetic tests. Relevant agencies should collaborate in an effort to develop an appropriate definition of health-related genetic tests that CMS could use as a basis for expanding its scope.

Clinical Utility

1) Information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions. SACGHS found a paucity of information on clinical utility of genetic testing. There is inadequate data on which to base utility assessments and only a few studies have been done of the clinical utility of specific genetic tests. More fundamentally, insufficient analysis has been done of the standard of evidence upon which the clinical utility of genetic tests should be evaluated and evidence-based methods applicable to genetic testing have been developed. Further policy analysis is also needed to define the process by which clinical utility assessments will be applied. To fill these needs SACGHS recommends the following:

A. HHS should create and fund a sustainable public/private entity of stakeholders to assess the clinical utility of genetic tests (e.g., building on CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative). This entity would:

1. identify major evidentiary needs;

2. establish evidentiary standards for different applications and types of decisions;

3. establish priorities for research and development;

4. augment existing methods for assessing clinical utility as well as analytical and clinical validity, such as those used by EGAPP and the U.S. Preventive Services Task Force, with relevant modeling tools;

5. identify sources of data and mechanisms for making them usable for research;

6. recommend additional studies to assess clinical effectiveness;

7. achieve consensus on minimal evidence criteria to facilitate the conduct of focused, quick-turnaround systematic reviews;

8. increase the number of systematic evidence reviews and make recommendations based on their results;

9. facilitate the development and dissemination of evidence-based clinical practice guidelines and clinical decision support tools for genetic/genomic tests;

10. establish priorities for implementation in routine clinical practice; and

11. publish the results of these assessments or make them available to the public via a designated HHS or other publicly supported website (e.g., GeneTests).

B. To fill gaps in the knowledge of analytic validity, clinical validity, clinical utility, utilization, economic value, and population health impact of genetic tests, a Federal or public/private initiative should:

1. develop and fund a research agenda to fill those gaps, including the initial development and thorough evaluation of genetic tests, and the development of evidence-based clinical practice guidelines for the use of those tests;

2. conduct research and surveillance on how that information can be translated into care practices that enhance the quality of care and health outcomes, including the dissemination and implementation of recommended genetic tests into clinical and public health practice, the evaluation of the extent and fidelity with which recommended applications are implemented in community settings, and the effect of implementation on population health; and

3. disseminate these findings to the public via a designated HHS or other publicly supported website (e.g., GeneTests).

2) Healthcare payers are increasingly requiring evidence of clinical utility before they will pay for genetic tests. Therefore, coverage and reimbursement decisions play a critical role in stimulating innovation and facilitating access to genetic testing. In February 2006, SACGHS issued a report that made recommendations for developing evidence of clinical utility and addressing other barriers to the coverage and reimbursement of genetic tests and services in the public and private sectors. SACGHS offers the following recommendation concerning the development of clinical utility evidence:

As the issues identified in the *Coverage and Reimbursement of Genetic Tests and Services* report are still current, SACGHS urges HHS to act on the report's recommendations. In addition, public and private healthcare payers should develop mechanisms, such as coverage with evidence development or phased reimbursement, to facilitate the collection of clinical utility evidence.

3) The value of genetic tests to patients is realized only when they are used appropriately. In addition, quality improvement processes are needed to assure that genetic tests are delivered consistently to appropriate patients. Furthermore, an ongoing process is needed to identify opportunities for improving the use of genetic testing, including the collection of postmarket outcome data. SACGHS, therefore, makes the following recommendations:

HHS should conduct public health surveillance to assess surrogate and health outcomes, practice measures, including appropriate utilization, and the public health impact of genetic testing.

1. Information should be linked to quality improvement practices that affect patient outcomes and the provision of health services.

2. Data on specific genetic testing results would be required to permit understanding of the significance of genetic variants and new detection methods to improve the utility of testing.

4) The clinical utility and value of genetic testing is inextricably linked to methods to improve care processes and decision support. Interoperable electronic health records will play a central role in the translation of guidelines into care practices through their decision support and educational functions. They will serve as a critical resource for assessing clinical utility and quality of care. SACGHS therefore makes the following recommendations:

HHS should ensure the coordination of efforts, including the deliberations of SACGHS and AHIC (particularly work groups addressing personalized health care, population health and clinical care connections, and confidentiality, privacy, and security), to advance the appropriate use of interoperable patient-level data for research and for enhancing the quality of decisionmaking.

Communication and Decision Support

1) There are documented deficiencies in genetic knowledge in all relevant stakeholder groups. Since current strategies are inadequate to address these deficiencies:

HHS should work with all relevant Governmental agencies and interested private parties to identify and address deficiencies in genetic knowledge and education of three key groups in particular: healthcare practitioners, public health workers, and consumers. These educational efforts should take into account the differences in language, culture, ethnicity, and perspectives on disability that can affect the use and understanding of genetic information.

2) Although FDA has asserted its authority over clinical decisions support systems, the extent to which the agency intends to regulate such systems is not clear. Given that clinical decisions support systems will be necessary to communicate information appropriately in the pre- and post-analytic period and because these systems contain elements that involve the practice of medicine, clarification of the nature and scope of FDA oversight of such support systems is critical. SACGHS recommends that:

FDA should engage with other relevant Federal agencies, working groups (e.g., AHIC), and stakeholders to gather perspectives on the appropriate regulatory framework for clinical decision support systems in light of the changing healthcare delivery and healthcare data collection systems. FDA should then prepare a guidance document articulating the basis of its authority to regulate clinical decision support systems as well as its rationale and approach to such regulation, explaining in particular which features of the system constitute a device.

3) The need for genetic expertise to support best genetic testing practices has been identified as an essential element for the provision and interpretation of appropriate genetic tests. Access to genetic expertise could be addressed in part by solving problems in the reimbursement of genetic tests and services. SACGHS recommends that:

HHS act on the recommendations in the 2006 SACGHS *Coverage and Reimbursement of Genetic Tests and Services* report.

4) There are extensive gaps in knowledge about genetic tests and their impact on patient care. Prioritizing activities under the authority of HHS would help to close these gaps and enhance the quality of patient care. SACGHS recommends that:

   HHS allocate resources to AHRQ, CDC, HRSA, and NIH to design and support programmatic and research efforts in order to encourage development and assist in the evaluation and dissemination of tools, particularly computerized tools, for clinical decision support in the ordering, interpretation, and application of genetic tests; and address current inadequacies in clinical information needed for test interpretation.

5) Direct-to-consumer advertising of genetic tests and consumer-initiated genetic testing have the potential for adverse patient outcomes and cost implications for the healthcare system. There is a gap in knowledge concerning the extent of this impact. SACGHS recommends an examination of these issues:

   HHS should step up its efforts through collaborations among relevant Federal agencies (e.g., FDA, CDC, NIH, and FTC), States, and consumer groups to assess the implications of direct-to-consumer advertising and consumer-initiated genetic testing, and as necessary, propose strategies to protect consumers from potential harm. Any additional oversight strategies that may be established should be attentive to cost and access issues that might prevent consumers from gaining benefits of wider access to genetic tests.

Chapter 1
Background and Scope

Introduction

Since the launch of the Human Genome Project, genetic testing has been adopted increasingly into standard practice for diagnosing and managing disease, expanding on its roles in predicting the risk of future disease and informing decisions about life planning and behavior change. Today, genetic tests use combinations of biochemical, cytogenetic, and molecular methods to analyze deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, proteins, and selected metabolites. Advances in genetics research are enabling improved prevention, treatment and disease management for common chronic conditions such as cancer, heart disease, and diabetes.

Drawing from some of these advances, pharmacogenomic testing is a relatively new form of genetic testing that is attracting great attention. Pharmacogenomics (PGx) attempts to uncover the genetic basis for individual differences in drug toxicity and efficacy to optimize drug design and drug therapy. Customized treatment choices and regimens can mean better responsiveness, reduced side effects, and more cost-effective drug development and use of drugs.[14]

As health professionals increasingly turn to genetic testing to assess disease risks and use the information to guide healthcare and public health decisions, it will be necessary to anticipate and adapt to the impacts of these advances on individual health care and public health. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS, or the Committee) has prepared this report with the goal of further integrating genetic testing into clinical and public health practice in a responsible manner, so as to minimize possible harms and maximize the benefits of these innovative existing and emerging testing technologies.

Over the past decade, in parallel with advances in science and the growth of health uses of genetic tests, various groups have called for increased Federal oversight of genetic testing and testing laboratories. In 1997, the Task Force on Genetic Testing, convened jointly by the National Institutes of Health (NIH) and Department of Energy (DOE), issued a report, *Promoting Safe and Effective Genetic Testing in the United States*, which made several recommendations regarding the oversight of genetic tests and testing laboratories.[15] The NIH-DOE Task Force also called for the formation of a standing committee to provide advice to the Secretary of Health and Human Services (HHS) about the level of scrutiny needed for genetic tests. This recommendation led to the chartering in 1998 of the Secretary's Advisory Committee on Genetic Testing (SACGT), which operated until 2002 when it was succeeded by SACGHS.

In 1998-2000, the Clinical Laboratory Improvement Advisory Committee (CLIAC) recommended the augmentation of regulations governing the quality of clinical laboratories generally and genetic testing laboratories specifically.[16] In May 2000, the Centers for Disease Control and Prevention (CDC) published a Notice of Intent soliciting public comments on plans to add a genetic testing specialty under

[14] World Health Organization (WHO). (2007). Ethical, legal, and social implications (ELSI) of human genomics: Pharmacogenomics. Geneva, Switzerland. See http://www.who.int/genomics/elsi/pharmacogenomics/en/. Accessed August 14, 2007.

[15] National Human Genome Research Institute. (1997). Promoting Safe and Effective Genetic Testing in the United States. Bethesda, MD. See http://www.genome.gov/10001733. Accessed August 14, 2007.

[16] CDC. Summary of September 16-17, 1998 CLIAC Meeting. Available from: http://www.phppo.cdc.gov/CLIAC/cliac0998.aspx. Accessed on November 5, 2007.

regulations of the Clinical Laboratory Improvement Act Amendments.[17] Later that year, SACGHS' predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT), issued a report, *Enhancing the Oversight of Genetic Tests*, which concluded that additional oversight of genetic tests was warranted and should be achieved through new, multifaceted, and innovative oversight mechanisms.[18] SACGT also agreed with CLIAC that a genetics specialty should be added to CLIA. In 2003, the CLIA regulations were amended in several general ways (e.g., to enhance confidentiality of laboratory practices and expand requirements for result reporting).[19]

SACGHS first identified the oversight of genetic tests as a priority area in 2004 based on the expanded use of genetic testing in clinical practice and public health and the pace and extent of technological change in the ways testing is performed. In addition, like SACGT, the Committee was concerned about the adequacy and transparency of the oversight system and whether there were gaps in it that could lead to harms in public health. In 2006, after several years of monitoring developments, SACGHS received public testimony expressing concern about the delay in the augmentation of CLIA and then learned that the Centers for Medicare & Medicaid Services had decided not to proceed with adding a genetics specialty to CLIA. In March 2007, SACGHS began gathering more extensive information about the oversight roles of Federal, State, and private sector entities concerning the analytical and clinical validity of genetic tests, private sector responsibilities for clinical laboratory accreditation, standard setting, and the development of clinical practice guidelines for genetic testing. A summary of these presentations is found in Appendix A (*to be inserted in the final draft*).

These efforts converged with the goals of Michael Leavitt, Secretary of Health and Human Services (HHS), when he identified personalized health care as a top national priority. The Personalized Health Care (PHC) Initiative, coordinated by the Office of the Secretary (OS), aims to improve health care in the United States by using genomics to help tailor health care to individual genetic characteristics. One of the main goals of the PHC Initiative is to ensure the analytic validity, clinical validity, and clinical utility of genetic tests used in healthcare practice.[20]

To synchronize the work of SACGHS with the Secretary's priorities, the OS charged the Committee on March 26, 2007, with investigating specific issues related to the adequacy of current oversight systems for genetic testing. The charge, designed to complement related efforts underway at the Federal level, also encompassed all sectors of the healthcare system concerning oversight, including the Federal Government, State Governments, and the private sector. Refined during Committee discussion, the charge is to:

> Undertake the development of a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. Consider and address the following questions:
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> - What evidence of harm exists regarding genetic tests? Is that harm attributable to analytic validity, clinical validity, or clinical utility of the tests? If evidence does not exist, what threats are not currently being addressed? What public health benefits are not accruing as quickly as they might?

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[17] 65 FR 25928-25934. Notice of Intent: Genetic Testing Under the Clinical Laboratory Improvement Amendments.

[18] SACGT. (2000). Enhancing the Oversight of Genetic Tests: Recommendations of SACGT. See http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf. Accessed November 5, 2007.

[19] 68 FR 3640-3714. Medicare, Medicaid, and CLIA Programs: Laboratory Requirements Relating to Quality Systems and Certain Personnel Qualifications: Final Rule.

[20] Personalized Health Care: Goals. Washington, DC: The Department of Health and Human Services. http://www.dhhs.gov/myhealth care/goals/index.html#Goal3. Accessed August 14, 2007.

- What distinguishes genetic tests from other laboratory tests for oversight purposes?
- What are the existing pathways that examine the analytic validity, clinical validity, and clinical utility of genetic tests? Consider the use of case studies.
- What organizations are currently involved with each of these aspects, and what are they doing to address these issues? Who should be responsible for each of these aspects?
- What resources (e.g., standards reagents/materials) are needed to develop proficiency testing kits or protocols for genetic tests? What is currently available in terms of proficiency testing kits or protocols for genetic tests? What information is provided by proficiency testing? Is the current level of proficiency testing for genetic tests adequate and are the results of such laboratory performance assessments sufficiently transparent?
- What are the potential pathways to communicate clear information to guide test and treatment selection by the provider?
- What new approaches or models should be considered for private and public-private sector engagement in demonstrating clinical validity and clinical utility for developing effectiveness measures of genetic tests in clinical practice?
- Would additional or revised Government oversight add value for patients, and if so, how and where?

This report focuses on the oversight of genetic testing and the application of genetic information in patient care and management. In developing the report, the SACGHS Oversight Task Force explored pathways to examine the analytic validity, clinical validity, and clinical utility of genetic testing, possible gaps in testing oversight that might lead to harms, evidence development for oversight of genetic and genomic tests, and new approaches for demonstrating the analytic validity, clinical validity, and clinical utility of genetic testing in clinical practice. The recommendations presented by SACGHS call for new models for private and public-private partnerships; additional efforts in research, public health surveillance, data sharing, information exchange, and clinical decision support; and enhanced Government oversight of genetic testing.

Like many new technologies, genetic testing has clinical and social implications. A broad ethical issue that concerns many Americans is the potential misuse of genetic information, primarily due to the potential for insurance and employment discrimination based on genetic information.[21] The pending Genetic Information Nondiscrimination Act of 2007 contains provisions that would prohibit discrimination on the basis of genetic information with respect to health insurance and employment. Although it was passed by the House of Representatives in April 2007, it has yet to be voted on in the Senate.[22]

As genetic tests become increasingly available, there are concerns that stigmatization on the basis of genetic makeup will grow. Psychological harms may also grow as more people learn about their risks for later onset diseases, particularly those that currently have no effective treatment.[23] These broader societal implications and potential harms of genetic testing are not, however, the subject of this report. This report focuses primarily on harms that may occur in the course of the testing process, including pre-analytic, analytic, and post-analytic phases of testing, from deficiencies in knowledge and understanding about the validity and utility of genetic tests, their appropriate use, interpretation, and communication.

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[21] Council for Responsible Genetics. (2001). Genetic Discrimination: Position Paper, update of the 1997 Position Paper on Genetic Discrimination. Cambridge, MA. See http://www.gene-watch.org/educational/genetic_discrimination.pdf. Accessed September 25, 2007.

[22] The Genetic Information Nondiscrimination Act. H.R. 493. 110th Congress, 1st Session. January 16, 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf. Accessed September 19, 2007.

[23] Ibid.

Definition of a Genetic Test and Intended Use

A genetic test involves the analysis of chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, or gene products (e.g., enzymes and other proteins) to detect heritable or somatic variations related to disease or health. Whether a laboratory method is considered a genetic test also depends on the intended use, claim, or purpose of a test. For example, amino acid analysis to detect metabolic disorders such as PKU is considered a genetic test, but use of this analysis to monitor general nutritional status is not.

Are Genetic Tests Different from Other Laboratory Tests?

One of the questions in the Secretary's charge relates to whether genetic tests should be treated differently from other laboratory tests for oversight purposes. In considering how genetic tests and the information they provide might be different, it is helpful to consider some of the characteristics of genetics and whether other medical information shares those characteristics.

On the one hand, genetic test results generally do not change over one's lifetime; they can provide predictive information about the risks of developing disease in the future; they have implications for family members; and the information can be stigmatizing. On the other hand, some medical tests, such as tests for cholesterol levels or infectious disease, can also provide information about factors that affect risk of developing disease and may have implications for family members. Other medical information, such as a diagnosis of a mental illness or a sexually transmitted disease, can be stigmatizing. Another potential difference is an incomplete understanding of the clinical validity and utility of many genetic tests and that many health professionals lack sufficient knowledge of genetics and are not prepared to use genetic tests appropriately. Although the extent may differ, incomplete understanding and provider knowledge can also be true of other medical tests when they are first introduced.

The idea that genetic information should be treated differently is known as "genetic exceptionalism," a term adapted from the previously coined term "HIV exceptionalism." The term was first used during deliberations of the Task Force on Genetic Information and Insurance, formed in 1991 by the Joint NIH-DOE Working Group on the Ethical, Legal, and Social Implications (ELSI) of Human Genome Research. There is extensive scholarship on the subject of genetic exceptionalism and the question of whether genetic information should be considered special or unique from a public policy perspective. (See box.) The scholarly and policy literature suggests that views on this issue are evolving.

A consensus appears to be emerging that, while genetic information may be different in some respects from other health information, the differences are not significant enough to warrant special treatment in every case or situation. Moreover, given the significant role of genetic variation plays in health and disease generally, it may be neither wise nor possible to render genetic information distinct from other health information. These views suggest that, although it may be appropriate and necessary for certain areas of public policy to address genetic information in a specific way (e.g., Federal protection against genetic discrimination in health insurance and employment), it is not necessary for every public policy to take such an approach. Genetic tests and the laboratories performing them should be expected to meet the same high standards of accuracy, validity, and utility to which other medical information is subject.

Evolving Perspectives on Genetic Exceptionalism

When considering whether genetic testing is different from other laboratory tests, it is important to understand the viewpoint known as "genetic exceptionalism," the perspective that genetic information is unique among other

health-related information and, therefore, deserves special considerations and protections.[24] Proponents of this perspective usually point to the following features of genetic information as being distinct from other types of health information:

- It can be used to make predictions about an individual's health future.
- It does not change throughout a person's lifetime.[25]
- It has the potential to reveal information about family members.
- There are instances in which it has been used to discriminate against individuals or selected populations.[26]

Genetic tests can provide diagnostic and predictive information about disorders that have no treatment or preventive measures.[27] This aspect raises questions about the clinical utility of such tests, their benefit to patients and concerns about their psychological well being.[28] Genetic information can be used to identify individuals based solely on genetic sequence.[29]

Concerns about the stigmatizing potential of genetic information can be greater due to the legacy of the eugenics movement of the early 20th century,[30] which sought to improve the fitness of the human race by eliminating perceived undesirable genes from the population.[31] Concerns persist today among minority and disability communities and others that technologies such as preimplantation genetic diagnosis and prenatal genetic testing can be applied beyond ethical norms, putting vulnerable groups at increased risk for discrimination.[32] These concerns have highlighted how the concepts of health and risk may lead some to consider genetic testing in a special light.

Contrasting perspectives note that other tests are also used for risk assessment and prediction of later onset diseases. High cholesterol and HIV-positive status can, to a certain extent, predict an individual's health future.[33] Moreover, a genetic test's predictive value can be affected by limited knowledge of the penetrance of disease-causing genes, gene-gene and gene-environment interactions, and difficulty in distinguishing between genetic and nongenetic causes of disease.[34,35] The potential to reveal information about family members, affect their health status, and invite discrimination and social stigma also exist with tuberculosis, HIV, and sexually transmitted diseases.[36] In today's information-rich, electronic environment, the risk of individual identification extends

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[24] Murray TH. (1997). Genetic Exceptionalism and "Future Diaries": Is Genetic Information Different From Other Medical Information? In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. Ed. Rothstein, M.A. Yale University Press: New Haven. p. 60-73.

[25] Hodge, J.G. Jr. (2004). Ethical issues concerning genetic testing and screening in public health. *American Journal of Medical Genetics Part C.* 125C(1):66-70.

[26] Annas G, Glantz L, Roch A (1995). Drafting the Genetic Privacy Act: science, policy, and practical considerations. The *Journal of Law, Medicine, and Ethics.* 23(4):360-6.

[27] Murray TH. (1997). Genetic Exceptionalism and "Future Diaries": Is Genetic Information Different From Other Medical Information? In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. Ed. Rothstein, M.A. Yale University Press: New Haven. p. 60-73.

[28] Annas G. (1995). Genetic prophecy and genetic privacy – can we prevent the dream from becoming a nightmare? *American Journal of Public Health.* 85(9):1196-1197.

[29] Murray TH. (1997). Genetic Exceptionalism and "Future Diaries": Is Genetic Information Different From Other Medical Information? In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. Ed. Rothstein, M.A. Yale University Press: New Haven. p. 60-73.

[30] Micklos D, Carlson E. (2000) Engineering American society: the lesson of eugenics. *Nature Review Genetics*. 1(2):153-8.

[31] Wickler D. (1999). Can we learn from eugenics? *Journal of Medical Ethics*. 25(2):183-94.

[32] Parens E, Asch A. (1999) The disability rights critique of prenatal genetic testing: Reflections and recommendations. *Hastings Center Report*. 29(5):S1-22. See http://geneticsandsociety.org/downloads/1999_parensasch_hastings.pdf. Accessed September 20, 2007.

[33] Green, M.J. and Botkin, J.R. (2003). "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests. *Annals of Internal Medicine*. 138: 571-575.

[34] Murray TH. (1997). Genetic Exceptionalism and "Future Diaries": Is Genetic Information Different From Other Medical Information? In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. Ed. Rothstein, M.A. Yale University Press: New Haven. p. 60-73.

[35] Hodge, J.G. Jr. (2004). Ethical issues concerning genetic testing and screening in public health. *American Journal of Medical Genetics Part C.* 125C(1):66-70.

[36] Green, M.J. and Botkin, J.R. (2003). "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests. *Annals of Internal Medicine*. 138: 571-575.

beyond genetic testing; many databases contain sufficient information, health-related or not, to identify individuals.[37]

Public fear of genetic discrimination has been cited as an argument in favor of genetic exceptionalism and as justification for legislators to adopt an exceptionalist approach to genetics policy. A 2007 survey conducted by the Genetics and Public Policy Center found that 92 percent of people are concerned that the results of genetic tests could be misused to harm the individual tested, and that less than a quarter of people would trust an insurance company or employer to have access to their genetic information.[38] A study of genetic counselors' experiences found that 38 percent of patients already seeking genetic testing were fearful of discrimination, a figure that does not include patients who opted out of genetic testing altogether due to fears of discrimination.[39] Public concerns about misuse of personal genetic information indicates a need for protections sufficient to allay individuals' reluctance to seek potentially beneficial genetic tests.[40,41] A majority of State legislatures have adopted additional protections for genetic information.[42] State policies include protections against discrimination in insurance and employment decisions, and penalties for violating genetic privacy.[43] Pending Federal legislation, the Genetic Information Nondiscrimination Act of 2007, would prohibit discrimination based on genetic information in health insurance and employment.[44]

Recent research studies suggest that the public's views may be evolving about the nature of genetic information. A recent study involving focus groups of members of a health maintenance organization suggested that they did not view genetic information as fundamentally different from nongenetic medical information. They did express strong opinions about the privacy and protection of their medical records, but did not limit their concerns to genetic information or indicate that genetic information deserved additional protections. Given the homogeneous composition of the focus groups, however, further research is needed to ensure the generalizability of the findings.[45]

Likewise, a nonexceptionalist approach has been taken with respect to Federal health privacy protections. The Federal Health Information Portability and Accountability Act (HIPAA) Privacy Rule, which became effective in 2003, treats genetic information as equally sensitive as other medical information and provides the same level of protection to genetic information and other types of personal health information.[46] Recent policy recommendations encourage movement away from genetic exceptionalism. Some States, including Michigan, Nebraska, South Dakota, and Washington, have enacted legislation that does not follow an exceptionalist

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37 Murray TH. (1997). Genetic Exceptionalism and "Future Diaries": Is Genetic Information Different From Other Medical Information? In *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. Ed. Rothstein, M.A. Yale University Press: New Haven. p. 60-73.

38 U.S. Public Opinion on Uses of Genetic Information and Genetic Discrimination. Washington, DC: Genetics and Public Policy Center, 2007. See http://www.dnapolicy.org/resources/GINAPublic_Opinion_Genetic_Information_Discrimination.pdf. Accessed August 21, 2007.

39 Hall, M.A. and Rich, S.S. (2000). Genetic privacy laws and patients' fear of discrimination by health insurers: the view from genetic counselors. *The Journal of Law, Medicine, and Ethics.* 28(3):245-57.

40 Nuffield Council on Bioethics, London. (2003). Pharmacogenetics: ethical issues. See http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/publication_314.html. Accessed August 21, 2007.

41 Glaser J, Henley DE. Letter to the American Health Information Community from the Personalized Health Care Working Group, July 31, 2007. Washington, DC: United States Department of Health and Human Services. See http://www.hhs.gov/healthit/ahic/materials/08_07/phc/recs.doc. Accessed August 21, 2007.

42 National Conference of State Legislatures (2007). Genetic Technologies Project. Washington, DC. See http://www.ncsl.org/programs/health/genetics.htm. Accessed August 1, 2007.

43 French, M.E. and Moore, J.B. (2003). Harnessing genomics to prevent disease and improve health: a State policy guide. Washington, DC: Partnership for Prevention. See http://genes-r-us.uthscsa.edu/resources/genetics/geneticsguide.pdf. Accessed September 24, 2007.

44 H.R. 493, S. 358 (110th Congress), 1st Session. January 16, 2007. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf Accessed September 19, 2007.

45 Diergaarde B, Bowen DJ, Ludman EJ, Culver, J.O., Press, N., and Burke, W. (2007). Genetic information: special or not? Responses from focus groups with members of a health maintenance organization. *American Journal of Medical Genetics Part A.* 143A(6):564-569.

46 Institute for Health Care Research and Quality. Genetics and privacy: a patchwork of protections. Oakland, CA: California Health care Foundation. See http://www.chcf.org/documents/ihealth/GeneticsAndPrivacy.pdf. Accessed July 24, 2007.

approach.[47] Washington explicitly includes genetic information under the definition of healthcare information.[48] Michigan prohibits certain genetic discrimination practices, but considers genetic information to be no more or less confidential than other health information.[49] International policy recommendations also discourage adopting genetic exceptionalism in developing policy. The U.K. Nuffield Council on Bioethics rejects genetic exceptionalism, but recognizes that specific policies may need to be adopted in response to patient beliefs and fears regarding genetic information. Consideration of special protections for genetic information could reveal areas where the protection provided for other personal health information is insufficient.[50]

More recently, the Personalized Health Care Workgroup of the HHS American Health Information Community has been considering whether genetic information should be treated differently in electronic health records (EHR) and the characteristics of genetic test information that should be considered in determining protections that should be in place for accessing data. The fluidity of knowledge and understanding of genetic tests and the evolving nature of societal perspectives about genetic information are key points that suggest the need for flexible policies that can also evolve over time. A paper reviewed by the Workgroup in October 2007 suggests that "Genetic test information in the near term should be treated as other sensitive information in the EHR, and the same policies regarding confidentiality, privacy and security should apply."[51]

Overview of the Report

To develop a report that responds adequately to the Secretary's complex charge, SACGHS formed a task force of SACGHS members, *ex officios* and *ad hoc* experts from the public and private sectors with knowledge of genetics, clinical laboratory practice and accreditation, test evaluation, diagnostic manufacturing, health information technology, law and public policy, and consumer perspectives. The Task Force was divided into working groups and given specific assignments for each chapter of the report. Each group was led by a SACGHS member responsible for overseeing progress. The chapters were developed as follows:

Chapter 2 provides an overview of the current landscape of systems of oversight that play a role in assuring the appropriate use and interpretation of genetic tests, including the key Federal and State agencies and public and private sector entities that play a role in these systems. Oversight of genetic tests and the information they provide relies on systems of multiple, interrelated activities that focus on specific aspects related to the delivery and use of genetics tests, such as test manufacturing, or on specific participants, such as physicians and clinical laboratories. These systems help to ensure that the risk of harms that may result from genetic tests is reduced. Federal and State statues governing the oversight and regulation of genetic tests are described, as well as the roles of public sector groups in ensuring and influencing the quality of genetic tests.

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[47] French, M.E. and Moore, J.B. (2003). Harnessing genomics to prevent disease and improve health: a State policy guide. Washington, DC: Partnership for Prevention. See http://genes-r-us.uthscsa.edu/resources/genetics/geneticsguide.pdf. Accessed September 24, 2007.

[48] National Conference of State Legislatures (2007). Genetic Technologies Project. Washington, DC. See http://www.ncsl.org/programs/health/genetics.htm. Accessed August 1, 2007.

[49] French, M.E. and Moore, J.B. (2003). Harnessing genomics to prevent disease and improve health: a State policy guide. Washington, DC: Partnership for Prevention. See http://genes-r-us.uthscsa.edu/resources/genetics/geneticsguide.pdf. Accessed September 24, 2007.

[50] Nuffield Council on Bioethics, London. (2003). Pharmacogenetics: ethical issues. See http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/publication_314.html. Accessed August 21, 2007.

[51] "Confidentiality, Privacy, and Security Issues As They Pertain to Genetic Test Information in Electronic Health Records," Confidentiality, Privacy, and Security Subgroup of the American Health Information Community Personalized Health Care Work Group. See http://www.hhs.gov/healthit/ahic/materials/10_07/phc/issues.html. Accessed on November 5, 2007.

Chapter 3 provides a brief history of the development of genetic testing technologies, from early biochemical analysis, e.g., PKU and chromosome analysis, to analysis of single nucleotide polymorphisms. The chapter describes how the intended use of analysis determines whether a technology is considered genetic testing. A broad overview is provided of key technologies used for genetic testing, along with examples of how these technologies are used and future trends. A brief description of laboratory personnel is also provided.

In accordance with the charge from the Office of the Secretary, Chapters 4, 5, and 6 identify harms and gaps associated with the current systems of oversight and develop recommendations to address them. Chapter 4 describes the current oversight framework for analytical validity, PT (an important component of analytical validity) and clinical validity; and defines key terms related to these concepts. The chapter describes the two most widely used models for providing genetic testing: commercial development of products (test kits) by in vitro diagnostics manufacturers for distribution to multiple laboratories after clearance or approval by the FDA, and laboratory developed tests (LDTs) that are used solely by the developing laboratory. The chapter also discusses the reference and quality control materials essential for validating the performance characteristics of a test, monitoring test performance, and detecting problems in the testing process. Activities and programs related to PT**,** as well as challenges related to meeting PT requirements are discussed. Case studies are presented that illustrate the complex issues surrounding analytic validity and clinical validity, which is influenced by multiple factors. These factors include the purpose of the test, the prevalence of the disease or condition for which the test is being conducted, and the adequacy of the information available to determine test accuracy in detecting or predicting risk for a health condition or phenotype.

Chapter 5 discusses the meaning of clinical utility and the processes for generating information about it, including clinical trials and observational studies using registries and other longitudinal datasets. The chapter addresses current mechanisms for collecting and synthesizing information, such as systematic evidence reviews, decision models, and expert opinion, as well as determination of appropriate care through clinical guidelines. Clinical utility relies heavily on effective translation of research into practice, which may necessitate a variety of incentives (e.g., insurance contracts, pay-for-performance) to promote quality improvement and adherence to clinical guidelines. While economic issues and their relation to clinical utility are beyond the scope of this report, Chapter 4 broadly discusses the challenges associated with identifying how genetic information can make a difference in health outcomes.

Chapter 6 addresses the need for clinical guidance on the use of genetic tests. Once confined to specialty settings and primarily applied to those affected by, or at risk for, rare diseases, genetic testing is now used in a variety of settings, including primary care. With the recent accelerated use of genetic tests, it is critical to provide clinicians with appropriate decision support as they consider the use and interpretation of genetic tests. Healthcare providers need to be able to identify which patients might benefit from genetic testing, determine the appropriate test, provide pre- and post-test information to the patient, and interpret test results accurately. Laboratories must also accurately interpret and effectively communicate test results to the ordering physicians. Professional societies play an important role in defining standards of practice. Effective use of electronic health records (EHRs) will play a great role in improving the quality and consistency of patient care. Several workgroups within the American Health Information Community (AHIC), such as the Personalized Health Care (PHC) Workgroup, are advancing the use of health information technology to integrate genomic test information into EHRs.[52] Clinical decision support is also a large part of PHC, making efforts to increase clinicians' effectiveness by providing resources to improve the quality of care, avoid adverse events, provide actionable guidelines, and help

[52] American Health Information Community, Personalized Health Care Work Group Update: Vision and Priorities, April 24, 2007 www.hhs.gov/healthit/documents/m20070424/phcslides_files/outline/index.html. Accessed on November 5, 2007.

integrate newly discovered information into clinical practice.[53] Chapter 6 addresses these issues and offers recommendations on effective communication and clinical decision support in the pre- and post-analytic phases of genetic testing. Chapter 7 sums up the Committee's findings, conclusions, and recommendations.

[53] Ibid.

Chapter 2
Systems of Oversight for Genetic Testing

The purpose of oversight for laboratory testing, including genetic testing, is to reduce the risk of harms that may accompany testing and test results, and to promote appropriate uses of testing that will maximize health benefits. The delivery and use of genetic testing relies on a range of activities spanning the research and development (R&D) of test technologies, performance of clinical laboratory testing procedures, and use of tests results to guide health and lifestyle decisions. The oversight system consists of various elements that pertain to particular activities, such as test development and commercialization, or specific participants such as physicians and laboratory personnel. Many elements of oversight apply generally to medical devices or other products and professional activities, but some are specific to genetic testing. Depending on the aspect of testing, oversight may be mandatory or voluntary, and it is provided by Government agencies, healthcare payers, professional associations, and/or other groups.

This chapter describes the basic elements required for an oversight system and then focuses specifically on those elements that address genetic testing. It also provides an overview of the public, professional, and private sector agencies and organizations that have roles in the oversight of genetic testing, including the Federal and State agencies that oversee the regulation of genetic tests and their use in clinical practice.

Elements of Oversight

This report distinguishes among three main elements of oversight that are necessary in virtually any context: information development and synthesis, standard-setting, and compliance mechanisms (i.e., mandatory, incentive-driven, and voluntary or informal compliance mechanisms).

Information Development and Synthesis

Information development and synthesis refers to data collection, scientific studies, and reporting requirements aimed at identifying and measuring potential benefits and harms. Spanning premarket and postmarket activities, it involves, for example, conducting studies of the performance characteristics and potential uses of new tests, gathering data on adverse events associated with tests already on the market, developing evidence-based guidelines for appropriate clinical use of tests, inspection of manufacturing facilities and clinical laboratories, and collection of clinical and population-level data on actual patterns of use and reimbursement of tests. It also involves identifying and assessing strategies to improve the balance of benefits and harms and monitoring the effectiveness of measures to implement those strategies. Further, it entails creation, maintenance, and dissemination of evidence and other information to guide providers, payers, patients, policymakers, and other decisionmakers participating in the delivery and use of genetic testing.

Standard-setting

Standards arise from identifying and describing the characteristics that a product or service should have in order to be regarded as offering an acceptable mix of benefits and risks. Standard-setting activities are frequently, but not always, carried out by a Governmental body or regulatory agency, and requirements for implementing them range from compulsory or voluntary. Examples include standards for:

- Establishing analytical or clinical performance for genetic tests;
- Safety and effectiveness that genetic testing products must meet before they can be marketed in interstate commerce;

- Clinical laboratories that are able to offer testing services to the public;
- Training and credentialing for medical professionals, counselors, and others involved in delivering genetic testing to the public;
- Physicians' professional care (e.g., appropriateness of offering genetic testing to a patient and responses to specific test results);
- Clinical care, best practices, and guidelines on appropriate application of testing in specific clinical contexts;
- Liability in State product-liability lawsuits against manufacturers and negligence suits against physicians and other providers of health-related services; and
- Reimbursement by Governmental payers and private health insurers (e.g., whether genetic testing should be covered and payment amounts for testing).

Compliance Mechanisms

Oversight frameworks vary widely in terms of compliance with the standards they establish. At one end of the spectrum is a traditional "command-and-control" regulatory approach, by which an oversight body establishes mandatory standards, monitors compliance, and requires a response or applies legal sanctions in the event of noncompliance. This approach is often associated with formal, Governmental regulatory oversight bodies that have been granted statutory authority to set and enforce standards. NonGovernmental oversight bodies, however, may achieve effective enforcement of standards through nonlegal sanctions, such as professional censure or expulsion of members that refuse to comply.

At the opposite end of this spectrum is an approach sometimes referred to as a "regulatory triangle," consisting of an oversight body, the industry or activity that is being overseen, and the public.[54] In this model, the Governmental or nonGovernmental oversight body plays an information management role, such as gathering information about the safety of various providers of a service and disseminating it to the public and decisionmakers, who can then factor it into their private decisions. In this model, the oversight body does not necessarily set standards and may rely on the public to draw its own conclusions about acceptable standards of performance**.** This approach can help promote good standards of behavior, but there is a risk that information development and standard-setting may have little impact if the oversight body lacks effective mechanisms for promoting compliance.

This report distinguishes three categories of compliance mechanisms: mandatory compliance that is legally enforceable under Federal and/or State statutes and regulations, incentive-driven compliance that is not legally mandatory, but which is supported by concrete financial or liability-related incentives, and informal or voluntary compliance.

Mandatory compliance mechanisms include empowering a Governmental regulatory agency to deny market access to testing products that fail to meet an established standard of safety and effectiveness, or requiring certification or licensing by a Governmental body that verifies compliance with a defined standard. Mandatory compliance requires a statutory or regulatory framework that applies a penalty or withholds a benefit in the event that the standard is not being met. Examples of penalties could include seizure of noncompliant products, removal of a license or certification that is required to conduct

[54] World Bank. Greening Industry: New Roles for Communities, Markets, and Governments. New York: Oxford University Press, 1999.

business, civil penalties such as fines, or criminal sanctions. Withholding of benefits could include denying a noncompliant party a commercial advantage, such as the ability to market its goods or carry on its business or profession.

Incentive-driven compliance mechanisms provide financial incentives to comply with a standard that is otherwise voluntary in nature. These incentives can be in the form of a financial benefit or reward, such as a tax break or eligibility for third-party payment, or an opportunity to avoid costs, such as by reducing lawsuit risks (tort liability). Incentives for compliance may be created via laws and regulations, even when compliance itself is not required by law. Incentive-based mechanisms have also been linked to healthcare quality improvement through pay-for performance programs (sometimes known as "P4P") or "value-based purchasing." One example is the Hospital Quality Incentive Demonstration (HQID), a pay-for-performance project led by the Centers for Medicare & Medicaid Services (CMS) and Premier Inc., which aims to determine if financial incentives can effectively improve clinical quality by rewarding bonuses to hospitals that demonstrate high quality care in several areas of acute care.[55] Congress has also shown some support for financial incentives by calling on CMS to develop a plan for hospital value-based purchasing by 2009. Despite these trends, research is still exploring the potential benefits of pay-for-performance mechanisms.[56]

Another example of an incentive-driven compliance mechanism is CMS's policy of granting "deemed" eligibility status for Medicare reimbursements to healthcare facilities that voluntarily undergo certification by the Joint Commission (formerly the Joint Commission for the Accreditation of Health Care Organizations).[57] While accreditation is not legally mandatory, the advantages of deemed eligibility status create a strong incentive for hospitals to participate in this voluntary accreditation program. By analogy, CMS reimbursement policies have the potential to play an important role in promoting incentive-driven compliance with voluntary standards established in the area of genetic testing. Because CMS's policies often influence coverage policies of private insurers, incentive-driven compliance mechanisms developed through the Medicare and Medicaid reimbursement framework have significant potential to extend to broader beneficiary populations through emulation by private insurers.

There are numerous examples of compliance incentives that flow from parties' desire to reduce their tort liabilities. In the United States, tort lawsuits are primarily matters of State law and include product liability suits against manufacturers and negligence suits against physicians, clinical laboratories, and other providers of health-related services. Liability rules vary considerably among States, but, in the aggregate, play a crucial role in establishing incentives for compliance with standards for safe, effective use of genetic testing. For example, some States allow clinical practice guidelines to be introduced as evidence in malpractice suits. A physician who complied with a guideline could use this compliance as a defense to a malpractice claim,[58] which provides an incentive for physicians to follow guidelines even when compliance is voluntary. The strength of this incentive differs among States, however, as States vary regarding whether and when they allow clinical practice guidelines to be introduced into evidence and how much weight they give to such guidelines.[59]

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[55] Centers for Medicare and Medicaid Services (CMS)/Premier Hospital Quality Incentive Demonstration Project: project overview and findings from year two. See http://www.premierinc.com/quality-safety/tools-services/p4p/hqi/resources/hqi-whitepaper-year2.pdf. Accessed September 18, 2007.

[56] Lindenaur PK, Remus D, Roman S, and Rothberg MB. (2007). Public reporting and pay for performance in hospital quality improvement. *New England Journal of Medicine.* 356(5):486-96. Epub 2007 Jan 26.

[57] Cite to Medicare regulation section on deemed status.

[58] Curran,WJ, Hall MA, Bobinski MA, Orentlicher D. Health Care Law and Ethics, 5th ed. New York: Aspen Law & Business, 1998, 365-7.

[59] Hall MA. (1991). The defensive effect of medical practice policies in malpractice litigation. *Law and Contemporary Problems.* 54(1-2): 119-45.

While legal incentives are a potential method for increasing compliance, it is also important to maintain high evidentiary standards when evaluating new therapies and how they will be utilized or covered by insurers. The use of high-dose chemotherapy with autologous bone marrow transplant (HDC-ABMT) for breast cancer patients a decade ago is one example where political pressures heavily influenced coverage decisions outside of the clinical trial setting. In the face of heavy lobbying and litigation, insurers were forced to provide coverage for HDC-ABMT before a sufficient body of rigorous research on its safety and effectiveness was prepared;[60] data, as they became available, did not bear out this decision. Coverage policies pertaining to tests and other procedures for detecting prostate cancer, breast cancer, low bone density, and other conditions have been redefined as payers apply greater scrutiny to available evidence.

Voluntary or informal compliance mechanisms. Even when standards are not legally enforceable and are not supported by clear financial or liability-related incentives, informal compliance mechanisms may help promote implementation of voluntary standards. Voluntary certification and self-regulation programs developed by professional bodies and industry groups sometimes can be highly effective, for example, if these bodies are able to mobilize their members via application of informal sanctions (e.g., censure of members who operate outside accepted standards). "Watchdog" activities by consumer advocacy organizations and fear of adverse publicity can promote compliance with good practices. Industry self-regulatory activities also can play a constructive role in oversight by drawing attention to potential issues within the industry and by mobilizing industry participants to adopt voluntary standards for addressing those issues. In some cases, self-regulatory schemes may include some form of intra-industry peer review (self-policing) to monitor whether members of the industry are complying with the adopted standards. Self-regulatory arrangements are subject to limitations inherent in their voluntary nature and possible conflicts of interest between the industry and public interests. While they can play a constructive role in oversight, they should not be regarded as a substitute for more formal regulation in the public interest.

Although informal compliance mechanisms can be effective in certain circumstances, they frequently prove inadequate. Over-reliance on informal compliance mechanisms can negate the efforts that oversight bodies invest in information development and standard-setting activities. An effective oversight framework must integrate all three elements: information development, standard-setting, and appropriate compliance mechanisms. This last element need not be a "command-and-control" mandatory compliance framework, but it does need to provide effective incentives for parties to act on available information and adopt the standards that the oversight framework has developed.

Overview: Governmental and NonGovernmental Oversight Bodies

Numerous Governmental and nonGovernmental bodies share responsibilities for the oversight of genetic testing. These include Federal and State legislatures, Federal and State regulatory agencies, State and Federal courts, and professional and industry oversight bodies. Table 1 summarizes key elements of jurisdiction and corresponding systems of oversight for genetic testing.

The U.S. Congress and State legislatures are directly involved in the oversight of genetic testing through statutes that establish regulatory standards, such as the "safety and effectiveness" standard that the Federal Food, Drug, and Cosmetic Act (FFDCA) requires for genetic tests that are regulated as medical devices, or the "reasonable and necessary" standard for Medicare coverage. At the Federal and State level, legislatures can delegate authority to Governmental regulatory bodies to interpret, apply, and enforce the statutory standards in particular cases and address particular uses and misuses of genetic

[60] Mello, M.M. and Brennan, T.A. (2001). The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. *Health Affairs* (Millwood). 20(5):101-17.

information (e.g., State[61,62] and proposed Federal[63] legislation prohibiting genetic discrimination in employment and insurance enrollment, and legislation addressing data privacy and information security[64]).

Federal and State regulatory agencies have powers delegated by Federal or State legislatures to oversee particular aspects of genetic testing. Regulatory agencies have a statutorily defined "jurisdiction," that is, specific sets of delegated powers and controls corresponding to specific issues, aspects of industry activity, and/or industry participants. These delegated powers may include: the power to engage in information development and standard-setting activities; a quasi-legislative power to issue rules that are legally binding in character (i.e., "regulations," which in the case of Federal agencies are recorded in the Code of Federal Regulations); quasi-executive powers to inspect, monitor, and enforce their standards; and quasi-judicial powers to adjudicate specific cases in which the regulations are applied to particular regulated parties. Key Federal and State regulatory agencies involved in the oversight of genetic testing are described later in this chapter.

State and Federal courts. State courts are the primary venue for tort lawsuits (product liability and negligence suits) in the United States and therefore play a crucial role in defining the standards of conduct to which manufacturers, clinical laboratories, physicians, counselors, and other parties will be held. State liability rules establish incentives for such parties to comply with regulatory standards (e.g., warnings in product labeling or evidence-based practice guidelines developed by a Federal agency) and informal standards (e.g., voluntary clinical practice guidelines). Federal courts are generally less involved in tort lawsuits. The statutes that authorize Federal regulatory oversight activities typically provide for Federal courts to hear appeals of regulatory decisions. In this capacity Federal courts may resolve disputes about the scope of a regulator's authority and handle appeals of disputed decisions by Federal regulators. Thus, State courts have continuous, ongoing involvement in oversight, via thousands of lawsuits in which aggrieved parties seek redress for alleged breaches of appropriate standards of conduct. The Federal courts' role in oversight is infrequent, but has the potential for great impact when it does occur.

Table 1. Key Elements of the Regulatory Oversight Framework for Genetic Testing

Area of Jurisdiction	Systems of Oversight
Regulation of clinical laboratories and testing services	**Federal:** CMS CLIA, with involvement of other federal agencies (e.g., FDA in categorization of tests and FTC in oversight of marketing) **Some States**: e.g., New York, Washington, California
Medical product regulation	**Federal:** FDA regulation of genetic tests and therapies used in conjunction with genetic tests, with oversight of marketing shared between FDA and FTC.
Regulations affecting reimbursement and access to genetic testing	**Federal:** CMS Medicare **State:** State health programs and insurance regulations affecting private insurers

[61] Williams ED, Sarata AK, Redhead CS. (2007). Genetic discrimination: overview of the issue and proposed legislation (RL33903, Mar. 7, 2007). U.S. Congressional Research Service. Ithaca, NY: Cornell University. http://digitalcommons.ilr.cornell.edu/cgi/viewcontent.cgi?article=1028&context=crs. Accessed October 30, 2007.

[62] Clayton, E.W. (2003). Ethical, legal, and social implications of genomic medicine. *New England Journal of Medicine.* 349(6):562-9.

[63] H.R. 493, S. 358 (110th Congress), 1st Session. January 16, 2007. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf Accessed September 19, 2007.

[64] Health Insurance Portability and Accountability Act of 1996. Public Law 104-191. 104th Congress. August 21, 1996. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation. Accessed September 20, 2007. http://aspe.hhs.gov/admnsimp/pl104191.htm.

	Informal/private sector: Medical necessity and utilization review practices, contracts
Clinical practice regulation (e.g., when, whom to test; physicians' claims and disclosures about tests)	**State law**: Medical practice & pharmacy regulations, consent laws, genetic privacy acts, tort law. **Informal regulation**: Voluntary guidelines and professional standards.
Regulation of specific uses and misuses of test results (e.g., privacy and data security; discrimination in employment and insurance)	**Federal:** Employment Retirement Income Security Act (ERISA), Health Insurance Portability and Accountability Act (HIPAA), Americans with Disabilities Act (ADA), etc. **State:** Statutes and tort law
Standards of patient responsibility	**State tort law:** Delineates when patients are responsible for protecting themselves as opposed to when they are entitled to rely on protection by other parties (e.g., manufacturers, physicians)

Professional and private sector oversight bodies. Professional societies, industry trade groups, and private-sector accreditation and oversight bodies play important roles in the oversight of genetic testing. The terms "informal regulation" and "informal regulatory bodies" are sometimes used to refer to these activities. In this report, the terms "regulatory" and "regulation" are reserved for formal, Governmental regulatory activities unless the term "informal" is expressly stated. Activities of key professional and private-sector oversight bodies in the area of genetic testing are described later in this chapter.

Oversight Role of Federal and State Regulatory Agencies

The United States has a bifurcated policy that requires prior regulatory review of safety and effectiveness for some, but not all, genetic and diagnostic tests. This situation reflects longstanding differences in the regulation of test products and testing services. At the Federal level, the Food and Drug Administration (FDA) and CMS have prominent oversight roles. In large part, their respective regulatory authorities derive from dual, yet sometimes overlapping, systems of regulating tests as medical devices as opposed to regulating testing services. Genetic testing products are medical devices subject to regulation under the FFDCA,[65] implemented by the FDA. Under FFDCA, the agency is mandated to ensure that medical devices are safe and effective.

Federal regulation of testing products. Genetic testing products, with limited exceptions, must pass through FDA's medical device premarket clearance or approval processes. As noted above, FDA's statutory mandate under the FFDCA is to ensure that medical devices are safe and effective.[66] FDA has interpreted this mandate as requiring a prior assessment of analytical and clinical performance of the device. This requirement is claims-driven, meaning the manufacturer must provide data supporting any analytical and clinical claims related to the use and/or effectiveness of a product. These claims are distinct from the payment claims used to seek reimbursement. Other chapters of this report discuss the specific requirements in terms of proof of analytical validity, clinical validity, and clinical utility. FDA

[65] Federal Food, Drug, and Cosmetic Act. Pub. L. no. 75-717, 52 Stat 1040 (1938). as amended, codified at 21 U.S.C. Sec.301-399. Baltimore, MD: US Social Security Agency, 2007. See http://www.ssa.gov/OP_Home/comp2/F075-717.html. Accessed October 30, 2007.

[66] In evidence-based medicine and related fields, the term "efficacy" refers to how well a technology works under ideal or well-controlled conditions of use, whereas "effectiveness" refers to how well a technology works under routine or general conditions. Although FFDCA uses the term "effective," the evidence required by FDA to support premarket clearance or approval of new technologies is typically generated under conditions that would demonstrate efficacy rather than effectiveness.

and the Federal Trade Commission (FTC) both play roles in regulation of marketing and promotion of testing products, i.e., protecting consumers from misleading or inaccurate information about the risks and benefits of genetic testing products.

Federal regulation of testing services. CMS has regulatory responsibilities for laboratory testing, including genetic testing, under the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA).[67] CMS oversees the administration of the many functions of CLIA, including the two main requirements for testing services: (1) registration with the CLIA program, and (2) certification by an approved accreditation body or CMS. Certification is intended to ensure that a clinical laboratory meets CLIA established standards for quality assurance, record maintenance, proficiency testing, personnel qualifications and responsibilities, and quality control. CLIA requirements for laboratory certification depend on the complexity of the tests performed; the more complex the test, the more stringent the requirements. FDA has been involved with CLIA since 2000, when it took over the responsibility of categorizing the complexity of certain diagnostic tests.[68] These tests are also subject to relevant FTC regulations for marketing.

CLIA gives CMS the authority to regulate laboratories that use laboratory-developed tests (LDTs), as well as FDA-approved or -cleared tests. Although a laboratory can use its LDTs to provide testing services to the public, it cannot sell its LDTs for use by others. CLIA requirements for LDTs and the FDA requirements of the 510(k) and premarket approval (PMA) review processes serve different purposes and use essentially different information sets, that is, FDA for safety and efficacy, and CLIA for accurate testing. Protocols instituted by each agency to meet their statutory responsibilities continue to be streamlined to reduce burden without compromising the integrity of each program's goals.

CLIA takes a process-oriented approach that focuses on factors such as credentials of laboratory personnel and laboratory testing procedures, rather than on data-driven regulatory clearance or approval for specific LDTs before they can enter clinical use. Thus, LDTs are not required to pass through an external regulatory review process to substantiate their claimed performance characteristics, although they generally do receive internal analytical validation by the laboratories that made them. CLIA surveyors do review analytical data (on quality control, proficiency testing, and quality assurance) for a sample of tests from all areas for which the laboratory is certified and the clients they serve. The emphasis of this review is on new tests or instruments or tests/requirements for which the laboratory has had problems in the past. Laboratories under CLIA are not discouraged from establishing clinical performance and validation of a new test. Even though it is not currently a regulatory requirement under this program, CLIA expects the laboratory director to assure that all tests offered by the laboratory are clinically relevant for the patient population being tested. CLIA inspectors have general expertise or training in clinical validation.

CMS has also established specific requirements for CLIA specialty areas such as microbiology and cytogenetics (the study of chromosomes and the diseases caused by numerical and structural chromosomal abnormalities), though genetic testing is not recognized as a CLIA specialty area.[69] In 1997, a joint National Institutes of Health (NIH)-Department of Energy (DOE) Task Force recommended that the Clinical Laboratory Improvement Advisory Committee (CLIAC) consider the creation of a genetic testing specialty for CLIA. The Task Force determined that, in the absence of a genetic testing specialty, "there is no assurance that every laboratory performing genetic tests for clinical purposes meets

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[67] CLIA Program. Baltimore, MD: Centers for Medicare & Medicaid Services. See http://www.cms.hhs.gov/clia/. Accessed May 1, 2006.

[68] CLIA Program. Baltimore, MD: Centers for Medicare & Medicaid Services. See http://www.cms.hhs.gov/CLIA/10_Categorization_of_Tests.asp#TopOfPage. Accessed November 5, 2007.

[69] CLIA Program. Baltimore, MD: Centers for Medicare & Medicaid Services. See http://www.cms.hhs.gov/clia/. Accessed May 1, 2006.

high standards." CLIAC made recommendations to strengthen genetic testing under CLIA pertaining to matters of informed consent, reuse of tested specimens, confidentiality, quality control, specimen integrity, proficiency testing, and personnel qualifications and responsibilities.[70] In the final rule promulgating CLIA in 2003, CMS addressed CLIAC's recommendations pertaining to enhanced confidentiality, expanded requirements for test result reporting and unidirectional workflow in its quality systems regulations, and quality control procedures for tests based on polymerase chain reaction, though not pertaining to proficiency testing.[71]

Although CMS had indicated that it would issue a Notice of Proposed Rulemaking that would establish a genetic testing specialty under CLIA, the agency announced in September 2006 that it would no longer pursue this path.[72] In explaining this decision, CMS Stated that CLIA already certifies genetic testing laboratories under requirements for existing specialties, and since the field is so dynamic, prescriptive standards for genetic testing likely would be outdated before they were published. CMS also expressed the view that a genetic testing specialty would not solve the lack of clinical validation of laboratory-developed genetic tests or address concerns about the lack of proficiency testing for genetic testing laboratories. CMS said there is not sufficient data indicating that genetic testing laboratories experience more problems than laboratories performing other types of tests and noted that there is no widely accepted definition of "genetic test." Further, the agency believed that additional CLIA regulations would not address the ethical, legal, and social issues associated with genetic testing. In lieu of a CLIA genetic testing specialty, CMS made plans to pursue the following options:

- Provide CMS surveyors with guidance on assessing genetic testing laboratories for compliance and technical training from genetic testing experts;
- Develop educational materials for and provide education to genetic testing laboratories;
- Maximize the expertise of CMS-approved accreditation organizations, some of which already have molecular diagnostic standards;
- Explore creative surveying alternatives;
- Develop alternative proficiency testing mechanisms (e.g., inter-laboratory comparisons) with the assistance of the Centers of Disease Control and Prevention (CDC) and FDA and encourage laboratories to participate in them;
- Seek assistance from FDA and CDC on the review of complex analytical test validations;
- Collect data on genetic testing laboratory performance;
- Work with CLIAC and the Clinical Laboratory Standards Institute on oversight concepts/issues; and
- Collaborate with CDC and FDA on ongoing oversight activities.

CLIAC accepted the CMS decision not to publish the NPRM, yet acknowledged the need to further examine the regulatory framework, with the goal of attaining enhanced oversight for genetic testing. They concluded that CMS and CDC should work with experts to clarify the critical issues.

In 2006, the Government Accountability Office (GAO) published a report on CMS's implementation of CLIA requirements and the related activities of several survey organizations, including the Joint Commission, CAP, and COLA (formerly the Commission on Office Laboratory Accreditation. The study

[70] CDC Summary of September 16-17, 1998 CLIAC Meeting. (http://www.phppo.cdc.gov/CLIAC/cliac0998.aspx) Accessed on August 14, 2007.

[71] 68 Federal Register 3640-3714. Medicare, Medicaid, and CLIA Programs: Laboratory Requirements Relating to Quality Systems and Certain Personnel Qualifications: Final Rule.

[72] CDC. CLIAC September 2006 Meeting. Atlanta, GA. September 20-21 Meeting Summary. http://wwwn.cdc.gov/cliac/cliac0906.aspx. Accessed July 1, 2007.

was not specific to genetic testing, but rather examined the quality of laboratory testing; the effectiveness of surveys, complaint investigations, and enforcement actions in detecting and addressing laboratory problems; and the adequacy of CMS's CLIA oversight. GAO recommended that CMS improve CLIA oversight by standardizing the reporting of survey deficiencies to permit meaningful comparisons across survey organizations; working with survey organizations to ensure that educating laboratory workers does not preclude appropriate regulation, such as identifying and reporting deficiencies that affect laboratory testing quality; and allowing the CLIA program to fully use revenues generated by the program to hire sufficient staff to fulfill its statutory responsibilities.[73] CMS and the affected accrediting organizations responded by stating that many of the report's recommendations were already in place or were in the process of being implemented.

Pre- and postmarket Federal regulation of testing products and services. In addition to having no mechanism for external review of the clinical validity and utility of tests, CLIA lacks the postmarket vigilance and adverse event reporting mechanisms that are provided in FDA's medical device regulations.[74] To date, there have been few documented cases in which patients experienced harm because of errors in a CLIA-regulated genetic test.[75,76,77] The lack of reports, however, may reflect the absence of a reporting requirement. CLIA provides for biennial inspections of laboratories, but these do not focus on the clinical performance records of the LDTs themselves. The FFDCA provides FDA with removal authority with respect to medical devices (including genetic tests). This authority allows the agency to take action to protect the public if, based on adverse event reports or other data, a test or device proves injurious in clinical use. If there are substantiated concerns about analytical accuracy and the laboratory does not correct them, CLIA does provide for sanctions. These sanctions include requiring the laboratory to cease testing or removing its certificate and Medicare payment when there is risk of harm to patients arising from a potentially faulty test result or in a problem testing area.

FDA may already have statutory authority to require data demonstrating the safety and effectiveness of LDTs, although this authority has been under debate. Within its enforcement discretion, FDA has declined in recent years to exercise this authority.[78,79,80,81] FDA, however, issued two draft guidances in September 2006 that indicate a shift of regulatory oversight for a small, yet growing number of complex tests, including some genetic tests. The guidances are likely to place these tests under the greater scrutiny of premarket review via the 510(k) or PMA processes.

The first guidance clarifies FDA's oversight of analyte specific reagents (ASRs), which are the building blocks used by clinical laboratories to develop LDTs. ASRs include antibodies, receptor proteins, nucleic acid sequences and other biological or chemical reagents that are used to identify or quantify substances in

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[73] U.S. Government Accountability Office. Report to Congressional Requesters. *Clinical Lab Quality: CMS and Survey Organization Oversight Should Be Strengthened*. See http://www.gao.gov/new.items/d06416.pdf. Accessed on August 10, 2007.

[74] 21 CFR 806 (providing for reporting of corrective changes made in medical devices and removals of devices from the market); 21 CFR 803 (establishing requirements for medical device reporting).

[75] Libby, E.N., Booker, J.K., Gulley, M.L. Garcia, D., and Moll,S. (2006). False-negative factor V Leiden genetic testing in a patient with recurrent deep venous thrombosis. *American Journal of Hematology*. 81(4): 284-289.

[76] Klein, R.D. and Mahoney, M.J. (2007). Medical legal issues in prenatal diagnosis. *Clinics in Perinatology*. 34(2): 287-297.

[77] Genetics and Public Policy Center. *Overview of Court Decisions Involving Reproductive Genetics.* See http://www.dnapolicy.org/resources/Overviewofcourtdecisions_Crockin.pdf. Accessed on November 2, 2007.

[78] Gutman S. (1999). Clinical Chemistry Forum: The Role of Food and Drug Administration Regulation of In Vitro Diagnostic Devices – Applications to Genetics. *Clinical Chemistry*. 45(5):746-9.

[79] United States Department of Health and Human Services. Final Rule, Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents. Fed Regist 1997 62: 62243, 62249.

[80] Ronald M. Johnson, *Presentation to the Association of Microbiological Diagnostics Manufacturers* (October 28, 1992).

[81] Schifreen, R.S. and Louth, C. (1996). Industry View on the Regulation of Ancillary Reagents. *Food and Drug Law Journal.* 51(1):155-159.

biological specimens.[82] The guidance, which was made final in September 2007, clarifies that a single ASR that is: (1) combined, or promoted for use, with another product such as other ASRs, general purpose reagents, controls, laboratory equipment, or software; or (2) promoted with specific analytical or clinical performance claims, instructions for use in a particular test, or instructions for validation of a particular test using the ASR, is considered by FDA to be test system and, thus, is not exempt from premarket notification requirements.[83] The draft guidance addresses industry efforts to market more complex combinations of ASR-based products under the less demanding requirements of single ASRs.[84,85]

The second guidance—first issued in September 2006 and revised in July 2007—explains FDA's oversight of a small number of LDTs known as in vitro diagnostic multivariate index assays (IVDMIAs).[86,87,88] IVDMIAs must meet pre- and postmarket device requirements under FFDCA and FDA regulations, including, when applicable, premarket review requirements for class II and III devices. IVDMIAs typically employ complex mathematical algorithms, often with the aid of computer software, to interpret large amounts of genetic or protein data to yield results that can be used to guide medical decisionmaking.[89] These tests include some of the complex genetic and proteomic tests, such as gene expression profiles that might predict cancer prognosis and guide the use of chemotherapy. In February 2007, FDA approved the first IVDMIA, MammaPrint. Marketed in The Netherlands since 2005, MammaPrint is a gene expression profiling test for predicting whether an existing cancer will metastasize in women with early stage breast cancer.[90] This guidance does not affect the many LDT genetic tests that do not fall within the multivariate index assays (IVDMIAs).

There have been various calls over the past decade to require a more rigorous external prior regulatory review process for LDTs. In 1997, the NIH-DOE Task Force recommended systematic, well-designed studies to assess the safety and effectiveness of genetic tests before they become routinely available and after they undergo significant modifications.[91] Three years later, the Secretary's Advisory Committee on Genetic Testing (SACGT) called for FDA to assume responsibility for premarket review, approval, and

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[82] Gutman SI. FDA's role in the regulation of in vitro diagnostic. Presentation May 10, 2003. Rockville, MD: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Device Evaluation and Safety, 2003. See http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html. Accessed September 1, 2007.

[83] Draft guidance for industry and FDA staff. Commercially distributed analyte specific reagents (ASRs): frequently asked questions. Rockville, MD: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. See http://www.fda.gov/cdrh/oivd/guidance/1590.pdf. Accessed September 1, 2007.

[84] Center sees "new era in oversight" of genetic tests in two new FDA draft guidances. Washington, DC: The Genetics and Public Policy Center, 2006. See http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=56. Accessed September 8, 2007.

[85] Gibbs JN. Regulations & standards: the past, present, and future of ASRs. Medical Devicelink, 2003. See http://www.devicelink.com/ivdt/archive/03/11/012.html. Accessed September 8, 2007.

[86] United States Department of Health and Human Services. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays [Docket No. 2006D-0347] (September 5, 2006). See www.fda.gov/OHRMS/DOCKETS/98fr/ch0641.pdf. Accessed September 25, 2007.

[87] Draft guidance for industry, clinical laboratories, and FDA staff: in vitro diagnostic multivariate index assays. Rockville, MD: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety, 2006. See http://www.fda.gov/cdrh/oivd/guidance/1610.pdf. Accessed September 8, 2006.

[88] Federal Register/Vol. 72, No. 143 /Thursday, July 26, 2007/Notices

[89] FDA, *FDA Drafts Regulatory Guidance to Industry and Labs for Group of Medical Tests*, FDA News P06-127 (September 5, 2006), at See http://www.fda.gov/bbs/topics/NEWS/2006/NEW01445.html. Accessed November 5, 2007.

[90] FDA clear breast cancer specific molecular prognostic test. Rockville, MD: U.S. Food and Drug Administration, 2007. Accessed September 8, 2007. http://www.fda.gov/bbs/topics/NEWS/2007/NEW01555.html.

[91] Task force on genetic testing: joint NIH-DOE ethical, legal and social implications working group of the Human Genome Project. Bethesda, MD: National Human Genome Research Institute, 1995. http://www.genome.gov/10001808. Accessed October 30, 2007.

labeling of all new genetic tests that have moved beyond the basic research stage.[92] SACGT envisioned data-driven reviews focusing on the analytical and clinical validity of genetic tests, as well as on any claims the developer plans to make about a test's clinical utility.[93] Despite these recommendations, it is likely that many types of CLIA- and FDA-regulated tests will remain subject to different approval standards, at least for the near future. As described below, most genetic tests that are newly available to U.S. consumers are entering the market by the CLIA pathway rather than through the FDA clearance/approval process. For example, commercial test kits—which are approved or cleared by FDA—generally are not available for rare genetic disorders. Also, testing methodologies used in genetic testing are rapidly evolving. By the time the studies required for FDA review are completed and the testing product or device has completed FDA review, the testing methodology will have likely advanced.

In general, FDA premarket review is more formal and detailed than that provided by CLIA or State regulations. FDA review also results in public posting of the final review memorandum in template form. This practice ensures transparency in the nature of analytical and clinical testing performed and gives healthcare providers information that may be of value in selecting conventional and off-label uses of a new test. Statutory regulation is a potential vehicle for providing changes in oversight, such as standardizing the reporting and labeling of information about genetic tests, which might help provide more information to interested stakeholders than is now available, particularly for tests brought to market without FDA review.

Two bipartisan bills recently introduced to Congress, but not yet passed, would place greater requirements on LDTs and renew a call for CMS to establish a genetic testing specialty under CLIA. The Genomics and Personalized Medicine Act (S.976),[94] introduced by Senators Barack Obama (D-IL) and Richard Burr (R-NC), would call for the Secretary of HHS to:

- Commission the Institute of Medicine to study and make recommendations on how Federal oversight and regulation of genetic tests can be improved if SACGHS does not submit its report to the Secretary of HHS by July 2008;
- Undertake a comparative analysis of CLIA and FDA review requirements and mandate a CLIA specialty in genetic testing;
- Develop a decision matrix for determining which genetic tests, including LDTs, should require review and determine the appropriate agency to have oversight of this review;
- Conduct postmarket public health surveillance of genetic tests with a focus on direct-to-consumer (DTC) tests;
- Establish a national biobanking database, biobank initiatives grant program, and mechanism for management and submission of pharmacogenomic data developed by FDA in collaboration with NIH and CDC.

[92] Secretary's Advisory Committee on Genetic Testing. Development of a classification methodology for genetic tests: conclusions and recommendations of the Secretary's Advisory Committee on Genetic Testing. Bethesda, MD: National Institutes of health. See http://www4.od.nih.gov/oba/sacgt/reports/Addendum_final.pdf. Accessed October 30, 2007.

[93] Ibid.

[94] S.976: Genomics and Personalized Medicine Act of 2007. http://www.govtrack.us/congress/billtext.xpd?bill=s110-976. Accessed Sept. 1, 2007.

The Laboratory Test Improvement Act (S.736), [95,96] introduced by Senators Edward Kennedy (D-MA) and Gordon Smith (R-OR) would put into place a comprehensive system of oversight for all laboratory-developed tests (LDTs), including genetic tests. In particular, it would:

- Grant explicit authority to FDA to regulate LDTs as medical devices;
- Require all laboratories using LDTs to register with FDA as medical device manufacturers, and to submit to FDA a list of tests offered by the laboratory, the intended uses of the tests, information on the tests' analytical validity, and information on the tests' clinical validity if they are intended for clinical use;
- Require laboratories offering DTC tests to submit their tests for FDA review;
- Make laboratories using LDTs subject to other requirements applicable to medical device manufacturers, such as reporting of adverse events resulting from the use of LDTs;
- Provide that compliance with CLIA regulations would satisfy FDA's Quality System Regulation requirements unless and until CLIA's requirements are found to be inadequate for protecting the public's health; and
- Create a genetic testing specialty under CLIA.

Critics of this bill argue that these submission requirements would present a burden for both laboratories and FDA and could threaten development and use of potentially beneficial tests.

State regulation of testing services.[97] At the State level, statutory regulation plays an important role in genetic testing. Twenty-six States have some degree of statutory authority for oversight of the practice of clinical laboratory medicine. New York and Washington are the only States that have CLIA-exempt status because their standards have been reviewed by CMS and approved to be at least equivalent to or more stringent than CLIA in accordance with the CLIA statute and regulations. New York State has specific standards for genetic testing, but Washington State does not—although it does review the clinical validity of certain tests. Through its Genetics Disease Branch and newborn screening and prenatal screening program, California has rigorous review of those types of assays, but its oversight does not generally extend to other genetic testing. New Jersey applies some personnel standards of the American Board of Medical Genetics to laboratories that perform genetic testing. With the exception of New York, no State requires review of validation data for individual assays, other than in the context of a physical on site inspection which, for most State programs, does not involve peer review. The Washington State program, however, does evaluate the clinical validity of tests.

New York is generally recognized as having the most stringent State laboratory standards in the country. Because New York is CLIA-exempt, laboratories having a New York license must only meet the State requirements in order to be in compliance with CLIA. A 1964 New York State statute, which predated CLIA, requires that the State oversee the practice of laboratory medicine for the testing of all specimens derived from the human body for all purposes. The statute holds that, "A laboratory shall perform only those assays that have been validated or verified at the site where the assay will be performed." It applies primarily to large, multi-site commercial entities that want to validate an assay at one site and then

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[95] Laboratory Test Improvement Act - Amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to deem a laboratory-developed test that is a direct-to-consumer test to be a prescription test if it satisfies the requirements of this Act. See http://www.thomas.gov/cgi-bin/bdquery/z?d110:SN00736:@@@D&summ2=m&. Accessed September 1, 2007.

[96] Senator Kennedy introduces the Laboratory Test Improvement Act. Genetics and Public Policy Center. See http://www.dnapolicy.org/news.enews.article.nocategory.php?action=detail&newsletter_id=20&article_id=78. Accessed Sept. 5, 2007.

[97] Willey AW. New York State Laboratory Specific Assay Validation Review and Approval as Applied to Genetic Testing. New York State Department of Health. Presentation to SACGHS meeting, March 26, 2007. See http://www4.od.nih.gov/oba/sacghs/meetings/Mar2007/Mon%20pm%20-%20Willey.pdf. Accessed October 18, 2007.

transfer it to other sites. They must reproduce the validation data at any site at which they intend to offer the test or ship all the specimens for that assay to one site. A laboratory must hold the appropriate permit category for the test.

New York has 26 specialties, with 70 different categories in which they issue permits. Every test falls into one or more of those categories. The laboratories must meet all other requirements related to personnel, proficiency testing (PT), and onsite inspection. New York State review of the validation of LDTs or assays using certain commercial reagents is part of an integrated program. Every category must have an assistant director or director holding specified credentials. They must be doctoral degreed individuals with a minimum of four years postdoctoral clinical laboratory experience and a minimum of two years in the specialty. All other personnel must meet relevant training experience. The laboratories are physically inspected every two years for their quality assurance program, quality control, reagents, equipment, and physical location. They are required to participate in New York's PT program and encouraged to participate in any other relevant proficiency tests.

Under the New York program, there are two types of tests: FDA-approved/cleared; and all other tests. The latter category includes tests for research or investigative purposes only and LDTs. LDTs are manufactured using ASRs.[98] The laboratory program must approve non-FDA-approved tests before they can be offered. New York has conducted approximately 450 reviews of genetic and nongenetic tests, which include both analytic and clinical validity. They also provide laboratory guidance on the materials needed for review. All reference laboratories in the country likely have a site in New York State, because any testing on a New York resident, regardless of where it takes place, is covered under New York law and their tests must be submitted there for approval. It is estimated that 75 percent of the genetic testing in the United States is subject to New York State oversight.[99]

The program in New York is divided into two segments: cytogenetics (since 1972) and genetics (since 1990). Cytogenetics includes clinical information about test selection and interpretation, patient consent, confidentiality, specimen retention times, and turnaround time. There are requirements that reports be signed by a cytogeneticist, that there be an interpretation suitable for a nongeneticist, and for prenatal and pre-implantation outcome verification. Laboratories are subject to the New York State PT program.

There are similar requirements for genetic testing, including clinical information about test selection and interpretation, patient consent, confidentiality, specimen retention times, and very detailed quality control procedures, with method documentation and retention of records. The reports must be signed by a geneticist. There must be an interpretation suitable for a nongeneticist physician and prenatal and pre-implantation outcome verification. In this case, PT requirements are the same as in CLIA. When PT material is not available, particularly for rare diseases, the laboratory is subject to alternative PT, if available, or review twice per year.

The New York process for validation review of non-FDA-cleared tests is not unique to genetics; it applies to any laboratory test, whether clinical chemistry, microbiology, or virology. The standards require that the laboratory submit validation data and clinical validity data. For genetic testing, only a very small number of cases are required. There must be a known clinical association with the genetic marker. All LDTs using ASRs require departmental approval, whether for genetics or microbiology. LDTs that do

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[98] Code of Federal Regulations. Specimen Preparation Reagents. 21 CFR 864.4020 Rockville, MD: The United States Food and Drug Administration, 2006. See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=864.4020. Accessed September 20, 2007.

[99] Willey AW. New York State Laboratory Specific Assay Validation Review and Approval as Applied to Genetic Testing. New York State Department of Health. Presentation to SACGHS meeting, March 26, 2007. See http://www4.od.nih.gov/oba/sacghs/meetings/Mar2007/Mon%20pm%20-%20Willey.pdf. Accessed October 18, 2007.

not use ASRs also require departmental approval because they are developed in-house and are not currently regulated by the FDA.[100]

State regulation of clinical use of genetic testing. The clinical use of genetic tests is primarily regulated at the State level. A complex web of State statutes, regulations, and liability rules will influence the extent to which patients benefit from genetic testing and are protected from harms. This web includes State medical practice acts, informed consent statutes, pharmacy regulations, State genetic testing statutes and privacy acts, and State tort liability rules that serve to define the physician's standard of care. State laws affect whom to test, when to test, which test to use, and what actions should be taken in response to specific test results.

Federal efforts to improve information development and standard-setting for genetic tests may have very little impact on day-to-day clinical practice unless States adopt regulations and liability rules that supply incentives to follow these standards. An example of this problem arises with physician compliance with safety warnings Stated in FDA-approved product labeling. Under the FFDCA, FDA decides whether medical products can lawfully be sold and approves their labeling, but does not require physicians to comply with the use standards (i.e., instructions and warnings) implicit in product labeling. Congress did not intend, when it passed the FFDCA in 1938, to authorize broad FDA regulation of the practice of medicine.[101,102] Courts have not subsequently found constitutional limits on FDA's power to regulate physicians, but FDA, as a matter of policy, has sought to avoid direct regulation of their activities.[103, 104,105] States were left to develop their own approaches for promoting physician compliance with warnings and instructions in labeling. States have not embraced a direct regulatory approach to this problem, and tort lawsuits are the main *de facto* compliance mechanism at the State level.[106] The result is a very weak set of incentives for physicians to heed warnings in product labeling,[107] since only some States treat compliance with labeling as the standard of care, and many States treat it as merely one factor to consider.[108,109]

Even if FDA's oversight duties were expanded to include all genetic tests (including LDTs), this would not necessarily ensure that patients would gain the public health benefits of genetic tests and be protected from potential harms. Sound State policies are crucial to these latter goals. In the case of genetic tests, FDA arguably has statutory authority to restrict how tests are used in clinical settings. The 1976 Medical Device Amendments[110] to the FFDCA authorized FDA to characterize a medical device as "restricted"

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[100] Wadsworth Center. Clinical Laboratory Evaluation Program. Albany, NY: New York State Department of Health, 2006. See http://www.wadsworth.org/labcert/TestApproval/submitguide.htm. Accessed September 20, 2007.

[101] Department of Health, Education, and Welfare, FDA, Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration (Notice of Proposed Rulemaking). 37 Federal Register 16503-5 (July 30, 1972).

[102] Joel E. Hoffman, *Administrative Procedures of the Food and Drug Administration*, *in* FUNDAMENTALS OF LAW AND REGULATION, (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds., 1999), at 17 – 24.

[103] David G. Adams, *The Food and Drug Administration's Regulation of Health Care Professionals*, *in* FUNDAMENTALS OF LAW AND REGULATION, at 423, 425-426.

[104] Department of Health, Education, and Welfare, FDA, 37 Fed. Reg. at 16503-4.

[105] William L. Christopher, *Off-label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247 (1993), at n. 6.

[106] Brennan, T.A. and Rosenthal, M. (1995). Medical Malpractice Reform: The Current Proposals. Journal *of General Internal Medicine*. 10: 212.

[107] Evans, B.J. and Flockhart, D.A. (2006). The unfinished business of US drug safety regulation. *Food and Drug Law Journal*. 61: 45-63.

[108] Sharp, Linda A., Annotation, Malpractice: Physician's Liability for Injury or Death Resulting From Side Effects of Drugs Intentionally Administered to or Prescribed for a Patient, 57 A.L.R. 5th 433 (1997, updated through 2004), §§ 2[a], 7.

[109] Minneman, David C., Annotation, Medical Malpractice: Drug Manufacturer's Package Insert Recommendations as Evidence of the Standard of Care, 82 A.L.R. 4th 166 (1990, updated through 2004), §§ 2 – 6.

[110] Pub. L. No. 94-295, 90 Stat. 539 (1976), codified at 15 U.S.C. § 55 *and* 21 U.S.C. *passim*.

and impose stringent limitations on its sale, distribution, or use.[111] To date, however, FDA has not exercised this authority for the purpose of restricting the clinical uses of genetic tests. Physicians are generally free to use an FDA-approved genetic test either in or out of compliance with its labeling, subject only to State tort liability for uses that prove positively injurious. Therefore, Federal efforts to improve prior review and labeling of genetic tests and genetically targeted drugs are almost entirely dependent on the States to supply clinical compliance mechanisms.

HHS cannot influence State laws, regulations, and liability rules directly, but the agency can play a valuable role in information development, for example, by funding surveys and data-gathering efforts to assess whether existing State policies encourage or discourage sound clinical application of genetic tests. These data would inform State policymakers and courts as they modernize outdated State liability rules and could help stimulate multi-State efforts to develop uniform model laws that promote appropriate clinical application of genetic testing. These data also could inform Congress regarding whether certain aspects of genetic testing merit statutory preemption of State laws, for the purpose of ensuring uniform national standards to protect all Americans.

Specific uses and misuses of genetic tests. Federal and State laws apply to specific uses and misuses of genetic tests and genetic information. The Federal Health Insurance Portability and Accountability Act (HIPAA), the associated HIPAA privacy regulations, and many State statutes affect storage and disclosure of genetic test results. State insurance regulations and the Federal Employee Retirement Income Security Act of 1974 (ERISA)[112] law may affect the use of test results by insurers. The Genetic Information Nondiscrimination Act of 2007 (GINA),[113] which was passed by the House in April 2007 but is pending in the Senate at this writing, would limit the use of genetic test results in insurance enrollment, premium-setting, and employment decisions. GINA is discussed in more detail later in this chapter.

Regulatory Status of Currently Available Genetic Tests

Data on genetic tests of all types. According to data submitted voluntarily to an online directory of genetic tests and the laboratories that offer them, more than 1,100 genetic tests are offered currently in 1,167 clinical laboratories.[114] The FDA has cleared or approved several dozen genetic tests to date (e.g., tests for factor V/II Leiden, cystic fibrosis, UGT1A1, CYP450 2D6 and 2C19, breast cancer prognosis gene expression test, bladder cancer fluorescence in situ hybridization (FISH), prenatal aneuploidy FISH, HER2 FISH.)[115] This figure refers to molecular genetic tests; when biochemical assays for genetic conditions (mainly for newborn screening) are added, the figure approaches 100. Although BRCA tests are widely used to predict patients' future risk of breast and ovarian cancer, no BRCA test has been approved by FDA.[116] A 2003 survey of U.S. molecular diagnostics laboratories found that genetic testing for inherited diseases was the second-largest diagnostic testing activity, representing 15 percent of the total volume of tests performed. Among the laboratories surveyed, 85 percent reported using at least one LDT.[117]

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[111] FFDCA §520(e), 21 U.S.C. § 360j(e). FDA's authority to restrict use of a device to certain categories of practitioners, however, is limited.

[112] 29 U.S.C. §1001 et seq.

[113] H.R. 493, S. 358 (110th Congress), 1st Session. January 16, 2007. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf Accessed September 19, 2007.

[114] GeneTests. See www.genetests.org. Accessed November 5, 2007.

[115] *Ibid.*

[116] National Academy of Sciences, National Cancer Policy Board, SAVING WOMEN'S LIVES: STRATEGIES FOR IMPROVING BREAST CANCER DETECTION AND DIAGNOSIS (2005), p. 225.

[117] Enterprise Analysis Corporation, MOLECULAR DIAGNOSTICS—AN IN-DEPTH SURVEY OF THE U.S. MOLECULAR DIAGNOSTIC LABORATORIES (Nov. 2003).

Data on pharmacogenomic and other tests used to guide drug-prescribing decisions. Pharmacogenomics attempts to reveal the genetic basis for individual differences in drug toxicity and efficacy to optimize design and drug therapy. Customized treatments can result in better responsiveness, reduced side effects, and more cost effective drug development and use of drugs.[118] In 1998, FDA approved the first molecular diagnostic test for use in detecting the HER2 protein, which is the target for the breast-cancer biologic therapy, trastuzumab (Herceptin®). The agency subsequently approved a test for this protein based on FISH technology. FDA also has cleared a test for genetic variations in HIV virus, for use in selecting appropriate therapies. It was not until December 2004 that FDA cleared a drug-metabolizing enzyme genotyping system, which is designed for use in detecting a patient's *CYP450* genotype.[119] In August, 2005, FDA cleared a second test of this type, for use in detecting variations in the *UGT1A1* gene that encodes the enzyme UDP-glucoronosyltransferase, which affects metabolism of the cancer drug, irinotecan.

***Federal regulation of drug labeling that includes genetic testing information*.** In addition to its role clearing and approving genetic testing products, FDA oversees the labeling of drug and biologic therapies (together, "drugs") that include pharmacogenomic information. Labeling information explains genetic factors that may affect individual drug response or provides instructions for using genetic tests to guide prescribing decisions. Recent FDA activities indicate that the agency has identified pharmacogenomics as an area of oversight priority. These activities involve the FDA Center for Drug Evaluation and Research (CDER) in conjunction with the Office of In Vitro Diagnostic Device (OIVD) Evaluation and Safety, the Office of Combination Products (OCP), and the Interdisciplinary Pharmacogenomics Review Group (IPRG).

In August 2007, FDA approved an updated prescription label, which includes information describing the role of genetics in warfarin dosing. The new label will reflect that "lower initiation doses should be considered for patients with certain genetic variations in *CYP2C9* and *VKORC1* enzymes."[120] SACGHS recently published a draft report that explores the opportunities for pharmacogenomics to advance the development of diagnostic, therapeutic, and preventive strategies to improve health and identifies challenges to the integration and application of pharmacogenomics to clinical practice and public health. The report makes recommendations to the Secretary of HHS in areas such as basic and translational research; the development process for pharmacogenomic products; clinical validity and clinical utility of pharmacogenomic technologies; use of pharmacogenomic technologies in clinical practice; and research on ethical, legal, and social issues.

At present, an estimated 120 drugs include some form of pharmacogenomic information in their labeling.[121] There are several examples in which a drug and a test are expressly cross-labeled for use together, so that the drug's labeling identifies specific tests and gives information on how to prescribe in response to test results.[122] In other cases, labeling notes that patient response may vary based on genetic factors, but lacks specific recommendations for testing and interpretation of test results.[123] Some labeling for drugs that are known to exhibit genetic variability of response do not yet provide such specific recommendations. Scientists and physicians have called for more information about genetic variability of

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[118] Ethical, legal, and social implications (ELSI) of human genomics: Pharmacogenomics. Geneva, Switzerland: World Health Organization, 2007. See http://www.who.int/genomics/elsi/pharmacogenomics/en/. Accessed June 4, 2007.

[119] FDA, *FDA Clears First of Kind Genetic Lab Test* (News release PO4-111, December 23, 2004).

[120] Food and Drug Administration. Coumadin label. http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf

[121] Rudman A. Pharmacogenomics: Update and Practical Regulatory Outset. Regulatory Affairs Professionals Society 2006 Annual Conference and Exhibition. October 18, 2006.

[122] *See, e.g.*, approved package insert for trastuzumab (Herceptin™), at http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp.

[123] *See, e.g.*, approved package insert for Atomoxetine HCl (Strattera™).

drug response to be included in drug labeling.[124] It is not clear that FDA has the authority to compel drug and test manufacturers to cross-label their products, unless they voluntarily agree to cooperate. Even if FDA has this authority, cross-labeling presents other legal and practical issues that are unresolved at present. It is unknown how many of the existing LDTs that have not received external, prior review of their analytical and performance characteristics would meet FDA's evidentiary standards for inclusion in drug labeling. Currently, even if a drug label includes pharmacogenomic information, this information does not indicate or guarantee that an FDA-cleared or -approved genetic test is commercially available.

Reimbursement Policies and Genetic Testing

Reimbursement policies play an essential role in determining whether and how genetic tests will be used. They affect whether patients will be covered for, and therefore have access to, genetic testing. Given that the revenue stream for test makers is largely determined by the volume of covered tests and the payment levels per test, reimbursement influences willingness to invest in the development of new tests.[125] While it would be desirable for payment levels to reflect such factors as the incremental innovation, effort required to conduct the test, and value to the patient (e.g., of the test itself or the effectiveness of treatment informed by test results), laboratory fee schedules and related payment mechanisms for tests are less discerning of those factors.

Reimbursement policies also affect whether appropriate courses of action will be taken in response to genetic test results when results are used to guide clinical decisions. Medical necessity determinations are a key point of control for ensuring that appropriate inferences are drawn in response to specific test results.[126] An example is the use of pharmacogenomic test results in medical necessity determinations, which may decide whether a patient will receive reimbursement for a particular drug. Before authorizing reimbursement for the drug, payers may require documentation that a pharmacogenomic test has been conducted and that there is a particular test result. A concern is that, given differences among analytical validity, clinical validity, and clinical utility of tests, some patients who are predicted by a pharmacogenomic test to respond favorably to a drug will not, whereas some patients who are predicted not to respond favorably to the drug may, in fact, respond well to it. Thus, patients who might have been good candidates for treatment with a given drug could be denied reimbursement for it. This risk can be minimized through appropriate oversight of tests and through information development and synthesis activities to strengthen the evidentiary base for reimbursement decisionmaking.

Medicare reimbursement. Current Medicare reimbursement provisions may have implications for genetic tests due to the limitations placed on the coverage of diagnostic tests. The Medicare statute restricts payment to items or services that are "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[127] Laboratory tests used only for screening purposes are not covered under Medicare unless Congress authorizes coverage for

[124] *See, e.g.,* Andersson, T, Flockhart, DA, Goldstein, *et al., Drug-metabolizing enzymes: evidence for clinical utility of pharmacogenomic tests,* CLINICAL PHARMACOLOGY & THERAPEUTICS 78: 559-581 (2005), at 560.

[125] Goodman C, Faulkner E, Gould C, et al. The value of diagnostics: innovation, adoption, and diffusion into health care. Washington, DC: The Advanced Medical Technology Association, 2005. See http://www.advamed.org. Accessed November 5, 2007.

[126] Evans, B.J. (2007). Finding a liability-free space in which personalized medicine can bloom. *Clinical Pharmacology & Therapeutics*. 82: 461-465.

[127] 42 U.S.C. §1395y.

specific tests.[128] Thus, most genetic tests will not be eligible for coverage unless they are performed on symptomatic patients or used to identify treatment-responsive subpopulations.

Establishing genetic tests as "reasonable and necessary" for diagnosis or treatment is often difficult. While determining analytical validity of genetic tests is usually straightforward, direct evidence of clinical utility and related healthcare outcomes as required by Medicare's core provisions can be more challenging. Studies on diagnostic and genetic tests often focus on test specificity, sensitivity and/or the ability to detect the presence of disease rather than on the impact of testing on clinical decisions, let alone on downstream health outcomes.[129] Many genetic tests provide information that may not be necessary for, or even relevant to, informing treatment decisions.

In recent years, Congress has sought to expand Medicare coverage to screening and other prevention-related services through amendments, including the Medicare Modernization Act of 2003.[130] These provisions, however, may have limited applicability to genetic tests. For example, pharmacogenomic tests using microarray or multiplex formats aim to detect genetic variations that may affect drug metabolism or susceptibility to adverse drug reactions. Coverage decisions for this class of genetic tests may rest on the ability to demonstrate that test results will provide information that is considered medically necessary. It also remains uncertain how specific genetic tests that target biomarkers that are known to be associated with treatment response will fare under Medicare's coverage criteria.[131]

Reimbursement by private insurers. A special concern relates to the clinical validity and utility of genetic tests whose results are used to inform medical necessity determinations by private insurers. Current State[132,133] and proposed Federal[134] laws on genetic discrimination in insurance prohibit the use of genetic information in insurance enrollment, underwriting, and premium-setting decisions. It is permissible, however, for insurers to condition reimbursement for specific medical treatments and procedures on genetic test results to the extent that those results reveal whether the person has a condition that makes the treatment medically necessary.[135] Thus, for example, it is permissible for an insurer to condition reimbursement for trastuzumab on documentation of a HER2 test showing that the patient would be a suitable candidate for this therapy. The Congressional Research Service, however, has suggested that there is uncertainty regarding insurers' uses of pharmacogenomic tests. Using pharmacogenomics to guide treatment of a manifested illness, while legally permissible, still may be controversial, e.g., when only one treatment is available and the patient is deemed not to be a candidate for that drug.[136] Harms to public health and to public confidence in the payment system may result if medical necessity determinations rely on tests with dubious clinical validity and utility.

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[128] Goodman C, Faulkner E, Gould C, et al. (2005). The value of diagnostics: innovation, adoption, and diffusion into health care. Washington, DC: The Advanced Medical Technology Association. See http://www.advamed.org. Accessed November 5, 2007.

[129] Recommendations for evaluating effectiveness: MCAC Executive Committee Working Group, 2004.

[130] Public Law 108-173; Medicare Prescription Drug, Improvement, and Modernization Act of 2003. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ173.108. Accessed on October 28, 2007.

[131] Goodman C, Faulkner E, Gould C, et al. (2005). The value of diagnostics: innovation, adoption, and diffusion into health care. Washington, DC: The Advanced Medical Technology Association. See http://www.advamed.org. Accessed November 5, 2007.

[132] Williams, E.D., Sarata, A.K. & Redhead, C.S., Genetic Discrimination: Overview of the Issue and Proposed Legislation (Congressional Research Service, RL33903, March 7, 2007), at CRS-1

[133] Clayton, E.W. (2003). Ethical, legal, and social implications of genomic medicine. *New England Journal of Medicine.* 349:562-569.

[134] H.R. 493, S. 358 (110th Congress), 1st Session. January 16, 2007. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h493ih.txt.pdf Accessed September 19, 2007.

[135] Report to Accompany S. 358, No. 110-48 (April 10, 2007), at 21.

[136] Williams *et al., supra* note 43 at CRS-31.

This issue presents a significant regulatory challenge. As applied by private payers, the term "medical necessity" is largely a matter of contract law subject to the terms of the specific insurance policies. No Federal regulation defines medical necessity for private insurers; only about a third of the States have any regulatory definition of the term,[137] and those that do rarely focus specifically on the use of genetic testing in medical necessity determinations. While accepting that medical necessity determinations are largely a matter of private contract law, HHS could play a valuable role in information development by supporting efforts to create an information base to inform the public and insurers about which tests have validity for use in guiding specific types of medical treatment decisions, monitoring how genetic tests are actually used in medical necessity determinations, and examining whether these uses are consistent with what is currently known about the tests' clinical validity and utility.

Roles of Federal Agencies in R&D and Evidence Synthesis

The success of the Human Genome Project has accelerated the translation of genomic information into clinical applications. The increasing number of genetic tests and other anticipated applications of genomic technologies for screening and prevention have the potential for broad public health impact.

Federal leadership by the NIH, the Agency for Healthcare Research and Quality (AHRQ), CDC, and the Health Resources and Services Administration (HRSA) is contributing to the initial part of the translational pathway, which begins with research on the genetic role in disease and ultimately leads to improved health outcomes. Several key Federal initiatives are advancing the translation of genetic tests and services into clinical and public health practice, some of which are described below. Although these Federal initiatives have made great strides in genetic testing, a more coordinated approach for effectively translating genomic applications into clinical practice and health policy is still needed.

The ACCE Project was a CDC-sponsored initiative carried out during 2000-2004 that generated a model process for evaluating data on emerging genetic tests. Taking its name from the four components of evaluation—analytic validity; clinical validity; clinical utility; and associated ethical, legal, and social implications—ACCE is intended to serve as a model process for evaluating data on emerging genetic tests. The process includes collecting, evaluating, interpreting, and reporting data about deoxyribonucleic acid (DNA) and related testing for disorders with a genetic component in a format that provides current and reliable information for decisionmaking.[138]

Evaluation of Genomic Applications in Practice and Prevention (EGAPP), another CDC initiative integrates knowledge and experience gained through ACCE and other processes, such as those of the U.S. Preventive Services Task Force (USPSTF). Launched in 2004, its goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice. EGAPP is an independent, non-Federal, multidisciplinary, Working Group that selects genomic applications for evaluation, establishes methods and process, monitors expert and peer review of commissioned evidence reports, and develops conclusions and recommendations based on the evidence. The project is supported by evidence reviews prepared by the Evidence-based Practice Centers program of AHRQ. To date, evidence reviews have been prepared on testing hereditary nonpolyposis colorectal cancer, genomics tests for ovarian

[137] U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administation, Special Report: Medical Necessity in Private Health Plans (2003).

[138] Department of Health and Human Services, Secretary's Advisory Committee on Genetic Testing. Request for public comment on a proposed classification methodology for determining level of review for genetic tests. *Federal Register*. 2000;65(236):76643-76645.

cancer detection and management, and testing for cytochrome P450 polymorphisms in the treatment of depression.[139,140]

The CDC Division of Laboratory Systems (DLS) has a mission to improve the quality of laboratory testing in the nation's clinical and public health laboratories by enhancing the use of evidence-based laboratory practices through policy development and laboratory health services research.[141] For example, DLS manages and receives advice from CLIAC, which is charged with advising the Department of Health and Human Services on matters related to CLIA and laboratory practices relevant to health care.[142] Currently, DLS is working with CLIAC and private and public partners to develop national guidance for laboratory practices associated with genetic testing.[143] This guidance will aid laboratories and CLIA surveyors to ensure quality and promote good laboratory practices in the area of genetic testing under the current CLIA framework. DLS has also organized several pivotal conferences to address challenges faced by laboratories including the need for laboratory control materials,[144] rare disease testing,[145] and biochemical genetic testing.[146] Several efforts are underway based on recommendations from these conferences, including establishment of the Genetic Testing Reference Materials (Get-RM) Coordination Program; Collaboration, Education, and Test Translation Program; and North American Laboratory Network.[147] DLS is also involved in promoting professional competency in the laboratory and clinical settings.[148]

The Collaboration, Education, and Test Translation (CETT) Program, which is overseen by the NIH Office of Rare Diseases, promotes the translation of tests for rare genetic diseases into clinical settings and works to encourage clinical laboratory and research collaborations. The program has active partnerships with Federal entities, including CDC, HRSA, and CMS. Collaborations also include many nonFederal groups, such as the Genetic Alliance, the American College of Medical Genetics (ACMG), and the Association for Molecular Pathology (AMP). Several tests have been approved for translation through CETT by various laboratories and commercial organizations using multiple methodologies. Recently, CETT addressed the issue of biochemical genetic testing and recommended improved training of laboratory and clinical personnel; guideline development to ensure the quality of testing, result

[139] Evaluation of Genomic Applications in Practice and Prevention (EGAPP). See http://www.egappreviews.org. Accessed on October 29, 2007.

[140] Genetic Testing. Atlanta, GA: The Centers for Disease Prevention and Control. See http://www.cdc.gov/genomics/gtesting.htm. Accessed September 25, 2007.

[141] Division of Laboratory Systems, Centers for Disease Control and Prevention. See http://wwwn.cdc.gov/dls/default.aspx. Accessed on September 10, 2007.

[142] Clinical Laboratory Improvement Advisory Committee, Centers for Disease Control and Prevention. See http://wwwn.cdc.gov/cliac/default.aspx. Accessed on September 10, 2007.

[143] Clinical Laboratory Improvement Advisory Committee, Minutes of Full Committee Meeting, February 2007. See http://wwwn.cdc.gov/cliac/cliac0207.aspx. Accessed on September 10, 2007.

[144] Chen B, O'Connell C, Boone DJ, Amos JA, Williams LO, et al. (2005). Developing a Sustainable Process to Provide Quality Control Materials for Genetic Testing. *Genetics in Medicine*. 7:534-549.

[145] Access to Quality Testing for Rare Diseases: A National Conference, September 26-27, 2005, Washington D.C. See http://rarediseases.info.nih.gov/QTRD/. Accessed September 10, 2007.

[146] Quality, Access, and Sustainability of Biochemical Genetic Testing, October 6-7, Atlanta, Georgia. http://wwwn.cdc.gov/dls/genetics/qualityaccess/default.aspx. Accessed September 10, 2007.

[147] National Laboratory Network for Rare Disease Genetic Testing. See http://www.rarediseasetesting.org/index.php. Accessed on September 10, 2007.

[148] Funding Opportunity Announcement, Genetics in Clinical Practice: A Team Approach. Funding Opportunity Number: CDC-RFA-CI07-707, Catalog of Federal Domestic Assistance Number: 93.064. See http://www.cdc.gov/od/pgo/funding/CI07-707.htm. Accessed on September 10, 2007.

interpretation, and diagnosis for inherited metabolic disorders and other genetic diseases; enhancement of quality assurance measures for various laboratory tests; and international collaboration in research.[149]

AHRQ's Evidence-based Practice Centers Program generates evidence reports in support of EGAPP, among other agency and organization initiatives for which it prepares evidence reports and technology assessments. In conjunction with the CDC, AHRQ has commissioned a study on monitoring use and outcomes of gene-based applications in the U.S. healthcare system. AHRQ also administers the USPSTF, an independent panel of experts in primary care and prevention that systematically reviews evidence of effectiveness and develops recommendations for clinical preventive services. USPSTF has conducted reviews of relevant genetics topics, including BRCA testing and hereditary hemochromatosis.[150]

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (SACHDGDNC), supported by HRSA's Maternal and Child Health Bureau, is a committee that advises the Secretary of HHS on appropriate guidelines for States to improve their newborn screening programs. HRSA also supported the development of a report on the financing mechanisms employed by State newborn screening programs using case studies in seven States.

The National Institute of Standards and Technology (NIST), a nonregulatory Federal agency within the U.S. Department of Commerce, supports measurement procedures and reference materials for traditional biomarkers, such as cholesterol and calcium in serum, and new protein-based markers, such as troponin, homocysteine, and folate, as well as DNA-based standards for HER2 testing standards and fragile X syndrome diagnosis. Recent efforts have addressed the development of reference measurement procedures and reference materials for new health status markers for IVD medical devices.[151]

Department of Veterans Affairs (VA) has launched a major research and care initiative related to genomic medicine. As VA has more than 7.7 million enrolled veterans and sees 5.5 million of them yearly in a system of 156 hospitals and over 900 outpatient clinics, the potential impact is fairly substantial. The program receives guidance from a Genomic Medicine Program Advisory Committee that advises the Department on both research and care. The research effort includes large-scale genomic association studies and implementation research among its program areas.

Professional and Industry Organizations

Professional societies, industry organizations, and other groups can mobilize attention to highlight the importance of genetics issues for their members, including laboratory oversight. Many diverse organizations are involved in improving the quality of laboratory practices and in developing clinical practice guidelines to ensure appropriate genetic testing. Private-sector accreditation organizations can apply for "deemed status" under CLIA and thus, they can survey laboratories for CMS, as long as their standards are at least equivalent to CLIA. The following professional organizations are among those involved in accreditation of laboratories, guideline and standard development, advancement of best practices, PT programs, promotion of health professional education in human genetics, and other efforts that improve health care through laboratory medicine.

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[149] CETT Program – a new paradigm. Bethesda, MD: The National Institutes of Health. See http://www.cettprogram.org/paradigm.aspx. Accessed August 14, 2007.

150 U.S. Preventive Services Task Force. Rockville, MD: Agency for Health care Research and Quality. See http://www.ahrq.gov/clinic/uspstfix.htm/. Accessed August 14, 2007.

[151] National Institute of Standards and Technology. Gaithersburg, MD: National Institute of Standards and Technology, 2007. See http://www.nist.gov/. Accessed August 14, 2007.

The American College of Medical Genetics (ACMG) develops clinical practice guidelines; establishes uniform laboratory standards, quality assurance, and proficiency testing; and serves as a voice for the medical genetics profession. ACMG's voluntary standards and guidelines are educational resources to assist medical geneticists in providing accurate and reliable diagnostic genetic laboratory testing consistent with current technologies in clinical cytogenetics, biochemical genetics, and molecular diagnostics.[152]

The College of American Pathologists (CAP) is the world's largest association composed exclusively of pathologists and is widely considered the leader in laboratory quality assurance. Approximately 6,600 laboratories are accredited by the CAP and approximately 23,000 laboratories are enrolled in its PT programs.[153] The goals of the CAP accreditation program are to ensure that tests are analytically and clinically valid, that there is patient safety and patient access to testing, and that there is innovation and improvement of LDTs.

The Clinical and Laboratory Standards Institute (formerly NCCLS) develops best practices in clinical and laboratory testing and promotes their use using a consensus-driven process that balances the viewpoints of industry, Government, and the healthcare professions.[154] CLSI has approximately 2,000 member organizations and 2,000 volunteers that collaborate to develop CLSI consensus documents.

The Association of Public Health Laboratories (APHL) works to strengthen public health laboratories in the United States and abroad. It advances laboratory systems and practices and promotes policies that support healthy communities, such as State newborn screening programs and the oversight of genetic tests. Membership includes State and local public health laboratories, environmental laboratories, and others that conduct testing of public health significance.[155]

The Association for Molecular Pathology (AMP) is dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and basic and translational research based on the applications of genomics and proteomics. AMP supports the development of new technologies in molecular biology to be used in laboratory medicine, including diagnosis, treatment, and prognosis of genetic disorders. AMP aims to inform and educate its members about advances in, and applications of, DNA-, ribonucleic acid (RNA)-, and protein-based diagnostics.[156]

The American Association for Clinical Chemistry (AACC) is a professional society dedicated to improving health care through laboratory medicine. Its nearly 10,000 members are clinical laboratory professionals, physicians, research scientists, and others involved in developing tests and directing laboratory operations. AACC publishes the scientific journal *Clinical Chemistry*, maintains the patient-

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[152] Mission Statement. Bethesda, MD: American College of Medical Genetics, 2007. See http://www.acmg.net/AM/Template.cfm?Section=Mission_Statement&Template=/CM/HTMLDisplay.cfm&ContentID=2103 Accessed August 14, 2007.

[153] College of American Pathologists. Northfield, IL: College of American Pathologists. See http://www.cap.org. Accessed August 14, 2007.

[154] Clinical Laboratory Standards Institute. Wayne, PA: Clinical Laboratory Standards Institute, 2007. See http://www.nccls.org/. Accessed August 14, 2007.

[155] Association of Public Health Laboratories. Silver Spring, MD: Association of Public Health Laboratories. See http://www.aphl.org/about_aphl/Pages/default.aspx. Accessed August 14, 2007.

[156] Mission and Vision. Bethesda, MD: Association for Molecular Pathology. See http://www.amp.org/AboutAMP/mission.htm. Accessed August 14, 2007.

centered website Lab Tests Online, and hosts the world's largest conference on laboratory medicine and technology.[157]

The American Society of Human Genetics (ASHG) provides venues for investigators to share their research findings in human genetics; informs health professionals, legislators, health policymakers, and the general public about all aspects of human genetics; and facilitates interactions between geneticists and other communities including policymakers, industry, educators, and patient and public advocacy groups. Its membership of nearly 8,000 professionals includes researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, and nurses.[158]

The National Coalition for Health Professional Education in Genetics (NCHPEG) is an "organization of organizations" committed to a national effort to promote health professional education and access to information about advances in human genetics. NCHPEG members are an interdisciplinary group of leaders from more than 140 diverse health professional organizations, consumer and volunteer groups, Government agencies, private industry, managed care organizations, and genetics professional societies. NCHPEG is not a policy, standard-setting, or regulatory organization. Its goals are to integrate genetics content into the knowledge base of health professionals and students of the health professions, develop educational tools and information resources to facilitate the integration of genetics into health professional practice, and strengthen and expand its interdisciplinary community of organizations and individuals.[159]

The National Society of Genetic Counselors (NSGC) promotes the recognition of the genetic counseling profession as an integral part of healthcare delivery, education, research, and public policy. It promotes the professional interests of genetic counselors and provides a network for professional communications. NSGC encourages local and national continuing education opportunities and the discussion of all issues relevant to human genetics and the genetic counseling profession.[160]

The International Society of Nurses in Genetics (ISONG) is dedicated to fostering the scientific and professional growth of nurses in human genetics and genomics worldwide. ISONG promotes caring for people's genetic and genomic health.[161]

Public Policy and Consumer Advocacy Organizations

Through the involvement of advocacy groups, organizations, and individuals, the public is engaged in issues pertaining to genetic testing. Patient advocacy groups, as well as individuals and families affected with genetic conditions, play an important role in setting standards and in developing guidelines through advocacy and the monitoring of healthcare practices. Other organizations monitor and analyze developments in genetics that affect health care and serve as sources of information for the public, the media, and policymakers. Examples of such organizations are described briefly, below.

The Genetics and Public Policy Center helps policy leaders, decision makers, and the public better understand the rapidly evolving field of human genetics and its application to health care. New

[157] American Association for Clinical Chemistry. Washington, DC: American Association for Clinical Chemistry. Accessed August 14, 2007. http://www.aacc.org/AACC/

[158] American Society of Human Genetics. See http://www.ashg.org. Accessed November 5, 2007.

[159] National Coalition for Health Professional Education in Genetics. Lutherville, MD: National Coalition for Health Professional Education in Genetics. See http://www.nchpeg.org. Accessed August 14, 2007.

[160] Our Society's Vision and Mission Statements. Chicago, IL: National Society of Genetic Counselors. http://www.nsgc.org/about/visionMission.cfm. Accessed September, 2007.

[161] International Society of Nurses in Genetics. Pittsburgh, PA: International Society of Nurses in Genetics. See http://www.isong.org/about/Statements.cfm. Accessed August 14, 2007.

diagnostic tools and treatments raise a host of ethical, legal, and social concerns. The Center surveys public attitudes about genetics issues, conducts analyses of the existing regulatory landscape, monitors the transition of genetic applications into clinical practice, and presents options and likely outcomes of key genetics policies.[162]

The Genetic Alliance is a coalition of more than 600 advocacy organizations serving 25 million people affected by some 1,000 conditions. The organization works to transform leadership in the genetics community to build capacity in advocacy organizations and to educate policymakers by leveraging the voices of individuals and families. The interactions of its member groups are intended to accelerate translational research; improve the climate for the development of technologies; encourage cohorts for clinical trials; increase the availability of linked, annotated biological resources; and ultimately lead to improved human health.[163]

The National Breast Cancer Coalition (NBCC) is the country's largest breast cancer advocacy group. Its trained advocates have lobbied at the national, State and local levels for public policies that affect breast cancer research, diagnosis, and treatment. This grassroots advocacy effort has hundreds of member organizations and tens of thousands of individual members working toward increased Federal funding for breast cancer research and collaboration with the scientific community to implement new models of research, improve access to high-quality health care and breast cancer clinical trials for all women, and expand the influence of breast cancer advocates.[164]

The Marti Nelson Cancer Foundation/CancerActionNow (CAN) works to make effective and safe cancer treatments available to cancer patients. Because the drug development timeline is lengthy, CAN supports compassionate use or expanded access to programs that provide experimental treatments to patients once a treatment is shown to be relatively safe and effective.[165]

The Ovarian Cancer National Alliance comprises seven ovarian cancer groups that joined in 1997. Their primary goal is to establish a coordinated national effort to place ovarian cancer education, policy, and research issues prominently on the agendas of national policymakers and women's healthcare leaders.[166]

Overarching Recommendation

SACGHS' analysis of the U.S. system of oversight of genetic testing found a complex system involving many dedicated, hard-working public and private sector entities at both the national and State levels. Nonetheless, the Committee also found significant gaps in the system that could lead to harms. The Committee formulated a number of recommendations that, if implemented and sufficiently supported, could help close these gaps. A critical theme in many of the recommendations is that new and enhanced collaborations and public partnerships between the Federal Government and the private sector are needed. In the Committee's view, it is also important for the HHS to enhance interagency coordination so that the agencies with regulatory roles (CMS and FDA) are working synergistically with one another, with other

[162] Genetics and Public Policy Center. Washington, DC: Genetics and Public Policy Center, 2006. See http://www.dnapolicy.org/. Accessed August 14, 2007.
[163] About us. Washington, DC: Genetic Alliance, 2007. See http://www.geneticalliance.org/ws_display.asp?filter=about. Accessed August 14, 2007.
[164] National Breast Cancer Coalition. Washington, DC: National Breast Cancer Coalition. See http://www.natlbcc.org/. Accessed August 14, 2007.
[165] CancerActionNow.org. Davis, CA: Cancer Action Now. See http://www.canceractionnow.org/. Accessed August 14, 2007.
[166] Ovarian Cancer National Alliance. Washington, DC: Ovarian Cancer National Alliance. See http://www.ovariancancer.org/. Accessed August 14, 2007.

regulatory agencies (FTC), and with the knowledge generation agencies (AHRQ, CDC, HRSA, and NIH). Such coordination would help enhance the consistency and complementarity of Federal programs and ensure the most efficient and effective use of the public-private partnerships that will be key to closing gaps in the oversight of genetic testing. To this end, SACGHS recommends that:

> The HHS Secretary take steps to enhance interagency coordination of the activities associated with the oversight of genetic testing, including policy and resource development, education, regulation, and knowledge generation.

Chapter 3
Technologies Used To Conduct Genetic Tests

Introduction

A genetic test, as defined in this report, involves the analysis of chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, and gene products (e.g., enzymes and other types of proteins) to detect heritable or somatic variations related to disease or health. In addition, it is important to consider the intended use, claim, or purpose of a test in determining whether a laboratory method is considered a genetic test. For example, amino acid analysis to detect metabolic disorders such as phenylketonuria (PKU) is considered a genetic test but using this analysis to monitor general nutritional status is not. Hemoglobin analysis to diagnose sickle cell disease or carrier status is a genetic test, but it is not regarded as genetic testing when used to detect modified hemoglobin that is associated with diabetes. Another example is immunohistochemistry staining of tissue for the purpose of identifying p53 tumor suppressor protein with an increased half-life due to gene mutations, which is considered a genetic test. The same technique for detection of cytomegalovirus (CMV) antigens in tissue to diagnose CMV disease in transplant patients, however, is not regarded as a genetic test. Considering intended use will help define the types of laboratory techniques and procedures that are considered genetic tests.

Overview and History of Types of Genetic Tests

Genetic tests use biochemical, cytogenetic, and molecular methods, or a combination of these methods, to analyze DNA, RNA, chromosomes, proteins, and certain metabolites. The history of analyzing the genetic basis of health conditions spans more than a century. This history demonstrates that genetic tests evolve and expand with available technologies and advancing knowledge. Emerging technologies are providing increasingly detailed information about genetic variations, but interpretation of this information is becoming more complex and its significance in health is not always clear. (See Appendix B for additional resources related to genetic testing.)

Biochemical Tests

Biochemical tests do not directly evaluate DNA, but measure products of genes such as enzymes and hormones. The history of the biochemical characterization of inherited disease begins with Archibald Garrod's 1901 description of "black urine disease" (alkaptonuria) and his 1908 lecture explaining its chemistry.[167] The clinical use of biochemical genetics was firmly established, in the form of newborn screening, in the 1960s with the introduction of the Guthrie test to detect phenylketonuria in newborns. In the ensuing decades, several assays that screened for hormone and enzyme deficiencies and hemoglobinopathies were added to the Guthrie test. Following the introduction of tandem mass spectrometry (MS/MS) technology in the late 1990s, newborn screening rapidly expanded. MS/MS enables screening for 30 or more metabolic disorders in a single analysis from one small disk of dried blood.[168] Biochemical tests are used after the newborn period for screening and diagnosis of inherited disorders, and they are also applied prenatally for the screening and diagnosis of metabolic disorders using specimens of amniotic fluid, maternal serum, or chorionic villi.[169]

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Cytogenetic Tests

Cytogenetic tests evaluate changes in the number or structure of chromosomes. The clinical cytogenetic era began with pioneers such as Theodore Boveri who described polyploidy in human tumors in 1914.[170] Although several investigators studied human chromosomes in the first half of the 1900s, the medical use of cytogenetics did not begin to flourish until 1956 when the human chromosome count in diploid cells was established as 46. Prior to this period, the human chromosome number was thought to be 48. Technical improvements such as colchicine treatment to arrest cells during division and use of hypotonic solutions to swell cells and spread out their contents made it easier to visualize and count chromosomes. These improvements, along with the development of photomicroscopy to document chromosome content accurately, stimulated the use of cytogenetics in a clinical setting.

By the end of the 1950s, numerical chromosomes abnormalities had been reported in patients with Down,[171] Turner,[172] and Klinefelter[173] syndromes and in XXX females.[174] In 1960, Nowell and Hungerford described the Philadelphia chromosome in patients with chronic granulocytic leukemia,[175] the first report of a structural chromosomal change associated with human cancer (although at the time it was reported as a chromosomal deletion instead of a translocation[176]). In 1966, Steele and Breg reported a method, still widely used today, to analyze the chromosome content of fetal cells cultured from amniotic fluid.[177] The field of medical cytogenetics was greatly advanced in the early 1970s with the introduction of chromosome banding,[178] a chemical treatment that produces differentially stained regions on chromosomes. Banding provided a means to identify individual chromosomes and their subregions, and to describe chromosomes rearrangements, inversions, duplications, and/or deletions as etiologies for numerous syndromes. By the mid-1970s, high resolution banding techniques emerged that improved the resolution from 500 bands to more than 1,000 bands per karyotype.[179] High resolution banding facilitated the detection of subtle duplications and deletions and the identification of contiguous gene syndromes, such as Prader-Willi syndrome and velocardiofacial syndrome.

Today, even with numerous technological advances, cytogenetics is often the first tier of genetic testing for assessment of a child with multiple congenital abnormalities and/or developmental delay, prenatal detection of chromosome anomalies, detection of mosaicism, or evaluation of a cancerous tumor.[180]

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Molecular Tests

Molecular genetic tests evaluate DNA or RNA for alterations such as nucleotide substitutions, deletions, or insertions, or changes in the amount of DNA. Quantitative measurements of DNA began in the 1930s with Caspersson's pioneering work using ultraviolet absorption methods. In the 1960s, techniques emerged that quantified DNA by measuring fluorescence of a DNA-specific stain instead of stain absorbance. In the late 1970s, quantification by fluorescence was integrated into flow cytometry methodologies. For flow cytometry, nuclei in suspension are stained with a DNA-specific fluorochrome and their fluorescence is measured against a known standard by passing the stained nuclei through the path of a laser of a specific wavelength.[181] Flow cytometry is useful for detecting abnormal DNA content, particularly in tumor cells.[182] In the 1990s, image analysis densitometry technology began to emerge and has been shown to be particularly useful for DNA quantification for cancer diagnosis and prognosis,[183, 184]

The 1970s brought two pioneering discoveries that have become ubiquitous tools in molecular genetic testing—restriction enzyme digestion and hybridization. Restriction enzymes cut DNA at sequence-specific sites, called restriction sites, which generates specific and reproducible DNA fragments (restriction fragments). In 1970, Smith and Wilcox demonstrated that the restriction enzyme endonuclease R cleaved the bacteriophage T7 to produce specific fragments of DNA,[185] and Smith and Kelly determined the restriction site recognized by this enzyme.[186] A year later, Danna and Nathans reported that endonuclease R cleaved simian virus 40 to produce specific fragments of DNA that could be separated from one another by electrophoresis.[187] Danna and Nathans foresaw several potential applications of restriction enzymes such as mapping genes, DNA sequencing, detection of mutations, and DNA fingerprinting for forensic purposes.[188] By the mid-1970s restriction enzymes were an integral element in recombinant DNA technology. The use of restriction enzymes can be applied clinically to detect certain disease-related mutations, such as the genetic variation that causes sickle cell anemia, as these mutations alter a restriction site and the pattern of restriction fragments when separated by electrophoresis.

As predicted by Danna and Nathans, restriction enzymes also became important reagents in DNA sequencing. In 1977, reports of two different methods of DNA sequencing were published, although both methods used restriction enzymes to generate fragments of DNA for sequencing. The Maxam and Gilbert method[189] used restriction fragments labeled at one end with a radioisotope (^{32}P) and particular chemicals that broke the DNA chain at adenine-, guanine-, cytosine-, or thymine-specific sites. This base-specific

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cleavage produced a set of radioactive fragments that were separated by electrophoresis, and the sequence could be read from the pattern of bands. The Sanger method[190] used restriction fragments as primers for newly synthesized DNA. The restriction fragments were mixed with DNA polymerase, radiolabeled deoxyribonucleoside triphosphate (e.g., ^{32}PdATP), and inhibitors (dideoxy bases) that terminated the newly synthesized DNA chain at specific residues (i.e., adenine, guanine, cytosine, or thymine). This method produced DNA chains of varying length that were separated by electrophoresis, and the sequence could be determined from the pattern of bands. The Sanger method is the basis of current automated sequencing techniques. DNA sequencing is used to identify gene mutations in numerous disorders.

Hybridization was in its infancy in the early 1970s but had matured by the 1980s and was integrated into clinical use by the 1990s. Hybridization involves the interaction of complementary nucleic acid strands, which can occur between two strands of DNA or between DNA and RNA strands. The sequence of one strand is labeled, usually with a fluorescent tag, and is called the probe. The complementary strand is called the target. Hybridization is the basis of many molecular techniques such as the Southern blot, a technique that separates DNA fragments by electrophoresis and transfers the fragments to a nylon or nitrocellulose membrane for enhanced visualization. Used clinically, target DNA from a patient is hybridized to a matching probe to detect point mutations, microdeletions, or other types of genetic changes such as inversions. For example, hybridization can be used to detect an inversion in the F8 gene, which causes hemophilia A.[191]

Molecular testing was further revolutionized in the 1980s by the advent of DNA amplification. Amplification involves repeated cycles of copying a DNA sequence of interest, through a technique called polymerase chain reaction (PCR), to generate millions of copies of that particular sequence. In a short time, PCR became a fundamental tool with many applications such as detecting the presence or absence of a sequence or to measure its size. For example, using PCR for DNA sequences specific to the Y chromosome can confirm or rule out the presence of XY cells in females with Turner syndrome, as such cells in the gonads can become malignant.[192] Quantitative fluorescence (QF) PCR allows detection of common aneuploidies—such as trisomy 13, 18, and 21, and those involving the sex chromosomes—within 1 or 2 days. This short timeframe for analysis is especially attractive for prenatal diagnosis.[193]

Numerous methods for amplifying targets to detect nucleic acids are now available, and all have advantages and disadvantages. A unified approach to amplification and detection is emerging. A large number of commercial and laboratory developed tests combine amplification with detection in the form of real time PCR technology utilizing hybridization or hydrolysis probe approaches. These technologies allow for detection and quantitation of nucleic acids with exquisite sensitivity and specificity but also allow identification of specific nucleic acid sequences for the purpose of genotyping.

Completion of the Human Genomic Project (HGP) in 2003[194] shifted molecular analysis from single-gene alterations to a simultaneous examination of large numbers of DNA and RNA sequences. In the post-HGP era, many laboratory methods rely on the essential technologies of amplification and hybridization discussed above.

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A large number of hybridization tests performed simultaneously forms the basis of microarray technology. Microarrays, which were first introduced in the 1990s, consist of hundreds to thousands of different DNA probes anchored to a solid support such as glass slides, silicon chips, nylon membranes, or beads. Genomic microarrays are gradually being applied to clinical genetics. One type of microarray uses sequence variations known as single nucleotide polymorphisms (SNPs). Polymorphisms are natural DNA sequence variations that occur in more than 1 percent of a population. SNPs are estimated to affect 1 in 300 nucleotides in the human genome[195] and serve as fingerprints of our genome. SNP microarrays show great promise in identifying individuals with variations that affect drug efficacy. For example, a microarray known as the AmpliChip P450 can identify 29 polymorphisms in the CYP2D6 gene and two polymorphisms in the CYP2C19 gene. These genes play a role in the metabolism of approximately 25 percent of prescription drugs.[196] This type of testing could potentially help physicians select appropriate drugs for their patients and adjust dosage based on test outcomes.

Combined Technologies

With the development of new technologies, combined methodologies such as molecular cytogenetics have emerged. Molecular cytogenetics is a type of genetic test in which molecular techniques are combined with classical cytogenetics. For example, a technique called fluorescence in situ hybridization (FISH) uses fluorescently labeled DNA probes applied to chromosome preparations.[197] By the mid-1990s, FISH was providing an accurate means for detecting microdeletions and microduplications, cryptic rearrangements, and marker chromosomes.[198] Improved resolution is an important advancement in the development of FISH assays. Resolution improved from about 5 megabases (Mb) for whole chromosomes in metaphase spreads to 50 kilobases (kb) – 2 Mb for interphase nuclei and was later refined to 5 kb – 500 kb for chromatin strands using fiber FISH. Labeling strategies that allowed the simultaneous visualization of all 24 human chromosomes, each in a different color, was another advancement. Specific technologies that use these strategies are multiplex-FISH (M-FISH), spectral karyotyping (SKY), and combined binary ratio labeling (COBRA).[199]

Comparative genome hybridization (CGH) is another means to evaluate chromosome abnormalities. CGH is particularly useful for characterizing tumors with complex rearrangements, and it is also used to identify the loss or gain of critical genetic regions involved in microdeletion/microduplication syndromes and subtelomeric regions associated with developmental delay.[200] CGH, however, is not well suited for balanced genetic alterations such as inversions or balanced translocations, or for the detection of low-level mosaicism. Array CGH emerged in the late 1990s.[201, 202] Instead of hybridizing a labeled probe to

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metaphase chromosomes, thousands of well-characterized probes, representing entire chromosomes or genomes, are affixed in an ordered manner onto a solid surface such as a glass slide to form a genetic array. DNA from a patient is fragmented, labeled in a certain color, mixed with the same amount of reference DNA (labeled in a different color), and hybridized to the DNA probes on the array.[203] DNA that does not hybridize is washed off, and the ratio of patient to reference DNA is analyzed to detect gains or losses of DNA sequences.[204]

Requirements for Laboratory Personnel

Most genetic testing is performed in a laboratory that does high-complexity testing and as such must meet Federal regulations for laboratory personnel.[205] (Several States also have State laboratory licensure laws.) For example, Federal regulations require that the laboratory director for high-complexity testing must be a doctor of medicine (M.D.), doctor of osteopathy (D.O.), or doctor of podiatry (D.P.M.) currently licensed to practice in the State in which the laboratory is located, or have a doctoral degree (Ph.D.) in a chemical, physical, biological or clinical laboratory science. All Ph.D. laboratory directors must also be Board certified (for example, certified in clinical molecular genetics by the American Board of Medical Genetics). Laboratory directors may also be pathologists who are certified in clinical or anatomic pathology (by the American Board of Pathology), and all directors must have experience in a high-complexity testing laboratory. The laboratory director is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures; recording and reporting test results promptly, accurately, and proficiently; and for assuring compliance with all applicable regulations. The regulations for laboratory personnel provide a detailed explanation of the qualification and responsibilities for the laboratory director.[206]

Laboratories that perform high-complexity testing also have a technical supervisor, clinical consultant, general supervisor, and testing personnel. If qualified, the laboratory director may also perform the duties required by these positions. The qualifications of the technical supervisor are similar to the laboratory director; the technical supervisor must be a currently licensed doctor or have a doctoral degree in a biological science, and have proper training and relevant experience to provide technical services. The technical supervisor's duties include selecting the test methodology that is appropriate for the clinical use of the test results; establishing a quality control program appropriate for the testing performed, including enrollment and participation in proficiency testing; resolving technical problems; and evaluating the competency of the laboratory staff. Federal regulations provide a detailed list of the technical supervisor's qualifications and responsibilities.[207]

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[206] Clinical Laboratory Improvement Amendments (CLIA), Subpart M—Personnel for Nonwaived Testing: Standard, Laboratories performing high complexity testing; laboratory director. See http://wwwn.cdc.gov/clia/regs/subpart_m.aspx#493.1441. Accessed on October 2, 2007.

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Laboratories that perform high-complexity testing must also have a clinical consultant who can discuss the appropriateness of the test(s) ordered; the interpretation of the test results; and the diagnosis, treatment, and management of patient care with the laboratory's clients. The clinical consultant must be qualified as a laboratory director or be a M.D., D.O., or D.P.M. currently licensed to practice in the State in which the laboratory is located. Laboratories performing high-complexity testing must also have one or more general supervisors who provide day-to-day supervision of testing personnel and reporting of test results. Testing personnel for high-complexity testing are responsible for specimen processing, test performance, and reporting test results. Each individual performs only those high complexity tests that are authorized by the laboratory director and are commensurate with the individual's education, training or experience, and technical abilities. Federal regulations provide a detailed list of qualifications and responsibilities for the clinical consultant,[208] general supervisor,[209] and testing personnel.[210]

Future Trends

New genetic testing technologies are rapidly emerging. While current genetic tests may be applicable to about 2 percent of the general population, genetic testing in development promises future applicability to more than 60 percent of the population.[211] Advancing knowledge of the human genome coupled with rapidly evolving technologies is leading to new opportunities to assess common, multifactorial disorders such as heart disease, diabetes, asthma, and mental illness, which likely involve multiple genes and environmental factors. One such opportunity is genome-wide association studies (GWAS), which analyze a large set of SNPs across the genome (in some studies, 500,000 to a million SNPs) to identify genetic variants that influence health and disease. Additionally, emerging technologies will help to decipher complex phenomena such as gene-gene interactions; epigenetic effects, which are heritable changes in gene function that do not alter the DNA sequence (e.g., DNA methylation); copy number variations that involve the gain or loss of large segments of DNA (ranging in size from thousands to millions of DNA bases), and the influence of environmental factors such as diet and exposure to exogenous substances (e.g., allergens, toxic chemicals) on gene expression.

Protein and antibody microarrays, which allow the simultaneous evaluation of multiple sets of proteins, show potential for improving diagnosis, prognosis, and management of a variety of diseases including cancer, cardiovascular disease, vision disorders, and neurological disease.[212] Recently developed array technologies allow multiplex protein analyses using a planar or bead-based approach. Planar microarrays involve a two-dimensional surface such as a glass slide or microchip that has defined reaction loci for individual analyses. For example, an antibody microarray test, which measures expression levels of three proteins associated with angiogenesis, invasion, and metastasis of tumors, has been developed for the diagnosis of breast cancer.[213] Multiplex bead-based microarrays, also called liquid arrays, employ

[208] Clinical Laboratory Improvement Amendments (CLIA), Subpart M—Personnel for Nonwaived Testing: Standard, Laboratories performing high complexity testing; clinical consultant. See http://wwwn.cdc.gov/clia/regs/subpart_m.aspx#493.1453. Accessed on October 2, 2007.

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suspensions of microsphere sets in which each set represents an individual analytical test. This approach has been used to identify disease-specific profiles for vitreoretinal disorders based on the analysis of cellular mediators such as cytokines, chemokines, and growth factors.[214]

Another application of protein microarrays is to characterize the effect of gene alterations on the function of the resulting protein. For example, microarray technology can be used to quantify the effect of cancer-associated mutations and polymorphisms in the p53 gene on the DNA-binding function of the p53 oncoprotein.[215] Microarrays that use small nucleic acid molecules called aptamers, which specifically bind proteins, have been developed for protein detection. Aptamers, due to their stability and binding specificity, hold great promise for the development of new classes of protein arrays for the combined detection of protein and nucleic acids.[216]

Small RNA molecules, known as microRNAs, are also likely to play a role in genetic testing, particularly as a tool to classify cancers[217] and provide information about cancer progression and response to treatment.[218] MicroRNAs are short segments of RNA (about 20 nucleotides) that do not encode proteins but instead play a role in regulating gene expression. MicroRNAs attach to certain sites on messenger RNA, which blocks the production of proteins. It is estimated that one-third of human protein-encoding genes are regulated by microRNAs.[219] MicroRNAs also play a role in controlling the replication and latency of viruses such as HIV.[220, 221]

Research studies have shown that levels of particular microRNAs can be used to differentiate between normal and cancerous tissues and also to help determine the stage of the cancer. For example, Bloomston et al.[222] compared expression patterns of microRNAs in pancreatic cancer to those of normal pancreas and chronic pancreatitis. They found that pancreatic cancer may have a distinct microRNA expression pattern that is distinct from normal pancreas and chronic pancreatitis. Their findings also suggested that microRNAs expression patterns may be able to distinguish between long- and short-term survivors. Research by Shell et al.[223] indicates that levels of the microRNA let-7 could be used as a predictor of cancer progression. In the cells they studied, let-7 reduced the expression of the HMGA2 gene, which is typically overexpressed in cancer cells. Cells from benign ovarian tumors had high levels of let-7 and low levels of HMGA2 expression, compared to tumor cells from advanced ovarian cancers. Levels of let-7 and HMGA2 were better predictors of ovarian cancer prognosis than established markers such as

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[221] Triboulet, R., Mari, B., Lin, Y., Chable-Bessia, C., Bennasser, Y., Lebrigand, K., Cardinaud, B., Maurin, T., Barbry, P., Baillat, V., Reynes, J., Corbeau, P., Jeang, K., and Benkirane, M. (2007). Suppression of microRNA-silencing pathway by HIV-1 during virus replication. *Science*. 315(5818): 1579-1582.

[222] Blooomston, M,m Frankel, W.L., Petrocca, F., Volinia, S., Alder, H., Hagan, J.P., Liu, C.G., Bhatt, D., Taccioli, C., and Croce, C.M. (2007). MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA*. 297(17): 1901-1908.

[223] Shell, S., Park, S.M., Radjabi, A.R., Schickel, R., Kistner, E.O., Jewell, D.A., Feig, C., Lengyel, E., and Peter, M.E. (2007). Let-7 expression defines two differentiation stages of cancer. *Proceedings of the National Academy of Sciences*. 104(27): 11400-11405.

vimentin and E-cadherin. Research evidence indicates that let-7 also acts as a tumor suppressor in other types of cancer such as lung cancer.[224] A test for let-7 levels is not available for clinical use, but the technology is rapidly advancing.[225]

Important advancements have also been made in the area of instrument automation. High throughput, accuracy, speed, and flexibility are the main reasons for the interest in these automated instruments. The introduction of fully automated platforms will make it possible for more laboratories to implement genetic testing because the need for specialized technical training will be minimized. Until recently the clinical application of nucleic acid based technology has been restricted to high complexity laboratories with specialized staff trained to design and run these assays. In 2006, however, self-contained, fully automated products were introduced, making nuclei acid analysis available to all hospitals, as well as moderate complexity laboratories in physician offices and clinic settings. An example of this automated technology is Cepheid's GeneXpert assay to detect BCR-ABL gene fusion in neoplastic cells of chronic myeloid leukemia patients.[226]

In addition to automation, the future of genetic testing will likely embrace improvements in miniaturization technologies. Nanotechnology, the science of building miniature devices that use small particles such as individual atoms, molecules, viruses, or cells, merges biology with information technology. Nanotechnology promises to affect the clinical laboratory industry through the development of miniaturized components and devices for chemical processing and measuring sensors. This technology could prove to be extremely useful in the movement toward developing small, versatile point-of-care tests.[227]

As current advances in sequencing become more widely available, with increased speed and decreased cost, it is likely that sequence-based approaches for the analysis of chromosome arrangements will become more important and widely used. Genome-wide analysis of DNA methylation and histone acetylation in addition to copy number changes will become an integral part of genetics.[228]

Continued refinement in the application of existing technologies and introduction of novel methodologies, along with an advanced understanding of the human genome, will expand the genetic diagnostic tool box available to healthcare providers, patients, and in some cases the general U.S. population seeking better healthcare choices. Genetic testing is also a key element in personalized medicine. If wisely developed and used, genetic testing has the potential to shift the American healthcare paradigm from reactive to proactive or preventive. This shift will pose significant challenges such as ensuring valid testing procedures and educating the lay public, healthcare providers, third-party payers, and policymakers about the optimal use of genetic technologies.

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[224] Yanaihara, N., Caplen, N., Bowman, E., Seike, M., Kumamoto, K., Yi, M., Stephens, R.M., Okamoto, A., Yokota, J., Tanaka, T., Calin, G.A., Liu, C.G., Croce, C.M., and Harris, C.C. (2006). Unique microRNA profiles in lung cancer diagnosis and prognosis. *Cancer Cell*. 9(3): 189-198.

[225] The University of Chicago Medical Center. New genetic marker characterizes aggressiveness of cancer cells. See http://www.uchospitals.edu/news/2007/20070625-let-7.html. Accessed on October 3, 2007.

[226] Jobbagy, Z., van Atta, R., Murphy, K.M., Eshlemann, J.R., and Gocke, C.D. (2007). Evaluation of Cepheid GeneXpert BCR-ABL assay. *Journal of Molecular Diagnostics.* 9(2): 220-227.

[227] Gau, V. and Wong, D. (2007). Oral fluid nanosensor test (OFNASET) with advanced electrochemical-based molecular analysis platform. *Annals of the New York Academy of Sciences*. 1098: 401-410.

[228] Speicher, M.R. and Carter N.P. (2005). The new cytogenetics: blurring the boundaries with molecular biology. *Nature Reviews Genetics*. 6: 782-792.

CHAPTER 4
ANALYTICAL VALIDITY, PROFICIENCY TESTING, AND CLINICAL VALIDITY

This chapter describes two key elements of genetic tests—analytical validity and clinical validity, as well as proficiency testing (PT), which is an important component of quality assurance (QA) programs. In addition, it explains various elements in the current oversight framework designed to ensure that genetic tests are analytically and clinically validated prior to use in patient care. The chapter concludes with a discussion of the gaps in this framework and makes recommendations that might help close those gaps. The following questions in the Secretary's charge are addressed in this chapter:

- What evidence of harm exists regarding genetic tests? Is that harm attributable to the analytic validity or clinical validity of the tests? If evidence does not exist, what threats are not currently being addressed?

- What are the existing pathways that examine the analytic validity and clinical validity of genetic tests?

- What organizations are currently involved with each of these aspects, and what are they doing to address these issues? Who should be responsible for each of these aspects?

- What resources (e.g., standards reagents/materials) are needed to develop proficiency testing (PT) kits or protocols for genetic tests? What is currently available in terms of PT kits or protocols for genetic tests? What information is provided by proficiency testing? Is the current level of proficiency testing for genetic tests adequate and are the results of laboratory performance assessments sufficiently transparent?

- What new approaches or models should be considered for private and public-private sector engagement in demonstrating clinical validity for developing effectiveness measures of genetic tests in clinical practice?

- Would additional or revised Government oversight add value for patients, and if so, how and where?

Assuring analytical and clinical validity is paramount for genetic testing because predictive and susceptibility genetic testing is often performed on asymptomatic persons and the interpretation of results may not be supported by other findings. Moreover, genetic testing for a particular heritable condition or disorder is typically performed once and not repeated or confirmed.

Background[229]

Like all other laboratories that test human specimens for the purpose of assessing health, diagnosis, and treatment, genetic testing laboratories are regulated by the 1988 Clinical Laboratory Improvement

[229] The GAO report, *Clinical Lab Quality: CMS and Survey Organization Oversight Should be Strengthened,* provides an excellent overview of how clinical laboratories are regulated.

Amendments (CLIA).[230] The implementation of CLIA requirements is overseen by the Centers for Medicare & Medicaid Services (CMS). Genetic testing laboratories must undergo inspections (also called surveys) every two years to assess their compliance with CLIA quality requirements such as personnel qualifications and responsibilities, quality control (QC) standards, PT, QA, and record keeping. Laboratories have a choice of being surveyed by an agency in their State department of health that is under contract with CMS to conduct inspections or by one of six private accrediting organizations[231] approved by CMS as having standards equivalent to CLIA. The State agencies use CLIA requirements for their surveys; however, New York and Washington operate State laboratory certification programs that have CLIA-exempt status because they are considered by CMS to be equal to or more stringent than the CLIA requirements. Therefore, New York and Washington States and the six private accrediting organizations use their own requirements, which have been approved by CMS, to survey laboratories. In addition to the biennial surveys, laboratories must participate in PT three times a year. If proficiency testing is unavailable, laboratories must perform a different type of assessment called an alternative assessment (AA).[232] (PT and AA are discussed in more detail later in this chapter.)

Under CLIA, deficiencies that are identified during CMS surveys are classified as "standard-level" or "condition-level." Generally, standard-level deficiencies are in stand-alone, unique requirements that may not be serious, while condition-level deficiencies indicate serious and/or comprehensive problems and are comprised of standard-level requirements. A serious problem is one that adversely affects (or has the potential to affect adversely) the accuracy and reliability of a patient's test results. When deficiencies are found, laboratories are required to submit a plan detailing how they will address the deficiencies, and they are given an opportunity to correct the deficiencies before sanctions are imposed. CMS can impose an armamentarium of sanctions that are composed of two types—alternative or principal. Of the two, alternative sanctions are less severe and usually include monetary penalties or onsite monitoring. Principal sanctions include revocation of a CLIA certification, cancellation of Medicare payments, or imposition of limitations on testing. Sanctions are selected based on the history of the laboratory's performance, and the severity and pervasiveness of the problem's impact on patient health and safety.

The Food and Drug Administration (FDA) categorizes laboratory tests by the complexity of the assay. The categories are: waived tests or non-waived tests (which can be of moderate- or high-complexity). Waived tests are examinations or procedures that are simple to perform and have little likelihood of erroneous results, including those approved for home use. Facilities performing only waived tests are not subject to routine surveys or the quality standards under CLIA, but must follow the manufacturer's instructions for test performance. Non-waived tests have more stringent requirements to meet under CLIA (such as routine surveys, personnel qualifications, QA, QC, and PT) than do waived tests. Currently, most genetic tests are categorized as high-complexity tests and are subject to the most stringent standards.

Like any other laboratory tests, the process of performing a genetic or genomic test can be divided in three different phases. The three phases are the pre-analytic phase, analytic phase, and post-analytic phase. The pre-analytical phase includes activities such as appropriate test selection and ordering tests for the clinical condition being evaluated, provision of appropriate clinical and demographic information, specimen collection, handling, and processing. The analytical phase encompasses the steps necessary to perform the test itself, quality control, and collection of analytical test results. The post-analytical phase

[230] CLIA. (1988) http://www.cms.gov/clia/. Accessed June 20, 2007.
[231] The six private CLIA-accrediting organizations are the American Association of Blood Banks (AABB), American Osteopathic Association (AOA), the American Society of Histocompatibility and Immunogenetics (ASHI), the College of American Pathologists (CAP), COLA, and the Joint Commission.
[232] 42 CFR § 493.801(a) (2) (ii) and 42 CFR 493.1236 (c)(1).

includes the necessary evaluation steps to analyze and interpret results obtained during the analytical phase, and reporting the test results to the person who ordered the test or will use those results.

Pathways for Bringing Genetic Tests to Clinical Practice

Currently, there are two pathways for bringing genetic tests into clinical practice. One pathway is through commercial product development, and the other is the provision for tests developed within a laboratory as a service. These pathways are subject to distinct regulatory requirements. Commercial products are developed by in vitro diagnostic device (IVD) manufacturers for distribution to multiple laboratories. In the service pathway, laboratories provide genetic tests by developing and validating tests for use solely in that laboratory. These types of tests are called laboratory developed tests (LDTs). (Such tests have also been known as in-house tests or home brew tests, but these terms are no longer in favor.)

Analyte specific reagents (ASRs) are used in the development of many genetic tests, and FDA regulates ASRs that are sold to laboratories.[233] ASRs are specific substances such as antibodies, receptor proteins, ligands, or nucleic acid sequences that are used as active ingredients in tests that identify or quantify a particular chemical entity in patient specimens. All manufacturers and suppliers of commercially distributed ASRs are required to register with FDA, provide a list of the ASRs they supply to laboratories for use in developing LDTs, meet current good manufacturing practices (cGMPs), comply with medical device report requirements, and report adverse events related to ASRs,[234] as well as comply with a number of other requirements included with FDA's definition of general controls.

Most ASRs are regulated by FDA as Class I exempt devices, subject to general controls but exempt from premarket review. A small number of ASRs are classified as Class II devices, which are subject to general and special controls, or Class III devices, which are subject to premarket approval. Only laboratories certified by CLIA to perform high-complexity tests can provide tests using ASRs, and only physicians or other healthcare practitioners authorized by applicable State law are permitted to order LDTs using ASRs. In addition, the labels on commercially distributed ASRs must indicate that the analytical and performance characteristics of the ASR are not established.

Test kits contain quality-controlled reagents for the performance of the test for a particular clinical condition. For example, a kit might include the reagents necessary for nucleic acid isolation, amplification, and detection/quantitation. FDA regulates test kits as in vitro diagnostic devices, and if the classification of the test indicates that premarket review is required, then they must be cleared or approved before they can be marketed and commercially distributed. There are numerous class I exempt test kits that are exempt from premarket review, but none of these are genetic tests. FDA premarket review of test kits focuses on their analytical validity and clinical plausibility. FDA reviews the claims made and the labeling provided for the kit, and test manufacturers are subject to registration, listing, and adverse event reporting requirements, among other requirements.

Manufacturers may market similar product designs that have not undergone FDA review with a label indicating that the products are for research use only (RUO), not for use in diagnostic procedures. These products are not intended for clinical laboratory use in diagnostic testing. Devices for which the design

[233] Food and Drug Administration. Analyte Specific Reagents [21CFR 809.10(e), 809.30, and 864.4020]. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm. Accessed on August 8, 2007.

[234] Food and Drug Administration. Analyte Specific Reagents [21CFR 864.4020]. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=864.4020&SearchTerm=asr. Accessed on August 8, 2007.

phase is complete, but for which performance data are not established, may be offered with appropriate labeling and other controls for investigational use only (IUO).

A laboratory verifies that the system performs as claimed when used by the persons who routinely perform patient testing. They also verify that the established performance specifications (e.g., accuracy, precision) are achieved. Specific activities required for assay verification may be outlined in CLIA regulations or standards governing laboratories, such as the College of American Pathologists (CAP) Checklist for Molecular Pathology: 2006.[235] If a laboratory chooses to modify elements of an FDA-approved or –cleared IVD for "off label" use, then the laboratory must perform an analytical validation for the modification prior to patient testing to establish performance specifications.

LDTs are developed using reagents that are entirely produced within the laboratory and/or use ASRs and general purpose reagents (GPRs) purchased from a variety of manufacturers. FDA considers LDTs to be medical devices and, as such, LDTs are products subject to FDA regulatory oversight. There is some opposition, however, to this position in a number of quarters.[236, 237, 238, 239] With a few exceptions, FDA has not exercised its regulatory authority in this area, a decision based on the limited resources available to the FDA and the understanding that laboratories developing LDTs for clinical use are regulated by CLIA.[240]

In a departure from previous years, when the FDA decided not to exercise regulatory authority over most LDTs, the FDA recently published a draft guidance for vitro diagnostic multivariate index assays (IVDMIAs).[241] The draft guidance addresses FDA's regulatory approach to IVDMIAs as a discrete category of devices, even those offered as LDTs. As defined in this guidance, an IVDMIA is a device that combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a classification, score, index). These devices are intended for use in the diagnosis of disease and other conditions, or in the cure, mitigation, treatment, or prevention of disease, providing a result whose derivation is nontransparent and cannot be independently derived or verified by the end user. IVDMIAs raise concerns about safety and effectiveness because they are based on observed correlations between multivariate data and clinical outcome, and the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests. The draft guidance clarifies that IVDMIAs must meet pre- and postmarket device requirements appropriate to their level of risk, including premarket review requirements for Class II and III devices. FDA estimates that only one or two dozen products of this type may be on the market now, or are close to being marketed.

The breadth involved in analytically validating an LDT is similar, but more involved, than verification of a commercial IVD. Verification of an FDA-approved or –cleared test under CLIA means that the laboratory must confirm that the laboratory is within the manufacturer's specifications for accuracy,

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[235] American College of Medical Genetics. Laboratory Standards and Guidelines for Clinical Genetics Laboratories. 2006 Edition. http://www.acmg.net/Pages/ACMG_Activities/stds-2002/g.htm. Accessed on June 16, 2007.

[236] Washington Legal Foundation. *WLF criticizes FDA efforts to regulate clinical laboratories, ASRs.* March 2007. See http://www.wlf.org/upload/030907RS.pdf. Accessed on August 17, 2007.

[237] American Clinical Laboratory Association letter to HHS Secretary Tommy Thomson; September 12, 2002; comments on the Secretary's Advisory Committee on Genetic Testing (SACGT) report: *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT.*

[238] Washington Legal Foundation. Citizen Petition Regarding FDA Regulation of Laboratory Developed Tests. September 28, 2006. See http://www.wlf.org/upload/Clinical%20Labs-%20FDA%20Citizen%20Petition.pdf. Accessed on August 17, 2007.

[239] Docket 2006D-0347: Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—In Vitro Diagnostic Multivariate Index Assays. See http://www.fda.gov/ohrms/dockets/dockets/06d0347/06d0347.htm. Accessed on September 13, 2007.

[240] CLIA. (1988) http://www.fda.gov/cdrh/clia/ Accessed June 20, 2007.

[241] Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—In Vitro Diagnostic Multivariate Index Assays. See http://www.fda.gov/cdrh/oivd/guidance/1610.html. Accessed on September 13, 2007.

precision, reference range, and reportable range (i.e., the test works appropriately in the laboratory). If a test is modified by the laboratory (any change that impacts the test's performance specifications), is not FDA-cleared or -approved (including LDTs), or the performance specifications are not provided by the manufacturer, the laboratory must validate the test. Validation means that the laboratory must "establish" the specifications for their laboratory for the above four parameters, as well as for specificity and sensitivity. The validation plan for an LDT considers the analytic performance characteristics as well as regulatory requirements such as those put forth by CLIA. In addition, some laboratories voluntarily address international standards such as the ISO 13485:2003, a comprehensive quality management system for the design and manufacture of medical devices published in 2003 by the International Organization of Standardization (ISO). The validation of an LDT often will also need to meet requirements of other regulatory and guidance frameworks (e.g., CLIA,[242] ISO 17025: 2005,[243] ISO 15189: 2007,[244] CLSI MM01,[245] and CLSI MM07[246]).

Analytical Validity

When a laboratory test is performed, the manufacturer, regulatory agencies, credentialing organizations, the laboratory, the ordering physician, and the patient need to have a high level of confidence that reported results are reliable.

In 2005, the United Kingdom (U.K.) National Measurement Institute[247] issued a set of principals that describe the important aspects of making reliable analytical measurements.

1. Analytical measurements should be made to satisfy an agreed requirement.
2. Analytical measurements should be made using methods and equipment that have been tested to ensure they are fit for purpose.
3. Staff making analytical measurements should be both qualified and competent to undertake the task.
4. There should be a regular independent assessment of the technical performance of the laboratory.
5. Analytical measurements made in one location should be consistent with those made elsewhere.
6. Organizations making analytical measurements should have well-prepared quality control and quality-assurance procedures.

One aspect of assay reliability is the validity of the analytical method itself. In laboratory medicine, the medical device used to perform the measurement needs to meet an accepted standard of quality to ensure that the results are reliable. It is important to understand that any measurement is subject to some level of uncontrollable variation inherent to the particular measurement method employed. This is called the measurement uncertainty.

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[242] Centers for Medicare and Medicaid Services. Interpretive guidelines for laboratories. See http://www.cms.hhs.gov/CLIA/03_Interpretive_Guidelines_for_Laboratories.asp. Accessed on August 16, 2007.

[243] International Organization for Standardization. General requirements for the competence of testing and calibration laboratories (ISO 17025: 2005). See http://www.iso.org/iso/en/CatalogueDetailPage.CatalogueDetail?CSNUMBER=39883. Accessed on August 16, 2007.

[244] International Organization for Standardization. Medical laboratories—particular requirements for quality and competence (ISO 15189: 2007). See http://www.iso.org/iso/en/CatalogueDetailPage.CatalogueDetail?CSNUMBER=42641. Accessed on August 16, 2007.

[245] Clinical and Laboratory Standards Institute. *Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition.* CLSI document MM01-A2. 2006. Clinical and Laboratory Standards Institute: Wayne, PA.

[246] Clinical and Laboratory Standards Institute. *Fluorescence In Situ Hybridization (FISH) Methods; Approved Guideline—First Edition.* CLSI document MM07-A. 2004. Clinical and Laboratory Standards Institute: Wayne, PA.

[247] Valid Analytical Measurement Programme. Middlesex, UK: LGC. http://www.vam.org.uk. Accessed September 28, 2007.

Key Terms and Concepts

The quality of a measurement (i.e., its analytical validity) is a function of its:

Accuracy: the closeness of agreement between a test result and true value of what is being measured (see Figure 1 below).

Precision: the closeness of agreement between independent results of measurements obtained under stipulated conditions[248] (see Figure 1 below).

Uncertainty: a parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand;[249] it is a formal quantitative statement of the confidence in the result of an assay.

Traceability: a property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties.[250]

Robustness: the ability of a method to remain unaffected by small fluctuations in assay parameters, it is often assessed through interlaboratory comparison studies or by varying parameters such as temperature and relative humidity to determine the operating range of the method.

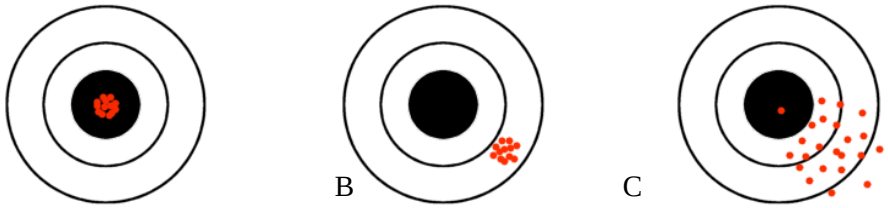

Figure 1. Reference Values

This figure shows three "targets" in which the center of the target is the true or reference value. Each of the dots indicates a repeated test measurement from an individual. Target A shows results that are both precise (all results are close together) and accurate (in the center of the target). Target B is precise, but not accurate. Target C is neither precise nor accurate.[251] [Adapted from Med4You[252] with permission from Dr. Wolfgang Hübl.]

Validation is established by assessing various assay performance parameters specific to each test. Because of the breadth of tests covered by this report, a detailed discussion is not possible regarding all aspects of analytical validation. In general, assay validation addresses quality parameters related to the:

- analytical method (e.g., PCR, microarray, gene sequencing for nucleic acids, and immunoassay of proteins, or analytical chemistry for metabolites);

[248] ISO. *International Vocabulary of Basic and General Terms in Metrology*. 1993. International Organization for Standardization: Geneva.
[249] ISO. *International Vocabulary of Basic and General Terms in Metrology*. 1993. International Organization for Standardization: Geneva.
[250] Traceability – NIST policy and supplementary materials. Gaithersburg, MD: National Institute of Standards and Technology, 2001. http://ts.nist.gov/traceability/ Accessed October 1, 2007.
[251] Diagrams from EurogenTesthttp://www.EuroGentest.org/).
[252] Med4You. See http://www.med4you.at/laborbefunde/allgemeines/lbef_qualitaet.htm#Pr. Accessed on October 15, 2007.

- measurand – the analyte (e.g., genetic sequence, protein or metabolite) being measured in a particular matrix or type of sample; and
- type of result being reported, which can be either:
  - quantitative – a numerical value is reported as the result and is obtained by running the patient sample against an available set of internationally accepted and traceable standards (e.g., the amount of thyroid stimulating hormone in human serum)
  - qualitative – the result is reported as to whether the analyte is present (positive) or absent (negative) in the sample or if the test was not able to definitively determine a result (equivocal) (e.g., the presence or absence of a genetic mutation in a particular sample of the patient's DNA.).

Wherever possible, a medical laboratory measurement should be validated against a standard reference method using reference materials that are traceable to an internationally recognized certified standard reference material.[253] Unfortunately, relatively few standard reference methods and certified reference materials are available. Overall, however, the analytic performance of genetic tests is good, when specific tests have been examined,[254, 255] but many genetic tests have not undergone examination.

Analytical sensitivity describes how effectively a test can detect all true positive specimens, as determined by a reference method. For example, in testing samples of deoxyribonucleic acid (DNA), analytic sensitivity is how well an assay can detect certain mutations when they are present. This description is most often used for tests that yield a qualitative result. The concept can also be expressed as the test's false negative rate (1-sensitivity), or how often a test incorrectly reports the absence of a DNA alteration when in fact that alteration is present in the sample.

Analytical sensitivity can also be defined as a change in the response of a measurement system (analyte change) divided by the corresponding change in the stimulus (analyte).[256] The most critical point in this regard is usually limit of detection (LoD), which can be defined by the lowest amount of analyte that can be measured accurately (limit of quantitation) or by the lowest amount of analyte in a sample that can be detected, but not quantified as an exact value.[257, 258] This definition is most often used for tests that yield a quantitative result. Different assays will have different limits of sensitivity.

Analytic specificity is defined as the ability of a measurement procedure to measure solely the analyte of interest.[259] Two important aspects of analytical specificity are interference by endogenous or exogenous substances other than the analyte of interest and cross-reactivity of the analytical system with substances other than the intended analyte of interest.

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[253] Joint Committee for Traceability in Laboratory Medicine (JCTLM). See http://www.bipm.org/en/committees/jc/jctlm/. Accessed on September 26, 2007.

[254] Palomaki, G.E., Bradley, L.A., Richards, C.S., and Haddow, J.E. (2003). Analytic validity of cystic fibrosis testing: a preliminary estimate. *Genetics in Medicine*. 5: 15-20.

[255] Palomaki, G.E., Haddow, J.E., Bradley, .LA., Richards, C.S., Stenzel, T.T., and Grody, W.W. (2003). Estimated analytic validity of *HFE* C282Y mutation testing in population: the potential value of confirmatory testing. *Genetics in Medicine.* 5: 440-443.

[256] ISO. *International Vocabulary of Basic and General Terms in Metrology*. 1993. International Organization for Standardization: Geneva.

[257] WHO. Expert Committee on Biological Standardization. *Glossary of Terms for Biological Substances Used for Texts of the Requirements*. 1995. WHO unpublished document BS/95.1793. World Health Organization: Geneva.

[258] Clinical and Laboratory Standards Institute. *Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline—First Edition.* CLSI document EP-17A. 2004. Clinical and Laboratory Standards Institute: Wayne, PA.

[259] ISO. *International Vocabulary of Basic and General Terms in Metrology*. 1993. International Organization for Standardization: Geneva.

Interference may result from contamination, admixture, and presence of exogenous substances in samples, which can occur for a variety of reasons such as poor sampling, lack of sample stabilizer (where appropriate), cross-contamination during sample processing, inclusion of normal, non-diseased tissue with the diseased tissue of interest, tissue from a source additional to the desired sample (e.g., maternal cells obtained during fetal specimen collection), or failure to remove exogenous substances (e.g., anticoagulants used during blood collection, residual reagents used during sample processing). Laboratories and IVD manufacturers account for the effects of contamination, admixture and interfering substances during assay validation testing. FDA requires manufacturers to assess the potential for interference by using substances that are likely to be problematic. The American College of Medical Genetics (ACMG) has published technical standards and guidelines for prenatal testing to require an ancillary test be used to verify the absence of contributing maternal DNA to a prenatal diagnostic result;[260] these guidelines may also apply to other mixed specimens.

Cross-reactivity of an assay with analytes other than the ones it is designed to measure should also be assessed. FDA requires manufacturers to assess the potential for cross-reactivity by using substances that are likely to be problematic. It is important to consider analytes that have a non-negligible probability of being present in any of the target population's specimen collection site/sample type.

Challenges Related to Analytic Validity

Emerging Technologies

New technology such as microarray and highly multiplex technology have been used to study several tumor types, most notably breast, ovary, colon, gastric, leukemias, malignant lymphoma, prostate, lung, and malignant melanoma. Almost daily, there is an announcement of a new genomic association of specific SNP patterns or gene expression patterns to different diseases such as cancer, cardiovascular disease, and diabetes. Analytical and accurate clinical interpretation from the currently available data is a challenging task, as there are numerous inter-experimental variations that can significantly influence the interpretation of results.

Proper statistical analysis with an adequate number of well characterized patients and independent validation in large series of patients is one way to address this dilemma. Most of the molecular signatures are based on retrospective studies but will need to be based on prospective studies in representative populations. Technologies for gene-expression profiling for breast cancer are gradually being implemented in the clinic. Prognostic factors that have been used for over 20 years to help clinicians guide adjuvant therapy treatment for breast cancer and microarray technology for gene-expression profiling may become an important adjunct to the known prognostic factors. For breast cancer, two relevant gene-expression profiles associated with prognosis have been identified: a 70-gene classifier (Mammaprint™) and a 21-gene signature (OncotypeDx™).

In addition, emerging technologies will pose a continuous challenge in the availability of quality control materials and materials available for PT. The continued development of molecular genetic tests, performed by an extensive number of different methods, challenges vendors to stay abreast of PT requirements for comprehensive and suitable testing materials that assess laboratory performance for newly discovered genetic mutations and recently introduced technologies. Vendors have partnered with others to assist in development of PT strategies. One example is the recently developed and clinically implemented microarray testing for cancer diagnosis, prognosis, and treatment planning. U.S. Governmental agencies are actively working with physicians as well as academic and commercial

[260] American College of Medical Genetics. Laboratory Standards and Guidelines for Clinical Genetics Laboratories. 2006 Edition. http://www.acmg.net/Pages/ACMG_Activities/stds-2002/g.htm. Accessed on June 16, 2007.

institutions to understand the complexities, proficiency testing needs, and possible regulatory changes that are needed to ensure quality laboratory testing and patient safety in this rapidly evolving area.[261, 262]

An example of the cooperative nature of the above interactions is the MicroArray Quality Control (MAQC) Project, an evaluation of current gene expression profile testing. This collaborative project has shown "intra-platform consistency across test sites as well as a high level of inter-platform concordance in terms of genes identified as differentially expressed. Furthermore, the project provides a resource that represents an important first step toward establishing a framework for the use of microarrays in clinical and regulatory settings."[263] This project has also developed and used two batches of whole human genome ribonucleic acid (RNA) sample types that are supplied at no cost to appropriate individuals and/or institutions. These same specimen batches will be supplied by their manufacturers for the next several years. Eventually, these two extensively characterized RNA sample sets can form the basis of a reasonable PT program in this area.[264, 265, 266]

Other newly emerging areas of clinical molecular genetics/genomics include gene dosage (comparative genomic hybridization, CGH) and single nucleotide polymorphism (SNP) arrays, described in Chapter 3. There are several key issues involved in these areas, as well as in the microarray area.

Regulatory Harmonization

Most genetic tests are LDTs and must be analytically validated by the laboratory according to CLIA. Laboratories that test samples from New York patients or return results within New York must submit their validation documentation for review and approval by the New York State Department of Health (NYSDOH). Oversight would be enhanced by greater consistency of State and Federal requirements.

In addition, due to limited test availability, not all genetic tests for U.S. citizens are performed in the United States. While there are a few CLIA-certified laboratories operating outside the United States, for the most part these laboratories have no routine U.S. oversight (unless performing testing on specimens from New York or are accredited). For these laboratories, an internationally accepted set of mutually recognized requirements for analytical validity becomes important. CMS is evaluating various options and alternatives for the routine oversight of foreign laboratories.

Will the U.S. professional and Government communities accept an international assessment of laboratory capability to perform genetic testing? How would the analytical validity be established for non-U.S. performed tests? However the process of oversight is achieved by blending professional, Government,

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[261] Dasciano, D.A. and Woodcock, J. (2006). Empowering Microarrays in the Regulatory Setting. *Nature Biotechnology*. 24:1103-1104.

[262] Frueh, F.W. (2006). Impact of Microarray Data Quality on the Genomic Data Submissions to the FDA. *Nature Biotechnology*. 24:1105-1107.

[263] MAQC Consortium. (2006). The MicroArray Quality Control (MAQC) Project Shows Inter-and Intraplatform Reproducibility of Gene Expression Measurements. *Nature Biotechnology*. 24:1151-1161.

[264] Canales, R.D., Luo, Y., Willey, J.C., Austermiller, B., Barbacioru, C.C., Boysen, C., Hunkapiller, K., Jensen, R.V., Knight, C.R., Lee, K.Y., Ma, Y., Maqsodi, B., Papallo, A., Peters, E.H., Poulter, K., Ruppel, P.L., Samaha, R.R., Shi, L., Yang, W., Zhang, L., and Goodsaid, F.M. (2006). Evaluation of DNA Microarray Results with Quantitative Gene Expression Platforms. *Nature Biotechnology*. 24:1115-1122.

[265] Shippy, R., Fulmer-Smentek, S., Jensen, R.V., Jones, W.D., Wolber, P.K., Johnson, C.D., Pine, P.S., Boysen, C., Guo, X., Chudin, E., Sun, Y.A., Willey, J.C., Thierry-Meig, J., Setterquist, R.A., Wilson, M., Lucas, A.B., Novoradovskaya, N., Papallo, A., Turpaz, Y., Baker, S.C., Warrington, J.A., Shi, L., and Herman, D. (2006). Using RNA Sample Titrations to Assess Microarray Platform Performance and Normalization of Techniques. *Nature Biotechnology*. 24:1123-1131.

[266] Tong, W., Lucas, A.B., Shippy, R., Fan, X., Fang, H., Hong, H., Orr, M.S., Chu, T.M., Guo, X., Collins, P.J., Sun, Y.A., Wang, S.J., Bao, W., Wolfinger, R.D., Shchegrova, S., Guo, L., Warrington, J.A., and Shi, L. (2006). Evaluation of External RNA Controls for the Assessment of Microarray performance. *Nature Biotechnology*. 24:1132-1139.

and international activities, the goal is to assure that all genetic tests have their analytical validity established for all health assessment purposes and the established analytical validity is considered to be sufficient for its specific intended use.

Professional Guideline Development

Although professional societies play an important role in developing clinical guidelines and standards, they cannot keep up with the pace of development of genetic tests. Thus, there are and always will be gaps in current standards until professional organizations are given the support needed to develop guidelines for every genetic test.[267]

Proficiency Testing

The CLIA regulations require laboratories to maintain a level of quality and accuracy in performing tests. CLIA requires laboratories to have quality assurance programs in place, and all of the CLIA quality standards together help to facilitate test accuracy and reliability. A key component of such programs is PT.[268] There are two ways in which PT is performed: regulated PT via a CMS-approved PT program or AA. AA is a twice yearly assessment of the laboratory's testing performance when regulated or routine PT is not available.

PT is an external assessment of laboratory competence. PT performance reflects the accuracy of the laboratory's testing process and can also serve as an educational activity for the laboratory staff. It determines testing performance by comparing the laboratory's results obtained by testing unknown challenge specimens to an external standard. The external standard is generally the mean of values obtained by other laboratories using the same test method, but it may be assigned by a reference method or some other procedure. Laboratories engage in PT three times a year, and their results are graded by a CMS-approved PT program. A list of CMS approved PT programs can be found on the CMS CLIA web site.[269]

Examples of AA are split-sample testing between two or more laboratories sharing test results with all participants, repeat testing on previously analyzed specimens whose earlier results are blinded to the laboratory technical staff, enrollment in a non-approved PT program, or testing by a different method.[270]

Most genetic testing laboratories are not required by CLIA to perform formal PT unless they are testing regulated analytes that are listed in the CLIA regulations in Subpart I,[271] irrespective of the fact that genetic tests are high complexity tests. CMS enforces the formal PT performance requirement only for laboratories offering any of the 83 regulated analytes. According to CLIA regulations, AA must be performed for all other tests.

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[267] Sue Richards presentation to SACGHS, March 2007. See http://www4.od.nih.gov/oba/SACGHS/meetings/Mar2007/SACGHSMar2007meeting.htm. Accessed on September 20, 2007.

[268] External Quality Assessment (EQA) is a term equivalent with PT but more commonly used in Europe.

[269] Clinical Laboratory Improvement Amendments: Overview. Baltimore, MD: Centers for Medicare and Medicaid Services, 2007. http://www.cms.hhs.gov/clia. Accessed October 2, 2007.

[270] Clinical and Laboratory Standards Institute. *Assessment of Laboratory Tests When Proficiency Testing is Not Available; Approved Guideline—First Edition.* CLSI document GP29-A. 2002. Clinical and Laboratory Standards Institute: Wayne, PA.

[271] Clinical Laboratory Improvement Amendments (CLIA), Subpart I—Proficiency Testing Programs for Nonwaived Testing. See http://wwwn.cdc.gov/clia/regs/subpart_i.aspx. Accessed on August 9, 2007.

Genetic testing laboratories that are accredited by a CMS-deemed organization may be required by that organization to carry out PT (if available) for all the tests they offer, including genetic tests. This requirement is applied regardless of whether the analyte is regulated by CLIA (an analyte for which PT is specifically required by regulation) or nonregulated. For example, one such accrediting organization, CAP, currently accredits approximately 6,600 laboratories, of which about 6,400 are in the United States. If PT is not available, then AA is required.

Value of PT Testing

Congress recognized the importance of PT in 1988 when the CLIA program was authorized. According to the law's legislative history, Congress wanted proficiency testing to "be the central element of determining a laboratory's competence since it purports to measure actual test outcomes rather than merely gauging the potential for accurate outcomes."[272]

Since the earliest days of proficiency testing the contribution to improvement of laboratory practice has been substantiated. Laboratories utilize PT as a tool for quality management through comparison of a laboratory's test result and interpretation to that of a larger group or reference method, education of laboratory personnel, monitoring of internal processes, evaluation of summary data to compare method performance, and a source of continuing laboratory education.[273]

A satisfactory PT result, however, is only one measure of laboratory performance. Initial validation of a method, periodic recalibration of instruments, contemporaneous quality control testing, a well-functioning quality assurance plan, and onsite inspection by external organizations all supplement the assurance provided by a record of satisfactory PT performance. Nevertheless, ongoing monitoring of PT allows the laboratory to assess the quality of day-to-day operations and trends by identifying testing problems that may not surface with other control activities. Such information enables the laboratory to take preventative action and prevent future unacceptable results or inaccuracies in patient testing.[274] Likewise, the investigation of unacceptable results can identify clerical errors, methodological problems, equipment problems, technical problems, problems with the PT material, and problems with test interpretation.

For genetic testing, PT materials also provide to the laboratory a source of continuing education. More specifically, PT materials include commentaries that accompany the participant summary reports, evaluations of educational or ungraded specimens, and recommendations for improvement of test method and utilization of proper nomenclature.[275, 276]

Current PT Programs and Related Activities

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[272] House Committee on Energy and Commerce, Clinical Laboratory Improvement Amendments of 1988, 100th Cong., 2nd Sess., 1988, H.Rep 100-899 [legislative history].

[273] Tholen, D.W., Berte, L.M., Boone, D.J., Cooper, W.G., Gun-Munro, J., Noble, M.A., Sarewitz, S.J., and Williams, M.L. Using Proficiency Testing to Improve the Clinical and Laboratory; Approved Guideline – Second Edition. Clinical and Laboratory Standards Institute GP27-A2, Vol. 27(8).

[274] Tholen DW, Berte LM, Boone DJ, Cooper WG, Gun-Munro J, Noble MA, Sarewitz SJ, Williams ML. Using Proficiency Testing to Improve the Clinical and Laboratory; Approved Guideline – Second Edition. Clinical and Laboratory Standards Institute GP27-A2, Vol. 27(8).

[275] Mascarello, J.T., Cooley, L.D., Davison, K., Dewald, G.W., Brothman, A.R., Herrman, M., Park, J.P., Persons, D.L., Rao, K.W., Schneider, N.R., and Vance, G.H. (2003). As currently formulated, ISCN FISH nomenclature is not practical for use in clinical test reports or cytogenetics databases. *Genetics in Medicine*. 5(5): 370-377.

[276] Gulley, M.L., Braziel, R.M., Halling, K.C., His, E.D., Nikiforova, M.N., Nowak, J.A., Silverman, L., Tubbs, R.R., Van Deerlin, V.M., Vance, G.H., and Versalovic, J. (2007). Clinical Laboratory Reports in Molecular Pathology. *Archives of Pathology and Laboratory Medicine*. 131:852-863.

PT Program of the College of American Pathologists

CAP is a professional organization of board-certified pathologists. Shortly after its inception in 1947, the Board of Governors issued a directive to institute national proficiency testing. In 1949, the CAP Chemistry Survey enrolled 515 participant laboratories. By 1963, 1,400 laboratories were participating in six surveys including microbiology, immunohematology, toxicology, hematology, urinalysis, and nuclear medicine. In 2007, the College enrolled 23,000 national and international laboratories in one or more of 530 PT products. PT surveys for genetic testing are produced for cytogenetics, molecular and biochemical genetics, and molecular pathology. A complete list of these products can be found in Appendix C (Table 1: CAP Products for Proficiency Testing). Approximately 700 laboratories are enrolled in the molecular pathology PT products and 250 laboratories in the cytogenetic PT products. New products under development include an array format for pharmacogenetic testing of warfarin and cytochrome P450 variants, and a comparative genomic hybridization array format for detecting copy number variants.

CAP provides individual laboratories with unknown "challenge" specimens for testing. Most typically, five challenge specimens are sent to PT subscribers in a single mailing, and three mailings are sent per year. CAP offers challenges for approximately 20 genetic disorders.

Each PT survey is developed within one or more CAP scientific resource committees of the College's Council on Scientific Affairs. The College partners with other medical specialty organizations in producing PT programs. For example, the Cytogenetic and Molecular/Biochemical Genetic Resource committees are jointly sponsored with the ACMG. These resource committees are also responsible for the grading of PT.

As previously discussed, grading of PT challenges is generally with reference to the mean of values obtained by other laboratories using the same test method but may also be assigned by a reference method or some other procedure. Quantitative tests are expected to perform within two standard deviations of the mean or within a specified percentage deviation from the mean to be considered acceptable. For qualitative tests, agreement with the response provided by 80 percent of peer laboratories or 80 percent of referee laboratories is required for acceptable performance.

Performance on a mailing is considered "satisfactory" when at least 80 percent of a laboratory's responses to challenges in a single mailing (sometimes called an "event" or a "cycle") are acceptable. For certain high-risk analytes, such as ABO testing, satisfactory performance requires that all responses (100 percent) be acceptable. Some challenge specimens are sent for educational value and are not designed to be graded. When laboratory responses to a challenge cannot be graded because of technical considerations or lack of either referee or participant consensus, the challenge is also considered educational and not factored into the determination of a laboratory's acceptable performance. When a PT survey is developed for a new analyte or new testing method/technology, the entire survey may be considered educational and not graded for one or more years, assuring field validation.

Periodically, supplementary questionnaires are sent to laboratories enrolled in PT surveys. These questionnaires solicit information about a variety of laboratory procedures and practices including laboratory accession methods and reporting formats and pre- and post-analytic variables. Compilation of responses provides insight into pre- and post-analytic laboratory practices being used by clinical

laboratories. Summaries of PT challenges and supplementary evaluations prepared by the scientific resource committees are found in the literature.[277, 278, 279]

PT Monitoring of CAP-Accredited Laboratories

Laboratories performing moderate and high complexity testing (non-waived) must hold either a certificate of compliance or a certificate of accreditation if surveyed by a CMS-deemed accrediting agency. (CMS issues all certificates; however, the deemed agencies may also issue an accreditation to laboratories.) Accreditation is granted by a nonprofit organization, such as CAP, that has been approved ("deemed") by CMS to have requirements that are equal to or more stringent than key (condition-level) CLIA requirements.[280]

CAP's Laboratory Accreditation Program (LAP) is responsible for monitoring PT performance in CAP-accredited laboratories. This oversight occurs in two venues. The Continuous Compliance Committee (CCC) of CAP's Commission on Laboratory Accreditation monitors laboratory PT performance and intervenes when a laboratory does not enroll in PT, enrolls in a PT survey but does not submit PT results, or demonstrates unsatisfactory PT performance. When performance is unacceptable, an escalating series of responses is initiated (Appendix C, Figure 1). If a laboratory has two unacceptable testing events within three successive PT cycles, then the laboratory is given a choice to either cease testing for that analyte with failed PT or submit to the CAP a credible plan of corrective action for testing. If the laboratory chooses to provide a plan of corrective action and that plan is acceptable to the CCC, then the laboratory is permitted to continue testing until the next PT event. If the laboratory's result on the next event is unsatisfactory, the laboratory must cease testing for that analyte. If the laboratory performs satisfactorily on the next two PT events, the laboratory can continue testing for the analyte. The opportunity to submit a credible plan of correction (no other penalty) is allowed only on the first unsuccessful performance. Subsequent unsuccessful performance would require an immediate cessation of testing.

Laboratory PT performance for CAP-accredited laboratories is also assessed during the on-site laboratory inspection performed by a team of external inspectors once every two years. During the inspection process, the inspector reviews enrollment, PT performance, documentation, and laboratory review of PT. The laboratory must retain documentation of its corrective action for each unacceptable PT result. If documentation is absent or the laboratory has not engaged in corrective action, the laboratory is cited for a deficiency. All PT deficiencies are set as Phase II, which means that the laboratory must respond to CAP within 30 days of the inspection with a corrective plan of action. That plan is reviewed by technical and professional staff and a decision is rendered as to whether the plan is acceptable or not. If the plan is not acceptable, the laboratory accreditation may be withheld or revoked. Laboratories are normally subjected to external inspection every two years, but laboratories with a history of poor PT performance, inspection deficiencies, or other problems may be inspected more frequently. Results of failed PT and inspection

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[277] Cell Markers and Cytogenetics Committee, CAP. (2002). Clinical laboratory assays for HER2/neu amplification, quality assurance, standardization, and proficiency testing. *Archives of Pathology and Laboratory Medicine.* 126: 803-808.

[278] Mascarello, J.T., Brothman, A.R., Davison, K., Dewald, G.W., Herrman, M., McCandless, D., Park, J.P., Persons, D.L., Rao, K.W., Schneider, N.R., Vanc,e G.H., and Cooley, L.D. (2002) Proficiency testing for laboratories performing fluorescence in situ hybridization with chromosome-specific DNA probes. *Archives of Pathology and Laboratory Medicine.* 126: 1458-1462.

[279] Nikiforova, M.N., Hs,i E.D., Braziel, R.M., Gulley, M.L., Leonard, D.G.B., Nowak, J.A., Tubbs, R.R, Vance, G.H., Van Deerlin, and V.M. (2007). Detection of clonal IGH rearrangements: summary of molecular oncology surveys of the College of American Pathologists. *Archives of Pathology and Laboratory Medicine*. 131:185-189.

[280] P.Valenstein (*Editor*). Quality Management in Clinical Laboratories-Promoting Patient Safety Through Risk Reduction and Continuous Improvement. College of American Pathologists, 2005; p56.

decisions from an out-of-cycle inspection, if conducted, are included in the inspector's packet for the next inspection.

All CAP-accredited laboratories must participate in PT for analytes designated by CAP.[281] This requirement is applied regardless of whether the analyte is regulated by CLIA (an analyte for which PT is specifically required by regulation) or nonregulated. For analytes not on the CAP list, the laboratory must engage in an alternative assessment of testing proficiency, and the laboratory must document this activity. The documentation is reviewed during the on-site laboratory inspection. If the laboratory has failed to perform, document results, or review results for alternative assessment, then the laboratory is cited with a deficiency as described above.

CAP Reporting of PT Results

The CAP Surveys Department, as an approved CMS PT provider, sends laboratory PT performance data to CMS for all enrolled laboratories (referenced by CLIA ID) for the 83 regulated analytes. These results are available to the public upon request to CMS. Alternative assessment results are not required to be reported to CMS, but are assessed during onsite inspections and cited as appropriate. Anyone can request and obtain a laboratory's inspection report from CMS and evaluate alternative assessment performance based on a deficiency citation.

PT Monitoring of Non-CAP Accredited Laboratories

Authority for ensuring compliance with CLIA is vested in CMS. In addition to the CAP, CMS has delegated (or "deemed") authority to several other nonprofit accrediting organizations to inspect laboratories on its behalf, although CAP inspects the large majority of laboratories with genetic testing capabilities. As explained above, CMS monitors laboratory PT regularly for enrollment and satisfactory performance and during routine biennial surveys. AA performance is assessed during routine biennial onsite laboratory inspections that are conducted by the State agencies with which CMS contracts. Each approved accrediting organization is expected to do the same for the laboratories it evaluates.

PT Monitoring of New York Certified Laboratories

The New York clinical laboratory reference system has operated PT programs in clinical laboratory disciplines since its inception in 1964. Cytogenetics proficiency testing was added in 1972. This program currently sends test challenges to more than 70 cytogenetics laboratories nationwide that perform cytogenetic testing on New York specimens. This testing program is largely method based, examining laboratories' ability to reach the correct cytogenetic diagnosis from a variety of tissue types collected from patients with varied reasons for clinical referral. In addition to the correct test result as specified by the International System of Cytogenetic Nomenclature (ISCN), the program also reviews the actual karyotypes prepared in support of the diagnosis and the test report that must be written with an interpretation suitable for the nongeneticist physician. The New York program also conducts PT in molecular oncology (acquired genetic changes associated with cancers) on a similar basis.

Laboratories performing constitutional genetic testing are required to design and execute alternative proficiency assessments for each of their analytes at least two times per year. They may use other external proficiency tests to meet this requirement partially. The greatest challenge to proficiency testing for genetic tests is that external proficiency testing relies on grading of performance based on a correct

[281] CAPS Laboratory Accreditation Program. *PT Enrollment Guide 2007*. See http://www.cap.org/apps/docs/laboratory_accreditation/2007_pt_enrollment_guide.pdf. Accessed on September 14, 2007.

response established by a peer group of laboratories performing the particular analysis. To date the New York program has not identified a critical mass of laboratories performing any one assay using common methods that would warrant distribution of a test-specific proficiency test challenge. This finding would suggest the use of method-based proficiency testing, which entails sending a specimen and asking the laboratory to test it for any gene mutation or genetic marker that the laboratory has on its test menu. Correct response would be determined by peer grading. Similar issues arise in molecular oncology as new markers are added and in cytogenetics where no panel of test specimens will evaluate the performance of all fluorescence in-situ hybridization (FISH) probes used by each laboratory. Therefore, the use of alternative assessments with careful review of the results and evaluation of this performance evaluation tool at the time of laboratory inspection remains of vital importance.

New York proficiency testing results are available preferably from the individual laboratories. Results, however, are also available from the program under the Freedom of Information Law (FOIL). The status of the laboratories permit is publicly posted, which would imply overall successful proficiency performance in all permitted categories.

CDC's PT Workgroup

In 2006, CDC formed a working group to assess the effectiveness of clinical laboratory proficiency testing for regulatory, educational, and quality improvement purposes. Membership to this working group was selected to provide a balance among PT users, PT providers, and accrediting organizations. Recommendations were generally developed to be applicable to the broad area of clinical laboratory testing. For genetic testing, the report recognizes the rapid growth of molecular diagnostics and rare disease testing and suggests alternatives to traditional PT need to be explored in certain instances, such as when only a few laboratories offer a particular test. The report suggests that an independent advisory body be formed and charged with considering innovative approaches to PT in such situations. The workgroup did recommend that one approach to explore was the development of a PT program based on the process of testing (i.e., a platform-based approach) rather than measurement of specific analytes. The final report of the workgroup is expected to be available toward the latter part of 2007.

Organized Alternative Assessment Programs

In summer 2007, the CAP initiated an internet-based registry service designed to connect genetic testing laboratories performing low volume genetic tests.[282] The need for this service arose in the context of the nonavailability of proficiency testing for new genetic tests together with the importance of supporting quality practices. Laboratories enroll online, and when three laboratories are identified as testing for the same genetic disorder, the CAP will facilitate contact among them so that the exchange may be negotiated.

The CAP/ACMG Biochemical and Molecular Genetics Committee provides scientific support to the CAP Registry through provision of tools as well as though supplementary educational materials. This information is also included in the Molecular Genetics Survey's Participant Summary Report as a benefit to subscribers.

The Association of Molecular Pathology (AMP) facilitates sample exchange between laboratories through its listserv, CHAMP. Laboratories seeking others to test performance on specific analytes contact

[282] College of American Pathologists. See http://www.cap.org. Accessed on August 9, 2007.

one another via the listserv. The laboratories are responsible for establishing testing parameters and facilitating exchange of specimens and test results.

Performance on PT and Alternative Assessment

Laboratories participating in CAP PT for genetic testing have performed well. Aggregate data for 2006 molecular genetics PT demonstrates that on a cumulative basis for the two PT events (MGL 2006 A & B), 93 percent of laboratory responses to challenges were acceptable (Appendix C, Table 2). Analytes in these two surveys included the highest volume genetic tests: factor V Leiden, prothrombin, methylenetetrahydrofolate reductase, fragile X mental retardation, cystic fibrosis, Prader Willi/Angelman syndromes, hemochromatosis, Duchenne muscular dystrophy, and hemoglobin S/C genes. Interpretation of the analytic result was also evaluated, and 94 percent of participant laboratory responses were acceptable. Additionally, cumulative PT result data spanning 5 years (2002-2006) for cytogenetics (four components) and molecular pathology and genetics demonstrates improving trends of performance (Appendix C, Table 3). In surveys and continuous reviews conducted by CMS of 27,558 U.S. laboratories between January 2004 and September 2006, 1.5 percent of these laboratories were cited for unsuccessful PT at the condition level, and 3.6 percent were cited for non-enrollment in PT for regulated analytes.[283]

For those genetic tests without available PT survey material, laboratories are required to perform an AA. The laboratory AA program must be documented. Results must be recorded and reviewed by the laboratory. Corrective action taken for unsuccessful performance must be documented and available for review during the laboratory's external biennial inspection performed by CMS or a CMS-deemed accrediting agency. Failure to perform AA or document AA results, review results, or take corrective action taken for an unacceptable performance will lead to a deficiency citation upon laboratory inspection. In 20,722 CMS surveys (2004-2006), 7.1 percent of laboratories were not in compliance with this requirement. Deficiency citations are reported to CMS and available to the public upon request to CMS.

In a 2006 survey of 190 genetic testing laboratories, Hudson et al.[284] found wide variations in laboratory performance, as measured by the number of deficiencies in formal proficiency testing and the number of incorrect test results reported by a laboratory. The survey further found that these quality measures were related to the extent of the laboratory's participation in PT. It reported that when a formal PT program is not available, 23 percent of laboratories did not always perform an AA (which the survey referred to as informal PT). Overall, the survey found that about one third of laboratories offered some genetic tests for which they performed no formal PT or AA. Moreover, PT deficiencies decreased significantly with increasing use of PT and AA, and the number of PT deficiencies experienced by a laboratory correlated positively with the number of incorrect test results reported by the laboratory.

Bonini et al. (2002)[285] reviewed seven studies of general clinical laboratory practice and found that most laboratory errors occurred in the pre-analytic phase (31-75 percent), followed by the analytic (4-40 percent) and post-analytic phases (9-31 percent). The 2006 survey by Hudson et al. went beyond these studies and found that laboratories whose most common error was an analytical error were more likely to perform genetic tests without either formal PT or AA.

[283] Judy Yost, personal communication.

[284] Hudson, K.L., Murphy, J.A., Kaufman, D.J., Javitt, G.H., Katsanis, S.H., and Scott, J. (2006). Oversight of US genetic testing laboratories. *Nature Biotechnology*. 24(9): 1083-1090.

[285] Bonini, P., Plebani, M., Ceriotti, F., and Rubboli, F. (2002). Errors in Laboratory Medicine. Clinical Chemistry. 48(5): 691-698.

Newborn Screening Quality Assurance Program

Newborn screening is the largest genetic testing effort in the nation and is primarily performed by State public health laboratories. State laboratories, their associated laboratories, or private laboratories routinely screen dried-blood-spot (DBS) specimens for inborn errors of metabolism and other disorders that require intervention. For more than 28 years, CDC, with its co-sponsor, the Association of Public Health Laboratories, has conducted research on materials development and assisted laboratories with QA for these DBS screening tests. The annual summary report as well as the quarterly reports for most of the PT programs can be found online at http://www.cdc.gov/labstandards/nsqap.htm.

The Newborn Screening Quality Assurance Program (NSQAP) at CDC is the most comprehensive QA program worldwide for newborn screening of analytes in the DBS matrix. It provides certified DBS QC materials, PT for more than 35 disorders, training and consultations for problem solving, and filter paper quality assurance. The QC program enables laboratories to achieve high levels of technical proficiency and continuity that transcend changes in commercial assay reagents while maintaining the high-volume specimen throughput that is required. The PT program provides laboratories with quarterly panels of blind-coded DBS specimens and gives each laboratory an independent external assessment of its performance. All laboratories in the United States that test DBS specimens participate voluntarily in NSQAP, free of charge.[286] Since it is a voluntary program, there is no requirement to participate other than possibly satisfying CLIA or State requirements. CLIA requires AA,[287] and laboratories can utilize NSQAP to meet this standard.

Newborn screening analytes and the DBS matrix are not regulated by CLIA. Therefore, no process exists to obtain CLIA-approved PT provider status for the NSQAP. NSQAP, however, exceeds most of the operation requirements of a CLIA-approved PT provider in terms of the number of challenges distributed per year.

NSQAP prepares and distributes more than 500,000 DBS per year to national laboratories. DBS materials for QC and PT are certified for homogeneity, accuracy, stability, and suitability for all assays from different commercial sources. The program also serves as a central repository of critical QA data, as an unbiased point of coordination and communication, and as a reference resource for the nation's screening laboratories. False positive and false negative reports are received and handled each quarter. CDC provides immediate notification and consultation to laboratories that misclassify a specimen so that corrective actions may be taken to maintain high-quality test results.

Genetic Testing Reference Materials (GeT-RM) Coordination Program

The CDC, in partnership with the genetics community, has established the GeT-RM Coordination Program.[288] The goal of this program is to improve the supply of publicly available and well-characterized genomic DNA that can be used as reference materials for PT, QC test development/validation, and research studies.

Well characterized reference materials are fundamental to laboratory QA programs including both external assessment by PT and internal QA activities including QC and test development/validation.

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[286] Centers for Disease Control and Prevention, Newborn Screening Quality Assurance Program. See http://www.cdc.gov/labstandards/nsqap_program_background.htm. Accessed on July 18, 2007.

[287] 42 CFR § 493.1236

[288] Centers for Disease Control and Prevention, Genetic Testing Reference Materials Coordination Program. See http://wwwn.cdc.gov/dls/genetics/qcmaterials/default.aspx. Accessed on July 19, 2007.

Several types of reference materials exist and the selection of appropriate material is based on the needs of the assay, test methodology, and availability. For example, human genomic DNA provides the closest approximation of an actual patient sample, but can typically only control for a few genotypes at a time. Other sample types such as synthetic DNA controls—short fragments of DNA synthesized in a laboratory—are useful when human DNA is not available or when multiple alleles or genotypes need to be monitored simultaneously.

Currently, characterized reference or QC materials are not available for the vast majority of clinical genetic tests. PT program vendors usually solicit large hospital centers or commercial vendors to obtain blood and tissue specimens from affected patients to support the PT programs. These materials must be validated prior to use. For some genetic tests, including many disorders in the CAP PT surveys, sufficient and appropriate material is not publicly available. For example, until very recently genomic DNA materials for allele repeat lengths representing important phenotypic classes and diagnostic cutoffs for fragile X were not publicly available. The absence of such materials for routine QC, PT, and test development may have accounted for the differences in laboratory performance in some recent CAP PT fragile X surveys.

The GeT-RM program has recently characterized 57 cell lines to be utilized as reference materials for disorders such as fragile X syndrome, Huntington disease, and disorders on the Ashkenazi Jewish panel (i.e., Bloom syndrome, Canavan disease, Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Neimann Pick disease and Tay-Sachs disease). These materials are (or soon will be) publicly available from Coriell Cell Repositories, which houses several NIH-funded collections of essential research reagents. A characterization study of 14 DNA materials with important mutations causing cystic fibrosis is currently underway in six collaborating clinical laboratories.

Additionally, the GeT-RM program is characterizing a panel of DNA specimens with identifiable gene mutations for confirmatory testing in disorders included in State newborn screening panels. This includes disorders such as congenital adrenal hyperplasia, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease, cystic fibrosis, and galactosemia. Additional materials are in development for gene mutations found in Gaucher, Tay-Sachs disease, Canavan disorders. Development of materials will soon be initiated for other disorders, including inherited breast cancer (BRCA1 and 2), alpha-1 antitrypsin deficiency, and type 2 multiple endocrine neoplasia (MEN2).

To date, the GeT-RM has focused its efforts on DNA-based testing for inherited genetic disorders. Other areas of genetics, including molecular oncology, molecular infectious disease testing, and biochemical genetic testing, however, are also facing a paucity of reference and PT materials. To address these needs, the GeT-RM, together with the genetics community, professional organizations, and other Governmental agencies outside of the CDC, are trying to assess what reference materials are currently available for laboratory QA programs and are beginning to formulate plans for collecting and characterizing materials where shortages exist.

United Kingdom National External Quality Assessment Service (UKNEQAS)

The UKNEQAS[289] is a nonprofit organization whose members comply with the UKNEQAS Code of Practice. Organized in the United Kingdom, members are defined as External Quality Assessment (EQA) schemes or groups of schemes that have been accepted for membership. The program aims to provide optimal patient care by facilitating the availability of reliable laboratory investigations through (1) the

[289] United Kingdom National External Quality Assessment Service. See http://www.ukneqas.org.uk/new.htm. Accessed on September 20, 2007.

provision of objective assessment of laboratory performance, (2) professional advice, and (3) assistance when appropriate. The genetic testing schemes of UKNEQAS are comprised of two programs: Clinical Cytogenetics and Clinical Molecular Genetics.

The Clinical Cytogenetics program was organized in 1982. Participant laboratories are sent standardized slides for chromosome analysis on a wide variety of tissues that include prenatal, constitutional, and neoplastic disorders. Participants also submit slides for review to assess slide quality. Approximately eight samples are distributed on a quarterly basis. Laboratories are not only evaluated for their analytic performance but also for turn-around-times, success rates, and abnormality rates. Laboratory reports are submitted to assess accuracy of interpretation and communication of abnormal findings. Approximately 37 clinical laboratories from the U.K. are enrolled as well as 24 non-U.K. laboratories located in Australia, China, South Africa, and throughout Europe.

The Clinical Molecular Genetics program, organized in 1991, sends out specimens for DNA analysis for carrier detection, diagnosis, presymptomatic testing using linkage analysis, and mutation detection. Four to five samples are distributed twice a year. Participant laboratories are assessed for their performance in (1) detecting genotype, (2) interpretation of result, and (3) clerical accuracy. Reports are also reviewed for conformity to guidelines set forth by the Clinical Molecular Genetics Society. There are approximately 32 participant laboratories from the U.K. and 11 non-U.K. laboratories.

Other European groups have established episodic external quality control programs for molecular genetic testing of the CFTR gene in cystic fibrosis. Dequeker and Cassiman report on the results of a series of three testing events from 1996-1998.[290] Six DNA samples with common CFTR mutations were distributed to 136-159 laboratories. Data on mutation detection, test methodology, and interpretation were collected. Similarly, Salvatore et al. published the results of an external quality assessment in Italy conducted by the Italian External Quality Control Programme between 2001 and 2004.[291] For each of six DNA samples, the laboratories were required to establish results and provide a report of molecular analysis including proper nomenclature.

Challenges Related to PT

Education vs. Regulation

How can PT best detect laboratory error in the short term in order to improve testing quality in the long term? When performance problems are identified, the PT provider should be able to give technical assistance to the laboratory in developing the remediation plan. As new categories or new analytes are tested, it is generally advisable to offer ungraded but thoroughly evaluated proficiency challenges to make certain the tested laboratories know what is expected and to make sure the PT provider understands the potential issues to be identified. What is the balance of education versus punitive action for PT? Punitive regulatory action may result in adverse actions, including a decrease in the number of laboratories subscribing for non-required PT and pressure to lessen the difficulty of PT challenges to ensure a satisfactory passing percentage.

Breadth of PT

[290] Dequeker, E. and Cassiman, J.J. (2000). Genetic testing and quality control in diagnostic laboratories. *Nature Genetics*. 25:259-260.

[291] Salvatore, M., Falbo, V., Floridia, G., Censi, F., Tosto, F., Bombieri, C., Castaldo, G., Pignatti, P.F., Rosatelli, M.C., and Taruscio, D. (2007). The Italian External Quality Control Programme for cystic fibrosis molecular diagnosis: 4 years of activity. *Clinical Chemistry Laboratory Medicine*. 45:254-260.

Whenever possible, PT should include a formal assessment of the laboratory's pre-analytic analysis of real specimens and its post-analytic analysis based on the laboratory report and supporting materials. In this way, laboratories are scored for performance on accession data and interpretation of the test result. The Molecular Oncology and Molecular Genetic surveys produced by the CAP do include scoring of interpretive responses. Additionally, periodic summary evaluations are included with PT materials that inquire about laboratory accession and result reporting.

Sufficient Specimens

There must be a sufficient volume of uniform testing specimens so that laboratories are testing the same reagent/tissue/analyte. With the new HER2 guidelines published in 2007,[292] there has been an increase in PT participation for the CAP immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) surveys. Laboratory enrollment in HER2 PT has increased by 153 percent for IHC and 10 percent for FISH. Providing sufficient uniform material to be utilized in these surveys required CAP to seek assistance from the National Cancer Institute (NCI), and private and commercial anatomic pathology laboratories to supply sufficient tissue specimens.

The lack of test kits and standards means each laboratory has its own LDTs, so methods may be different between laboratories and the outcome of PT may be different as well. Therefore, clinical interpretation of the result is as important as the analytic interpretation with regard to limitations of each test and the sensitivity/specificity for the disease in question.

The CAP PT program usually sends out cell lines (or extracted DNA or RNA) for nearly all of its genetic PT surveys but may use residual clinical specimens when available. Access to abundant, high quality patient specimens is limited and, in part, is being addressed by the GeT-RM program. Funding is needed to expand the scope of this type of work so that additional cell lines and tissues are developed, obtained and characterized for use in PT for genetics, oncology, and pharmacogenetic testing.

Cost of PT Programs

There is little financial motivation for vendors to produce PT materials for genetics because of the relatively low volume of subscribers compared to the high cost of producing the PT challenges. Vendors must not only supply materials for PT but the supporting infrastructure as well including marketing, staff assistance, scientific and statistical expertise, and communication formats. Professional organizations such as CAP see it as a longer term investment in promoting laboratory quality and patient safety.

Vendors also witness declining participation in existing PT products due to gene patents and exclusive licensing agreements, such as with BRCA1 and BRCA2. As a result, the ACMG/CAP PT program for exclusively licensed genetic tests (such as BRCA1, BRCA2, SCAs, and FRDA) may become extinct due to prohibitive cost. Additionally, vendors see increasing costs of materials from cell banks and repositories such as the American Type Culture Collection (ATCC).

[292] Wolff, A.C., Hammond, E., Schwartz, J.N., Hagerty, K., Allred, D.C., Cote, R., Dowsett, M., Fitzgibbons, P.L., Gutman, S., Hanna, W., Keegan, P., Langer, A., McShane, L.M., Paik, S., Pegram, M.D., Perez, E.A., Press, M.F., Rhodes, A., Sturgeon, C., Taube, S., Tubbs, R., Vance, G.H., van de Vijver, M,, Wheeler, T., Yost, J., and Hayes, D.F. (2007). American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for HER2 Testing in Breast Cancer. *Journal of Clinical Oncology*. 25(1):118-143.

Increased costs to the vendor are passed on to the laboratory. As the cost of PT increases, the number of laboratory participants (especially low volume laboratories) may decrease due to declining reimbursement for laboratory tests. Most reimbursement is drifting downward to Medicare or sub-Medicare levels as well as insufficient Medicare reimbursement for many molecular current procedural terminology (CPT) codes.

Transportation of Biological Material

Transportation restrictions imposed on shipping biological material across State lines raises problems for access of PT specimens for PT products. For example, blood products obtained for the sole purpose of use in PT products is subject to licensing requirements applicable to interstate commerce, which means the blood collection must take place at an establishment that is registered with the FDA and also licensed to collect source plasma. It is usually not possible to coordinate collection of specimens representing rare genetic abnormalities at these designated locations, however. It is also questionable whether such products fall under the definition of a diagnostic biologic since the specimen will not be "used for purposes of diagnosis" or "applicable to the prevention, treatment, or cure of diseases or injuries of man," further complicating the coordination of specimen collection.

Clinical Validity

The clinical validity of a genetic test refers to the test's accuracy in detecting the presence of, or predicting risk for, a health condition or phenotype.[293] When a test is use diagnostically, clinical validity measures the association of the test result with the disorder. When a test is used to identify genetic susceptibility, clinical validity measures the accuracy with which it predicts a future clinical outcome. This property corresponds to the gene-disease associations measured in epidemiological studies.

Key Terms and Concepts

Along with the elements of analytic validity, the six elements listed below are relevant to assessing clinical validity.[294, 295]

Clinical sensitivity (or the clinical detection rate) measures the proportion of individuals for whom the test result correctly identifies or predicts the presence of a well-defined disorder. In genetic tests, this is often seen as the relationship between genotype and phenotype. The clinical sensitivity of some genetic tests depends on the number of mutations that the test is able to identify (e.g., a test for only the p.F508 mutation will identify fewer individuals with CF compared to a test that detects the entire ACMG recommended panel of 23 mutations).

Clinical specificity measures the proportion of individuals for whom the test result correctly detects or predicts the absence of a well-defined clinical disorder.

Positive and negative predictive values are the probabilities that people (within a defined population) with positive test results will get the disease (positive predictive value, PPV) and that people (within a

[293] Adapted from the NIH/DOE Task Force: Promoting Safe and Effective Genetic Testing in the United States
[294] ACCE. See http://www.cdc.gov/genomics/gtesting/ACCE.htm. Accessed on September 20, 2007.
[295] EGAPP. See http://www.cdc.gov/genomics/gtesting/EGAPP/about.htm. Accessed on September 20, 2007.

defined population) with negative results will not get the disease (negative predictive value, NPV). These values are useful ways to present clinical validity data to clinicians.

Prevalence measures the proportion of individuals in the selected setting or population who have the phenotype.

Penetrance defines the relationship between genotype and phenotype. It is the probability or likelihood that the condition (or phenotype) will be expressed when a particular genotype is present.[296] It is expressed numerically, e.g., if 100 individuals all have a particular gene mutation but only 80 of them have the condition associated with that mutation, then the mutation is said to be 80 percent penetrant. For example, Duchene muscular dystrophy is considered 100 percent penetrant, as virtually 100 percent of individuals with disease-causing mutations in the DMD gene will develop Duchene muscular dystrophy, whereas hereditary nonpolyposis colorectal cancer (HNPCC) is considered 75 percent penetrant as about 75 percent of people with HNPCC-causing mutations develop this cancer.

Modifiers include other genetic or environmental factors that may interact with the genetic alteration being studied and the outcome of interest. Modifiers can affect expressivity, which refers to the variability of signs or symptoms that occur with a phenotype.

Types of Genetic Tests

Genetic tests may have a number of purposes, and some tests are used for more than one purpose (see Table 1).

Table 1. Types of Genetic Tests

Test Type	Description
Tests for gene mutations with high penetrance	
Diagnosis of genetic disease	Testing patient with indicative clinical findings of a specific disease to establish the diagnosis
Newborn screening	Testing of newborn to identify the presence of condition(s) that require immediate initiation of treatment to prevent death or disability
Carrier tests	Testing is performed in an asymptomatic adult to identify if the individual is a carrier for an autosomal or X-linked recessive condition(s)
Prenatal tests	Testing to identify a fetus with a genetic disease or condition. Testing is usually initiated due to family history or maternal factors. Some prenatal testing are routinely offered such as testing for Down Syndrome
Tests for adult onset of a genetic condition or disease	Testing of young adults to identify a genetic condition that will occur later in life such as Huntington disease
Tests for gene variants that are associated with genetic susceptibility	
Test to predict drug response	Testing to identify individuals likely to have a reduced or increased response to a particular drug, or reduced or increased risk of adverse reaction to a drug
Assess genetic risk for common complex disease-disorder	Testing to identify individuals at risk for developing a disease or disorder in the future, such as heart disease or diabetes
Test to evaluate prognosis	Testing to evaluate the likely outcome or course of a disease, particularly cancers.

[296] Constantin, C.M., Faucett, A., and Lubin, I.M. (2005). A primer on genetic testing. *Journal of Midwifery and Women's Health*. 50(3): 197-204.

A test's clinical validity is influenced by a number of factors, including the purpose of the test, the prevalence of the disease or condition for which the test is being conducted, and the adequacy of the information available to determine how accurate the test is in detecting or predicting risk for a health condition or phenotype.

The acceptable levels for clinical sensitivity and specificity may vary depending on the purpose for which the test is used. For example, tests that diagnose a condition in clinically symptomatic individuals may place more emphasis on sensitivity and less emphasis on high specificity because of the high *a priori* likelihood (high prevalence). For example, testing for three *HFE* mutations in individuals with clinical and biochemical evidence of hereditary hemochromatosis may be warranted, even though two of the three mutations are of low penetrance. Although the identification of two *HFE* mutations can be useful for diagnosis, treatment is likely to be based on biochemical measurements such as serum ferritin. Alternatively, tests that are used in the general population often stress specificity over sensitivity, especially if the disorder of interest is relatively uncommon (low prevalence). According to recommendations from ACMG, identifying carrier couples as part of the prenatal diagnosis of cystic fibrosis via CFTR testing should be limited to 23 mutations that are known to cause classic cystic fibrosis. Although such a panel will have lower clinical sensitivity than a much larger panel, higher clinical specificity will be achieved as the possibility of false positive results due to nondeleterious polymorphisms being interpreted as classic mutations will be reduced.

Evaluating Clinical Validity

Evaluation of the clinical validity of the genetic test is a complex process that might be incomplete at the time of offering the service. The evaluation that led to the recommendations for cystic fibrosis screening provides a useful example. In April 2001, ACMG's Cystic Fibrosis Carrier Screening Working Group issued recommendations for a population screening program to determine carrier status within the CFTR gene using a panel of 25 mutations and variants that were known to have an allele frequency of greater than 0.1 percent among North American patients with CF. This recommendation was the result of an NIH CF Consensus Conference that CF carrier screening be offered to all couples before conception or prenatally. At that time, the Working Group recognized limitations in understanding the population frequencies of several CF alleles but still recommended population screening to determine CFTR carrier status for couples before conception or prenatally. In light of this understanding, the Workgroup proposed to review mutation distribution data after the first two years of the program. In 2004, this mutation panel was ultimately revised by the ACMG CF Carrier Screening Working Group based on 2-year laboratory data derived from general population screening.[297, 298, 299, 300, 301]

Existing programs—such as the Collaboration, Education and Test Translation (CETT) program,[302] which focuses on rare diseases—or new models of private or public-private partnerships could spur evaluation

[297] National Institutes of Health Consensus Statement: Genetic Testing for Cystic Fibrosis. (1997). See http://consensus.nih.gov/1997/1997GeneticTestCysticFibrosis106html.htm. Accessed on September 20, 2007.

[298] American College of Obstetricians and Gynecologists Committee opinion: Update on carrier screening for cystic fibrosis. (2005). *Obstetrics and Gynecology.* 106(6):1465-1468.

[299] Grody, W.W., Cutting, G.R., Klinger, K.W., Richards, C.S., Watson, M.S., Desnick, R.J., Subcommittee on Cystic Fibrosis Screening, Accreditation of Genetic Services Committee, American College of Medical Genetics. (2001). Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genetics in Medicine*. 3(2):149-154.

[300] American College of Obstetricians and Gynecologists and American College of Medical Genetics. (2001). Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines. Washington DC: ACOG.

[301] Watson, M.S., Cutting, G.R., Desnick, R.J., Driscoll, D.A., Klinger, K., Mennuti, M., Palomaki, G.E., Popovich, B.W., Pratt, V.M., Rohlfs, E.M., Strom, C.M., Richards, C.S., Witt, D.R., Grody, W.W. (2004). Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genetics in Medicine.* 6(5):387-391.

[302] The Collaboration, Education and Test Translation Program. See http://www.cettprogram.org/. Accessed on July 17, 2007.

of the clinical validity of genetic tests without adversely affecting innovation. For example, an experienced group of genetic experts could be tasked to review preliminary data submitted by a laboratory and to provide specific recommendations to strengthen the scientific claims. Similar approaches for review and certification have been successfully implemented in other areas of medicine. For example, in an effort to promote the adoption of electronic health records (EHRs) while ensuring minimum levels of interoperability, functionality and security, HHS contracted with a consortium of private-sector entities, the Certification Commission for Health Information Technology (CCHIT), to develop and implement a voluntary, transparent certification process for EHRs. Through a collaborative, multi-stakeholder process, certification standards were adopted, and currently, approximately 40 percent of companies with ambulatory EHR products have had their products certified by CCHIT. Potential purchasers of EHR products can now purchase such products with greater certainty of their effectiveness, and EHR companies remain free to innovate.

A voluntary certification process could also be considered for genetic tests as an incremental, market-oriented mechanism for enhanced oversight that would complement the existing regulatory framework. HHS could contract with a private consortium representing multiple stakeholders (a "Genetic Test Certification Commission") to adopt consensus standards for the effectiveness of specific genetic tests and to establish a transparent certification process. Companies offering genetic tests could voluntarily submit their tests for certification, and once certified such tests could be performed as "certified laboratory-developed genetic tests." As such, companies with noncertified laboratory-developed genetic tests could continue to perform their tests and innovate, but would have an incentive to meet the consensus standards represented by certification. Such a certification process could potentially enhance public confidence in the clinical validity of genetic tests while avoiding the loss of innovation that could result from new and disruptive regulatory mandates.

Clinical Validity: A Case Study

Clinical validity is certainly an issue of great complexity and importance in the case of genetic testing. The issue becomes increasingly problematic for genetic tests that are rapidly being marketed to a broad segment of the population through direct-to-consumer (DTC) advising, despite the fact that clinical validity has not been established in all population groups. The following Case Example of BRCA1 and BRCA2 helps illustrate the nuances involved in this topic.

Case Example: BRCA1 and BRCA2

Mutations in two genes, BRCA1 and BRCA2, are implicated in 5-10 percent of all breast cancers. Mutations in these genes also predispose patients to ovarian and prostate cancers (BRCA1) or pancreatic cancer (BRCA2). The BRCA1 gene was identified in 1990 and sequenced in 1994, [303] the same year that the BRCA2 gene was located. [304] BRCA1 and BRCA2 mutations have been estimated to induce approximately 45 percent of breast cancer susceptibility syndromes that are transmitted as an autosomal dominant trait and are usually associated with a younger age of onset. These discoveries were important, as they led to tests for women with a strong family

[303] Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P.A., Harshman, K., Tavtiqian, S., Liu, Q., Cochran, C., Bennett, L.M., Ding, W., Bell, R., Rosenthal, J., Hussey, C., Tran, T., McClure, M., Frye, C., Hattier, T., Phelps, R., Haugen-Strano, A., Katcher, H., Yakumo, K., Gholami, Z., Shaffer, D., Stone, S., Bayer, S., Wray, C., Bogden, R., Dayananth, P., Ward, J., Tonin, P., Narod, S., Bristow, P.K., Noriss, F. H., Helvering, L., Morrison, P., Rosteck, P., Lai, M., Barrett, J.C., Lewis, C., Neuhausen, S., Cannon-Albright, L., Goldgar, D., Wiseman, R., Kamb, A., and Skolnick, M.H. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*. 266(5182): 66-71.

[304] Wooster, R., Neuhausen, S.L., Mangion, J., Quirk, Y., Ford, D., Collins, N., Nguyen, K., Seal, S., Tran, T., Averill, D., Fields, P., Marshall, G., Narod, S., Lenoir, G.M., Lynch, H., Feunteun, J., Devilee, P., Cornelisse, C.J., Menko, F.H., Daly, P.A., Ormiston, W., McManus, R., Pye, C., Lewis, C.M., Cannon-Albright, L.A., Peto, J., Ponder, B.A.J., Skolnick, M.H., Easton, D.F., Goldgar, D.E., and Stratton, M.R. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science*. 265(5181): 2088-2090.

history of breast cancer that can determine if they have mutations in these genes. Even though genetic testing was available, there were a significant number of uncertainties on how to proceed in the management of patients and family members of patients with breast cancer. There were also ethical issues raised regarding who should be tested.

There was a lack of consensus for BRCA testing, partly due to the considerable uncertainty about the penetrance of BRCA1 and BRCA2 mutations. Studies have estimated the lifetime risk of breast cancer associated with BRCA1 and BRCA2 mutations that range from 36 to 85 percent, while the variation in cancer phenotype (i.e., breast cancer, ovarian cancer, both, or neither) remains unexplained.[305, 306, 307, 308] Second, the efficacy of the interventions offered to BRCA1 and BRCA2 mutation carriers—early mammography, ovarian cancer screening, prophylactic surgery—was uncertain and based largely on expert opinion.[309] Furthermore, the intervention with the most efficacy data, prophylactic mastectomy,[310] was accepted by only a minority of eligible women.[311] As a result, there were uncertainties about key parameters, clinical validity and clinical utility.

Today we know that inheritance of the mutation does not necessarily convey a certainty of developing cancer, indicate the type of cancer, or the age of onset. The average cumulative risk of breast cancer mutations in either the BRCA1 gene or BRCA2 gene is about 27 percent to age 50 and 64 percent to age 70. Both environmental and other genetic factors play a role in the development of breast or other cancers in the mutation-positive patients, as does the type of DNA mutation in BRCA1 or BRCA2. Mutations in these genes are heterogeneous and located throughout each gene, with more than 1,600 different mutations identified to date. Interestingly, the range of mutations varies greatly among different populations, with founder mutations observed in many ethnic groups. Testing for disease-associated mutations is made difficult by the heterogeneity of the disease-causing mutations and the complexity of the BRCA1 and BRCA2 genes. Moreover, the clinical significance of some observed variants is unknown and in some cases observed variants may be benign. The issue of possible differences in the clinical outcome of the BRCA-mutation carriers compared to that of woman with sporadic breast cancer has been addressed by a number of different studies but results have been conflicting, with some reports of worse prognosis related to BRCA1 mutational status and others highlighting no substantial differences.

Continuing uncertainties regarding BRCA1 and BRCA2 genetic testing prompt the development of practice guidelines and recommendations by professional societies and the Government. Guidelines for assessment, counseling, and testing for genetic susceptibility for breast and ovarian cancer have been developed by ACMG and the New York Department of Health.[312] The U.S. Preventive Services Task Force developed a set of

[305] Easton, D.F., Ford, D., and Bishop, D.T. (1995). Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *American Journal of Human Genetics*. 56(1): 265-271.

[306] Struewing, J.P., Abeliovich, D., Peretz, T., Avishai, N., Kaback, M.M., Collins, F.S., and Brody, L.C. (1995). The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genetics. 11(2): 198-200.

[307] Ford, D., Easton, D.F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D.T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M.D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T.R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B.A.J., Gayther, S.A., Birch, J.M., Lindblom, A., Stoppa-Lyonnet, D., Bignon, Y., Borg, A., Hamann, U., Haites, N., Scott, R.J., Maugard, C.M., Vasen, H., Seitz, S., Cannon-Albright, L.A., Scholfield, A., Zelada-Hedman, M., and the Brest Cancer Linkage Consortium. (1998). Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *American Journal of Human Genetics*. 62: 676-689.

[308] Thorlacius, S., Struewing, J.P., Hartge, P., Olafsdottir, G.H., Sigvaldason, H., Tryggvadottir, L., Wacholder, S., Tulinius, H., and Eyfjord, J.E. (1998). Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet*. 352(9137): 1339-1339.

[309] Burke, W., Daly, M., Garber, J., Botkin, J., Kahn, M.J., Lynch, P., McTiernan, A., Offit, K., Perlman, J., Petersen, G., Thomson, E., Varricchio, C. (1997). Recommendation for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *JAMA*. 277(12): 997-1003.

[310] Hartmann, L.C., Schaid, D.J., Woods, J.E., Crotty, T.P., Myers, J.L., Arnold, P.G., Petty, P.M., Sellers, T.A., Johnson, J.L., McDonnell, S.K., Frost, M.H., Jenkins, R.B. (1999). Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *New England Journal of Medicine*. 340(2): 77-84.

[311] Lerman, C., Hughes, C., Croyle, R.T., Main, D., Durham, C., Snyder, C., Bonney, A., Lynch, J.F., Narod, S.A., and Lynch, H.T. (2000). Prophylactic surgery decisions and surveillance practices one year following BRCA1/2 testing. *Preventive Medicine*. 31(1): 75-80.

[312] American College of Medical Genetics Foundation and the New York State Department of Health. (1999). *Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling, and Testing Guidelines*. See http://www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm. Accessed on September 20, 2007.

recommendations entitled *Genetic Risk Assessment and* BRCA *Mutation Testing for Breast and Ovarian Cancer Susceptibility*[313] that provided recommendations for screening for BRCA1 mutation carriers and mutations.

Challenges Related to Clinical Validity

For many genetic tests, particularly those that are predictive or presymptomatic, prospective knowledge of the test's clinical validity may be incomplete for many years after the test is developed, although the probable clinical validity can usually be estimated using retrospective data. When information that may affect clinical validity is incomplete, the potential harms of the test may increase and must be considered more carefully.[314] Even with incomplete data, however, there may be sufficient information to warrant offering the test in addition to the fact that even greater harm may be caused by denying testing. Nonetheless, to minimize harms, it is important to collect data over time. Because the data for clinical validity are often incomplete, innovative approaches involving many organizations and disciplines working together to collect and share data and analyses may be needed. Such approaches may require new policy and programmatic constructs and resources. CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative[315] (discussed in Chapter 2) and the CETT program[316] are examples of current activities that successfully evaluate clinical validity. Long term follow-up is also needed to ensure that the test has clinical utility, which is discussed in Chapter 5.

Numerous challenges exist to collecting postmarket data. Multi-site research projects and longitudinal follow-up studies are often necessary. There is also the need to link laboratory results with clinical data, which is particularly challenging with regard to issues of privacy and confidentiality. Additionally, it is important to have broad access to data for secondary analysis and dissemination. Possible models include the CETT program, the Human Variome Project,[317] and dbGaP (in which genotype-phenotype information is accessible in an up-to-date database).[318]

Assessing clinical validity may be particularly challenging in the case of tests for ultra-rare diseases. As relatively few people have these diseases, gathering statistically significant data can be extremely challenging. Thus, prevalence is a factor in determining how much data on test performance should be available before a test is offered in patient care.[319]

Many different organizations provide clinical practice guidelines using different processes and methodologies, but their approaches are not always transparent. Evidence may be lacking when the guidelines are issued, and as new data emerge, revisions are necessary. In the field of genetics, technology is evolving rapidly and the quality of evidence builds over time.[320] Increasingly,

[313] U.S. Preventive Services Task Force. (2005). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Annals of Internal Medicine*. 143(5): 355-361.
[314] Secretary's Advisory Committee on Genetic Testing (SACGT). Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT. See http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf. September 20, 2007.
[315] Evaluation of Genomic Applications in Practice and Prevention (EGAPP). See http://www.egappreviews.org/. Accessed on August 1, 2007.
[316] The Collaboration, Education and Test Translation Program. See http://www.cettprogram.org/. Accessed on July 17, 2007.
[317] The Human Variome Project. See http://www.variome.org/. Accessed on July 17, 2007.
[318] National Center for Biotechnology Information. dbGAP. See http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap. Accessed on August 16, 2007.
[319] Secretary's Advisory Committee on Genetic Testing (SACGT). Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT. See http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf. September 20, 2007.
[320] Wylie Burke presentation to SACGHS, March 2007. See http://www4.od.nih.gov/oba/SACGHS/meetings/Mar2007/SACGHSMar2007meeting.htm. Accessed on September 20, 2007.

multidisciplinary approaches to guideline development (e.g., by professional organizations with a clinical and/or laboratory focus) may have advantages.

Current Oversight System for Assuring the Validity of Genetic Tests and the Quality of Laboratories

Genetic testing laboratories must comply with regulations set forth by Federal and State (if applicable) agencies as they apply to LDTs and manufacturers of commercially distributed test kits. Agencies and organizations involved in standards development also provide a critical element in oversight by providing quality control (QC) and reference materials (RM) that are essential for validating performance characteristics of laboratory tests. Knowledge generation and synthesis agencies play a crucial role in oversight by collecting data and analyzing research findings to determine the appropriate use of genetic tests. Several professional societies are actively involved in improving the quality of laboratory practices and developing clinical guidelines to ensure the appropriate use of genetic testing.

Federal Regulatory Agencies

Oversight at the Federal level includes activities carried out by both the FDA and CMS (under CLIA). A broad discussion of oversight is provided in Chapter 2.

Centers for Medicare & Medicaid Services and CLIA

CLIA regulations are designed to assure the quality of laboratory testing. These regulations require laboratories to verify/establish the test's analytical performance characteristics before laboratories can offer a new test and report patient results. The regulations do not require that a laboratory follow specific procedures or protocols, as long as the laboratory can assure that its test results are accurate, reliable, timely, and confidential, and there is no risk of harm to patients. CMS, however, does provide guidance and resources in its Interpretive Guideline for Laboratories[321] to help laboratories achieve compliance.

Analytical Validity

CLIA regulations for analytical validity apply to FDA-cleared and –approved products, modified tests that use cleared or approved products, and LDTs. The CLIA survey process does not evaluate every test in the laboratory every two years, but instead evaluates the laboratory operation as whole, using a sample of tests for all of the laboratory's systems and processes. For recertification, surveyors examine samples of validation procedures and data for LDTs, other noncleared or approved tests, and FDA-cleared or –approved tests. They also review new tests and specialties instituted since the last inspection process and any that were previously problematic. CLIA requires that all non-waived tests introduced into the laboratory after April 24, 2003 (previously, this requirement applied only to high complexity tests) have performance specifications or analytical validity verified or established prior to reporting patient test results.[322] As discussed earlier in this chapter, there are two different sets of requirements—for verification or validation—dependent on whether the test is FDA-cleared, -approved, or neither. CLIA also requires that the laboratory determine calibration and control procedures based on the performance specifications it verified or validated. In this determination, the laboratory must consider test system stability, test frequency, the method's technique dependence, QC failure frequency, training, experience

[321] CLIA. See http://www.cms.hhs.gov/clia. Accessed on September 14, 2007.

[322] Center for Disease Control and Prevention. Laboratory Standards: Establishment and verification of performance specifications [45 CFR Part 1253]. Available at: http://wwwn.cdc.gov/clia/regs/subpart_k.aspx#493.1253. Accessed on July 16, 2007.

and competency of testing personnel. All performance specification verification or validation efforts must be documented. CLIA does not specify how the laboratory must meet this requirement or a required number of specimens due to the variations in laboratory operations, patient populations, and test volume, but CMS does offer interpretations, clarifications of terms (which are not always compatible with CLSI and ISO terminology), and suggestions to facilitate compliance in its "Interpretive Guidelines" and brochures.[323] CMS State surveyors will look to determine if the test is providing accurate and reliable results in that laboratory as a result of the laboratory's evaluation of analytical validity.

Proficiency Testing

All non-waived laboratories must enroll annually in PT with a CMS-approved PT provider for the regulated analytes, specialties, and subspecialties in which the laboratory performs testing. The testing disciplines and 83 regulated analytes are listed in the CLIA regulations at subpart I.[324] None of the 83 analytes are DNA or RNA but other materials such as proteins. For laboratories with multiple testing sites, each site with a separate CLIA certificate must enroll in its own PT survey and must demonstrate successful performance. When a laboratory measures an analyte by more than one test method, PT is required only for the primary test method in use. In addition, the laboratory must also:

- Notify Health and Human Services (HHS) of which PT program(s) they have selected,
- Participate in those program(s) at least one year prior to changing PT providers,
- Establish and re-validate accuracy at least twice per year (using either an external PT program or an AA procedure) for tests that a laboratory performs that are not listed in subpart I, and
- Authorize the release of laboratory PT data to HHS to:
    - Enable ongoing monitoring of laboratory performance and
    - Make laboratory PT results for the 83 regulated analytes available to the public upon request.

A laboratory must test PT samples in the same manner as its patient specimens along with routine patient workload by personnel who regularly test these patients, using the laboratory's standard methods. The laboratory must not engage in inter-laboratory communications regarding PT results until after they are reported back by the PT program. The laboratory must not send PT samples to another laboratory for testing or its certificate will be revoked for one year. Laboratories receiving PT samples for testing from another laboratory must notify HHS. Intentional referral of PT to another laboratory or communication with another laboratory about PT results during a PT event automatically results in certificate revocation for one year, and the laboratory director (owner/operator) is unable to direct any laboratory for two years.

Each laboratory performing any of the non-waived tests listed in subpart I of the CLIA regulations must successfully participate in PT, which requires three PT test events with 5 challenges/events each year. Unsuccessful PT performance is defined as failure to attain the minimum satisfactory score (usually 80 percent) for the same analyte, specialty or subspecialty for any two of three consecutive testing events evaluated in a rolling timeframe. Clerical errors will also result in failed PT.

Enforcement action is taken by CMS when a laboratory fails to pass PT. For the initial failure to perform, CMS may direct the laboratory to undertake training and technical assistance, unless there is risk of harm to patients, a history of repeated failure, or the laboratory does not correct the root cause of the failure.

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[323] Centers for Medicare and Medicaid Services. Clinical Laboratory Improvement Amendments, available at: http://www.cms.hhs.gov/CLIA/03_Interpretive_Guidelines_for_Laboratories.asp. Accessed on August 10, 2007.

[324] Clinical Laboratory Improvement Amendments (CLIA), Subpart I—Proficiency Testing Programs for Nonwaived Testing. See http://wwwn.cdc.gov/clia/regs/subpart_i.aspx. Accessed on August 9, 2007.

For subsequent failures, the laboratory's certificate will be revoked or limited and its Medicare payments suspended or cancelled. The laboratory must cease testing in the area of failure for six months and demonstrate sustained satisfactory performance for two consecutive PT events before resuming clinical testing. Failure to enroll in PT and perform successfully is considered a condition-level deficiency and will be cited on a deficiency statement and appropriate enforcement actions imposed when identified. CMS is in the process of enhancing the CLIA website so that information on laboratory performance is easily accessible to the public.

Laboratories must review and evaluate PT results received from PT programs and must verify the accuracy of testing for the following circumstances:

- Analytes in subpart I that have not been scored by the PT program,
- Analytes for which the laboratory receives a zero score for nonparticipation or late result return, and
- Analytes that are not included in subpart I and must have their accuracy verified twice per year, at a minimum.

Laboratories must take effective corrective actions for any unacceptable PT test results.
PT evaluation and verification activities must be documented and records must be maintained for two years. A laboratory's PT enrollment and results are regularly monitored by CLIA surveyors and during routine biennial onsite inspections by CMS or other deemed-status accreditation organizations to verify PT enrollment or AA activity and testing results.

Further information and guidance about PT performance and surveyor compliance assessment can be found on the CMS CLIA website at: www.cms.hhs.gov/clia under Interpretive Guidelines.

Clinical Validity

The CLIA program is not designed to assess the clinical validity of laboratory tests. CLIA regulations under 42 CFR § 493.1445(e), however, require the laboratory director to ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this regulation is the responsibility of the laboratory director to use medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies could not be said to be "required for patient care." In addition, CLIA requires that directors of high complexity laboratories must have a M.D., D.O., or Ph.D. degree, with board certification. Laboratory directors are also responsible overall for ensuring test quality and that the laboratory engage qualified, competent personnel to oversee and perform tests. Each of the CLIA-required positions for high complexity laboratories has educational, experiential, and training requirements, in addition to responsibilities that correspond to CLIA quality standards. CLIA regulations[325] provide more detail on these positions that include clinical consultant, technical supervisor, general supervisor, and testing personnel. The personnel requirements are designed to ensure on-going quality in the performance of testing. For example, CLIA requires the laboratory to have a clinical consultant, who "must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care."[326] The responsibilities of the clinical consultant include providing information "regarding the appropriateness of the testing ordered

[325] CLIA, Subpart M—Personnel for Nonwaived Testing. See http://wwwn.cdc.gov/clia/regs/subpart_m.aspx. Accessed on August 17, 2007.
[326] CLIA, Subpart M—Personnel for Nonwaived Testing. See http://wwwn.cdc.gov/clia/regs/subpart_m.aspx#493.1455. Accessed on September 24, 2007.

and interpretation of the test results."[327] Because there is no CLIA genetic testing specialty, however, no specific personnel requirements are in place for genetic testing laboratories.

Notwithstanding these requirements, analytical validity is the only performance measure that CLIA fully enforces or has ever enforced. CLIA does not assess laboratory performance in clinical validity or utility, and CMS is not required to enforce any requirements except those related to analytical validity per the CLIA statute. According to CMS, moreover, Congress intended the CLIA regulations to assure the "accuracy of testing" and, therefore, it did not expect CLIA to assure the clinical validity of the tests. Adding clinical validity requirements to the CLIA regulations would have been to create duplicative roles for FDA and CLIA[328] where FDA has implemented its authority for the oversight of clinical validity or safety and effectiveness.

The U.S. Government Accountability Office (GAO) has examined clinical laboratory quality and issued its report (GAO-06-416), *Clinical Lab Quality: CMS and Survey Organization Oversight Should be Strengthened*[329] in June 2006, along with the accompanying testimony before Congress (GAO-06-879T).[330] GAO made several recommendations to improve the oversight of laboratory tests. GAO was asked to examine (1) the quality of laboratory testing; (2) the effectiveness of surveys, complaint investigations, and enforcement actions in detecting and addressing laboratory problems; and (3) the adequacy of CMS's CLIA oversight. GAO made recommendations to CMS to improve CLIA oversight including (1) standardizing the reporting of survey deficiencies to permit meaningful comparisons across survey organizations; (2) working with survey organizations to ensure that educating laboratory workers does not preclude appropriate regulation, such as identifying and reporting deficiencies that affect laboratory testing quality; and (3) allowing the CLIA program to use fully the revenues generated by the program to hire sufficient staff to fulfill its statutory responsibilities. CMS concurred with most of GAO's recommendations and noted that the report provided insights into areas where it can improve, augment, and reinforce oversight. Since the report was issued, CMS has made significant inroads in accomplishing these recommendations.

CMS has considered adding a genetic testing specialty under CLIA that would identify standards for laboratories performing genetic testing but decided that mechanisms other than adding a specialty could be used more effectively to address gaps in oversight.[331] Additionally, the genetic testing specialty would not address issues such as the PT sample paucity and lack of clinical validity assessment. CMS' decision has received mixed reactions from the laboratory community. For example, ACMG released a position statement[332] in July 2007 supporting the specialty, while the American Clinical Laboratory Association

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[327] CLIA, Subpart M—Personnel for Nonwaived Testing. See http://wwwn.cdc.gov/clia/regs/subpart_m.aspx#493.1457. Accessed on September 24, 2007.

[328] Personal communication from Judy Yost, CMS

[329] U.S. Government Accountability Office. Report to Congressional Requesters. *Clinical Lab Quality: CMS and Survey Organization Oversight Should Be Strengthened*. See http://www.gao.gov/new.items/d06416.pdf. Accessed on August 10, 2007.

[330] U.S. Government Accountability Office. Testimony Before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, House of Representatives. *Clinical Labs: CMS and Survey Organization is Not Sufficient to Ensure Lab Quality*. See http://www.gao.gov/new.items/d06879t.pdf. Accessed on August 10, 2007.

[331] Secretary's Advisory Committee on Genetics, Health, and Society. Presentation by Thomas Hamilton and Judith Yost, November 13, 2006. See http://www4.od.nih.gov/oba/SACGHS/meetings/Nov2006/SACGHSNov2006meeting.htm. Access on September 10, 2007.

[332] American College of Medical Genetics, *Position Statement of the American College of Medical Genetics on the Regulatory Oversight of Genetic and Genomic Tests.* July 29, 2007. See http://www.acmg.net/AM/Template.cfm?Section=ACMG_Newsletter_The_ACMG_Medical_Geneticist&Template=/CM/ContentDisplay.cfm&ContentID=2112. Accessed on October 9, 2007.

(ACLA) issued a letter[333] in September 2007 supporting CMS' decision not to establish a new genetic testing specialty. SACGHS agrees with CMS that a genetic testing specialty under CLIA may not be the best approach to improve the oversight of genetic testing. The recommendations in this report suggest enhancements to current regulatory mechanisms and propose new approaches to strengthen the oversight of genetic testing.

Food and Drug Administration

The Federal Food, Drug and Cosmetic Act,[334] as amended, authorizes the FDA to regulate medical devices, such as reagents, test kits, and instruments used by clinical laboratories to conduct testing.

Analytical Validity

The FDA reviews analytical validation prior to approval or clearance of commercially marketed reagents, test kits, and/or instruments. For an unmodified FDA-approved or -cleared IVD, in which FDA has reviewed validation data and cleared or approved the test, the laboratory must only verify that the established performance specifications (e.g., accuracy, precision) are achieved when the IVD is used by persons who routinely perform patient testing. If a laboratory chooses to modify elements of an FDA-approved or –cleared IVD for "off label" use, then the laboratory must perform a full validation for the modification prior to patient testing. For example, if a test product is cleared for cystic fibrosis carrier screening but is used for diagnosing cystic fibrosis, then the diagnostic test must be validated. The laboratory takes full responsibility for performance, which must be disclosed in test reports.

FDA seeks specific analytical performance information for tests kits (including genetic tests) as outlined in the 510(k) decision summaries posted on the Office of In Vitro Diagnostics (OIVD) web site.[335] When applicable, FDA recommends the following six distinct types of information be provided to establish analytical performance for a new test:

- Precision/reproducibility—information on total variability for each specimen type, including information on sites (if applicable), lots, users, instruments, and other sources of variation;
- Linearity/reportable range—information on the linearity of quantitative tests and the reportable range over which reliable results can be expected;
- Traceability, stability, expected values (controls, calibrators, or methods)—information on source, value assignment, and credentials of materials and methods used to control and calibrate the test system;
- Detection limit—information describing minimum sample requirements and limits of detection for measurement;
- Analytical specificity—studies to evaluate both interference and cross reactivity of relevant substances or samples, including carry-over studies when appropriate; and
- Assay cut-off—information to demonstrate how the assay cut-off was chosen and whether an equivocal zone may be warranted.

[333] American Clinical Laboratory Association. *ACLA Supports CMS Response on Genetic Specialty*. September 5, 2007. See http://www.clinical-labs.org/documents/PressreleaseSpetember52007onGeneticSpecialty.pdf. Accessed on October 9, 2007.

[334] Federal Food, Drug, and Cosmetic Act. Available at http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm. Accessed on August 8, 2007.

[335] Food and Drug Administration, Office of In Vitro Diagnostic Device (OVID) Evaluation and Safety. OIVD Decision Summaries for Products Cleared or Approved Since November 2003. See http://www.fda.gov/cdrh/oivd/decisionsummaries.html. Accessed on August 8, 2007.

FDA also requires method comparisons to establish accuracy (trueness) or bias of the test when compared to a reference or standard working method. The comparative method can vary depending on the nature of the test being studied, but for classic genetic tests, bi-directional sequencing is usually the most appropriate comparative method. For other kinds of tests, alternative comparative methods may be appropriate, and for some tests (e.g., complex genetic signatures) there may be no reference method. If no reference method is available, test performance stability, and clinical performance comparison to some measure of clinical truth serve as mechanisms for establishing the performance of a new analytical system.

FDA analytical performance evaluation is usually assessed in the context of information on the device design and description and includes an analysis of software and hardware performance. While FDA prefers analytical studies be carried out on natural patient samples, the agency does recognize that for rare alleles or substances meeting this requirement may not be possible. In these cases, contrived or spiked samples may sometimes be used to supplement or replace actual specimens. These samples should be matrix specific and as close to real-life samples as possible.

FDA review of analytical performance data is conducted by one or more scientific reviewers. If appropriate, consultation is sought from medical officers, statisticians, and/or engineers to ensure comprehensive evaluation of the test's performance and labeling. Following review, design, analytical, and clinical information about the test is posted in a standardized summary on the OIVD web page. This procedure allows healthcare providers and other interested stakeholders to assess what studies were done to support claims made in product labeling and to review the thoroughness and rigor of the data being used to establish analytical performance.

FDA also regulates ASRs that are commercially distributed for use by laboratories or by IVD manufacturers for development of tests or kits. Because these products are ingredients, and not tests themselves, they have no defined performance characteristics in isolation. Thus, there is no requirement to validate class I ASRs. When an ASR is used in a laboratory test, the test must be validated under the appropriate oversight framework (i.e., CLIA), and labeling for the test must comply with the requirements of the appropriate Federal regulations.

Clinical Validity

As noted earlier, FDA has exercised enforcement discretion over genetic tests that are developed as LDTs. Most genetic tests are currently offered as LDTs, which means that the FDA is not currently assessing the clinical validity of most genetic tests. Thus, FDA's current role in assessing clinical validity applies primarily to test kits.

Although clinical validity is a term defined in this document and often used in discussing test performance, law and regulations do not define clinical validity as a parameter to be reviewed by the FDA. Instead, the FDA is charged with assessing the safety and effectiveness[336] of the device or test itself. These parameters are generally tied to assessment of analytical and clinical performance of the test or device. The FDA may assess clinical performance of genetic tests in several different ways, depending

[336] For FDA, the term "effectiveness" means that based on information provided, "it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device" (FFDCA, section 513(a)(3)(A)) This is informally interpreted as "do the performance data provided adequately support the intended use claimed by the sponsor?" Elsewhere in this report, the term effectiveness is used as a measure of how well the test performs in "real-world" clinical settings and "efficacy" is used for outcomes seen in controlled research settings.

on the nature of the test, its intended use, and the amount of existing information about the association of the genetic marker(s) being tested with a clinical diagnosis.

For tests that are subject to premarket clearance or approval, the information that the FDA seeks to support clinical performance of a genetic test is claims-driven and is based on the intended use and the indications for use of the diagnostic device being reviewed. In order for a test manufacturer to meet regulatory requirements to demonstrate safety and efficacy, there must be information on clinical performance in relation to what the manufacturer claims as the intended use. Ideally, this information provides a description of test sensitivity and specificity in clinical specimens as compared to known clinical status, or "clinical truth." In instances where clear "clinical truth" cannot be measured, the FDA may accept a clear description of surrogate endpoints for truth. In any case, for genetic tests, it is important for the manufacturer to account for prevalence of the marker in different populations, the penetrance of the marker, and for other elements of variability that might affect the applicability or value of the test result.

FDA will often accept analytical testing on specimens from enriched populations of patients with the genetic variation or condition in question, together with a listing of the relevant literature, as the basis for an assertion of "clinical validity," or a likelihood of acceptable clinical performance. In these cases, an analytical signal for a genetic marker is well established, easily understandable in terms of clinical use, and the published literature provides evidence that the marker is well-associated with a particular phenotype.

If the genetic marker is new, not amenable to direct interpretation in clinical use, or has unknown clinical performance parameters, FDA may request clinical data from one or more clinical studies to demonstrate that the marker is predictive of the disease or condition in the populations for which the test is intended. These data may need to be collected in a prospective study in some cases, but often an analysis of well-credentialed stored samples (i.e., specimens with well-documented, agreed-upon clinical status) may be sufficient.

FDA does not require evidence of beneficial clinical outcomes for genetic tests but does expect new diagnostic tests to have medically plausible benefits to meet its effectiveness definition.

For tests with sufficient performance data, FDA generates a letter authorizing marketing and establishes a classification for the test that includes a general classification number and a product code. This letter, along with the registration and listing information, allows for devices to be tracked postmarket to assure analytical performance is maintained consistently over time, for problems to be identified and remedied (through notifications to customers or through recalls), and for appropriate medical device reports of adverse events to be made.

State Regulatory Agencies

Oversight of analytical validity at the State level varies. New York has one of the most stringent State-level oversight systems. NYSDOH requires pre-approval prior to offering clinical testing. Other States have little to no oversight of analytic validation and rely on oversight provided by Federal authorities and guidelines provided by professional societies.

NYSDOH oversees the analytical validity of testing performed on all patient samples. They use a licensing process prior to making a test available. Subsection 58-1.10 of Part 58 of Title 10 (Health) of the Official Compilation of Codes, Rules and Regulations of the State of New York states that all

technical procedures employed in a laboratory shall be of proven reliability and generally accepted by leading authorities in the specialties of laboratory medicine and/or approved by the Department.[337] The laboratory must submit an application along with the validation summary and raw data to NYSDOH for all modified FDA-approved assays, IUO and RUO assays, and LDTs with or without ASRs for genetic assays. Once the analytic validation is approved, laboratories are licensed to perform testing on N.Y. patient samples.

The NYSDOH review process starts with the basic scientific premise of the assay, generally based on the published literature establishing an association of the marker to be tested (e.g., deletion detected by FISH, gene mutation, enzyme level) and the disease of interest. This process also forms the basis of the clinical validity for most of the assays submitted. The actual procedural method is reviewed for clarity of the instructions to the analyst, correct concentrations of reagents, and complete materials and equipment list. The analytical validity data for the selected normal and abnormal case materials are reviewed. A critical component of this review is determining how the specimen is characterized as to the expected result. This determination could be by comparison to a gold standard method or by clinical characterization of the patient source that is independent of the result of the assay being studied. Reproducibility and robustness of the assay as well as inter- and intra-run or lot variation must be submitted. All educational materials for the patient and ordering physician are submitted and reviewed along with sample normal and abnormal reports. As New York Civil Rights Law requires, explicit written informed consent for genetic testing and the consent documents are also submitted for review. The majority of submissions are not approved on first submission, and some have required as many as six re-submissions for missing data.

In New York State, tests that must be reviewed prior to being offered include commercially distributed assays labeled for research use only, those using ASRs, FDA-approved assays or IUO assays that have been modified from their intended use or investigational device exemption (IDE) approval from the FDA, and any LDT. A change in the specimen type, the type of analysis (e.g., qualitative or quantitative), the purpose of the assay (e.g., screening, diagnosis, prognosis, monitoring, confirmation), or the target population outlined in the FDA-cleared or -approved or package insert is considered a change in an intended use. The materials submitted for validation review must include:

- The target population(s);
- The purpose (e.g., diagnostic, prognostic, screening, predictive);
- Whether the result is qualitative or quantitative;
- The performance evaluation method (e.g., comparability to an established method or correlation of results to clinical status of test subjects);
- Practitioner/patient information, including limitations of the test;
- Indication of clinical validity (generally, as reported in the literature);
- For germ line genetic tests, policy and compliance documents relevant to informed consent; sample reports for both normal and abnormal samples, including all necessary disclaimers;
- Scientific references; and
- Performance characteristics of the assay (e.g., accuracy, precision, reportable ranges, sensitivity, and specificity)

In cases where performance evaluation is based on the clinical outcome of test subject status, additional information is needed on protocols to establish clinical status, protocols to blind specimen evaluation from clinical status, how discrepant results are resolved, and how predictive value calculation is done. New York State standards also require that cytogenetics and genetics laboratories report with an

[337] New York State Department of Health. Clinical Laboratory Evaluation Program. http://www.wadsworth.org/labcert/TestApproval/submitguide.htm. Accessed on June 16, 2007.

interpretation suitable for a nongeneticist physician, reference ranges (e.g., for germ line genetics of single gene disorders, the heterozygote and homozygote results), and whether the assay predicts disease state.

All laboratories that solicit and receive specimens from New York are subject to New York clinical laboratory permit requirements, including approval of LDTs. The program currently certifies over 70 cytogenetics laboratories, including six pre-implantation genetic testing laboratories that are not subject to CLIA requirements. Over 200 biochemical and DNA-based genetic testing laboratories, 100 molecular oncology laboratories, and 30 paternity identity or forensic DNA laboratories are included in the program. All large commercial reference laboratories do business in New York and thus must have New York laboratory permits. This list includes Quest Diagnostics, Laboratory Corporation of America, Genzyme, Mayo, and ARUP laboratories. While there are many other laboratories performing rare genetic tests, the vast majority of them perform cytogenetic, common biochemical genetic (e.g., Tay Sachs carrier testing), and DNA-based mutation (e.g., CFTR mutations, fragile X triplet repeats) tests. Therefore, although as few as 30 percent of the genetic testing laboratories are regulated by New York, it has been estimated that as much as 75 percent of all cytogenetic and genetic testing performed in the United States (numbers of specimens tested, not number of laboratories) is subject to New York State oversight.

For rare genetic tests not available from any New York permitted laboratory, the program will issue a letter authorizing the New York provider, physician, or referring permitted laboratory to send the particular specimen on the particular patient to that non-permitted laboratory. This letter includes caveats for the ordering physician and the patient regarding the lack of any review of the validity of the promised test. The program also sends communication to the reference laboratory to inform them of the New York permit process and requirements. If the program receives over 50 requests for a single test to be sent to one laboratory, that laboratory is informed they will no longer be authorized to accept New York specimens and continued acceptance can result in fines. If a provider, specifically a New York permitted laboratory continues to submit specimens to a laboratory without New York permit or that has not validated the assay, New York will send that referring laboratory a cease and desist letter and a warning that they will be fined $2,000 per specimen for continued operation.

Although about half of the States have some degree of statutory authority for oversight of the practice of clinical laboratory medicine, only two other States besides New York requires some review of clinical validity data for individual assays. California reviews genetic tests used in newborn and prenatal screening. This evaluation is based largely on the published literature establishing an association of the marker to be tested (e.g., deletions detected by FISH, gene mutation, enzyme level) and the disease of interest. Washington State also has a program that evaluates the clinical validity on an as needed basis when there is doubt about a specific test.[338]

Standards Development Organizations

QC and RMs are essential for validating the performance characteristics of a laboratory test, monitoring test performance, and detecting problems in the testing process. Unlike other areas of the clinical laboratory testing for which these materials are readily available, well characterized cell lines, DNA materials, or residual clinical specimens with mutations or polymorphisms that should be detected by the intended genetic test are not always readily obtainable. FDA has cleared QC materials for only two genetic tests: cystic fibrosis testing and cytochrome CYP450. Not all alleles commonly included in these tests are represented in the FDA-cleared QC materials, however. Laboratories must obtain and verify

[338] Washington Administrative Code, Chapter 246-338, Medical test site rules. See http://apps.leg.wa.gov/WAC/default.aspx?cite=246-338. Accessed on September 10, 2007.

QC/RMs for all alleles included in their test panels. To do this, they often utilize residual patient samples, cell lines, or synthetic DNA materials.

The National Institute of Standards and Technology (NIST) and the CDC, through the GeT-RM Coordination Program, are working to address these QC and RM needs. Commercial companies are also developing these materials.

NIST, a nonregulatory agency of the U.S. Department of Commerce, develops and certifies physical and chemical standards in support of national commerce, manufacturing, and science. In its role supporting U.S. science and industry, the NIST responds to specific standards needs, most recently for medically and biologically important analytes. Broad-based consensus developed through interdisciplinary NIST workshops initiated development of NIST-certified DNA standards. Standard Reference Materials (SRMs) are highly characterized, high-order reference materials that are produced in small quantities. Such materials serve the diagnostic community and help manufacturers benchmark a variety of DNA diagnostic testing platforms.

One of NIST's first efforts in the clinical genetics area was the development of a SRM for fragile X testing (SRM 2399). This SRM contains a set of nine different PCR products or amplicons with varying CGG repeat sizes along the normal to premutation range for the FMR1 gene. Due to the difficulty in manufacturing and the cost, this SRM is intended for use during assay validation or for assay calibration but not for daily use as a QC material. Until recently, SRM 2399 was the only SRM available for molecular genetic testing, although a few others are in development. There is a critical need for additional materials for use as calibrators and for analytical validation of new genetic tests.

The CDC GeT-RM program, AMP, and nine laboratories from the molecular genetics community have engaged in an effort to obtain and characterize reference materials for fragile X syndrome testing. This effort entailed the evaluation of 16 cell lines deposited at Coriell containing clinically relevant FMR1 alleles in the normal and premutation range. DNA from the 16 fragile X cell lines, as well as five control samples, were characterized by nine clinical genetic laboratories using both laboratory-developed assays and a research use only platform to determine the allele size of the different cell lines.[339] This project was coordinated by the GeT-RM program, infrastructure and logistics were provided by AMP, and the nine laboratories volunteered reagents and personnel for the evaluation. Similar characterization projects were also completed to create 14 Huntington RMs,[340] 31 Ashkenazi Jewish Panel RMs, and studies are currently underway for other disorders such as cystic fibrosis. These studies have been extremely well received by the genetic community but have only provided a limited amount of validated materials. There is still a significant need for additional reference materials but limited funding for participating laboratories have hampered these efforts. Funding for validation of additional reference materials should be identified and made available on a competitive basis.

Commercial vendors of QC materials provide both synthetic and cell line based that can be used for both assay validation/verification and daily QC. Many of these vendors are listed on the GeT-RM website.[341]

[339] Amos, W. J,, Pratt, V.M., Phansalkar, A., Muralidharan, K., Highsmith Jr, W.E., Beck, J.C., Bridgeman, S., Courtney, E.M., Epp, .L, Ferreira-Gonzalez, A., Hjelm, N.L., Holtegaard, L.M., Jama, M.A, Jakupciak, J.P., Johnson, M.A., Labrousse, P., Lyon, E., Prior, T.W., Richards, C.S., Richie, K.L., Roa, B.B., Rohlfs, E.M., Sellers, T., Sherman, S.L., Siegrist, K.A., Silverman, L.M., Wiszniewska, J., and Kalman, L.V. Consensus Characterization of 16 FMR1 Reference Materials: A Consortium Study by the Fragile Xperts. *Journal of Molecular Diagnostics.* (submitted).

[340] Kalman, L. (2007). *Genetics in Medicine*. In press.

[341] http://wwwn.cdc.gov/dls/genetics/qcmaterials/

The FDA regulates commercial QC vendors.[342] The cost of FDA-cleared QC materials can be significant to both the manufacturer during development and to the laboratory during use, which may impede both the development and use of these materials.

Knowledge Generation Agencies

Federal research agencies such as the Agency for Healthcare Research and Quality (AHRQ), CDC, the Health Resources and Services Administration (HRSA), and NIH, play a critical role in determining the genetic contribution to disease and in collecting data and generating, analyzing, and summarizing knowledge to support the appropriate use of genetic tests. Such work advances understanding of the clinical validity of genetic tests and is an essential part of determining their safety and effectiveness. The initiatives of AHRQ, CDC, HRSA, and NIH that relate to genetic testing are discussed in Chapter 2.

Additional activities include an NIH focus on studying small differences (at the level of individual bases) in individual genomes, and investing in whole genome-wide association research that attempts to correlate genetic variations with specific disease. The application of this knowledge will contribute to the clinical validity of genetic tests. To this end, the Human Genome Epidemiology Network (HuGENet),[343] an international collaborative effort established at CDC, promotes the synthesis, interpretation, and dissemination of population-based data on human genetic variation in health and disease, providing summary data to inform clinical validity assessments.

While the efforts of these agencies are significant, most Federal resources in genetics and genomics are focused on basic research. Fewer resources are applied to translation research and surveillance activities for genetic tests and other genetic discoveries entering clinical practice and public health, nor are there requirements for this type of research to be performed prior to a test being offered clinically. Current programs that explicitly targets clinical validity in the context of test translation are CETT[344] and EGAPP.[345]

In 2001, SACGHS' predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT)[346] began an assessment of HHS efforts to increase knowledge of clinical validity and utility of genetic tests both before and after a test is marketed. As part of its fact-finding, SACGT gathered data from AHRQ, CDC, FDA, HRSA, and NIH about their agencies' roles and activities in supporting primary and secondary data collection efforts from fiscal year 1996 to fiscal year 2000. The activities were categorized as primary research, secondary data analysis, summary information development, and information dissemination.[347]

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[342] U.S. Food and Drug Administration. Guidance for Industry and FDA Staff—Assayed and Unassayed Quality Control Material. See: http://www.fda.gov/cdrh/oivd/guidance/2231.html. Accessed on July 31, 2007.

[343] Human Genome Epidemiology Network. See http://www.cdc.gov/genomics/hugenet/default.htm. Accessed on November 1, 2007.

[344] The Collaboration, Education and Test Translation Program. See http://www.cettprogram.org/. Accessed on July 17, 2007.

[345] Evaluation of Genomic Applications in Practice and Prevention (EGAPP). See http://www.egappreviews.org/. Accessed on August 1, 2007.

[346] Archive of the Secretary's Advisory Committee on Genetic Testing, available at http://www4.od.nih.gov/oba/SACGT.HTM. Accessed on July 17, 2007.

[347] The categories were defined as follows: Primary research – the generation of original data to increase knowledge of the analytical validity, clinical validity, and clinical utility of genetic tests; Secondary data analysis – systematic reviews and meta-analyses combining data from a number of studies in order to increase knowledge of the analytical validity, clinical validity, or clinical utility of genetic tests; Summary information development – the development or updating of information summaries on the analytical validity, clinical validity, or clinical utility of genetic tests for clinicians, laboratory personnel, policy-makers, patients/consumers, and the general public; Information dissemination – dissemination of information about the analytical validity, clinical validity, or clinical utility of genetic tests to professionals and the public.

Over the 5-year period, the agencies supported 1,068 projects and activities spanning the range of genetic test development and application, from the identification of a genetic component in a disease or condition to the education of health professionals. Seventy-two percent of the projects (766) focused on one of 184 diseases/conditions; the most common diseases/conditions to be funded were cancer-related, with breast cancer as the most common (89 projects). Some of the non-disease topics included education, technology development, and quality assurance. NIH supported 94 percent of the reported projects, totaling more than $1.03 billion. Eighty-eight percent of the projects were categorized as primary research with NIH supporting more than 98 percent. Among the agencies, NIH also supported most of the secondary data analysis, summary information development, and information dissemination.

Professional Societies

Professional societies that contribute to the oversight system include ACMG, CAP, and CLSI. CAP develops standards for its membership under LAP and operates proficiency testing programs. CLSI, formerly the National Committee on Clinical Laboratory Standards (NCCLS), develops consensus recommendations for standardization of test methodologies. Other organizations, such as ACMG, the American Society of Human Genetics (ASHG), the American Academy of Pediatrics, American College of Obstetrics and Gynecology, AMP, and National Society of Genetic Counselors are also involved in the development of guidelines and recommendations regarding the appropriate use of genetic tests. These guidelines may be evidence-based, best practices, or based on expert opinion. For example, ACMG and ASHG published practice guidelines for the appropriate clinical use of genetic testing for colon cancer.[348] Clinical guidelines help make sense of thousands of articles on a given clinical topic. They help clinicians deal with complex decisions, improve the quality of decision-making, and provide justifications to patients, payers, and the legal system about why decisions are made. Guidelines are useful for transmitting medical knowledge, assisting with patient and physician decisions, setting clinical norms, and contributing to quality improvement projects in hospitals and group practices. They can also be used for privileging and credentialing, payment, cost control, and medicolegal evaluation. Chapter 5 discusses their role in communication and appropriate use of tests.

Some professional societies work in partnership with CMS and the CDC. CMS is willing to work with developers of guidances to place references to these documents in Surveyor Interpretive Guidelines and/or to include all or parts of these documents. In doing so, laboratories might accept them more readily, but the guidances still would not have the force of regulations. Most of the oversight provided by professional societies is offered as recommendations for laboratories. With the exception of CAP's LAP program of accreditation, these recommendations are not enforced. Appendix D summarizes available guidelines and standards for molecular diagnostics testing.

ACMG develops clinical practice guidelines focusing on medical practice as well as technical standards and guidelines on laboratory practice for clinical laboratories (see www. acmg.net). The ACMG guidelines include tests performed with FDA-cleared or -approved kits, as well as LDTs. The ACMG recommends that validation with well-characterized samples is critical.[349]

A section on test validation is included in the technical standards and guidelines that relates to clinical validity.[350] The document recommends, in accordance with CLIA 1988, that each laboratory is

[348] Joint Test and Technology Transfer Committee Working Group. (2000). Genetic testing for colon cancer: Joint statement of the American College of Medical Genetics and American Society of Human Genetics. *Genetics in Medicine*. 2(6): 362-366.
[349] American College of Medical Genetics. Laboratory Standards and Guidelines for Clinical Genetics Laboratories. 2006 Edition. http://www.acmg.net/Pages/ACMG_Activities/stds-2002/g.htm. Accessed on June 16, 2007.
[350] ACMG Technical S&G for Clinical Genetics Labs, Section C8.1 Test validation overview, 2006.

responsible for validating each new test before introduction into clinical use, including tests performed with FDA-cleared or -approved kits, as well as LDTs (reagents homemade or purchased under analyte-specific reagent rules). First, it is necessary to define the clinical disorder being tested for as well as the intended use or clinical setting of the test (e.g., diagnostic testing, screening) because clinical validity can vary based on the clinical setting.

Validation of each test in a specific clinical setting is focused on the collection of data to establish analytic validity, clinical validity, and clinical utility. The process involves (1) reviewing professional guidelines and relevant literature; (2) performing and evaluating analytic and clinical correlation studies within the laboratory to establish validity; (3) defining the limitations of the test; (4) determining the variables that must be monitored to maintain a high level of performance; (5) identifying and addressing relevant ethical, legal and social issues, and collecting information about the clinical utility of the test in order to inform patients and providers about appropriate test usage. ACMG also notes that for some test applications, gaps in knowledge may exist, and these gaps should be identified. They recommend that the laboratory provide justification for offering the test in a clinical setting based on the information and data currently available.

ACMG is also developing a Quality Watch program that will facilitate communication when laboratories have problems with products such as reagents, tests kits, or equipment. Quality Watch will be a new feature on the ACMG website[351] and is expected soon. Laboratorians who encounter a problem will fill out and submit an online form describing the problem. Submissions will be monitored, and when appropriate, e-mails will be sent out through ListServs asking other laboratories that have encountered the same problem to fill out a Quality Watch form. The responses will be reviewed to determine if a single product is likely causing the problem. If so, laboratorians will be encouraged to contact the manufacturer. This program is based on an incident in which a company making syringes changed the coating. Cell cultures from amniocentesis samples failed when samples were sent to the laboratory in these syringes. Using a cytogenetics ListServ, the problem was pinpointed within a week. The problem was discussed with the manufacturer and resolved.

AMP provides published recommendations for in-house development and operation of molecular diagnostic tests, including genetic testing.[352] In addition, AMP continuously provides workshops at its annual meeting regarding assay standardization, analytical and clinical validation of genetic tests, development of quality control materials, and other related topics. AMP has provided significant support for the CDC sponsored Fragile Xperts working group, to analytically validate a number of different cells lines that can be used for quality control for fragile X syndrome testing. Furthermore, AMP has undertaken three sample exchanges for real-time PCR assessment for BCR/ABL involving 36 laboratories across North America. A manuscript describing results from the sample exchanges and proposed test standardization and reporting guidelines is currently being drafted.

CAP provides guidelines on the analytical performance of each assay in accordance with CLIA 1988 (see above). CAP evaluates the analytical validity of an assay by using checklists and a laboratory inspection process after the assay has been made available. The analytical validation must include an evaluation of the performance characteristics such as analytic sensitivity, analytic specificity, precision, linearity (for

[351] American College of Medical Genetics. See http://www.acmg.net. Accessed on August 16, 2007.
[352] Association for Molecular Pathology statement. Recommendations for in-house development and operation of molecular diagnostic tests. (1999). American Journal of Clinical Pathology. 111(4): 449-463.

quantitative tests), reportable range of patient test results, reference range (normal values), and any other applicable performance characteristic.[353]

The CAP LAP also provides mechanisms for assuring the clinical validity of genetic tests. For example, CAP expects laboratories to demonstrate how the tests they offer have been clinically validated. CAP looks for whether there is documentation that validation studies have been performed to establish the performance characteristics of the LDT. It determines whether clinical performance characteristics of each assay are documented, using either literature citations or a summary of internal study results and whether final reports include an appropriate summary of the methods, the loci or mutations tested, the analytical interpretation, and clinical interpretation (if appropriate), and a summary statement, signed by the laboratory director or designee, that documents the review of validation studies and approval of the test for clinical use.[354]

CLSI provides voluntary consensus standards and guidelines for the healthcare community (see Table 2). These standards and guidelines are often used by laboratories during the validation process, but are neither mandatory nor enforced. CLSI recommends identifying and characterizing the critical analytic performance properties relevant to ensuring consistent and reliable results. At a minimum, the analytic sensitivity, analytic specificity, robustness, and precision/reproducibility of the assay should be evaluated. The test should be validated for all specimen types (e.g., blood, chorionic villus sample (CVS), fibroblasts) that will be utilized for testing. The analytic performance should first be characterized using known, well-characterized specimens. Then the assay should be reassessed using clinical samples or control materials to optimize the procedure. The laboratory is recommended to identify any limitations and contraindications for use of the test, including factors that impact adversely on accuracy of test interpretation (e.g., allelic mutations that cannot be detected by the test, less than optimal analytic performance) and any technical limitations of the assay such as interferences or inhibitors.[355]

The term clinical validity is not used in the CLSI MM1, a guideline that specifically addresses diagnostic methods for genetic diseases. CLSI uses the ISO definitions for global harmonization. Diagnostic performance is "the ability of the test to correctly measure or predict the diagnostic endpoint of interest (e.g. clinical outcome, phenotype, and genetic status, genotype)." For the purposes of this discussion, these definitions of diagnostic performance and clinical validity are viewed as having the same components (i.e., diagnostic sensitivity and specificity, or clinical sensitivity and specificity, and positive- and negative-predictive values). The CLSI document is technical and describes how to assess diagnostic performance, referring readers to the ACMG Standards and Guidelines for Clinical Genetics Laboratories for a more in depth discussion of what is required of genetic laboratories. Certain CLSI documents are accepted by FDA as "special controls" and as recognized standards, and, as such, they may also have a limited regulatory role.[356]

Gaps in the Oversight of Analytical and Clinical Validity

[353] College of American Pathologists. Molecular Pathology Checklist. December 2006. See http://www.cap.org/apps/docs/laboratory_accreditation/checklists/molecular_pathology_december2006.pdf. Accessed on June 16, 2007.

[354] Gail Vance presentation to SACGHS, March 2007. See http://www4.od.nih.gov/oba/SACGHS/meetings/Mar2007/SACGHSMar2007meeting.htm. Accessed on September 20, 2007.

[355] Clinical and Laboratory Standards Institute. *Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition.* CLSI document MM1-A2. 2006. Clinical and Laboratory Standards Institute: Wayne, PA.

[356] Clinical and Laboratory Standards Institute. *Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition.* CLSI document MM1-A2. 2006. Clinical and Laboratory Standards Institute: Wayne, PA.

- It is estimated that more than 1,100 genetic tests are currently offered in clinical laboratories. This estimate is based on data submitted voluntarily to Gene Tests, an on-line directory of genetic tests and the laboratories that offer them.[357] AMP also maintains a voluntary registry.[358] There is no complete or official source of information on the number and types of genetic tests that are clinically available in the United States. No Federal agency or national organization maintains a complete list. AMP also provides a list of FDA-approved tests for inherited or somatic genetic disorders.[359]

  For the vast majority of these tests, no publicly available validated QC materials are available. Therefore, laboratories must improvise to obtain these reagents and, in some cases, develop and run assays without adequate controls. Samples are often derived from residual patient specimens, synthetic samples, or cell lines. The laboratory must validate these materials prior to use as QC or reference materials. It should be noted that most of the common mutations in the common genetic disorders do have reference materials available for analytic validation.

  In addition, some laboratories use reagents that are manufactured in-house, and/or reagents marketed "for research use only" to develop laboratory-developed genetic tests. There is no national mechanism for reporting these reagents when they are faulty because manufacturers are not required to be registered or to list these products with FDA. ACMG's soon-to-be-launched Quality Watch Program for reporting problems associated with reagents/assays could serve as a model, however. CAP's Council on Scientific Affairs has developed a process designed around patient safety issues detected from summary PT data. Similarly, if a laboratory-developed test is faulty due to design or validation failures, there is no mechanism to report the faulty test.

- Variation in allele and polymorphism frequencies in the general population and by race/ethnicity have been well described in the literature for some population groups (e.g., HFE), while others have much less information available.[360, 361] Some of these allelic variances or polymorphisms could have an impact on the ability to detect or classify clinically significant genetic variants in the process of providing genetic testing services.

- Some laboratories offering health-related tests are not required to follow CLIA regulations. These include in vitro fertilization clinics, which use genetic tests to diagnose a genetic disorder in a pre-implantation embryo. Laboratories offering tests whose purpose is solely to assess or guide lifestyle related matters (e.g., nutrigenomic tests) or to determine the gender of a fetus are not covered by CLIA. Questions also exist about whether SNP profiles, currently offered by a few laboratories and provided to patients' clinicians on a CD are covered by CLIA. These tests are being marketed with claims that physicians will be able to interpret the data and predict medical needs. CLIA regulations cover only the testing of a human specimen for the purpose of assessing health, diagnosis, and treatment. Since such tests can have health-related implications, assuring their accuracy and validity is important. Concerns have been raised among health professionals, Federal agencies, Congress, and the public about whether consumers may be harmed by these unregulated tests.

[357] Gene Tests. Seattle, WA: University of Washington, 2007. http://www.genetests.org Accessed October 1, 2007.
[358] Association for Molecular Pathology. Bethesda, MD: Association for Molecular Pathology. http://www.amp.org. Accessed October 1, 2007.
[359] FDA cleared/approved molecular diagnostic tests. Bethesda, MD: Association for Molecular Pathology, 2007. http://www.amp.org/FDATable/FDATable.doc. Accessed October 1, 2007.
[360] Le Gac, G. and Ferec, C. (2002). The molecular genetics of haemochromatosis. *European Jounal of Human Genetics.* 13(11):1172-85.
[361] Worwood M. (2002). HFE mutations as risk factors in disease. *Best Practice and Research. Clinical Haematology*. 15(2):295-314.

- Currently, there are no Federal (CLIA) requirements that laboratories establish or verify the clinical validity of each test offered.

  Laboratories are not required by CLIA to document the performance characteristics, including clinical sensitivity, specificity and predictive values, in relevant patient groups and populations. While at present clinical validity for the more common genetic tests can in fact be estimated by use of published literature, there will be some tests that are proprietary for which published literature addressing clinical validity is lacking.

  CLIA does not address clinical validity, in part because Congress recognized that adding clinical validity requirements to CLIA would be duplicative of FDA regulations. Very few LDTs, however, are reviewed by FDA, and the agency does not currently have sufficient resources to carry out such reviews for all tests if existing review mechanisms are used. Moreover, some observers consider FDA's review to involve an assessment of "clinical plausibility" rather than the more rigorous assessment of clinical validity.

- CLIA inspectors may not be sufficiently trained to evaluate laboratory developed genetic tests, a problem that CMS is addressing through training of CMS inspectors and contracting with specially trained personnel. CAP provides trained inspectors for genetics specialty laboratories upon director request.

- Establishing the analytical and clinical validity of an ever-increasing number of genetic tests with greater complexity may require a different framework than the processes in place today. Elements of the CETT and EGAPP initiatives might be adapted for such a framework.

- Most of the analytes that pertain to genetic testing (and the thousands of other clinical tests that are in use in U.S. laboratories) are not among the 83 analytes regulated by CLIA. Therefore, prescriptive PT enrollment is not required for genetic testing analytes although all laboratories must at least perform AA for all analytes on their testing menu. Congress intended HHS to require PT of all laboratories for each type of clinical test they performed, unless the Secretary determined that was not feasible. Congress did not intend for the Secretary to exempt analytes from proficiency testing merely because such testing is not currently available or because it is difficult to obtain consensus on the best method of proficiency testing.

  While CDC is willing to assist in developing alternative means to achieve PT for genetic tests, the resources, funding, and means to develop formal PT for all genetic tests are lacking. CMS currently has a system to compile regulated PT scores for surveyor review and will make them available to the public upon request. Information regarding laboratory deficiencies in PT for the 83 regulated analytes and deficiencies in AA are also publicly available upon request. The certification status of a laboratory is available to the public, and CMS is in the process of making that information more readily available on the CLIA website so that it is possible to know if a laboratory has been certified to comply with CLIA requirements.

- No data exist on the effectiveness of PT versus AA.

- PT based on test methodologies such as sequencing, which exists in European laboratories, has not been developed in the United States. CAP offers method-based PT for conventional and molecular cytogenetics, biochemical, and molecular testing. It is not known at this point if PT based on test methodology can be of benefit.

- In general, the research agendas of Federal research agencies are not directly tied to translation of genetic tests into clinical practice. The CETT program supported by CDC and NIH is an exception.

Evidence of Harms and Potential Harms

Inadequate Knowledge of the Analytical Validity of Genetic Tests

- Excessive false positive or negative results may occur due to the test not being adequately analytically validated. This problem arises from a lack of knowledge regarding the different sequence variations or the lack of postmarket surveillance data for new sequence variations, which have not been clinically validated, but might affect the analytic validity of the test. Variations in allele and polymorphism frequencies in the general population in addition to variations by race/ethnicity have been well described in the literature for some population groups such as the HFE gene.[362,363,364,365,366] Other allelic variations, however, have much less information available. Some of these allelic variances or polymorphisms could have an impact in the ability to detect or classify clinically significant genetic variants in the process of providing genetic testing services. Laboratories should make efforts to report allelic frequencies as well as polymorphisms that could interfere with test analysis. Even though this is important information for the healthcare community there is no formal mechanism for collection and dissemination of this information.

- Excessive false negative or positive results can occur due to lack of method optimization and standardization. Even though false-negative results for factor V Leiden (fVL) mutation are unusual, some studies[367] have reported false negative results in cases of patients with a history of deep venous thrombosis. This report brings attention to the need for standardization of optimized fVL genetic testing methods.

- Excessive false positive or negative result may occur when an assay is not analytically validated due to the lack of appropriate reference materials.[368]

- Inaccurate test results may occur due to faulty reagents or instruments.

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[362] In 1999, Jeffrey *et al.* reported that a previously described HFE polymorphism, 5569A, was associated with misdiagnosis of C282Y/5569A heterozygotes as C282Y homozygotes. The reason for the misdiagnosis was due the presence of a single base pair polymorphism located in the primer binding site for the C282Y wild type allele in exon 4. Since only the mutant allele would then be amplified, this could result in the appearance of a C282Y homozygote, and a false positive result. Subsequently, two other laboratories reported misclassification of C282Y heterozygotes as homozygotes. Because this polymorphism is relatively common (allele frequencies as high as 13 percent), this report raised immediate concern about C282Y results in genotyping studies worldwide and led some laboratories to re-analyze previous results.

[363] Jeffrey, G.P., Chakrabarti, S., Hegele, R.A., and Adams, P.C. (1999). Polymorphism in intron 4 of HFE may cause overestimation of C282Y homozygote prevalence in haemochromatosis. Nature Genetics. 22(4): 325-326.

[364] Totaro, A., Grifa, A., Carella, M., D'Ambrosio, L., Valentino, M., Roth, M.P., Borot, N., Coppin, H., Roetto, A., Camaschella, C., Gasparini, P. (1997). Hereditary hemochromatosis: a HpaI polymorphism within the HLA-H gene. *Molecular and Cellular Probes*. 11(3): 229-230.

[365] Gomez, P.S., Parks, S., Ries, R., Tran, T.C., Gomez, P.F., Press, R.D. (1999). Polymorphism in intron 4 of HFE does not compromise haemochromatosis mutation results. *Nature Genetics*. 23(3): 272.

[366] Somerville, M.J., Sprysak, K.A., Hicks, M., Elyas, B.G., and Vicen-Wyhony, L. (1999). An HFE intronic variant promotes misdiagnosis of hereditary hemochromatosis. *American Journal of Human Genetics*. 65(3): 924-926.

[367] Libby, E.N., Booker, J.K., Gulley, M.L., Garcia, D., and Moll, S. (2006). False-negative factor V Leiden genetic testing in a patient with recurrent deep venous thrombosis. *American Journal of Hematology*. 81(4): 284-289.

[368] Baum M. New NIST reference material reinforces fragile-x screens. Gaithersburg, MD: National Institute of Standards and Technology Tech Beat, 2005. http://www.nist.gov/public_affairs/techbeat/tb2005_0224.htm#new. Accessed October 1, 2007.

Inadequate or Misapplied Knowledge of the Clinical Validity of Genetic Tests

- The potential risks of positive test results include the exposure of individuals to unnecessary treatments; possible social, psychological, and economic harms, including altered self-image, impact on family relationships, stigmatization, and exclusion from health insurance and employment; and identification of risk status in other family members (though this may also be a potential benefit). In the event of false positive test results, individuals may be exposed to unnecessary screening or treatment. A false negative test result could give false reassurance regarding risk due to nongenetic causes or induce psychological effects such as survivor guilt. False negative test results may delay diagnosis, screening, and treatment.

- In some cases, genetic test results that are correct and valid could be misapplied, for example by a poorly trained healthcare provider, and lead to adverse actions such as inappropriate medical management, denied insurance or denied employment.

- Significant harms (real or potential) can occur if a genetic test is used before its clinical validity is understood. For many genetic tests, particularly those that are predictive or presymptomatic, knowledge of the test's clinical validity may be incomplete for many years after the test is developed. When information that may affect clinical validity is incomplete, the potential harms of the test may increase and must be considered more carefully. The following examples illustrate real harms that can be attributed to applying a genetic test without proper documentation that the clinical validity is adequate for the test's intended use.

    - Applying a test with established clinical validity for one condition to an unrelated condition for which clinical validity had never been established. Burlington Northern Santa Fe Rail Company applied a genetic test that is clinically valid for a peripheral nerve condition called hereditary neuropathy with liability to pressure palsies to identify workers with carpal tunnel syndrome. The clinical validity of this test for carpal tunnel syndrome has not been established. The harm resulted when employees were threatened with dismissal from the company if they did not have the test. (They were not informed that a genetic test was being done). Presumably, if the test came back positive the employees would have been denied coverage for treatment of carpal tunnel syndrome based on a "pre-existing condition."[369, 370, 371]

    - HLA-B27 can be useful in diagnosing the genetic disorder axial spondyloarthritis. Available data from the literature was used to develop a diagnostic algorithm for the use of HLA-B27 in the subset of patients with low back pain who also had inflammatory back pain. In the clinical setting of inflammatory back pain, the HLA-B27 test had very good positive predictive value for axial spondyloarthritis. However, if the HLA-B27 test was applied to all patients with low back pain, regardless of inflammation, the positive predictive value is significantly lower (i.e., the test has less clinical validity). Several harms resulted, including increased use of resources relating to testing (by testing all rather than a subset), exposure of

[369] http://www.washingtonpost.com/ac2/wp-dyn/A34877-2001Apr18?language=printer. http://www.pbs.org/newshour/bb/health/jan-june01/genetest_06-07.html.

[370] Clayton, E.W. (2003). Ethical, legal, and social implications in genomic medicine. *New England Journal of Medicine.* 349(6): 562-569.

[371] Schulte, P.A. and Lomax, G. (2003). Assessment of the scientific basis for genetic testing of railroad workers with carpal tunnel syndrome. *Journal of Occupational and Environmental Medicine*. 45(6): 592-600.

patients without axial spondyloarthritis to anti-inflammatory therapies with less benefit and an increased harm from adverse drug events, and exposure to additional diagnostic tests.[372]

- Ordering a test in an inappropriate clinical setting is another potential harm. For example, thrombophilia assessments are being done in individuals with arterial disease, which is not indicated, since the impact of thrombophilic factors is in venous disease, not arterial.[373] Assessing protein C and S levels during acute thrombotic events can result in abnormal results in patients with arterial disease. In a recent study,[374] 62 percent of tests were ordered at an inappropriate time. At least 40 tests had abnormal values of protein C and/or S, all of which proved to be secondary to the illness or treatment as opposed to an intrinsic deficiency. Harms included inappropriate classification as deficient (with attendant medical and insurance implications), inappropriately aggressive treatment based on perception of increased risk, diagnostic odyssey, and waste from cost of doing a test at an inappropriate time.

RECOMMENDATIONS

1) For a number of years, CMS had been planning to address gaps in the oversight of laboratories that conduct genetic tests with the addition of a genetic testing specialty under CLIA. Recently, CMS changed direction and is now addressing these gaps with a multi-faceted action plan. SACGHS considered CMS' rationale and reviewed the agency's action plan. SACGHS carefully considered the recommendations of prior groups as well as the perspectives of stakeholders who support the specialty. In the end, the Committee came to the conclusion that identified gaps can be addressed without the creation of a genetic testing specialty. SACGHS proposes the following recommendations to support and/or augment the CMS action plan:

   A. Currently, CLIA requires all non-waived tests to undergo some form of performance assessment, but only 83 specific analytes, none of which are genetic tests per se, are required to undergo the type of assessment called proficiency testing (PT). PT is currently considered to be the most rigorous form of performance assessment. In principle, genetic tests and all other high-complexity tests should be required to undergo PT. However, such a goal may not be achievable. Consequently, the following actions should be taken:

      1. HHS should fund studies of the effectiveness of other types of performance assessment methods to determine whether they are as robust as PT and support innovations in the way PT is performed such as through methodology-based processes.

      2. In the interim, steps need to be taken to increase the use of PT for genetic tests.

         a. CMS should amend the CLIA regulation to expand the list of regulated analytes to include genetic tests for which PT products are available. In addition, CMS should restructure the PT provision of the rule to enable the list to be updated more rapidly and assure an efficient process to review new PT products.

[372] Rudwaleit, M., van der Heijde, D., Khan, M.A., Braun, J., and Sieper, J. (2004). How to diagnose axial spondyloarthritis early. *Annals of the Rheumatic Diseases*. 63(5):535-43.

[373] Intermountain Healthcare personal communication and Semin. Hematol. 2007 Apr;44(2):106-13. Inherited thrombophilia in arterial disease: a selective review. de Moerloose P, Boehlen F.

[374] Somma, J., Sussman, I.I., and Rand. J.H. (2006). An evaluation of thrombophilia screening in an urban tertiary care medical center: A "real world" experience. *American Journal of Clinical Pathology*. 126(1):120-7.

b. CMS should seek advice from an appropriately constituted group of relevant experts to determine which genetic tests should be added to the list of regulated analytes.

c. HHS should develop incentives for PT providers to expand PT products for those genetic tests.

B. CMS should consult or contract with experts in the field to train inspectors of genetic testing laboratories. Training by such experts will enhance inspectors' understanding of the technologies, processes, and procedures utilized by genetic testing laboratories and equip them to assess compliance with CLIA requirements. In addition, CMS should identify and evaluate innovative, alternative mechanisms to inspect genetic testing laboratories.

C. As recommended in a 2006 Government Accountability Office report on clinical laboratory quality, CMS should use revenues generated by the CLIA program to hire sufficient staff to fulfill CLIA's statutory responsibilities and the program should be exempted from any hiring constraints imposed by or on the agency.

2) Currently, there are gaps in the extent to which analytical validity and clinical validity data can be generated and evaluated for genetic tests. To address these gaps, SACGHS recommends supporting public resources for genetic testing through the following actions:

A. In consultation with relevant agencies, HHS should assure funding for development and characterization of reference materials, methods, and samples (e.g., positive and negative controls and samples from different ethnic/geographic populations) for assay validation, quality control, and performance assessment.

B. HHS should assure funding for the development of a mechanism to establish and support a laboratory-oriented consortium to provide a forum for sharing information regarding method validation, quality control, and performance issues.

C. HHS agencies, including NIH and CDC, should continue to work with public and private partners to support, develop, and enhance public reference databases to enable more effective and efficient collection of mutation and polymorphism data and expand clinical reference sequence databases, and provide summary data on gene-disease associations to inform clinical validity assessments (e.g., RefSeqGene, HuGENet).

D. HHS should support the development by professional organizations of additional standards and guidelines for applying genetic tests in clinical practice.

3) Today, there continue to be considerable information gaps about the number and identity of laboratories performing genetic tests and the specific genetic tests being performed. In the Committee's view, registration efforts are needed to understand the universe of genetic tests being offered and to enhance the transparency of this field. SACGHS reviewed a number of proposals of both a voluntary and mandatory nature. SACGHS recommends:

A. The establishment of a voluntary system of genetic test registration through a public-private partnership. Specifically,

1. HHS should provide additional funding to expand GeneTests to include genomic applications with the potential for broad public health impact, including those related to

pharmacogenomics, and somatic genetic disorders and other types of testing methods (e.g., biochemical testing).

2. HHS should provide incentives to encourage laboratories to register with GeneTests, and this information should be easily accessible to the public.

3. After five years, HHS should assess the completeness and adequacy of the voluntary system. If the system is found to be inadequate, HHS should consider whether registration should be mandatory.

4) There has been much debate in the past decade regarding FDA's role in regulating laboratory developed tests (LDTs). SACGHS supports FDA regulation of LDTs and the flexible risk-based approach the agency is taking to prioritize genetic LDTs, an approach that should be robust enough to accommodate new genetic testing technologies and methodologies. SACGHS agrees that applying the same regulatory framework to every genetic test is infeasible given the number of tests in use and in development and the costs and resources that would be needed to support such a structure. Moreover, such a policy could unnecessarily delay patient access to important new technologies. FDA has taken an important step forward in defining the type of LDTs that will be subject to premarket review. However, SACGHS suggests that further analysis, deliberation, and consultation are needed to determine whether the appropriate weight has been apportioned to the risks associated with the novelty and complexity of the testing platform and technology. SACGHS recommends that:

A. HHS convene relevant HHS agencies, including FDA, CMS, CDC, AHRQ, and NIH, as well as stakeholders to provide further input into the development of a risk-based framework for the regulation of LDTs.

B. For LDTs that will not be subject to FDA review and clearance processes, SACGHS recommends that:

1. HHS encourage and support the development of new and transparent models for private sector efforts or public-private partnerships that could assess the analytical and clinical validity of laboratory developed genetic tests.

2. Laboratory developed tests that have undergone such an assessment would be certified as having been through the process. Such certifications should be made publicly available and could be included as part of the test's listing in GeneTests. For a test whose assessment is negative, i.e., it is found to lack analytical validity and/or clinical validity, HHS should determine the appropriate course of action.

5) SACGHS' fact finding also identified gaps in the enforcement of existing regulations. The following steps should be taken to address them:

A. Further efforts are needed to prevent laboratories from performing genetic tests without appropriate CLIA certification. In addition, although the CLIA program has an array of enforcement actions available, those actions cannot be imposed on uncertified laboratories. Instead, CMS must report the laboratory to the HHS Inspector General for action. HHS should explore mechanisms and seek or develop new authorities and resources to enable CMS to strengthen its enforcement efforts against laboratories that perform genetic tests for clinical purposes without proper CLIA certification. CMS should step up its efforts to make publicly available a list of laboratories that have been cited by CLIA for condition-level deficiencies.

B. Appropriate Federal agencies, including CDC, CMS, FDA, and FTC, should strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about genetic tests.

6) SACGHS is concerned about certain types of health-related genetic tests that are marketed directly to consumers and appear to fall outside the scope of CLIA. Some nutrigenomic tests (e.g., a test for caffeine metabolism) and tests to determine the gender of a fetus are examples of health-related genetic tests that are skirting the boundaries of CLIA's authority. There is insufficient oversight of laboratories offering such tests and their potential impact on the public health is an increasing concern. SACGHS recommends that:

CLIA regulations, or if necessary, CLIA's statutory authority, should be expanded to encompass the full range of health-related genetic tests. Relevant agencies should collaborate in an effort to develop an appropriate definition of health-related genetic tests that CMS could use as a basis for expanding its scope.

Chapter 5
Development and Evaluation of Evidence for the Clinical Utility of Genetic Tests

Introduction

The potential value of a genetic test is only realized when it provides a meaningful benefit to patients, families, or society. This chapter will discuss the meaning of clinical utility and processes for generating information about clinical utility, including clinical trials and observational studies using registries, epidemiologic studies, and other longitudinal datasets. Current mechanisms for synthesizing information, such as systematic evidence reviews, decision models, and expert opinion will also be discussed, as well as the determination of appropriate care through clinical guidelines. This chapter addresses the following questions in the Secretary's charge:

- What evidence of harm exists regarding genetic tests? Is there harm attributable to issues concerning the clinical utility of the tests? If evidence does not exist, what threats are not currently being addressed?
- What are the existing pathways that examine the clinical utility of genetic tests?
- What organizations are currently involved with each of these aspects, and what are they doing to address these issues? Who should be responsible for each of these aspects?
- What new approaches or models should be considered for private and public-private sector engagement in demonstrating clinical utility for developing effectiveness measures of genetic tests in clinical practice?
- Would additional or revised Government oversight of clinical utility add value for patients, and if so, how and where?

In response to these questions, specific recommendations are presented for reducing harms. The application of clinical utility to decision support systems is discussed in Chapter 6. However, the application of clinical utility to quality improvement and coverage decisions is beyond the scope of this report. Yet it should be recognized that clinical utility and an understanding of the magnitude of impact is critical to priority setting and efforts to improve clinical care and disease prevention processes. Similarly, economic evaluation, which combines clinical utility with measures of economic cost, is outside the scope of this report, but plays an important role in priority setting, selection of alternative uses of resources, and enhancing the efficiency of our public health and clinical care system.[375]

Definition of Clinical Utility

Within the field of genetics, clinical utility represents a balance between health-related benefits and the harms that can ensue from a genetic test. In other settings, clinical utility is usually referred to as clinical effectiveness. In general, the benefits and harms of genetic testing compared to the best alternative to genetic testing and the additional net benefit or net harm that would be achieved is called the incremental benefit or incremental harm. Those benefits and harms should be considered at the individual, family, and societal levels.

[375] SACGHS. *Coverage and Reimbursement of Genetic Tests and Services.* February 2006. Available at http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf. Accessed on June 28, 2007.

The analytic validity and clinical validity of tests are important prerequisites for assessing clinical utility. Until the clinical utility and value are known, however, the use of a test is at best conjectural. Some laboratory testing has achieved extraordinary levels of precision and tests frequently have high analytic sensitivity and specificity. The clinical utility, however, is often inadequately documented, which leads to a poor understanding of which tests should be ordered and how results can be applied.

Since there is a harm associated with almost every clinical intervention, it is important to understand the health-related benefits that can result from appropriate clinical diagnosis and intervention and evaluate whether the expected benefits are likely to exceed the harms, and for whom. Harms, at a minimum, will include the time and cost incurred as a result of the intervention. The challenge is to have sufficient information to determine the magnitudes of expected benefits and harms. Ideally, findings from well designed and suitably conducted research that addresses important clinical and public health issues are used in evidence-based processes to determine the most appropriate clinical and preventive practices.

Currently, much of clinical practice is not based on high-quality evidence or evidence-based assessments, and even the promulgation of evidence-based guidelines is often limited in scope and speed of implementation. For single-gene disorders, high-quality clinical studies and evidence-based guidelines are even less common. The most rigorous evidence-based assessments reflect both the magnitude of effect and certainty of the evidence. These assessments are conducted by organizations such as the U.S. Preventive Services Task Force (USPSTF) and the Grading of Recommendations Assessment, Development and Evaluation Working Group and are generally restricted to common disorders and interventions. As a result, reaching that level of rigor is a challenge for many clinical decisions, particularly in genetics. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) process is an attempt to bring that level of rigor to genetic testing in a timely way.

Assessment of scientific evidence and development of evidence-based clinical guidelines have been used not only to inform clinical management, but also insurance coverage decisions, quality improvement initiatives and policy decisions. Guidelines provide general recommendations that need to be integrated with specific patient needs and preferences. Since providers and patients are not always comfortable with guidelines, they may disregard them if the guidelines fail to endorse popular practices. In many cases, insurance coverage decisions may be influenced more by employers' willingness to pay for services, provider/consumer demand, and what is considered “standard of care” than by evidence-based clinical guidelines or evidence reviews.

Clinical Utility and Value

In this report, clinical utility for clinical decisionmaking is defined as the balance between the benefits and harms of testing and the ensuing follow-up evaluation, treatment, or prevention. Clinical utility must be evaluated within a specific context, including the clinical variables, availability of resources, acceptability and values, and patient preference.[376] Moreover, the same genetic test can be used in very different ways (e.g., for population or family screening, risk assessment, diagnosis, or prognosis) and its utility may vary depending on available alternatives. While the test may have adequate utility in one situation, it may not in another. For example, the clinical utility of BRCA1 and BRCA2 testing is established for women with a family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in the BRCA1 or BRCA2 gene.[377,378] BRCA1 and BRCA2 testing in the

[376] Lomas J, Culyer T, McCutcheon C, McAuley L, Law S. *Conceptualizing and Combining Evidence for Health System Guidance*, May 2005. Available at http://www.chsrf.ca/other_documents/pdf/evidence_e.pdf. Accessed on June 28, 2007.

[377] U.S. Preventive Services Task Force. (2005). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation Statement. *Annals of Internal Medicine*. 143: 355-361.

general population, however, is not recommended because of the low risk for developing breast or ovarian cancer associated with BRCA1 or BRCA2 mutations in the absence of a family history of these cancers.

Once clinical utility has been assessed, the critical issue becomes how to translate the certainty and net benefit of the test into specific decisions. Decisionmakers such as regulators, payers, patients and providers, place different emphasis on various factors.[379] Table 1 illustrates some of the factors these decisionmakers may consider.

Table 1. Considerations for the Application of Clinical Utility by Type of Decisionmaker

Decisionmakers	Factors Considered
Public Health	Effectiveness Safety Comparative effectiveness Cost and cost-effectiveness Population characteristics Legal and ethical considerations Social preferences Feasibility
Payers	Effectiveness Comparative effectiveness Cost and cost effectiveness Clinical situation (e.g., population tested, stage of illness, natural history of condition, test purpose (e.g., prediction/predisposition, prevention, diagnosis, treatment, monitoring)) Legal and ethical considerations (e.g., precedent, malpractice, Federal and State laws and regulations) *To a lesser extent:* Patient values and preferences Feasibility (e.g., infrastructure requirements) Stakeholder interests
Clinical Guideline Developers	Safety Efficacy Effectiveness Comparative effectiveness Clinical situation *To a lesser extent:* Legal and ethical considerations Feasibility
Quality Improvement Organizations	Effectiveness

[378] U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation Statement. 2005. See http://www.ahrq.gov/clinic/uspstf05/brcagen/brcagenrs.htm. Accessed on August 6, 2007.

[379] Teutsch S. Issues in Adjusting the Evidence Framework to Decision Needs. Presentation during the Institute of Medicine Workshop, *Judging the Evidence: Standards for Determining Clinical Effectiveness*, February 5, 2007, Washington, DC. Available at http://www.iom.edu/Object.File/Master/40/367/Steve%20Teutsch.pdf. Accessed on June 28, 2007.

	Clinical situation Administrative options (e.g., tools for targeting or limiting use to those most likely to benefit) Feasibility
Patients, Families and Providers	Effectiveness Cost and cost effectiveness Clinical situation Values and preferences

The assessment of clinical utility presumes that a minimum threshold of analytic and clinical validity has been established. Without an analytically valid test that accurately predicts disease or treatment outcomes, it is unlikely that clinical utility can be established. Nonetheless, important clinical and reimbursement decisions often are made on the basis of analytical and clinical validity before evidence regarding clinical utility is established. By the same token, it is easy to imagine that the evidence required to bring a product to market may differ substantially from what is needed to include that test in clinical guidelines, and may further differ from that needed for reimbursement decisions. Therefore, one needs to consider where to "set the bar" in terms of net benefit and certainty of that net benefit for each situation. A taxonomy of decisions is lacking, however, along with agreement on the level of evidence needed for net benefit and certainty, and the types of study designs that would suffice for each decision.[380] Such a taxonomy could provide guidance on the types of studies that are best suited for each situation, help shape research priorities, and provide guidance as to their appropriate use given the State of knowledge.

In general, systems and considerations for assessing the clinical utility of genetic tests do not differ substantially from other technologies. They are, however, a harbinger of issues that the healthcare system will be facing. Hence, confronting these challenges can help to address other medical issues. Though not unique to genetic testing, the issues that these technologies raise include the following:

An information explosion. The number of genetic variants, their penetrance, genetic pleiotropy, polygenic interactions, and interactions with individual behaviors and environmental exposures pose enormous challenges to understanding all the information and integrating it so that clinical utility is realized at the population as well as individual level. Because these challenges could be an overwhelming task, they need to be managed intelligently.

Medicalization. As more genetic risk characteristics are identified, there is likely to be increased medicalization of previously unknown conditions and risk factors linked to important health conditions. In hyperlipidemia, for example, low density lipoprotein (LDL) cholesterol thresholds for high-risk individuals have been decreased to a target as low as 70 mg/dL, well below what was previously considered "normal." The consequence is that many more individuals now have a medical condition (hyperlipidemia) that will lead to clinical management.

Timeliness. Capitalizing on all the information and making new knowledge available in a timely manner will continue to be challenging. The more time that passes between clinical availability of a test and evidence of clinical utility, the more likely practice patterns of use will be established and hard to modify, as was seen with routine chest X-ray and Venereal Disease Research Laboratory (VDRL) screening.

[380] Teutsch S.M., Berger, M.L., and Weinstein, M. (2005). Comparative Effectiveness: Asking the Right Question. Choosing the Right Method. *Health Affairs* 24:128-132.

Rare conditions. Single-gene high penetrance conditions are typically rare, and the challenges associated with these have been discussed in other reports[381]. The need for personalized health care is likely to expand with improved knowledge of population subgroups that are at risk for genetic conditions, respond differentially to therapy, or require tailored follow up. Subgroups that are large enough can be studied with traditional clinical epidemiologic methods. On the other hand, such studies for rare conditions may be impractical. Systems for managing those conditions will also be needed.

Need for methods development. Clinical utility is generally established by clinical trials and observational studies conducted specifically for that purpose. The large number of de novo studies and evidence syntheses that would be required to provide comparable evidence for the burgeoning number of gene-based technologies and clinical issues may not be practical. It may be necessary to prioritize such evaluations. Other methods to assess utility of laboratory tests using postmarketing strategies are also needed, such as making inferences on the basis of pathophysiologic mechanisms and using vast databases that may emerge from electronic health records (EHRs) or other information systems.

Family, community, and social consequences. Although not unique to genetic testing, the clinical utility of genetic tests for families, communities, and society has ethical and social consequences that cannot be ignored. For example, there is potential for stigmatization among population subgroups that are targeted for screening of genetic disorders or genetic variants that occur with a higher frequency within these subgroups compared to the general population. These issues will need to be systematically addressed as part of clinical utility.

Development of Evidence of Clinical Utility

There are several existing processes to generate evidence of clinical utility. The first step in evaluating the impact of a genetic test is to understand the natural history of the underlying disease or condition and the clinical validity of the test in predicting or diagnosing that disease or condition. This evaluation is typically done through longitudinal epidemiology studies typified by cohort studies funded by the National Institutes of Health (NIH), case-control studies, and global integration efforts, such as the Human Genome Epidemiology Network (HuGENet™),[382] which is sponsored by the Centers for Disease Control and Prevention (CDC). The next step is to evaluate the impact of interventions that occur as a consequence of genetic testing.

Although individual studies assess efficacy or effectiveness to varying degrees, clinical utility is primarily concerned with effectiveness. Efficacy outcomes (often short-term surrogate outcomes) are measured in an ideal-world setting, whereas effectiveness outcomes (often long-term health outcomes) are measured in a real-world setting in which variations in provider training, education, and skills affect appropriate choice and delivery of an intervention. Other factors, such as the affected individual's age and sex, access to intervention, adherence to an intervention, presence of co-morbidities and other treatments, dietary and behavioral activities, cost of the intervention, and other factors also may have a large impact on the outcomes. FDA's use of the term "effectiveness", as in the phrase "drugs are safe and effective," corresponds to this report's use of the word "efficacy."

[381] Sanderson, S., Zimmern, R., Kroese, M., Higgins, J., Patch, C., and Emery, J. (2005). How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. *Genetics in Medicine*. 7(7): 495-500.

[382] Centers for Disease Control and Prevention, Human Genome Epidemiology Network (HuGENet™). See http://www.cdc.gov/genomics/hugenet/default.htm. Accessed on August 1, 2007.

Data on therapies are typically generated by pharmaceutical and biotechnology companies to gain FDA approval, though some interventions could be lifestyle modifications to improve diet, decrease tobacco use, and increase physical activity. Typically, these studies are randomized controlled trials (RCTs) that focus on surrogate, short-term outcomes in select patient populations, making it difficult to understand the applicability of these results in the general population. Thus, these studies often have good internal validity but poor external validity or applicability. Additionally, these studies are not designed to evaluate rare or long-term outcomes. These deficiencies have lent support for conducting practical clinical trials (also called large simple trials) with large sample sizes, broad inclusion criteria, and modest data collection leading to estimates of effectiveness in typical care settings.[383, 384] Many practical clinical trials are in the fields of behavioral disorders,[385, 386] cardiovascular disease,[387] and mental illness.[388, 389, 390] Practical clinical trials are typically funded by NIH, but some are supported by private funding.[391]

As relatively few practical clinical trials have been conducted, the relevant data are often collected through observational studies using existing data sources, such as insurance claims or electronic medical records. These studies are necessarily performed after the test or intervention has been released into clinical practice. Such studies can be funded by Federal agencies, such as the Agency for Healthcare Research and Quality (AHRQ), the Department of Veterans Affairs (VA), CDC and NIH, or private sources, such as pharmaceutical companies or health plans. While this method is less costly, it has some drawbacks, since there are limited study design options to control for bias with data that have already been collected.[392] For example, the Oncotype DX®[393] test entered the clinical market based on retrospective analyses,[394] but Kaiser of Northern California is still conducting a 5-year prospective study of this test.

Most studies measuring the clinical utility of genetic tests are conducted in the premarket approval phase and there is often less evidence generated in the postmarket phase. Lack of postmarket evidence constrains the ability to understand the impact of tests and therapies after they enter clinical and public health practice. Even beyond the area of genetic testing, there is a recognized need for more postmarket research and surveillance, particularly in the area of safety, where there have been high-profile examples

[383] Glasgow, R.E., Magid, D.J., Beck, A., Ritzwoller, D., and Estabrooks, P.A. (2005). Practical clinical trials for translating research to practice: design and measurement recommendations. *Medical Care*. 43(6): 551-557.

[384] Tunis, S.R., Stryer, D.B., and Clancy, C.M. (2003). Practical clinical trials: increasing the value of clinical research for decisionmaking in clinical and health policy. *JAMA*. 290(12): 1624-1632.

[385] Weiss, M.D., Gadow, K., and Wasdell, M.B. (2006). Effectiveness outcomes in attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*. Suppl 8: 38-45.

[386] Glasgow, E., Davidson, K.W., Dobkin, P.L., Ockene, J., and Spring, B. (2006). Practical behavioral trails to advance evidence-based behavioral medicine. *Annals of Behavioral Medicine*. 31(1): 5-13.

[387] Strandberg, T.E., Pitkala, K.H., Berglind, S., Nieminen, M.S., and Tilvis, R.S. (2006). Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine I the Elderly (DEBATE) study: a randomized, controlled trial. *American Heart Journal*. 152(3): 585-592.

[388] Perkins, D.O. (2006). Clinical trials in schizophrenia with results for the real world. *CNS Spectrums*. 11(7 Suppl 7): 9-13.

[389] March, J.S., Silva, S.G., Compton, S., Shapiro, M., Califf, R., and Krishnan, R. (2005). The case for practical trials in phychiatry. *American Journal of Psychiatry*. 162(5): 836-846.

[390] March, J.S., Silva, S.G., Compton, S., Anthony, G., DeVeaugh-Geiss, J., Califf, R., and Krishnan, R. (2004). The Child and Adolescent Psychiatry Trials Network (CAPTN). *Journal of the American Academy of Child and Adolescent Psychiatry*. 43(5): 515-518.

[391] Hahn, D.L. and Plane, M.B. (2004). Feasibility of a practical clinical trial for asthma conducted in primary care. *The Journal of the American Board of Family Practice*. 17(3): 190-195.

[392] Manolio, T.A., Bailey-Wilson, J.E., and Collins, F.S. (2006). Genes, Environment and the Value of Prospective Cohort Studies. *Nature Reviews Genetics*. 7(10): 812-20.

[393] *Genomic Health: Oncotype DX Breast Cancer Assay.* Available at http://www.genomichealth.com/oncotype/default.aspx. Accessed on June 24, 2007.

[394] Paik, S., Shak, S., Tang, G., Kim, C., Baker, J., Cronin, M., Baehner, F.L., Walker, M.G., Watson, D., Park, T., Hiller, W., Fisher, E.R., Wickerham, D.L., Bryant, J., and Wolmark, N. (2004). A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *New England Journal of Medicine*. 351:2817-26.

of product recalls and changes to labeling.[395] In addition to harms to patients, harms may be incurred by practitioners, industry, and society through lawsuits, withdrawal of medication, resources spent on medications, treatment of complications, and the resultant impact on families and businesses.

From a practical standpoint, understanding the clinical utility of an intervention requires an assessment of the balance of benefits and harms in outcomes in order to guide decisions on its use. The outcomes of interest are determined by the disease or condition as well as the clinical intervention, setting, perspective and purpose. The outcomes of interest may be categorized into different types: health, surrogate (or intermediate), process, efficiency, and quality. This report will focus on many of the health-related outcomes as described in Table 2, which summarizes an outcomes lexicon developed by the EGAPP Working Group. Some of these outcomes, however, are outside the scope of this report. The appropriate choice of an outcome depends on the perspective and context of the decisionmaker. A broad range of examples of surrogate and health outcomes for some common and rare conditions are provided in Table 3. For the purposes of this report, however, the focus is on outcomes related to the clinical management of individuals.

Table 2. Examples of Types of Health-Related Outcomes[396]

Potential Outcomes	Examples
Diagnostic Thinking/ Health Information Impact	Ending diagnostic odyssey Knowledge of prognosis/disease course Long-term planning Distress (increased or decreased) Satisfaction with testing services Increased/decreased sense of control Stigmatization or discrimination Incidental information (unwanted information) Changes in family dynamics Cultural, ethnic identity
Therapeutic Choice	Changes in preventive or therapeutic strategies Adherence to therapeutic regimen Satisfaction with treatment choice Health behavior (test recipients)
Patient Outcomes Impact	Mortality Morbidity Change in response to therapy Incidence of adverse outcome(s) following testing Severity of adverse outcome(s) following testing Health-related quality of life Pregnancy termination decisions Prenatal interventions
Familial and Societal Impact	Impact on health disparities Healthcare utilization by family members Disabilities perspective Fostering genetic determinism in society

[395] Committee on the Assessment of the US Drug Safety System. Baciu A, Stratton K, Burke SP (e*ds*). *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: National Academies Press, 2007.

[396] Botkin, J.R., Teutsch, S., Kaye, C.I., Hayes, M., Bradley, L.A., Szegda, K., and Dotson, W.D. on behalf of the EGAPP Outcomes Working Group. Outcomes of interest in evidenced-based evaluations of genetic tests. Manuscript in preparation.

	Eugenics attitudes in society Technology innovation Population health interventions

Table 3. Examples of Health and Surrogate Outcomes for Specific Conditions

Indication for Testing	Gene/ Marker	Surrogate Outcomes	Health Outcomes
Familial adenomatous polyposis	APC	Colorectal polyps	Colorectal cancer mortality Quality of life
Alpha 1-antitrypsin (AAT) deficiency	SERPINA1	Serum AAT levels Loss of lung tissue measured by computed tomography (CT) scan	Shortness of breath Morbidity and mortality from cirrhosis
Chronic myelogenous leukemia	BCR, ABL	BCR-ABL level White blood cell (WBC) level	Mortality Morbidity from suppressed immunity
Warfarin treatment	VKORC1, CYP2C9	International normalized ratio (INR) level	Mortality and morbidity from insufficient anticoagulation (stroke and pulmonary embolism) or over anticoagulation (hemorrhage)

To support evidence development, AHRQ and CDC are jointly conducting a needs assessment of existing systems and databases for monitoring the utilization and outcomes of gene-based applications, including tests and related interventions in the U.S. healthcare system.[397] This assessment, expected in May 2008, will identify characteristics of an optimal database or linkages between databases that would enable assessment of utilization and outcomes of gene-based applications, inventory existing databases and assess their strengths and limitations in identifying outcomes, and provide options for ascertaining outcomes of gene-based applications.

Assessment of Evidence of Clinical Utility

An important premise of clinical utility is that each intervention has predictable and unpredictable consequences that can either be beneficial or have the potential to cause harm. Therefore, an assessment of benefits and harms is necessary prior to recommending use of an intervention to ensure that effective interventions are provided and that harmful or ineffective ones are not.

Evaluation of the evidence and decisionmaking involves two separate steps. Recognizing that there are tradeoffs between timeliness and rigor, the first step is a systematic, explicit, transparent, rigorous, and reproducible evidence assessment, accomplished through a systematic evidence review (SER) as part of a technology assessment (TA). SERs are useful for clarifying the variety of evidence sources and quality of data and identifying gaps in the evidence to prioritize research. They provide information about clinical and/or economic benefits and harms of interest to stakeholders. In addition, TAs often examine the social, ethical, and economic implications of the development, diffusion, and use of technologies. Table 4 provides examples of organizations conducting SERs and TAs.

[397] Agency for Health care Research and Quality. Needs Assessment to Establish an Infrastructure for Monitoring the Utilization and Outcomes of Gene-Based Applications in the United States Health Care System (Research Abstract). See http://effectivehealth care.ahrq.gov/reports/topic.cfm?topic=0&sid=29&rType=2. Accessed on August 13, 2007.

Table 4. Examples of Organizations Conducting SERs and Technology Assessments

Groups Performing SERs/TAs	Funders	Purpose
Evidence-Based Practice Centers (EPC)[398]	AHRQ/CDC	Reviews all relevant scientific literature on clinical, behavioral, and organizational and financing topics to produce evidence reports and technology assessments. These reports are used to inform and develop coverage decisions, quality measures, educational materials and tools, guidelines, and research agendas.
The Cochrane Collaboration[399]	International independent not-for-profit organizations	Cochrane Reviews investigate the effects of interventions for prevention, treatment and rehabilitation in a healthcare setting. Most Cochrane Reviews are based on RCTs, but other types of evidence may also be taken into account if appropriate.
Technology Assessment Organizations associated with or used by third-party payers	Blue Cross Blue Shield, Technology Evaluation Center, ECRI[400], Hayes, Drug Effectiveness Review Project	Provide healthcare decisionmakers with timely, rigorous, and credible assessments that synthesize the available evidence on the diagnosis, treatment, management and prevention of disease.

The second step in assessing clinical utility is an evidence-based decisionmaking process. Ideally, the evidence assessment is done by a team independent of decisionmakers, such as clinical guideline development panels or advisory committees. Although the two steps are closely linked, they are usually independent. The outcomes of interest and scope of review is clarified by the decisionmakers, the evidence assessment is done by the evidence-review team, and the balance of benefits and harms is determined by the decisionmakers.[401] EGAPP and USPSTF are existing processes that incorporate these steps into the assessment of clinical utility. For example, the EGAPP Working Group commissions evidence reports to independent review teams or evidence-based practice centers, specifying and outcomes of interest and providing input through participation in technical expert panels. The subsequent EGAPP Working Group recommendation Statements are developed independently of the evidence review team but with direct linkage to the evidence. Realistically, this separation frequently does not occur, particularly in the realm of genetic testing for rare disorders. Table 5 gives examples of several existing guideline developers that create clinical guidelines based on an evaluation of clinical utility.

Table 5. Examples of Groups That Develop Guidelines

[398] Agency for Health care Research and Quality, Evidence-based Practice Centers (EPC). See http://www.ahrq.gov/clinic/epc/. Accessed on August 1, 2007.
[399] The Cochrane Collaboration. See http://www.cochrane.org/index.htm. Accessed on August 1, 2007.
[400] ECRI Institute. See http://www.ecri.org/. Accessed on August 1, 2007.
[401] Teutsch, S. and Berger, M. (2005). Evidence Synthesis and Evidence-Based Decisionmaking: Related, But Distinct Processes (editorial). *Medical Decisionmaking*. 25:487-9

Guideline Developers	Supporter	Purpose	Process for Development
Consensus development panels[402]	NIH	• Evaluates the available scientific information on a biomedical issue • Develops a Statement that advances understanding • Useful to health professionals and the public	• Broad-based, independent panel of experts considers information provided by experts and the public • Composes a Statement to address a set of predetermined questions.
USPSTF[403]	AHRQ	• Evaluates the benefits of individual services based on age, gender, and risk factors for disease; • Makes recommendations about which preventive services should be incorporated into primary medical care and for which populations.	• Systematically assembles and reviews the evidence, estimates the magnitude of benefits and harms for each preventive service • Determines the net benefit for each preventive service, secures external reviews • Issues a recommendation
EGAPP Working Group[404]	CDC	• Seeks to develop a sustainable process for evaluating genetic tests and other genomic applications using an evidence-based approach • First reports from this group will be released in 2007 • Only group with a focus exclusively on the evaluation of genetic tests	• Establishes methods and processes • Prioritizes and selects topics for review based on systematic evidence reviews • Develops and publishes conclusions or recommendations • Provides guidance and feedback on other project activities.
Clinical Efficacy Assessment Project[405]	American College of Physicians	• Reviews the clinical literature on a specified topic • Presents information so that practitioners can readily determine the usefulness of diagnostic tests, procedures, or treatments	• Systematically reviews the literature, • Seeks critical review • Develops a manuscript and guideline
Guideline Panels	Professional specialty societies	• Most common mechanism for creating practice guidelines. • Groups consist primarily of "decision makers" • Can potentially reflect practitioner bias	• Make recommendations based on varying levels of literature review and expert opinion.

[402] NIH Consensus Development Program. See http://consensus.nih.gov/. Accessed on August 1, 2007.
[403] AHRQ U.S. Preventive Services Task Force (USPSTF). See http://www.ahrq.gov/clinic/uspstfix.htm. Accessed on August 1, 2007.
[404] Evaluation of Genomic Applications in Practice and Prevention (EGAPP). See http://www.egappreviews.org/. Accessed on August 1, 2007.

When ascertaining the strength of evidence for a key question or domain, the evidence assessment should take into account the quality, quantity, and consistency of studies and attempt to ascertain the magnitude of benefits and harms. Attention should also be paid as to whether the intervention or test was studied in conditions or situations that are the same as, or similar to, the proposed clinical application. Studies can be ranked on these characteristics based on the study design and methodology. RCTs are usually placed at the top of the hierarchy, since they have the least potential for bias and confounding, minimizing the potential for making erroneous conclusions. Case reports and expert opinions are typically placed at the bottom of the hierarchy, since they have the greatest potential for making an erroneous conclusion. Observational studies, such as cohort and case-control studies, are somewhere in the middle of the hierarchy. The study population, clinical setting, duration, primary outcomes evaluated, and conduct of a study also influence the conclusions drawn from study findings and, thus, are important in determining the strength of evidence. A well-designed and well-executed nested, case-control study can provide more definitive results than a poorly designed RCT. Additionally, a study that more accurately models the application of the test or intervention in a "real-world" delivery system might provide more relevant information about the effectiveness of the test or intervention than a highly controlled RCT. The gap between theoretical efficacy and practical effectiveness can be large, with concomitantly smaller net benefit in real-world practice.

Types and Levels of Evidence Considered

- *Study designs*. Experimental (trial), observational, prospective, retrospective, cohort, case-control, cross-sectional, case series
- *Purpose*. Hypothesis-generating or hypothesis-testing; magnitude of effect size and degree of precision needed; coverage or regulatory decision; State-mandated (newborn screening) or not
- *Levels*. Strength of evidence for a key question or issue can be good/fair/poor depending upon study design, execution and applicability to question (includes population being studied, type of test/therapy and details of its administration, outcomes, comparator, setting)
- *Magnitude of benefits and harms*. Screening/prevention or treatment

Guideline developers examine the strength of evidence and magnitude of benefits and harms to assess the magnitude of net benefit and degree of certainty of the magnitude. Focus is placed on evidence of the intervention's impact on clinically relevant health outcomes, such as mortality, morbidity, and quality of life. They typically consider the impact of an intervention on surrogate markers, such as biochemical or metabolic changes, only when the link between the surrogate marker and a health outcome is well-established. Formulation of guidelines for a broad population often requires extrapolation and generalization of the evidence.

While the principles of evidence-based guidelines are well established, they have only recently been adapted specifically to genetic testing by EGAPP[406] and ACCE.[407, 408] For example, evidence-based reviews usually contain a description of the condition's natural history, as well as current management

[405] American College of Physicians Clinical Efficacy Assessment Subcommittee. See http://news.acponline.org/clinical/guidelines/intro.htm. Accessed on August 1, 2007.

[406] CDC Website: National Office of Public Health Genomics. Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach. See http://www.cdc.gov/genomics/gtesting/egapp.htm. Accessed on June 24, 2007.

[407] Gudgeon, J.M., McClain, M.R., Palomaki, G.E., and Williams, M.S. (2007). Rapid ACCE: experience with a rapid and structured approach for evaluating gene-based testing. *Genetics in Medicine*. 9(7): 473-478.

[408] CDC Website: National Office of Public Health Genomics. ACCE Model System for Collecting, Analyzing, and Disseminating Information on Genetic Tests. See http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm. Accessed on August 14, 2007.

options; the EGAPP and ACCE processes have adapted these concepts to apply to genetic tests. Additionally, virtually no laboratory test is perfectly predictive of a condition or an outcome. In genetics, even a test that perfectly predicts a genotype may not predict the phenotype, which is what is clinically important, because of variable penetrance and expressivity.

A scarcity of evidence can have extraordinary consequences on the healthcare system. For example, autologous bone marrow transplantation for advanced breast cancer came into widespread use following a massive legal settlement despite the lack of evidence of effectiveness. Ultimately, the procedure was found to be ineffective and rapidly fell into disfavor, but countless women suffered needlessly and the cost to the healthcare system was massive.[409]

The Clinical Utility Spectrum

Currently, the degree to which clinical utility is established for various genetic tests varies widely. The widespread use and regulation of these tests often varies according to the type of test and the populations or conditions with which they are associated. The following examples illustrate a spectrum of evidence for clinical utility and associated challenges when evidence of utility is incomplete.

Tests with Proven Clinical Utility

The test for HER2/neu, or human epidermal growth factor receptor 2, is an example of a necessary test linked to a treatment with proven clinical utility. The HER2/neu receptor, which is produced from the ERBB2 gene, is involved in cell growth. Herceptin™ (trastuzumab) is a cancer drug that specifically targets the HER2/neuroceptor to inhibit its signaling pathway. The genetic test is used to identify HER2/neu-positive patients who would receive benefit from the drug and predict response to therapies such as hormone therapy and chemotherapy.[410, 411] In this case, the benefits of this test for the HER2/neu-positive subset of patients far outweigh the harms; the survival benefit has been quantified, and studies have demonstrated cost-effectiveness.[412, 413, 414] Postmarket studies continue to refine this application.

Mandated Tests and Uncertain Clinical Utility

Newborn screening, which is mandated in all States, is conducted for a panel of genetic disorders. The best-known example is the test for phenylketonuria (PKU). Early detection and treatment of PKU prevents the mental retardation associated with this disorder. Although the panel for newborn screening is determined at the State level, many States screen for the 29 disorders recommended in the American College of Medical Genetics (ACMG) report to the Health Resources and Services Administration (HRSA).[415] To be included in the panel recommended by ACMG, there must be "demonstrated benefits

[409] Rettig, R.A., Jacobson, P.D., Farquhar, C.M., and Aubry, W.M. False Hope: Bone Marrow Transplantation for Breast Cancer. New York: Oxford University Press, 2007.

[410] *Lab Tests Online: A Public Resource on Clinical Lab Testing From the Laboratory Professionals Who Do the Testing*. Available at http://www.labtestsonline.org/understanding/analytes/her2neu/test.html. Accessed on June 24, 2007.

[411] Colozza, M., de Azambuja, E., Cardoso, F., Bernard, C., and Piccart, M.J. (2006). Breast cancer: achievements in adjuvant systemic therapies in the pre-genomic era. *Oncologist*. 11(2): 111-125.

[412] Kurian, A.W., Thompson, R.N., Gaw, A.F., Arai, S., Ortiz, R., and Garber, A.M. (2007). A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. *Journal of Clinical Oncology*. 25(6): 634-641.

[413] Liberato, N.L., Marchetti, M., and Barosi, G. (2007). Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer. *Journal of Clinical Oncology*. 25(6): 611-613.

[414] Millar, J.A. and Millward, M.J. (2007). Cost effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a lifetime model. *Pharmacoeconomics*. 25(5): 429-442.

[415] Health Resources and Services Administration. *Newborn Screening: Toward a Uniform Screening Panel and System*. 2005. See http://mchb.hrsa.gov/screening/. Accessed on August 1, 2007.

of early detection, timely intervention and efficacious treatment of the condition being tested,"[416] although there is considerable disagreement about the standard of clinical utility and value of information that should be used.[417, 418] Furthermore, cost-effectiveness for several disorders included in newborn screening panels has been demonstrated.[419]

Rare Disease Testing and Emerging Evidence of Utility

People affected by rare inherited diseases may want information that is provided by genetic testing. The small market for these tests, however, limits their translation from research laboratories to clinical practice. When genetic tests for rare diseases are offered in research settings, CLIA regulations prohibit the return of results to patients. In clinical settings, most clinical laboratories performing rare genetic disease testing have limited monetary and personnel resources for the development of new tests and lack resources for data collection and development of educational materials, although many laboratories see this as the role of the clinician, not the laboratory. There also are issues with proficiency testing and quality assurance as previously discussed in Chapter 3. Finally, the ability to conduct clinical trials to assess the impact of testing on medical outcomes is limited by small numbers of patients and tests. For almost all rare genetic disorders, randomized trials of effectiveness are not conducted for practical reasons. All these factors contribute to decreased access to potentially useful tests. Identification of individuals with rare disorders through genetic testing could facilitate earlier diagnosis and referral to experts, and reduce or increase anxiety about the condition for the patient or the family.

The NIH Office of Rare Diseases and CDC established a pilot program to address these issues. As previously mentioned in Chapter 3, the Collaboration, Education, and Test Translation (CETT) program is a partnership between clinicians, laboratorians, researchers, and advocacy groups. Applicants provide information on the performance of the test (analytic validity), the clinical setting for which the test is appropriate with data supporting the test's use (clinical validity), and evidence concerning how the results of the test will impact the clinical management of the patient or family (clinical utility). In addition, it requires development of patient education materials; provider education materials in the form of a GeneReview;[420] template reports for positive, negative, and variants of unknown significance test results; ongoing collection of clinical data; analysis of these clinical data in the context of the genetic test result (genotype-phenotype correlation); storage of the data in a public database for a minimum of 5 years; and submission of progress reports to the CETT program staff at regular intervals. In return, the CETT program provides funding to assist in the development of a test in a clinical laboratory. While the impact of this type of program is unknown at present, the process may increase the understanding of the clinical utility of rare disease testing and provide solutions that may increase the benefits and reduce the harms.

Controlled Research Environment Versus Routine Clinical Use

Many tests or interventions, including genetic tests, that show a measurable improvement in the outcome of interest in a strictly controlled research environment do not show the same magnitude of effect when

[416] Health Resources and Services Administration. *Newborn Screening: Toward a Uniform Screening Panel and System*, Executive Summary, p. 6. 2005. See ftp://ftp.hrsa.gov/mchb/genetics/screeningdraftsummary.pdf. Accessed on August 1, 2007.

[417] Botkin, J.R., Clayton, E.W., Fost, N.C., Burke W., Murray, T.H., Baily, M.A., Wilfond, B., Berg, A., and Ross, L.F. Newborn Screening Technology: Proceed With Caution. *Pediatrics* 117:1793 - 1799.

[418] Grosse, S.D., Boyle, C.A., Kenneson, A., Khoury, M.J., and Wilfond, B.S. From public health emergency to public health service: The implications of evolving criteria for newborn screening panels. *Pediatrics* 2006;117:923-929.

[419] Grosse, S.D., Teutsch, S.M., and Haddix, A.C. (2007). Lessons from cost-effectiveness research for United States public health policy. *Annual Review of Public Health*. 28:365-391.

[420] GeneTests. See http://www.geneclinics.org/. Accessed on August 1, 2007.

translated into general clinical use. Reasons for this include less rigorous patient selection, expansion of the clinical setting, and variation from the ideal treatment protocol. Adenomatosis polyposis coli (APC) testing for conditions such as familial colorectal cancer can provide definitive information regarding risk for disease development in some patients and families if the test is appropriately interpreted. There are significant problems with misinterpretation of laboratory reports by nongenetics professionals, however.[421] Misinterpretation of results significantly alters the balance between benefits and harms of the test when compared with a setting in which the test is assured of accurate interpretation. So-called natural setting trials have been proposed as a possible way to address this issue.[422]

Pharmacogenomics and Incomplete Evidence of Clinical Utility

Pharmacogenomics addresses the influence of genetic variation on drug response, which can affect drug dosing decisions, effectiveness, and adverse drug reactions (ADRs).[423, 424] In theory, knowing how genetic variations affect pharmacokinetics and pharmacodynamics should allow clinicians to choose the most effective drug with the lowest risk of an ADR. In practice, this can be complicated. For example, a particular polymorphism in the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene predisposes patients to severe toxic reaction to the chemotherapeutic drug, irinotecan.[425] Advanced colorectal cancer patients with this polymorphism appear to be more responsive to chemotherapy, but are at increased risk of an abnormally low level of a type of white blood cells (a disorder known as neutropenia), especially when they receive a high-dose regimen of irinotecan. Since June 2005, the label for this drug warns that homozygosity for this particular polymorphism is a risk factor for severe neutropenia, and patients with this genotype should be treated with a reduced dose of irinotecan.[426] Even if one restricts the consideration of harms and benefits to patients undergoing chemotherapy, the situation is very complex. Identification of those at risk can lead to reduced dosage and less effective treatment or avoidance of the drug altogether. Had they received standard dosing, at-risk patients might sustain the risk of neutropenia, but also the potential for better tumor response. Would an alternative strategy of more frequent monitoring of the white blood count with dosage adjustment or treatment regimens that do not include irinotecan provide more utility than the genetic test? There are other permutations of this discussion that can be found in an upcoming EGAPP evidence report on this issue.[427]

Another topical example is CYP2C9 and VKORC1 testing for dosing of warfarin. In the United States, as many as a million people a year are started on this drug, but according to the FDA Adverse Event Reporting System, warfarin is among the 10 drugs with the largest number of serious adverse event reports submitted during the 1990 and 2000 decades.[428] Three polymorphisms seem to account for most of the genetic variability; however, these genetic factors account for at most 40 percent of the attributable risk for an adverse event. Other factors, such as weight, gender, renal function and other drugs, account for another 30 percent of the risk. Even if one combines all the known genetic and clinical factors, 30-40

[421] Giardello, F.M. (1997). Genetic testing in hereditary colorectal cancer. *JAMA*. 278(15):1278-81.
[422] Freund, C.L., Clayton, E.W., and Wilfond, B.S. (2004). Natural Settings Trials- Improving the Introduction of Clinical Genetic Tests. *The Journal of Law, Medicine, and Ethics*. 32(1):106-10.
[423] National Institute of General Medical Sciences. Frequently asked questions about pharmacogenetics. See http://www.nigms.nih.gov/Initiatives/PGRN/Background/pgrn_faq.htm. Accessed on August 6, 2007.
[424] National Center for Biotechnology Information. *One size does not fit all: the promise of pharmacogenomics*. See http://www.ncbi.nlm.nih.gov/About/primer/pharm.html. Accessed on August 6, 2007.
[425] Innocenti, F. and Ratain, M.J. (2004). "Irinogenetics" and UGT1A: from genotypes to haplotypes. *Clinical Pharmacology and Therapeutics*. 75: 495–500.
[426] Innocenti, F. and Ratain M.J. (2006). Pharmacogenetics of irinotecan: clinical perspectives on the utility of genotyping. *Pharmacogenomics*. 7(8): 1211-1221.
[427] EGAPP UGT1A1 Evidence Review (in development)
[428] Wysowski, D.K., Nourjah, P., and Swartz, L. (2007). Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Archives of Internal Medicine*. 167(13): 1414-1419.

percent of the variation in dosing response cannot be predicted. It is also noteworthy that current information focuses on the surrogate outcome, prediction of final dose. While it is reasonable to assume that arriving at the final dose faster should lead to a concomitant reduction in ADRs, this effect has not been demonstrated in clinical trials. Also, if trials do show efficacy, it is important to determine the impact of the turnaround time of the test result. Pharmacogenomic testing may not be feasible in certain clinical settings if test results are needed for the initial dosing decision. Since the cost-effectiveness of this intervention depends on the avoidance of ADRs and incorrect dosing, prevention of even a few ADRs may be difficult to justify, even if the cost of the test is modest. It should be noted that despite these gaps in evidence, CYP2C9 and VKORC1 testing is offered clinically in this country and the test is included in the FDA-approved warfarin label. A discussion of the ethical issues relating to pharmacogenomic testing can be found in Freund and Wilfond.[429] The issue is currently being studied in clinical trials sponsored by AHRQ and NIH.[430]

Tests for Which Information Alone Has Utility

Utility of a test need not be exclusively linked to a medical treatment or intervention. For example, despite the lack of a treatment, genetic testing for Huntington disease, when performed in conjunction with genetic counseling and patient consent, may result in decreased anxiety, opportunities for life-planning and improved quality of life, compared to individuals who choose not be tested, irrespective of whether the test result is positive or negative.[431, 432, 433] The true utility of information alone is difficult to quantify, since many patients do not want to know their test result.[434]

Incomplete knowledge of clinical utility can lead to wasted resources and jeopardize patient care. For example, clinical management could be diverted from effective strategies to those that are uncertain or even harmful. These situations can be characterized as "opportunity costs"—that is, the overall cost of decreasing or eliminating something of proven effectiveness (even if it may not be perfectly effective) to do something for which utility is still questionable.

Tests with incomplete evidence of clinical utility can lead to false expectations, or the fallacy of determinism. For example, some individuals with BRCA mutations who are not from known high-risk kindreds believe it is inevitable that they will develop cancer, even though the risk is far less than 100 percent. Conversely, women from a family with a history of BRCA mutations—but who do not have BRCA mutations themselves—may believe they will never develop breast cancer and do not follow routine surveillance recommendations, even though they still have a 1 in 8 risk of developing cancer (based on data of women born in the United States[435]).

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[429] Freund, C.L., Wilfond, B.S. (2002). Emerging Ethical Issues in Pharmacogenomics. *American Journal of Pharmacogenomics*. 2(4):273-81.

[430] See: (http://crisp.cit.nih.gov/crisp/CRISP_LIB.getdoc?textkey=7133487&p_grant_num=1R01HS016335-01&p_query=&ticket=43898079&p_audit_session_id=259418087&p_keywords=). Accessed September 9, 2007.

[431] Duncan, R.E., Gillam, L., Savulescu, J., Williamson, R., Rogers, J.G., and Delatycki, M.B. (2007). "Holding your breath": interviews with young people who have undergone predictive genetic testing for Huntington disease. *American Journal of Medical Genetics Part A*. [Epub ahead of print.]

[432] Cutler, S.J. and Hodgson, L.G. (2003). To test or not to test: interest in genetic testing for Alzheimer's disease among middle-aged adults. *American Journal of Alzheimer's Disease and Other Dementias*. 18(1): 9-20.

[433] Bookman, E.B., Langehorne, A.A., Eckfeldt, J.H., Glass, K.C., Jarvik, G.P., Klag, M., Koski, G., Motulsky, A., Wilfond, B., Manolio, T.A., Fabsitz, R.R., Leupker, R.V., and NHLBI Working Group. (2006). Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *American Journal of Medical Genetics Part A.* 140(10): 1033-1040.

[434] Hepburn, E.R. (1996). Genetic Testing and Early Diagnosis. *Journal of Medical Ethics.* 22(2):105-10.

[435] Ries, L.A.G, Melbert, D., Krapcho, M., Mariotto, A., Miller, B.A., Feuer, E.J., Clegg, L., Horner, M.J., Howlader, N., Eisner, M.P., Reichman, M., and Edwards, B.K. (eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD. See http://seer.cancer.gov/csr/1975_2004/. Accessed on August 7, 2007.

Available genomic test panels can detect dozens to hundreds or thousands of genetic variations, many of which have no known clinical consequence. Detection of multiple abnormal and unexpected genomic findings is similar to "incidentalomas" that are discovered in radiological studies (when imaging modes report on the area of clinical concern and, incidentally, on other organs in the field of view). These real but incidental findings can lead to aggressive diagnostic procedures and therapies in otherwise healthy people. The cost of genomic medicine can also increase substantially with little benefit to patients.[436]

Emerging genetic knowledge, such as data from genome wide association studies, has the potential to alter the currently large reactive medical paradigm to a proactive one that may optimize health and prevent or minimize medical problems through personalized health care and disease prevention. The medical and public health communities will need to determine and understand the clinical utility of genetic information that is probabilistic, or the era of personalized medicine may never come to pass. Family history is somewhat analogous in that the risk stratification provides probabilistic information of a future event. Studies have shown that this risk information can be conveyed to patients in an understandable fashion and that health behaviors change in response to this information, at least in some patients,[437,438] although individuals are notoriously poor at understanding risks and probabilities.[439]

Gaps and Challenges Concerning the Clinical Utility of Genetic Testing

Lack of Evidence, Assessment Tools, and Evidentiary Standards

As is unfortunately common in medicine, the widespread lack of high-quality evidence of benefit from prevention or treatment interventions is the primary gap in identifying net benefit for individuals who undergo genetic testing.

Clinical validity (discussed in Chapter 4) is an important component in an evidence base. A growing number of genetic tests, however, are inappropriately offered based on genetic association studies that have not been adequately validated. If a genotype does not predict disease phenotypes as depicted by test developers and marketers, the test will not support appropriate management decisions. For example, studies of the gene responsible for classic hemochromatosis (HFE) have cast doubt on claims that HFE mutations associated with hereditary hemochromatosis are associated with elevated risk of serious morbidity and mortality from diseases such as arthritis, diabetes, and heart disease; instead, evidence has focused more narrowly on the elevated risk of liver disease and associated mortality.[440] Consequently, there is doubt about the clinical utility of population screening for HFE mutations or iron overload phenotypes, even though phlebotomy is an effective and inexpensive treatment for established disease. To respond to this gap in knowledge, independent funding of large-scale studies of genotype-phenotype associations is essential.

Assuming that analytic validity and clinical validity are established, another gap in knowledge is a comparison of outcomes with and without intervention. Randomized trials are rarely available, and even

[436] Kohane, I.S., Masys, D.R., and Altman, R.B. (2006). The incidentalome: a threat to genomic medicine. *JAMA*. 296(2): 212-215.

[437] Katapodi, M.C., Lee, K.A., Facione, N.C., and Dodd, M.J. (2004). Predictors of perceived breast cancer risk and the relation between risk and breast cancer screening: a meta-analytic review. *Preventive Medicine*. 38(4): 388-402.

[438] Siddiqui, A.A., Patel, A., and Huerta, S. (2006). Determinants of compliance with colonoscopy in patients with adenomatous colon polyps in a veteran population. *Alimentary Pharmacology and Therapeutics*. 24(11-12): 1623-1630.

[439] Viscusi, W.K. (1998). Rational Risk Policy. Oxford: Clarendon Press.

[440] Whitlock, E.P., Garlitz, B.A., Harris, E.L., Beil, T.L., and Smith, P.R. (2006). Screening for Hereditary Hemochromatosis: A Systematic Review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 145(3):209-23.

when they are, may be underpowered or too short in duration to assess important outcomes or raise questions about external validity. Observational studies are prone to various types of bias, depending on the type of application, such as differential ascertainment and access to care in population screening. It can be costly, however, to collect data, especially for rare diseases. Pilot studies in which testing is provided in one geographic area and not in another, with the same level of clinical care, can be useful if data on outcomes are rigorously collected and estimates are adjusted for potential ascertainment bias. A good example is a recent study of outcomes of medium chain acyl-CoA dehydrogenase deficiency (MCADD) in Australian States with and without newborn screening using tandem mass spectrometry.[441]

Another challenge is when a condition has multiple adverse outcomes for which there is uneven evidence of effectiveness of interventions. Assessment of clinical utility requires not only evaluating the quality of conflicting evidence but also weighting the relative importance of different types of outcomes. For example, newborn screening for cystic fibrosis has been controversial because early identification has not been shown to reverse or even slow the primary pulmonary manifestations of the disease. A CDC review examined the risks and benefits of screening newborns for cystic fibrosis and concluded that there was evidence of moderate net benefit sufficient to endorse screening, but cautioned that screening should be conducted with adequate safeguards to minimize risks of harms.[442, 443] It is unclear, however, whether a nuanced assessment, such as Strength of Recommended Taxonomy (SORT) assessment, can shape the implementation of screening.

Another situation in which assessment of clinical utility can be problematic is where there is a continuum of risk and testing identifies individuals at risk for whom there is little evidence of the effectiveness of interventions to improve outcomes. For example, screening for hemoglobin disorders for the primary purpose of detecting sickle cell anemia has been shown to yield substantial clinical benefits for the primary target group. It is unclear to what extent individuals with other hemoglobin variants benefit from identification and treatment, however. Such issues have largely been ignored in assessments of hemoglobinopathy screening. Because the number of individuals with other variants greatly exceeds the numbers of individuals identified with sickle cell anemia, this is not a minor issue.[444]

Often, tests that have been approved by FDA have sparse information on clinical utility. A recent example is the use of cytochrome P450 (CYP450) testing in patients with depression. Among the clinically available tests to detect CYP450 variation is the FDA-cleared AmpliChip CYP450 test marketed by Roche Diagnostics, which detects variations in the CYP2D6 and CYP2C19 genes. EGAPP, through an AHRQ-sponsored EPC, conducted a review to determine whether testing for CYP450 polymorphisms in adults with nonpsychotic depression prior to treatment with selective serotonin reuptake inhibitors (SSRIs) led to improved outcomes. The researchers found no data that addressed whether testing for these polymorphisms led to an improvement in outcomes, or if testing results were useful in medical, personal,

[441] Wilcken, B., Haas, M., Joy, P., Wiley, V., Chaplin, M., Black, C., Fletcher, J., McGill, J., and Boneh, A. (2007). Outcome of Neonatal Screening for Medium-Chain Acyl-CoA Dehydrogenase Deficiency in Australia: A Cohort Study. *Lancet* 369(9555):37-42.

[442] Grosse, S.D., Boyle, C.A., Botkin, J.R., Comeau, A.M., Kharrazi, M., Rosenfeld, M., Wilfond, B.S., CDC. (2004). Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for State newborn screening programs. *Morbidity and Mortality Weekly Report. Recommendations and Reports.* 53(RR13):1-36.

[443] The National Guideline Clearinghouse. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for State newborn screening programs. See http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=5950&nbr=3919. Accessed on August 14, 2007.

[444] Pass, K.A., Lane, P.A., Fernhoff, P.M., Hinton, C.F., Panny, S.R., Parks, J.S., Pelais, M.Z., Rhead, W.J., Ross, S.I., Wethers, D.L., and Elsas, L.J. (2000). U.S. newborn screening system guidelines II: Follow-up of children, diagnosis, management, and evaluation: Statement of the Council of Regional Networks for Genetic Services. *Journal of Pediatrics.* 137(Suppl):S1-S46

or public health decisionmaking.[445] As new genetic testing technologies are approved and made available for clinical use, it is important to emphasize that FDA clearance or approval is based on test accuracy and evidence of an established link between a particular test result and prediction of clinical phenotype, rather than on demonstration of improved clinical outcomes.[446]

Additionally, as discussed in Chapter 3, many genetic tests are LDTs that have not undergone FDA review and approval prior to availability for clinical use. Thus, it is not uncommon for tests to be covered and reimbursed by insurers without having undergone FDA approval, which hampers development of evidence of clinical utility. Moreover, tests in wide clinical use, such as genetic testing for thrombophilia, frequently lack evidence of clear utility. The most recently published guidelines on antithrombotic therapy for venous thromboembolic disease makes recommendations on how to respond to patients presenting with thromboembolism who have one or more thrombophilic factors, despite sparse evidence.[447] It is likely, as part of value-based purchasing, that diagnostics, procedures, and devices will move to a tiered system similar to drugs, increasing pressure to generate evidence that demonstrate values and potentially lower costs.

Diverse Uses of Genetic Tests

Genetic tests are used for several different purposes, such as diagnosing disease, determining carrier status, helping to predict the risk of developing a particular disorder, providing prognostic information, and guiding therapeutic interventions. The prevalence of the genetic disorder and the varied levels of evidence for genotype-phenotype associations add to the complexity of genetic testing. The diverse uses of genetic tests applied to a range of genetic conditions present different risks, benefits, and oversight challenges, which may require substantially different regulatory approaches and oversight mechanisms. A "one-size-fits-all" oversight framework for all genetic tests may not be appropriate. The United States should continue to move toward a framework of "tailored oversight" that applies variable regulatory requirements and oversight mechanisms to different subclasses of genetic tests.

For rare disorders, it may be inherently infeasible to confirm the clinical utility of genetic tests prior to clinical use. Such tests may need a special framework that lets them be used clinically, subject to ongoing postmarket research requirements and informed consent provisions that require disclosure of the lingering uncertainties.

Assessing the clinical utility of pharmacogenomic tests and other tests that are designed for use in conjunction with another medical product (e.g., with a drug or biologic) can be challenging. As noted by Evans,[448] it may be difficult to characterize the clinical utility of a test, as distinguished from the utility of the drug itself or the drug/test combination. Inconsistent assessments of clinical benefit can create confusion about the appropriate use of pharmacogenomic tests. For example, physicians and their patients face tough dilemmas if FDA has approved a particular test but insurers and Medicare decline to reimburse it. This situation is further complicated if there are several competing tests, particularly if scientific evidence suggests that a newer, non-FDA-regulated test may be more reliable than an older, FDA-

[445] AHRQ. *Testing for Cytochrome P450 Polymorphisms (CYP450) in Adults with Non-Psychotic Depression Prior to Treatment with Selective Serotonin Reuptake Inhibitors (SSRIs).* January 2007. See http://www.ahrq.gov/clinic/tp/cyp450tp.htm. Accessed on August 1, 2007.

[446] Matchar, D.B. (2007). Is genetic testing for cytochrome P450 polymorphisms ready for implementation? *American Family Physician*. 76(3): 348-349.

[447] Albers, G.W, and Caro, .JJ. (2004). Optimizing Oral Anticoagulation in Managed Care. *The American Journal of Managed Care*. 10(14): 474-7.

[448] Evans, B.J. (2006). What will it take to reap the clinical benefits of pharmacogenomics? *Food and Drug Law Journal*. 61(4): 753-794.

approved test. There is a critical need for appropriate, consensus-based methodologies to evaluate the incremental safety, therapeutic, and economic benefits of using genetic tests to target drug and biologic therapies.

Labeling is an important clinical decisionmaking tool in determining the appropriate use of medical products. Genetic tests used in conjunction with drug interventions also raise issues of how to label both of the companion products to promote appropriate joint use of the test and the therapeutic product. A current example is HER2/neu testing to assess whether patients would benefit from treatment with the cancer drug Herceptin™. Genetic tests that are used alone, in the sense of not directing the use of another therapeutic product, do not raise the same labeling issues. An analysis by Evans raises several concerns.[449] Because these genetic tests can be used to direct treatment decisions, they are inevitably linked to the clinical practice of medicine and raise issues of how to draw the line between the regulation of medical products and regulation of medical practice. A key concern is to protect patients from unreliable tests and misleading claims about what the tests can do. Product labeling has been FDA's first-line of communication for indicated uses, instructions, and warnings. Traditional labeling may not be able to fulfill this role in the case of genetic tests that are used in conjunction with drugs or other biologic therapies. Clinicians need clear and timely instructions on how to target drugs, but there has been wide variation in this information in the drug/test products that FDA has approved. For example, the HER2/neu test and Herceptin™ are expressly cross-labeled for use together; the drug label identifies specific tests and provides information on how to vary prescribing based on test results.[450] For other drugs, labeling merely notes that patient response may vary based on genetic factors but provides no specific information about testing and interpretation of results.[451]

Off-label use of drug/test products also presents another complex set of issues. Off-label use may pertain to the drug, the genetic test, or both. FDA has traditionally declined to restrict off-label uses of the products it approves. Some off-label uses of drug/test combinations could be left to the physician's discretion, but made subject to informed consent, so that risks and benefits are disclosed to patients. Other uses, however, may need to be banned or discouraged by the FDA or through other mechanisms, such as denial of insurance reimbursements, State medical practice regulations and malpractice standards, or practice guidelines developed within the medical profession. Protecting the public from faulty targeting of medicines, while preserving the line between product and practice regulation, may require a careful coordination among FDA, State regulators, and the medical profession.

Implementing a tailored approach to the oversight of genetic testing implies the need for a risk-stratification, classification algorithm to determine which tests require which type of oversight. This classification algorithm would consider the following elements:

- The degree of risks and harms that could occur when clinical utility is uncertain;
- The potential benefits of allowing the test to be used and whether there are any currently available alternative ways to achieve those same benefits;
- Other characteristics of the test, such as whether the test is for a rare disorder;

[449] Evans, B.J. (2007). Distinguishing product and practice regulation in personalized medicine. *Clinical Pharmacology and Therapeutics*. 81(2): 288-293.

[450] Package insert for trastuzumab (Herceptin™), sections on "Clinical Studies: HER-2 Detection" and "Precautions," which cross-reference package inserts for the HercepTest™ IHC assay and the Pathvysion™ HER-2 DNA Probe Kit. See http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp. Accessed on August 15, 2007.

[451] Package insert for Atomoxetine HCL (Strattera™), sections on "Human Pharmacokinetics: Metabolism and Elimintation," "Drug-Drug Interactions," and "Precautions," noting that the drug is metabolized primarily through the CYP2D6 enzymatic pathway and commenting on the possible need for dosage adjustment when the drug is co-administered with certain CYP2D6 inhibitors.

- The seriousness of the condition that the test diagnosis or predicts;
- How the test will be delivered to patients (e.g., over-the-counter vs. a high-proficiency laboratory);
- How soon test results become available after a test is ordered; and
- Other characteristics that bear on the risks and benefits of allowing the test into widespread clinical use.

It will be a major challenge to develop an algorithm that will have a compact set of sorting criteria, yet yield consistent results, so that similarly situated tests receive consistent approaches to regulation and oversight. Another key challenge will be the design of a flexible oversight framework that acknowledges the health information technologies of today, but which can adapt as new technologies emerge. This framework must strike a balance that lets potentially beneficial new tests move into clinical use, while managing uncertainties until their clinical utility is resolved. The following goals should be considered in designing such a framework:

- Adopt a stratified approach that identifies the tests in which uncertainties about clinical utility pose the most serious threat of harm, and limit access to these tests until the uncertainties are further resolved.
- For tests where uncertainty about clinical utility poses less serious harms or threats, or for tests for rare genetic disorders, where resolution of uncertainty is infeasible without wider clinical use of the test, allow the tests to go into clinical use subject to requirements to confirm clinical utility through postmarket follow-up.
- Press forward with efforts to resolve uncertainties about the clinical utility of genetic tests at their source by putting in place the health information systems and adaptive, postmarket regulatory and data collection frameworks that ultimately are going to be required to support timely assessment of clinical utility in a real-time, adaptive manner as tests move into clinical use.

Recommendations

1) Information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions. SACGHS found a paucity of information on clinical utility of genetic testing. There is inadequate data on which to base utility assessments and only a few studies have been done of the clinical utility of specific genetic tests. More fundamentally, insufficient analysis has been done of the standard of evidence upon which the clinical utility of genetic tests should be evaluated and evidence-based methods applicable to genetic testing have been developed. Further policy analysis is also needed to define the process by which clinical utility assessments will be applied. To fill these needs SACGHS recommends the following:

   A. HHS should create and fund a sustainable public/private entity of stakeholders to assess the clinical utility of genetic tests (e.g., building on CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative). This entity would:

      1. identify major evidentiary needs;

      2. establish evidentiary standards for different applications and types of decisions;

      3. establish priorities for research and development;

4. augment existing methods for assessing clinical utility as well as analytical and clinical validity, such as those used by EGAPP and the U.S. Preventive Services Task Force, with relevant modeling tools;
5. identify sources of data and mechanisms for making them usable for research;
6. recommend additional studies to assess clinical effectiveness;
7. achieve consensus on minimal evidence criteria to facilitate the conduct of focused, quick-turnaround systematic reviews;
8. increase the number of systematic evidence reviews and make recommendations based on their results;
9. facilitate the development and dissemination of evidence-based clinical practice guidelines and clinical decision support tools for genetic/genomic tests;
10. establish priorities for implementation in routine clinical practice; and
11. publish the results of these assessments or make them available to the public via a designated HHS or other publicly supported (e.g., GeneTests) website.

B. To fill gaps in our knowledge of analytic validity, clinical validity, clinical utility, utilization, economic value, and population health impact of genetic tests, a Federal or public/private initiative should:

1. develop and fund a research agenda to fill those gaps, including the initial development and thorough evaluation of genetic tests, and the development of evidence-based clinical practice guidelines for the use of those tests;
2. conduct research and surveillance on how that information can be translated into care practices that enhance the quality of care and health outcomes, including the dissemination and implementation of recommended genetic tests into clinical and public health practice, the evaluation of the extent and fidelity with which recommended applications are implemented in community settings, and the effect of implementation on population health; and
3. disseminate these findings to the public via a designated HHS or other publicly supported (e.g., GeneTests) website.

2) Healthcare payers are increasingly requiring evidence of clinical utility before they will pay for genetic tests. Therefore, coverage and reimbursement decisions play a critical role in stimulating innovation and facilitating access to genetic testing. In February 2006, SACGHS issued a report that made recommendations for developing evidence of clinical utility and addressing other barriers to the coverage and reimbursement of genetic tests and services in the public and private sectors. SACGHS offers the following recommendation concerning the development of clinical utility evidence:

As the issues identified in the *Coverage and Reimbursement of Genetic Tests and Services* report are still current, SACGHS urges HHS to act on the report's recommendations. In addition, public and private healthcare payers should develop mechanisms, such as coverage with evidence development or phased reimbursement, to facilitate the collection of clinical utility evidence.

3) The value of genetic tests to patients is realized only when they are used appropriately. In addition, quality improvement processes are needed to assure that genetic tests are delivered consistently to appropriate patients. Furthermore, an ongoing process is needed to identify opportunities for improving the use of genetic testing, including the collection of postmarket outcome data. SACGHS, therefore, makes the following recommendations:

HHS should conduct public health surveillance to assess surrogate and health outcomes, practice measures, including appropriate utilization, and the public health impact of genetic testing.

1. Information should be linked to quality improvement practices that affect patient outcomes and the provision of health services.

2. Data on specific genetic testing results would be required to permit understanding of the significance of genetic variants and new detection methods to improve the utility of testing.

4) The clinical utility and value of genetic testing is inextricably linked to methods to improve care processes and decision support. Interoperable electronic health records will play a central role in the translation of guidelines into care practices through their decision support and educational functions. They will serve as a critical resource for assessing clinical utility and quality of care. SACGHS therefore makes the following recommendations**:**

HHS should ensure the coordination of efforts, including the deliberations of SACGHS and AHIC (particularly work groups addressing on personalized health care, population health and clinical care connections, and confidentiality, privacy and security), to advance the appropriate use of interoperable patient-level data for research and for enhancing the quality of decisionmaking.

Chapter 6
Effective Communication and Decision Support

Introduction

This chapter addresses issues relating to effective communication and clinical decision support in the pre- and post-analytic phases of genetic testing, discusses what is known about harms due to deficiencies in communication and interpretation, and identifies knowledge gaps that should be addressed to reduce these harms. It was developed in response to the following question from the Secretary's charge:

- What are the potential pathways to communicate clear information to guide test and treatment selection by the provider?"

The responsibility for the interpretation of laboratory tests has typically rested with the ordering clinician. While the laboratory clearly has a role in interpretation, as evidenced by inclusion of reference ranges in laboratory reports, there has been little study of the impact of communication of laboratory results on patient care.

As early as 1985, Zinder[452] noted that the increasing complexity of medical care necessitated a change in communication practice between the laboratory and the clinician, stating that the clinician's "…lack of knowledge of the laboratory… led (and still does lead) to erroneous, and sometimes life-threatening, decisions on his part, for which the laboratory is soundly denounced… The laboratory, on the other hand, has been content to give results which are usually accurate, precise and rapid…irrespective of the circumstances involved in obtaining and delivering it." The subject was raised again by Zinder in 1998.[453] A rarely cited portion of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) States that, "…all patients deserve accurate, consistent and confidential medical laboratory information."[454] Arguably, the nature and complexity of genetic testing requires a different degree of communication between the clinician and the laboratory both at the point of test ordering and when the result is reported.[455]

In addition, involvement of patients in shared medical decisionmaking is an increasingly important component of medical care. Zinder explicitly defined an important role for the patient in the communication and interpretation process for laboratory results.[456] This role is of particular relevance in genetic testing, given the complexity of the indications for testing as well as the interpretation. It is important to recognize that consumers can directly order laboratory tests in 27 States, with another 10 allowing consumer-ordered tests under defined circumstances.[457] The ability to self-order tests has led to direct-to-consumer (DTC) advertising campaigns for genetic testing, as described in previous chapters. While the impact of these campaigns is difficult to define at present, the increasing availability of a variety of genetic profile tests that claim to answer questions regarding cardiovascular risk, drug

[452] Zinder, O. (1985). Laboratory-clinician interaction and the interpretation of test results. *Contemporary Issues in Clinical Biochemistry*. 2:52-62.
[453] Zinder, O. (1998). New directions in laboratory-clinician communications. *Clinical Chemica Acta.* 278:83-94.
[454] HIPAA 1996. http://www.hipaa.org/ Accessed June 19, 2007.
[455] Struse H.M. and Montoya I.D. (2001) Health services implications of DNA testing. *Clinical Laboratory Science.* 14:247-51.
[456] Zinder, O. (1985). Laboratory-clinician interaction and the interpretation of test results. *Contemporary Issues in Clinical Biochemistry*. 2:52-62.
[457] Genetics and Public Policy Center. Survey of Direct-to-Consumer Statutes and Regulations. Available at http://www.dnapolicy.org/resources/DTCStateLawChart.pdf. Accessed on July 18, 2007.

metabolism, and DNA-informed diet suggests that patients will assume increasing responsibility in the interpretation and utilization of these tests results.[458,459] This trend has raised significant ethical concerns,[460] as well as prompting discussion of the role of both genetic professionals and clinicians who are not trained in genetics with patients who request interpretation of results.[461,462,463] The issue is now well enough accepted that examination of it has begun to appear in professional societies' policies.[464,465,466,467]

The topics discussed in this chapter should be interpreted in the context of general concerns about the translation of any new technology into medical care. The benefits of effective technologies are only realized when they are delivered to patients. "Translation into practice" is the phrase used to describe the processes for assessing technologies for their clinical utility and to ensure their appropriate delivery into clinical management. Chapter 5 reviews the assessment of clinical utility, which is generally seen as the first step in the translational process from research into practice. Based on assessments of clinical utility, evidence-based clinical guidelines are usually developed that form a foundation for defining the appropriate clinical application of technologies. The recommendations for practice in guidelines must, however, be tailored to the needs and preferences of individual patients.

The translational process requires that all parts of the healthcare system take an active role in ensuring the delivery of needed services, while minimizing misuse, overuse, or inappropriate use (i.e., getting the right service to the right patient at the right time). Some 40 years ago, Donabedian framed the quality improvement process based on structure, process, and outcome - a framework that serves us well today.[468] Recent literature describes the translation process[469] (and for genomics in particular[470]), providing models for understanding the components necessary for quality improvement. Translation requires a systems

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[458] Centers for Disease Control and Prevention (CDC). (2004). Genetic testing for breast and ovarian cancer susceptibility: evaluating direct-to-consumer marketing--Atlanta, Denver, Raleigh-Durham, and Seattle, 2003. *MMWR Morbidity and Mortality Weekly Report*. 53:603-606.

[459] Mouchawar J., Hensley-Alford S., Laurion S., Ellis J., Kulchak-Rahm A., Finucane M.L., Meenan R., Axell L., Pollack R., and Ritzwoller D. (2005). Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally-occurring experiment. *Genetics in Medicine*. 7:191-7.

[460] Wasson, K., Cook, E.D., and Helzlsouer, K. (2006) Direct-to-consumer online genetic testing and the four principles: an analysis of the ethical issues. *Ethics in Medicine*. 22:83-91.

[461] Mouchawar, J., Hensley-Alford, S., Laurion, S., Ellis, J., Kulchak-Rahm, A., Finucane, M.L., Meenan, R., Axell, L., Pollack, R., and Ritzwoller, D. (2005). Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally-occurring experiment. *Genetics in Medicine*. 7:191-7.

[462] Myers, M.F., Chang, M.H., Jorgensen, C., Whitworth, W., Kassim, S., Litch, J.A., Armstrong, L., Bernhardt, B., Faucett, W.A., Irwin, D., Mouchawar, J., and Bradley, L.A. (2006). Genetic testing for susceptibility to breast and ovarian cancer: evaluating the impact of a direct-to-consumer marketing campaign on physicians' knowledge and practices. *Genetics in Medicine*. 8:361-70.

[463] Wade, C.H. and Wilfond, B.S. (2006). Ethical and clinical practice considerations for genetic counselors related to direct-to-consumer marketing of genetic tests. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*. 142:284-92, discussion 293.

[464] American Society of Clinical Oncology policy Statement update: genetic testing for cancer susceptibility. (2003). *Journal of Clinical Oncology*. 21:2397-406.

[465] American College of Medical Genetics. Standards and Guidelines for Clinical Genetics Laboratories Edition 2006. See http://www.acmg.net/Pages/ACMG_Activities/stds-2002/b.htm. Accessed on June 8, 2007.

[466] American Society of Human Genetics. (2007). ASHG Statement on Direct-to-Consumre Genetic Testing in the United States. *American Journal of Human Genetics*. 81: 636-637. See http://www.ashg.org/genetics/ashg/news/dtc_Statement.pdf. Accessed on October 9, 2007.

[467] AMA (2007) House of Delegates Resolution: 522(A-07).

[468] Donabedian A. Evaluating the quality of medical care. (1966). *Milbank Memorial Fund Quarterly*. 44:166–206.

[469] Westfall, J.M., Mold, J., and Faqnan, L. (2007). Practice-based research—"blue highways" on the NIH road map. *The Journal of the American Medical Association*. 297:403-406.

[470] Khoury, M.J., Gwinn, M., Yoon, P.A., Dowling, N., and Bradley L. (in press) The continuum of translation research in genomic medicine: How can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genetics in Medicine*.

approach to quality improvement so that information, incentives, and systems are aligned to deliver recommended care. This process involves all participants in healthcare delivery and the perspectives of each will be discussed in this chapter.

Evaluation is needed to monitor the effectiveness of the translation process. This evaluation often takes the form of public health surveillance to monitor the delivery of services and, more importantly, whether the anticipated health outcomes are being realized.

Key Terms and Concepts

For the purposes of this chapter, "effective communication" is defined as, "A process by which test results are communicated by the laboratory in a format and with supportive information, when applicable, that promotes their appropriate use by the clinician and/or patient in making informed healthcare decisions."[471] Although not explicitly included in this definition, it is well known that, in many cases, proper interpretation of genetic tests requires the clinician to supply the laboratory with information that places the test in the proper clinical context.[472]

Another major concern is the appropriate use of genetic test results. "Appropriate use" within the context of health care can be defined as, "…application of the test result consistent with an established evidence base or, when this does not exist, in concert with expert opinion and/or experience."[473] Appropriate use has been recognized as a problem with laboratory tests in general for more than 20 years[474] and the complexity and probabilistic nature of genetic test results is likely to exacerbate this problem.[475] One proposed solution is to use clinical decision support systems within electronic medical records to facilitate communication from the clinician to the laboratory in the pre-analytic phase, and from the laboratory to the clinician once the test result is available.[476] "Clinical decision support" refers broadly to providing clinicians and/or patients with clinical knowledge and patient-related information, intelligently filtered, or presented at appropriate times, to enhance patient care.[477] This approach has been demonstrated to improve appropriate test ordering and interpretation of results with concomitant improvement in patient care and decreases in cost, particularly when evidence-based guidelines are embedded into clinical decision support tools that support best practice.[478]

Current Systems for Communication of Genetic Test Information

The science of genetics and genomics is providing important knowledge and tools that promise to advance health care in the United States and the world. Genetic tests, as with other medical tests, are used to assist clinicians and patients in making informed decisions about their health. A broad range of testing is encompassed that addresses heritable and somatic conditions and markers of drug metabolism. Genetic

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[471] Lubin, I.M. (2007). SACGHS workgroup on effective communication.
[472] Lyon, E. and Miller, C. (2003). Current challenges in cystic fibrosis screening. *Archives of Pathology and Laboratory Medicine.* 127:1133-9.
[473] Lubin, I.M. (2007). SACGHS workgroup on effective communication.
[474] Zinder, O. (1985). Laboratory-clinician interaction and the interpretation of test results. *Contemporary Issues in Clinical Biochemistry*. 2:52-62.
[475] Petersen, G.M. (2000). Genetic testing. *Hematologic and Oncolologic Clinics of North America*. 14:939-52.
[476] McNeely, M.D. (2002). The use of expert systems for improving test use and enhancing the accuracy of diagnosis. *Clinics in Laboratory Medicine*. 22:515-28.
[477] Adapted from Teich, J.M., Osheroff, J.A., Pifer, E.A., Sittig, D.F., Jenders R.A.; The CDS Expert Review Panel . (2005). Clinical decision support in electronic prescribing: recommendations and an action plan: report of the joint clinical decision support workgroup. *Journal of the American Medical Informatics Association*. 12:365-76.
[478] McNeely, M.D. (2002). The use of expert systems for improving test use and enhancing the accuracy of diagnosis. *Clinics in Laboratory Medicine*. 22:515-28.

testing, once relegated to specialty settings and primarily applied to those affected by or at risk for very rare diseases, is now used in a variety of settings, including that of primary care. In 2005, Acheson et al. reported that, nationwide, family physicians are addressing a variety of genetics issues with patients, particularly with respect to perinatal conditions and family cancers.[479] With the exception of population-based newborn screening tests, limited data are available about practices associated with the ordering and reporting of genetic tests and results.

As described previously in this report, laboratories are regulated under the Clinical Laboratory Improvement Amendments (CLIA), which provide minimum standards for quality assurance.[480] Genetic testing is currently regulated under the general CLIA requirements and a set of criteria mandates what information is to be requested when a test is ordered and reported when a result is determined. Some States, such as New York, through their Clinical Laboratory Evaluation Program (CLEP), have additional requirements.[481] Professional recommendations, such as those from the American College of Medical Genetics (ACMG) and the Clinical and Laboratory Standards Institute (CLSI), provide more detailed recommendations pertaining to the ordering of genetic tests and reporting of results.[482] For those laboratories choosing accreditation through the College of American Pathologists (CAP), specific practices must be in place for approval. In 2007, Gulley et al. published guidelines on behalf of CAP, providing guidance for molecular pathology reports.[483] Studies have not been published that describe the implementation of these guidelines into practice and their usefulness to the laboratory and end-user.

There are also no published studies that summarize clinicians' ordering practices for genetic tests. In 2001, the American College of Obstetricians and Gynecologists (ACOG), together with ACMG, published recommendations on testing for carrier status for cystic fibrosis in all couples that are pregnant or contemplating pregnancy.[484] As a consequence, some laboratories reported significant increases in test volume, with one particular laboratory reporting an increase from 1,000 test samples per month in 2001 to over 14,000 samples a month in 2003.[485] In 2005, Morgan et al. investigated the self-reported familiarity of genetic testing guidelines among practicing obstetricians and gynecologists (OB-GYNs and GYNs).[486] Approximately 90 percent of respondents to the survey saw the guideline as an important document, but only about 20 percent reported that they reviewed the guideline thoroughly. Eighty-two percent knew for whom screening should be offered, but only 22 percent could answer specific questions about genetic risk when integrating information about the sensitivity of the screening test. These limitations in knowledge have also been reflected in other studies.[487]

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[479] Acheson, L.S., Wiesner, G.L., Zyzanski, S.J., Goodwin, M.A., and Stange K.C. (2000). Family history-taking in community family practice: implications for genetic screening. *Genetics in Medicine*. 2:180-5.

[480] CLIA. (1988) http://www.fda.gov/cdrh/clia/ Accessed June 20, 2007.

[481] New York Department of Public Health, Clinical Laboratory Evaluation Program (CLEP), http://www.wadsworth.org/labcert/clep/clep.html. Accessed June 18, 2007.

[482] Clinical and Laboratory Standards Institute. *Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition.* CLSI document MM1-A2 [ISBN 1-56238-615-8]. (2006). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

[483] Gulley, M.L., Braziel, R.M., Halling, K.C., His, E.D., Kant, J.A., Nikiforova, M.N., Nowak, J.A., Ogino, S., Oliveira, A., Polesky H.F., Silverman, L., Tubbs, R.R., Van Deerlin, V.M., Vance, G.H., Versalovic, J.; Molecular Pathology Resource Committee, College of American Pathologists. (2007). Clinical laboratory reports in molecular pathology. *Archives of Pathology & Laboratory Medicine* 131:852-863.

[484] ACMG CF (2001) http://www.acmg.net/resources/policies/pol-005.asp Accessed June 19, 2007.

[485] Vastag, B. (2003). Cystic fibrosis gene testing a challenge: experts say widespread use is creating unnecessary risks. *Journal of the American Medical Association.* 289:2923-4.

[486] Morgan, M.A., Driscoll, D.A., Zinberg, S., Schulkin, J., and Mennuiti, M.T. (2005) Impact of Self-Reported Familiarity with Guidelines for Cystic Fibrosis Carrier Screening. *Obstetrics & Gynecology* 105:1355-1361.

[487] Hayflick, S.J., Eiff, M.P., Carpenter, L., and Steinberger, J. (1998). Primary care physicians' utilization and perception of genetics services. *Genetics in Medicine* 1:13-21.

These findings suggest that a significant percentage of clinicians may not be sufficiently familiar with guidelines for genetic testing to appropriately refer patients in some settings. Some experts have proposed that efforts are needed to make guidelines and other knowledge about testing available to clinicians in a useful format to promote appropriate use of tests.[488] In addition to a number of professional societies, the National Coalition for Health Professional Education in Genetics (NCHPEG), established in 1996 by the American Medical Association (AMA), the American Nurses Association (ANA), and the National Human Genome Research Institute (NHGRI) is an "organization of organizations," whose prime mission is to develop and promote professional education. As such, NCHPEG is engaged in several projects to enhance clinician understanding and appropriate use of genetic testing and information resources for clinicians have also been developed.

GeneTests (http://www.genetests.org), funded by the National Library of Medicine (NLM), was developed to provide a laboratory directory and expert peer-reviewed articles for a large number of molecular genetic tests. Studies of the utilization of this resource are limited by restrictions that prevent tracking who is accessing the site, how the site is being used to find information, and frequency of access. A voluntary survey was developed in 2005 to try to assess some of this information, but the data obtained was inadequate for analysis due to very low response rates.[489] Many clinical laboratories also provide web-based and written resources to clinicians, as well as consultation. ACMG has developed Action (ACT) sheets to provide guidance to providers that have patients with a positive newborn screening test.[490] What has not been studied is the extent to which clinicians, especially those less familiar with genetics, are aware of these resources, use them, and find them useful in informing clinical decisionmaking.

A recent study by Levy et al.[491] assessed the availability, completeness, and accuracy of answers provided by online databases to clinical questions for five genetic conditions commonly dealt with by primary care physicians. The study examined nine online databases including two genetic and seven nongenetic resources. Out of a total of 180 questions, these databases cumulatively provided complete answers only 33 percent of the time. Furthermore, wrong answers were given for these questions up to 15 percent of the time. Even among the most efficient databases in the study sample, the time required to find relevant information was twice as long as the time that providers are reportedly willing to spend looking for information. These findings suggest that current resources are not adequate to meet the needs of providers looking for information to assist with the interpretation of genetic tests.

The interpretation of genetic test results almost always requires information beyond the genotype, enzymatic activity, or cytogenetic result. While this is true for most medical tests, genetic test interpretation often requires information that is uniquely available from the laboratory, which the clinician is unlikely to have or be able to understand. For instance, laboratories performing DNA-based cystic fibrosis testing will report varying numbers of mutations depending on the methodology offered, which may result in differing detection rates.[492] This variation is particularly problematic when no mutation is found, and a patient's residual risk for having an undetected mutation must ultimately be determined and communicated. Other factors that can impact detection rates include race/ethnicity, family history, and

[488] Guttmacher, A.E., Porteous, M.E., and McInerney, J.D. (2007). Educating health-care professionals about genetics and genomics. *Nature Reviews Genetics* 8:151-157.
[489] Pagon, personal communication.
[490] Newborn Screening ACT sheets and confirmatory algorithms. See http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm. Accessed July 25, 2007.
[491] Levy, et al. (2007). 20 Questions in Genetic Medicine: An Assessment of Internet Databases for Genetics Information at the Point of Care. Manuscript in preparation. Used with permission of author.
[492] Grody, W.W., Desnick, R.J., Carpenter, N.J., and Noll, W.W. (1998). Diversity of cystic fibrosis mutation screening practice. *American Journal of Human Genetics* 62:1252–1254.

clinical information. The case of Tay-Sachs is another example from the field of biochemical genetics. While this disease is most closely associated with those of Ashkenazi Jewish decent, it does occur outside this ethnic/racial group. While Jewish Tay-Sachs carriers do exist, some non-Jewish individuals have experienced false positive results due to an unrelated mutation that reacts with certain assay types, interfering with the accuracy of the test.[493] Therefore, it is important for laboratories to know the race/ethnicity of the patient when selecting the test to run in order to appropriately interpret the results. It is conceivable that the absence of such information may lead to harms through misinterpretation. A limited number of studies have been published describing the extent to which laboratories request or collect such information to inform the development of the test result report.

Similarly, little work has been done to describe what is useful to clinicians in a genetic test report. In 2002, Andersson et al. assessed the adequacy of information content provided on test reports based on a cross-section of laboratories offering DNA-based testing for cystic fibrosis and factor V Leiden.[494] Findings showed that many reports failed to include information deemed essential by professional guidelines and recommendations. This study led to follow-up work by Krousel-Wood et al., which found that clinicians prefer reports that are sufficiently comprehensive to provide guidance for clinical decisionmaking.[495] The extent to which current reporting practices have led to adverse outcomes has not been documented.

Studies suggest that clinicians may not be well prepared to understand genetic testing, and in particular, results that are realistic, such as those relevant to genetic risk. In 1997, Giardiello et al. reported a study that described patients who underwent genetic tests for familial adenomatous polyposis. They found that these patients received inadequate counseling as a consequence of incorrect interpretation of the test results by physicians.[496] Another study by Sandhaus et al. in 2001 found that many physicians are unprepared to interpret genetic risk information relevant to results reported for BRCA.[497] Similarly, McGovern published results from a nationwide survey of genetic counselors in 2003, in which 83 percent of respondents indicated the need to contact the laboratory regarding clarification of the report interpretation.[498] These observations suggest the potential for harm due to miscommunication and/or misunderstanding of the meaning of a test result relevant to patient risk for disease. Currently, however, there is a paucity of data documenting actual harms related to the miscommunication of test results.

Another area of concern is in the interpretation of DNA-sequence data. With existing technology, laboratories can detect sequence variations, but laboratories and clinicians must still collaborate to understand the relationship between sequence variations and health conditions. ACMG developed a guideline that places findings from sequence analysis on a continuum, ranging from sequence variations known to have a strong correlation with a health condition, to those that are benign. They also identify sequence variations for which no data are available to support the presence or absence of an

[493] Triggs-Raine, B.L., Mules, E.H., Kaback, M.M., Lim-Steele, J.S., Dowling, C.E., Akerman, B.R., Natowicz, M.R., Grebner, E.E., Navon, R., and Welch, J.P. (1992). A pseudodeficiency allele common in non-Jewish Tay Sachs carriers: Implications for carrier screening. *American Journal of Human Genetics.* 51:793-801.

[494] Andersson, H.C., Krousel-Wood, M.A., Jackson, K.E., Rice, J., and Lubin, I.M. (2002). Medical genetic test reporting for cystic fibrosis (deltaF508) and factor V Leiden in North American laboratories. *Genetics in Medicine* 4:324-327.

[495] Krousel-Wood, M., Andersson, H.C., Rice, J., Jackson, K.E., Rosner, E.R., and Lubin, I.M. (2003). Physicians' perceived usefulness of and satisfaction with test reports for cystic fibrosis (deltaF508) and factor V Leiden *Genetics in Medicine* 5:166-171.

[496] Giardiello, F.M., Brensinger, J.D., Petersen, G.M., Luce, M.C., Hylind, L.M., Bacon, J.A., Booker, S.V., Parker, R.D., and Hamilton, S.R. (1997). The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *New England Journal of Medicine.* 336:823-7.

[497] Sandhaus, L.M., Singer, M.E., Dawson, N.V., and Wiesner, G.L. (2001). Reporting BRCA test result to primary care physicians. *Genetics in Medicine* 3:327-334.

[498] McGovern, M.M., Benach, M., and Zinberg, R. (2003). Interaction of genetic counselors with molecular genetic testing laboratories: Implications for non-geneticist health care providers. *American Journal of Medical Genetics* 119A:297-301.

association.[499] In the absence of such data, other criteria are sometimes applied to communicate a likelihood that a sequence variation may interfere with protein structure.[500,501] The challenge for the clinician is in understanding such inferences when presented and appropriately applying them to clinical decisionmaking. Inappropriate recommendations have the potential to harm patients. Formal studies and guidance are lacking in this area, although one study is currently addressing an aspect of this question.[502]

Communication of results from highly complex tests is also of concern. Tests that fall in this category analyze multiple parameters, including sequence variations, gene or protein expression levels, or a serum protein. Often, an algorithm is necessary to convert the data into clinically useful information. A number of platforms have been developed, many of which are still in development in research settings, although a few have been transitioned to clinical settings (see Chapter 2).[503,504] These tests can be divided into two categories: those in which a number of individual tests have been combined into a single platform and those in which the combination of measurements taken can be submitted to an algorithm able to provide clinically relevant information. An example of the former is the use of pharmacogenomic assays to establish a patient's metabolizer status for particular drugs. An example of the latter is in testing for RNA expression levels to inform decisions about a patient's risk for recurrence of cancer. Some of these assays fall under the FDA definition of an IVDMIA. Although some of these assays have transitioned to clinical settings and a few are FDA cleared or approved, there is significant debate concerning their utility compared to traditional regimens. Studies have yet to be published that would resolve such questions. As such, it is critical that the clinician using such tests have accurate information concerning what is known and not known about the result returned.

In some instances, pharmacogenetic testing could be considered of even higher complexity due to the multitude of factors considered when applying test results and determining how a particular patient will metabolize a specific drug.[505,506] In 2004, the Roche AmpliChip CYP450 test received FDA clearance.[507] The product is marketed to provide data on variants in the genes CYP2D6 and CYP2C19 and it provides patient classification of metabolizer status.[508] As an FDA-cleared kit, the user is provided with specific instructions for setting up the assay and evaluating the results to determine how a patient is likely to metabolize certain drugs. There can be patient-specific issues, however, that are important to recognize, and additional interpretation is needed to inform clinical decisionmaking. The National Academy of Clinical Biochemistry has prepared draft guidelines to address these issues.[509] The guidelines emphasize that decisions made as a consequence of the test results should be based on evidence in the scientific

[499] ACMG 2000. http://www.acmg.net/resources/policies/pol-027.pdf. Accessed June 20, 2007.

[500] Osorio, A., Milne, R.L., Honrado, E., Barroso, A., Diez, O., Salazar, R., de la Hoya, M., Vega, A., and BenÃtez, J. (2007). Classification of missense variants of unknown significance in BRCA1 based on clinical and tumor information. *Human Mutation*. 28:477-484.

[501] Gedge, F., McDonald, J., and Phansalkar, A. (2007). Clinical and analytical sensitivities in hereditary hemorrhagic telangiectasia testing and a report of de novo mutations. *Journal of Molecular Diagnostics* 9:258-265.

[502] NIH 1R01HG004064-01A1 Do Physicians Understand Uncertain Variants and Other Genetic Test Results? PI Plon SE.

[503] Hadd, A.G., Brown, J.T., Andruss, B.F., Ye, F., and WalkerPeach, C.R. (2006). Adoption of array technologies into the clinical laboratory. *Expert Review of Molecular Diagnostics*. 5:409-420.

[504] Anderson, J.E., Hansen, L.L., Mooren, F.C., Post, M., Hug, H., Zuse, A., and Los, M. (2006). Methods and biomarkers for the diagnosis and prognosis of cancer and other diseases: towards personalized medicine. *Drug Resistance Updates*. 9:198-210.

[505] Eichelbaum. M., Ingelman-Sundberg. M., and Evans. W.E. (2006). Pharmacogenomics and individualized drug therapy. *Annual Review of Medicine* 57:119-137.

[506] Kirchheiner, J. and Seeringer, A. (2007). Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. *Biochimica et Biophysica Acta*. 1770:489-94.

[507] Food and Drug Administration, Guidance for Industry and FDA Staff (2005). Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping Systems. See http://www.fda.gov/cdrh/oivd/guidance/1551.html. Accessed on October 28, 2007.

[508] Jain, K.K. (2005). Applications of AmpliChip CYP450. *Molecular Diagnosis*. 9:119-27.

[509] NACB (2006). Draft Guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice. Draft version 60806. See http://www.nacb.org/lmpg/LMPG_Pharmacogenetics.pdf. Accessed June 18, 2007.

literature. The draft guideline also raises the issue of drug-drug and drug-gene interactions. For example, Kirchheiner et al. have shown that persons possessing the CYP2C9 *2/*2 or *3/*3 genotype are typically labeled as poor metabolizers, but there are classes of drugs that do not fit this category.[510] Since many patients are on multiple drug regimens, drug-gene interactions sometimes need to be factored into the interpretation. For example, certain selective serotonin reuptake inhibitors (SSRIs) can inhibit some forms of cytochrome P450 enzymes, altering the metabolizer status determined from genotyping.[511] Thus, a question is raised over whose role it is to integrate this information into the interpretation of the test result. Furthermore, the laboratory's role must be determined. To date, no studies have documented the use of pharmacogenetic/pharmacogenomic testing in clinical settings. Such studies are essential for identifying gaps in information exchange, benefits achieved, and harms. This research would provide a firm grounding for identifying areas that might benefit from additional professional guidance and oversight.

Another type of highly complex test measures RNA expression levels from multiple genes.[512,513] In the past few years, two platforms have become available for prognosis in breast cancer: MammaPrint™ and OncotypeDX™. These tests are FDA-cleared to provide prognostic information for women who have stage I or stage II node-negative breast cancer. The tests analyze RNA expression levels from a panel of 70 and 21 genes, respectively. Algorithms are used to analyze the data and provide a score that classifies the patient into high, intermediate, or low likelihood of recurrence for breast cancer. Some physicians use these tests to identify patients that will benefit from chemotherapy to avoid recurrence and over-treatment of patients that otherwise would not have a remission. The studies that determined the effectiveness of these platforms used retrospective tumor specimens, coupled with known treatment and clinical outcomes in a specific subset of breast cancer patients.[514,515,516] A prospective clinical trial is currently underway. Despite the lack of prospective trial data, these tests are enjoying wide clinical use based on the retrospective analysis, even among women for whom the incremental predictive value is lacking. There is significant debate as to whether these and similar protocols, in their present format and with our current knowledge, do indeed influence patient outcomes. Studies have not yet been performed that report the impact of testing on patient outcomes or how clinicians integrate results into their decisionmaking process.[517] Another question raised is how these tests and similar ones compare in categorizing patients. It is also important to know whether differences exist across populations. Clearly, if the application of these tests based on current information proves to be inaccurate or incomplete, there is a potential for patient harm. In an evidence report prepared for the Agency for Healthcare Research and Quality

[510] Kirchheiner, J. and Seeringer, A. (2007). Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. *Biochimica et Biophysica Acta*. 1770:489-94.

[511] Spina, E., Scordo, M.G.,and D'Arrigo, C. (2003). Metabolic drug interactions with new psychotropic agents. *Fundamental & Clinical Pharmacology* 17:517-538.

[512] Hadd, A.G., Brown, J.T., Andruss, B.F., Ye, F., and WalkerPeach C.R. (2005). Adoption of array technologies into the clinical laboratory. *Expert Review of Molecular Diagnostics* 5:409-420.

[513] Modlich, O., Prisack, H., and Bojar, H. (2006). Breast cancer expression profiling: the impact of microarray testing on clinical decisionmaking. *Expert Opinion on Pharmacotherapy* 7:2069-2078.

[514] Paik, S., Shak, S., Tang, G., Kim, C., Baker, J., Cronin, M., Baehner, F.L., Walker, M.G., Watson, D., Park, T., Hiller, W., Fisher, E.R., Wickerham, D.L., Bryant J., and Wolmark N. (2004). A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *New England Journal of Medicine*. 351:2817-26.

[515] Lascal, J.C. (2007). How molecular biology can improve clinical management: the MammaPrint experience. *Clinical & Translational Oncology* 9:203.

[516] Floore, A., Delahaye, L.J., Wittenveen, A.T., Pover, R. C., Bakx, N., Lahti-Domenici, J.S., Bruinsma,, T.J., Wamoes M.O., Bernards, R., Wessels, L.F., and Van't Veer L.J. (2006). Converting a breast cancer microarray signature into a high throughput diagnostic test. *BMC Genomics* 7:278.

[517] Oratz, R. (in press) Impact of OncoType DX recurrence score on decisionmaking in early-stage breast cancer. *Journal of Clinical Oncology.*

(AHRQ) about genomic tests for ovarian cancer detection and management, the authors arrived at similar conclusions about available tests.[518] Other tests are emerging rapidly into clinical practice.[519]

The tests described above provide probabilistic risks, but other tests under development are designed to provide a likely diagnosis. In 2002, Petricoin et al. published a paper describing the use of mass spectrometry as a diagnostic tool for detecting early-stage ovarian cancer.[520] The test reportedly detected all patients with ovarian cancers in a set of 50 samples, while falsely identifying only 3 patients as being affected. This diagnostic method was a significant improvement over the use of CA-125, a biomarker that is FDA-cleared for use in monitoring after a diagnosis of ovarian cancer, but is not cleared for use in screening. Methods using CA125 in screening are reported to miss about half of the patients in the earliest stages of the disease.[521] Upon reanalysis of the data by biostatisticians at the University of Maryland, concerns were raised about the reproducibility of the data, particularly in reference to the interpretation of the mass spectroscopy data. It was concluded that since the technology was so new, the data collected were insufficient to document the potential benefits and limitations in clinical settings. For instance, it is possible that the proteomic profile could vary based on the patient's stress or drug regimen.[522] Clinicians having access to such tests are not likely to review the methodological issues and will focus on the test result, which, in this case, would be indicative of whether a patient had cancer. Without standards for ensuring that such tests are providing meaningful information to the clinician from such complex tests, potential harm can result from misidentifying patients as being affected or unaffected.

More complete data on current practices regarding how results are reported and their impact on health outcomes is lacking. As such, surveillance of practices and their links to patient outcomes is necessary to develop the evidence base necessary for understanding where resources should be allocated and where additional oversight and guidance would be useful.

Roles and Responsibilities in Genetic Testing

Healthcare Professionals Without Specialty Training in Genetics

In order to take advantage of the advances in genetics described above, nongenetics healthcare providers need to develop the skills to identify which patients may benefit from genetic testing, determine the appropriate test, provide pre- and post-test information to the patient, and interpret the test result accurately. Hayflick et al. proposed specific roles of primary care professionals in the provision of genetics services in a 1998 publication (see Table 1).[523] Interestingly, none of the proposed roles extend beyond identification of patients and the provision of basic information. Instead, the authors recommended that primary care providers work with genetics professionals to provide appropriate genetic services to their patients.

[518] AHRQ 2006. *Genomic Tests for Ovarian Cancer Detection and Management*, Structured Abstract. October 2006. Agency for Health care Research and Quality, Rockville, MD. See http://www.ahrq.gov/clinic/tp/genovctp.htm. Accessed June 18, 2007.

[519] Pusztai, L., Cristofanilli, M., and Paik, S. (2007). New generation of molecular prognostic and predictive tests for breast cancer. *Seminars in Oncology*. 34:S10-6.

[520] Petricoin, E.F., Ardekani, A.M., Hitt, B.A., Levine, P.J., Fusaro, V.A., Steinberg, S.M., Mills, G.B., Simone, C., Fishman, D.A., Kohn, E.C., and Liotta, L.A. (2002). Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 359:572-577.

[521] Check, E. (2004). Proteomics and cancer: Running before we can walk? *Nature* 429:496-497.

[522] Check, E. (2004). Proteomics and cancer: Running before we can walk? *Nature* 429:496-497.

[523] Hayflick, S.J., Eiff, P., Carpenter, L., and Steinberger, J. (1998). Primary care physicians' utilization and perceptions of genetics services. *Genetics in Medicine.* 1(1):13-18.

Table 1. Role Of Primary Care Professionals in the Provision of Genetic Services

- Identification of individuals who may benefit from genetics services
- Recognition of historical and physical features of common genetic conditions and susceptibilities that suggest a genetic disorder
- Monitoring of individual's health, in conjunction with genetics professionals
- Provision of basic genetic information to patients and families in a culturally competent manner using nondirective counseling approach
- Coordination of care for individuals and families with complex genetic service needs
- Recognition of special psychosocial issues for a family with members affected with genetic disorder or at risk
- Knowledge of available genetics services from which patient may benefit
- Referral of patients with additional genetics services needs
- Facilitation of use of genetics services

Although all health professionals are likely to be involved in providing some level of genetic services, most of the current studies have focused on primary care providers and oncologists. The extent of involvement of primary care professionals in ordering genetic tests will vary depending on physician knowledge, public awareness, uptake of tests, the type and prevalence of the disorder, precision of the test, and availability of therapy.[524] Two studies from the United Kingdom estimated that a general practitioner may have one to two patients per month that will require genetic services.[525] The prevalence of genetic testing, however, is projected to increase as the use of testing for pharmacogenomics and more genetic tests for common chronic disorders are incorporated into primary practice.

A survey conducted by the AMA reported that more than 70 percent of respondents Stated that their primary care doctor would be their first choice for information on a genetic disorder. About 80 percent said that they were very confident or somewhat confident that their primary care provider could advise them regarding a family member's risk of developing an inherited cancer, inform them about the availability of genetic testing for the cancer, and interpret the results from a genetic test.[526] During a medical errors study conducted by Baldwin et al., patients reported that they expected to be notified about their test results by someone who is knowledgeable enough to answer their questions.[527]

The National Cancer Institute (NCI), however, conducted a more recent study on a random sample of 1,251 physicians from 8 specialties, which found that only 40 percent of primary care physicians and 57 percent of tertiary care physicians felt qualified to recommend genetic testing for cancer susceptibility to their patients. Additionally, almost 25 percent of all the physicians surveyed perceived that genetic testing for cancer susceptibility had too many inaccurate or ambiguous results, and nearly 75 percent thought that clear management guidelines were not available when a patient had a positive test result.[528] Other studies reveal that the willingness of the physician to offer genetic services, including a genetic test,

[524] Kinmouth, A.L., Reinhard, J., Bobrow, M., and Pauker, S. (1998). Implications for clinical services in Britain and the United States. *BMJ* 316: 767-70.

[525] Emery, J., Watson, E., Rose, P., and Andermann, A. (1999). A systematic review of the literature exploring the role of primary care in genetic services. *Family Practice* 16 (4): 426-445.

[526] American Medical Association. *Genetic testing. A study of consumer attitudes.* Chicago, IL: Survey Center; 1998.

[527] Baldwin, D, Quintela, J, Duclos, C, Staton, E and Pace, W. (2005). Patient preferences for notification of normal laboratory test results: A report from the ASIPS Collaborative. *Biomedical Central Family Practice.* Available from: http://www.biomedcentral.com/1471-2296/6/11. Accessed on October 10, 2007.

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is correlated with the genetic knowledge of the primary care provider.[529,530,531,532,533] The SACGHS report on PGx States that the uptake of PGx testing and therapies will depend on acceptance by physicians, who are faced with complex concerns regarding their benefits, risks, and costs.[534] Also, providers are challenged with maintaining current knowledge of what tests are available; their accuracy, predictive validity, and cost; which patients are most appropriate for testing; and how test results should inform therapeutic decisions.[535] Further studies have revealed that many nongenetics healthcare providers have little training in genetics and do not feel knowledgeable enough to determine genetic risks and communicate the information to their patients. Wilkins-Haug et al. found that their nongenetics healthcare providers cite the rapidly changing knowledge about genetics as the greatest obstacle to providing information to their patients.[536,537,538,539,540]

The ability of healthcare professionals to interpret the genetic test results accurately and communicate this information effectively to families and healthcare providers is as important as determining and communicating information about the appropriate genetic testing. Studies such as the one by Giardiello et al. have found that only 68.4 percent of familial adenomatous polyposis (FAP) genetic testing results were correctly interpreted by nongenetics professionals.[541]

Even when the test result is interpreted correctly, many primary care physicians report an inability to discuss the details of the condition or management of the condition with their patients. This finding is true even for relatively routine testing, such as newborn screening.[542] Families also report that they do not receive educational materials to support their knowledge of genetic conditions in their families. A recent study found that 64 percent of 5,915 respondents reported receiving no genetics education materials from their provider responsible for managing the genetic condition in their family.[543]

[529] Weitz, R. (1981). Medical norms and medical innovation: adoption of genetic counseling and new drugs among primary care physicians. *Sociol Health Illness.* 3:207-219.

[530] Geller, G, Tambor, E, Bernhardt, B, and Chase, G. (1993). Physicians' attitudes toward disclosure of genetic information to third parties. *J Law Med Ethics.* 21:238-240.

[531] Hofman, KJ, Tambor, ES, Chase, GA, Geller, G, Faden RR, Holtzman, NA. (1993). Physicians' knowledge of genetics and genetic tests. *Acad Med.* 68:625-632.

[532] Modell, M, Wonke, B, Anionwu, E et al. (1998). A multidisciplinary approach for improving services in primary care: randomized controlled trial of screening for haemoglobin disorders. *Br Med J.* 317:788-791.

[533] Suther, S, Goodson, P. (2003). Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. *Genetics in Medicine.* 5(2):70-6.

[534] SACGHS. *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* Available at [Insert webpage when report is finalized]. Accessed on [Insert date].

[535] McCann, S, MacAuley, D, Barnett, Y, Bunting, B, Bradley, A, Jeffers, L, and Morrison, PJ (2007). Cancer genetics: consultants' perception of their roles, confidence and satisfaction with knowledge. *J Eval Clin Pract.* 13(2): 276-86.

[536] Hofman, KJ, Tambor, ES, Chase, GA, Geller, G, Faden, RR, Holtzman, NA (1993). Physician's knowledge of genetics and genetic tests. *Acad Med.* 68 (8): 625-32.

[537] Christianson, CA, McWalter, KM, and Warren, NS (2005). Assessment of allied health graduates' preparation to integrate genetic knowledge and skills into clinical practice. *J Allied Health.* 34(3): 138-44.

[538] Freedman, AN, Wideroff, L, et al (2003). US physicians' attitudes toward genetic testing for cancer susceptibility. *Am J Med Genet A.* 120(1): 63-71.

[539] Menasha, JD, Schechter, C, and Willner, J (2000). Genetic testing: a physicians prespective. *Mt Sinai J Med.* 67(2): 144-51.

[540] Wilkins-Haug, L, Hill, L, Schmidt, L, Holzman, GB, and Schulkin, J (1999). Genetics in obstetricians' offices: a survey study. *Obstet Gynecol.* 93(5 Pt 1): 642-7.

[541] Giardiello, FM et al (1997). The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *NEJM.* 336(12): 823-7.

[542] Kemper, AR, Uren, RL, Moseley, KL, and Clark, SJ (2006). Primary Care physicians' attitudes regarding follow-up care for children with positive newborn screening results. *Pediatrics.* 118(5): 1836-41.

[543] Harvey, EK et al (2007). Providers' knowledge of genetics: A survey of 5915 individuals and families with genetic conditions. *Genet Med.* 9(5): 259-267.

Merely using the term "genetic test" may lower the rate of adoption for a test by primary care physicians. One study of 1,120 physicians found that calling a proposed test "genetic" versus a "serum protein test" lowered the likelihood that the physician would offer it to their patients by 11 percent.[544] Even for genetic testing that has been part of a mandatory public health activity for over 30 years, such as newborn screening, physicians have difficulty communicating information about false positive results or positive carrier status results to parents. This difficulty can cause confusion about the disease State, medical complications associated with carrier status, and reproductive decisions.[545,546,547,548]

Studies of other allied health professionals report experiences similar to those of physicians in terms of genetics knowledge, skills, and abilities surrounding genetic testing for their patients.[549,550,551] For example, studies of nurses have revealed a lack of genetics education in this profession. Bankhead et al. found that over 96 percent of the 600 nurses surveyed collected a family history on their patients. The nurses reported, however, that they were unsure how to proceed when a family had a medical history of a disorder and would refer to a general practitioner.[552] Additionally, in a survey of individuals graduating from six allied health training programs, 78 percent reported that the genetics knowledge and skills covered in their training programs was marginal to none. Despite the lack of genetics education, these professionals reported that they were still responsible for providing genetics-related clinical services, such as taking family histories and discussing the genetic basis and impact of the disorder with the patients.[553]

Generally there is an expectation among patients and families that their primary healthcare provider is able to identify their risk for a genetic disorder and provide appropriate testing. Most patients are simply seeking an assessment and reassurance.[554] As such, it is important to equip primary care providers with the skills necessary to assess the genetic risk of disease and determine if any genetic testing is required. Ultimately, genetics education needs to be incorporated routinely in all healthcare provider training programs. The Association of American Medical Colleges (AAMC) recognizes the emerging importance of clinical training in genetics. As part of its Medical School Objectives Project, AAMC outlines specific recommendations on the attitudes, knowledge, and core skills that graduating medical students should achieve in genetics. AAMC also provides recommendations for future genetics-focused educational needs in residency and practice. The Accreditation Council for Graduate Medical Education, which is responsible for accrediting post-M.D. medical training programs, outlines common requirements for graduate programs in molecular genetics, including curriculum requirements and core competencies.

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[544] Shields, A, Blumenthal, D, Weiss, K, et al. (2005). Barriers to translating emerging genetic research on smoking into clinical practice. *J Gen Intern Med.* 20:131-138.

[545] Markel, H. (1998) Scientific advances and social risks: historical perspectives of genetic screening programs for sickle cell disease, Tay-Sachs disease, neural tube defects, and Down syndrome, 1970-1997. In Promoting Safe and Effective Genetic Testing. Ed. Holtzman, NA and Watson, MS, The Johns Hopkins University Press: Baltimore, MD. Pages 161-176.

[546] Kwon, C and Farrell, PM. (2000). The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med.* 154:714-718.

[547] Farrell, M, La Pean, A, and Ladouceur, L. (2005). Content of communication by pediatric residents after newborn genetic screening. *Pediatrics.* 116:1492-1498.

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[549] Lapham, EV, Kozma, C, Weiss, JO, Benkendorf, JL and Wilson, MA. (2000). The gap between practice and genetics education of health professionals: HuGEM survey results. *Genet Med.* 2:226-231.

[550] Bankhead, C, Emery, J, Qureshi, N, et al. (2001). New developments in genetics – knowledge, attitudes and information needs of practice nurses. *Fam Pract.* 18(5):475-486.

[551] Christianson, CA, McWalter, KM, and Warren, NS. (2005). Assessment of allied health graduates' preparation to integrate genetic knowledge and skills into clinical practice. *J Allied Health.* 34(3):138-44.

[552] Bankhead, C, Emery, J, Qureshi, N, et al. (2001). New developments in genetics – knowledge, attitudes and information needs of practice nurses. *Fam Pract.* 18(5):475-486.

[553] Christianson, CA, McWalter, KM, and Warren, NS. (2005). Assessment of allied health graduates' preparation to integrate genetic knowledge and skills into clinical practice. *J Allied Health.* 34(3):138-44.

[554] Thomas, S.M. Genomics: the implications for ethics and education. British Medical Bulletin 55(2): 429-45, 1999.

Additionally, genetics continuing education for practicing primary care providers needs to be offered using traditional methods (e.g., grand rounds, journal articles) and new technologies, such as distance learning.[555] Fortunately, efforts are underway to develop core competencies in genetics and incorporate genetics into allied health training programs.[556,557,558] Additional efforts are needed, however, for continuing education for practicing healthcare providers.

As far back as the 1976 American Academy of Pediatrics Genetic Screening Task Force report, many publications have emphasized a team approach to identifying patients at risk for genetic disorders, offering appropriate testing, and providing post-test information.[559,560,561,562,563] This team approach to providing genetic services should use a model of primary care access to geneticists, genetic counselors, and nurse specialists that can provide accurate information to guide the appropriate use of tests. Further discussion of the role of genetics professionals in genetic testing is provided in the following section. The genetics professions can also develop guidelines to aid the primary care provider in identifying patients that may benefit from a genetic test, choosing an appropriate test, and providing pre- and post-test information and resources for referral to genetics professionals. Several studies have indicated that primary care providers desire the development of these guidelines.[564,565,566]

Nongenetics healthcare professionals need resources to identify at-risk patients, determine appropriate genetic tests, and provide pre- and post-test information to families. Genetics education in training programs, continuing genetic education in practice, development of clear guidelines, and developing a working relationship with a team of genetics professionals are the components required to provide adequate support for nongenetics healthcare providers so that they can provide optimal genetic testing and follow up for their patients.

Genetics Professionals

The importance of access to formally trained genetics professionals has been an overarching concern and/or recommendation in each report developed by SACGHS for the Secretary of HHS. It is not surprising that many studies have revealed that genetics professionals are better equipped than primary care providers and other specialists to order appropriate genetic tests and provide genetic counseling

[555] Emery J, Watson E, Rose, P and Andermann A. (1999). A systematic review of the literature exploring the role of primary care in genetic services. *Fam Pract.* 16 (4): 426-445.
[556] Jenkins, J et al. (2001) Recommendations of core competencies in genetics essential for all health professionals. *Genet Med.* 3:155-159.
[557] National Association of Social Workers. (2003). NASW Standards for Integrating Genetics into Social Work Practice. Report from the NASW Genetics and Social Work Practice Standards Working Group.
[558] National Coalition for Professional Education in Genetics website (www.nchpeg.org). Accessed on June 15, 2007.
[559] American Academy of Pediatrics Task Force on Genetic Screening. (1976). The Pediarician and Genetic Screening (Every Pediatrician a Geneticist). *Pediatrics.* 58:757-764.
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[563] Knottnerus, JA. (2003) Community genetics and community medicine. *Fam Pract.* 20(5):601-6.
[564] Fry, A, Campbell, H, Gudmunsdottir, H, Rush, R, Porteous, M, Gorman, D, and Cull, A. (1999). GPs' views on their role in cancer genetics services and current practice. *Fam Pract.* 16(5):468-74.
[565] Emery, J and Hayflick, S. (2001). The challenge of integrating genetic medicine into primary care. *Brit Med J.* 322:1027-1030.
[566] Freedman, A, Wideroff, L, Olson, L, et al. (2003). US physicians' attitudes toward genetic testing for cancer susceptibility. *Am J Med Genet A.* 120 (1):63-71.

before and after testing.[567,568,569,570,571] Massachusetts has a State law that requires that all genetic testing be accompanied by a Statement that the person was informed about the availability of genetic counseling and was provided with written information identifying a genetic counselor or clinical or medical geneticist from whom the person might obtain counseling.[572]

The SACGHS Report on Coverage and Reimbursement of Genetic Services recognized that there are a wide range of providers of genetic counseling services, including M.D. geneticists, Ph.D. geneticists, Masters-level genetic counselors, genetics nurses, and other healthcare providers. It was noted that, "certain providers of genetic counseling services will be more appropriate than others, depending on the nature of the test and the condition for which the test is performed, the indications for testing, the complexity of the issues being discussed, and the education and qualifications of the provider."[573]

The Coverage and Reimbursement report also States that, "genetic counseling services can be provided prior to testing to collect and interpret family, genetic, medical, and psychosocial information, as well as to inform the patient of the various ethical, legal, and psychosocial issues raised by genetic testing."[574] It is important to add that information obtained during the genetic evaluation and counseling is essential in helping the genetics professional determine the appropriate genetic tests to offer and the sequence of testing that may need to occur. The Coverage and Reimbursement report emphasizes that "after a test is administered, genetic counseling services may be provided to discuss test results and the options of the patient based on those results."[575]

Training and Expertise of Genetics Professionals

The Coverage and Reimbursement report also presents information on the training, qualifications and credentialing of genetic service professionals, including the number of formally trained genetics professionals. At the time of publication, there were 1,178 M.D. clinical geneticists who were board certified by the American Board of Medical Genetics (ABMG) and 152 ABMG board-certified Ph.D. medical geneticists. The American Board of Genetic Counseling (ABGC) reported that there were 1,811 ABMG/ABGC board-certified genetic counselors. In addition, there were 39 individuals credentialed as either advanced practice nurses in genetics or genetic clinical nurses. Thirty nurses who are members of the International Society of Nurses in Genetics (ISONG) are also board certified in genetic counseling.[576]

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[571] Kemper, AR, Uren, RL, Moseley, KL, and Clark, SJ (2006). Primary Care physicians' attitudes regarding follow-up care for children with positive newborn screening results. *Pediatrics.* 118(5): 1836-41.

[572] *Massachusetts 2000 Session Laws. An Act relative to insurance and genetic testing and privacy protection* available at www.mass.gov/legis/laws/seslaw00/sl000254.htm. Accessed on June 8, 2007.

[573] Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). Report on Coverage and Reimbursement of Genetic Tests and Services. February 2006. Available at http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf. Accessed July 31, 2007.

[574] Ibid.

[575] Ibid.

[576] Ibid.

The report did not include the 224 genetic counselors that passed the 2005 ABGC board examinations, increasing the number of board certified counselors to 2,035.[577]

Genetics professionals are uniquely qualified by their training and board certification or credentialing to determine the appropriate genetic testing and communicate options to the family or healthcare provider prior to genetic testing. Their training also allows them to interpret the genetic test results accurately and provide information to the families and healthcare providers tailored to the recipient. All genetics specialties include competencies to determine appropriate testing, interpret test results accurately, and convey information appropriately to the intended recipient. Genetics professionals are also trained to continually update their knowledge base, since genetics continues to be a rapidly expanding field of knowledge. Below are the specific requirements for genetics professionals.

Qualifications of Genetics Professionals

M.D. Geneticists[1]

In order to be eligible for the ABMG board certification, a M.D. geneticist must have:

(1) 24 months of satisfactorily completed full-time training in an Accreditation Council for Graduate Medical Education (ACGME) accredited residency program in a specialty (other than clinical genetics) that is recognized by the American Board of Medical Specialties (ABMS) and an additional 24 months of satisfactorily completed full-time training in an ACGME-accredited clinical genetics residency program; or

(2) 48 months of satisfactorily completed full-time training in an ACGME-accredited 4-year clinical genetics residency. (Note: In this instance the 48 months of training satisfy both the graduate medical training requirement and the medical genetics training requirement); or

(3) 60 months of satisfactorily completed full-time training in an ACGME-accredited combined pediatrics/medical genetics or internal medicine/medical genetics residency. Upon successful completion of all requirements of the combined residency, a trainee is qualified to apply for certification by either or both the American Board of Pediatrics (ABP) and the ABMG OR either or both the American Board of Internal Medicine (ABIM) and the ABMG. Applicants must satisfactorily complete the specific credentialing requirements of each Board to be eligible to sit for the examination of that Board. Certification in one specialty is not contingent upon certification in the other.

Ph.D. Medical Geneticists[2]

An individual who holds an earned Ph.D. from a training program that also has an ABMG-accredited Ph.D. Medical Genetics training program may, at the discretion of the program director of the individual's ABMG-accredited medical genetics training program, apply for certification in the Ph.D. Medical Genetics specialty and one laboratory specialty after two years of combined medical genetics training in these two specialties in an ABMG-accredited program, if and only if:

(1) The earned Ph.D. is from a degree-granting program that is documented to be integrated with a postdoctoral program that is ABMG-accredited for at least PhD Medical Genetics and one laboratory specialty; and

(2) During the Ph.D. degree program, the individual has taken graduate course work including formal medical genetics and mathematical genetics, and the individual documents significant participation in clinical genetics: communicating with patients, communicating with referring physicians, and regularly attending clinical conferences. These activities must be documented and described in detail by the director of the ABMG-accredited medical genetics program and by the institution's director of the Ph.D. program granting the doctoral degree; and

(3) The applicant submits two logbooks, one of 150 cases for the laboratory specialty collected during the medical genetics fellowship training and one of 75 additional cases for the specialty of Ph.D. Medical Genetics (unrelated

[577] American Board of Genetic Counseling. Available at http://abgc.iamonline.com/english/View.asp?x=1418. Accessed on July 26, 2007.

to the laboratory specialty) also collected during the medical genetics fellowship training.

[1] American Board of Medical Genetics website. Available at http://www.abmg.org/genetics/abmg/cert-2007/requirements.htm. Accessed on June 9, 2007.
[2] American Board of Medical Genetics website. Available at http://www.abmg.org/genetics/abmg/cert-2007/requirements.htm. Accessed on June 9, 2007.

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Certified Genetic Counselors[3]

A genetic counselor must demonstrate competencies in the following areas to graduate from an ABGC accredited masters level genetic counseling program: (1) principles of human, medical, and clinical genetics; (2) psychosocial theory and techniques; (3) social, ethical, and legal issues; (4) healthcare delivery systems and principles of public health; and (5) teaching techniques and research methods.[1] Additionally to qualify to be board certified by the ABGC, a genetic counselor must have:
(1) Graduation from an ABGC accredited masters level genetic counseling program.
(2) A logbook of 50 distinct genetic counseling cases demonstrating a broad clinical training experience obtained after July 1, 1999 at approved genetic counseling training settings.
(3) Letters of reference from two board certified genetics professionals and the program director of the ABGC-accredited genetic counseling program.

Advanced Practice Nurse in Genetics[4]

Nurse genetics professionals can receive credentialing as an Advanced Practice Nurse in Genetics (APNG) or as a Genetics Clinical Nurse (GCN). In order to qualify for the APNG, a nurse has to be a master's level nurse and complete credentialing through successful completion of a professional portfolio review process. The credentialing requirements are:
(1) Proof of R.N. License in good standing.
(2) 300 hours of Genetic Practicum experiences as a clinical genetic nurse with greater than 50 percent genetic practice component.
(3) Completion of Log of 50 cases within five years of the application.
(4) 4 Written Case Studies reflecting International Society of Nurses in Genetics (ISONG) standards of clinical genetics nursing practice.
(5) Graduation from an accredited graduate program in nursing.
(6) 50 hours of genetic content in the past 5 years through academic courses or continuing education.
(7) Evidence of patient/family and/or client teaching absolutely required for credential award.

Genetics Clinical Nurse[5]

In order to qualify to be a GCN, credentialing is also obtained through successful completion of a professional portfolio review process. The credentialing requirements are:

(1) Proof of R.N. License in good standing.
(2) 5 years experience as a clinical genetic nurse with greater than 50 percent genetic practice component.
(3) Log of 50 cases within five years of the application.
(4) Written Case Studies reflecting ISONG standards.
(5) Graduation from an accredited Baccalaureate program in Nursing.
(6) 45 contact hours of genetic content within 3 calendar years of application through academic courses or continuing education.
(7) Evidence of patient/family and/or client teaching and evidence of genetics-related in-service education.

[3] American Board of Genetic Counseling website available at http://abgc.iamonline.com/english/View.asp?x=1667&mp=1664. Accessed on June 9, 2007.
[4] Genetic Nursing Credentialing Commission website. Available at http://www.geneticnurse.org/advancedpracticeapng.html. Accessed on June 9, 2007.
[5] Genetic Nursing Credentialing Commission website. Available at http://www.geneticnurse.org/geneticsnursegcn.html. Accessed on June 9, 2007.

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One of the primary tools for a genetics professional in determining appropriate testing for an individual or family is a three generation family history. Many nongenetics healthcare professionals, however, do not take such a family history. Additionally, studies have revealed that in genetic counseling sessions conducted with a three generational pedigree, up to 50 percent of the patients were found to have additional genetic risk factors that were not identified by the referring obstetrician.[578,579,580] Genetics professionals have the skills and current knowledge to identify accurately the genetic risks of the individual or family and determine appropriate genetic testing and options, but they may not be using all the tools available to provide complete and accurate guidance to patients.

Furthermore, some studies have even revealed that a patient's perception of a test result is influenced by whether the results are given by a geneticist or a nongenetics health professional. Johnson et al. found that genetic counseling by a genetics professional and testing increased overall patient adherence with recommended colon screening, especially for those with positive genetic test results. Another study by Michie et al.[581] found that 103 unaffected at-risk adults who received a negative predictive DNA test result for FAP attended bowel screening at a much higher rate when the results were received from a nongenetics professional, compared to patients given results by a genetics professional. Michie et al. attributed the difference to factors such as methods used to convey information about the accuracy of the test result, seriousness of the disease, and attitudes towards bowel screening.[582,583]

The training, skills, and knowledge of a genetics professional allows for the accurate interpretation and appropriate genetic counseling for the person or family receiving the test result. Genetic professionals can also provide the link between the primary care provider, who may not be knowledgeable about genetics, and the family in using the results to determine the options for treatment and management of a genetic disorder or risk for a genetic disorder.

Role of Laboratories in Providing Genetic Expertise

As noted above, given the complexity of genetic testing, the laboratory must play a role in interpreting and effectively communicating the test result to the ordering physician. This section reviews the role of the laboratory in providing genetic expertise in the genetic specialty laboratory and the nongenetic specialist laboratory. While the issues are the same for both, there are differences in practice that must be addressed in order to understand existing gaps and harms.

Genetic Specialty Laboratories

The pre- and post-analytic communication issues discussed above have led many genetic specialty laboratories to employ or contract with clinical genetic professionals to provide clinical consultation with ordering clinicians and patients. A clinical consultant is required by CLIA regulations for all laboratories.[584] This amendment provides the following definition of a clinical consultant:

[578] Frezzo TM, et al (2003). The genetic family history as a risk assessment tool in internal medicine. *Genet Med*. 5(2): 84-91.
[579] Cohn GM, et al (1996). The usefulness of a prenatal genetic questionnaire in genetic risk assessment. *Obstet Gynecol*. 88(5): 806-10.
[580] Koscica, KL, Canterino, JC, Harrigan, JT, Dalaya, T, Ananth, CV, and Vintzileos, AM (2001). Assessing genetic risk: Comparison between the referring obstetrician and genetic counselor. *Am J Obstet Gynecol.* 185: 1032-1034.
[581] Michie, S, Collins, V, Halliday, J and Marteau, TM (2002). Likelihood of attending bowel screening after a negative genetic test result: the possible influence of health professionals. *Genet Test.* 6(4): 307-11.
[582] Johnson, KA et al (2002). Impact of genetic counseling and testing on colorectal cancer screening ,behavior. *Genet Test.* 6(4): 303-6.
[583] Hadley, DW, Jenkins, JF, Dimond, E, de Carvalho, M, Kirsch, I and Palmer, CG (2004). Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol.* 22(1): 39-44.
[584] CLIA. (1988) http://www.fda.gov/cdrh/clia/ Accessed June 20, 2007.

§ 493.1417 Standard; Clinical consultant qualifications.

The clinical consultant must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care. The clinical consultant must:

(a) Be qualified as a laboratory director under § 493.1405(b) (1), (2), or (3)(i); Or

(b) Be a doctor of medicine, doctor of osteopathy or doctor of podiatric medicine and possess a license to practice medicine, osteopathy or podiatry in the State in which the laboratory is located.

While that standard States that the consultant "must be qualified" it does not specify the qualifications for any clinical consultant in general or clinical consultants in genetic laboratories in particular. The Standards and Guidelines for Clinical Genetic Laboratories (ed. 2006) of ACMG State, "The clinical consultant must be an American Board of Medical Genetics certified clinical geneticist, Ph.D. medical geneticist, or clinical laboratory geneticist. The laboratory director can fulfill this role. The clinical consultant is required to provide consultation but not counseling to the patient."[585] McGovern et al. published a survey on molecular genetic testing laboratories.[586] Of the 245 molecular laboratory directors who responded, 83 percent reported an affiliation with one or more doctoral-level genetics professionals. Approximately half of these affiliated geneticists provided clinical consultation to referring physicians while the rest provided consultation to patients. Additionally, 70 percent of the directors reported either employing (27 percent) or affiliating (43 percent) with clinical genetic counselors that provided similar consultative services to physicians and patients. A similar survey of biochemical genetics laboratories showed that of the 133 directors who responded, only 23 percent reported an affiliation with one or more doctoral-level genetics professionals. Of these affiliated geneticists, 89 percent provided clinical consultation to referring physicians and 72 percent to patients.[587] This study did not address the use of genetic counselors in the biochemical setting. Neither of these surveys specifically addressed how many laboratory directors fulfilled the clinical consultant role, which would meet the criteria of the ACMG Statement.[588] Nonetheless, the discrepancy between practices in the molecular laboratory compared to the biochemical laboratory is notable.

It is a measure of the perceived importance of these services that most genetic testing laboratories employ or contract with clinical genetic professionals, despite the inability to be directly reimbursed for their services. In theory, these costs could be distributed across the tests offered as an indirect overhead expense reflected in the charge for the service. In practice, given that many laboratories contract to accept payment at a discounted rate and that third-party payers such as Medicare set maximum allowable charges that do not cover the laboratory's costs for testing, it is unlikely that this indirect approach results in coverage of this expense, although there are no published data to support this conclusion.

[585] American College of Medical Genetics. Standards and Guidelines for Clinical Genetics Laboratories Edition 2006 (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/b.htm) Accessed on June 8, 2007.

[586] McGovern M.M., Benach M.O., Wallenstein S., Desnick R.J., Keenlyside R. (1999) Quality assurance in molecular genetic testing laboratories. *Journal of the American Medical Association*. 281:835-40.

[587] McGovern M.M., Benach M., Wallenstein S., Boone J., Lubin I.M. (2003B) Personnel standards and quality assurance practices of biochemical genetic testing laboratories in the United States. *Archives of Pathology and Laboratory Medicine Part B*. 127:71-6.

[588] American College of Medical Genetics. Standards and Guidelines for Clinical Genetics Laboratories Edition 2006 (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/b.htm) Accessed on June 8, 2007.

Furthermore, there are few data indicating whether the clinical genetic consultant improves appropriate testing, interpretation, and use of the test result. McGovern et al. tried to indirectly answer this question by surveying genetic counselors regarding their interaction with molecular genetic testing laboratories.[589] Of the 758 counselors that responded to this survey, over 80 percent indicated that they contacted a laboratory after receiving the results of a test for a variety reasons, including clarification of report interpretation (83 percent), information about methodology used (82 percent), interpretation of results (81 percent), and revised risk based on a negative test result (69 percent). A total of 57 percent of the respondents indicated that they contacted a genetic counselor employed by the laboratory. Other contacts included the client services employee (19 percent), laboratory director (16 percent), clinical consultant (12 percent) and laboratory supervisor (7 percent). Of the 758 genetic counselors, 21 percent indicated that the laboratories were not always able to answer a question and 28 percent reported a "frequent need" to clarify reports prior to providing information to a patient.

The authors specifically raise the concern that despite the high level of training of the genetic counselors and the fact that over 90 percent worked with a doctoral-level clinical geneticist, only 72 percent felt that the reports contained enough information to explain test results. A total of 76 percent of respondents indicated receiving a test report that did not have an interpretation, despite the ACMG requirement that genetic test reports contain a Statement interpreting the data, and that the interpretation should be understandable to a nongeneticist professional.[590] The authors conclude that, "It could be reasonably expected that the perceived deficiencies in laboratory reports articulated by these trained genetics professionals may pose an even greater challenge to primary care physicians." It may be expected that consumers who have ordered their own genetic tests would experience similar challenges. This concern was echoed by Malinowsky and Blatt.[591] The only published test highlighting this concern was in a study by Giardiello et al., which reported that 17 percent of patients had "inappropriate" indications for testing and over 31 percent of physicians misinterpreted the results of an APC gene test.[592] Some research has also indicated that a number of identified genetic testing laboratories are not in compliance with the recommendation that a clinical consultant be available.[593,594] If these findings represent a decrease in the quality of patient care, this is a potential harm.

An approach that was developed to address similar problems in anatomic pathology reporting is synoptic reporting.[595] Focused on the reporting of tumor pathology, this approach has had a dramatic impact on improving the quality of patient care. The Cancer Committee of CAP developed a series of cancer protocols that culminated on January 1, 2004, with mandatory compliance to Standard 4.6 of the American College of Surgeons Commission on Cancer (COC). This standard requires that pathologists at COC-approved cancer programs include all scientifically validated or regularly used data elements of the

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[589] McGovern M.M., Benach M., Zinberg R. (2003A) Interaction of genetic counselors with molecular genetic testing laboratories:implications for non-geneticist health care providers. *American Journal of Medical Genetics Part A*. 119:297-301.

[590] American College of Medical Genetics. Standards and Guidelines for Clinical Genetics Laboratories Edition 2006 (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/b.htm) Accessed on June 8, 2007.

[591] Malinowski M.J., Blatt R.J. (1997) Commercialization of genetic testing services: the FDA, market forces, and biological tarot cards. *Tulane Law Review*. 71:1211-312.

[592] Giardiello F.M., Brensinger J.D., Petersen G.M., Luce M.C., Hylind L.M., Bacon J.A., Booker S.V., Parker R.D., Hamilton S.R. (1997) The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *New England Journal of Medicine.* 336:823-7.

[593] McGovern M.M., Benach M.O., Wallenstein S., Desnick R.J., Keenlyside R. (1999) Quality assurance in molecular genetic testing laboratories. *Journal of the American Medical Association*. 281:835-40.

[594] McGovern M.M., Benach M., Wallenstein S., Boone J., Lubin I.M. (2003B) Personnel standards and quality assurance practices of biochemical genetic testing laboratories in the United States. *Archives of Pathology and Laboratory Medicine Part B*. 127:71-6.

[595] Leslie K.O., Rosai J. (1994) Standardization of the surgical pathology report: formats, templates, and synoptic reports. *Seminars in Diagnostic Pathology*. 11:253-7.

CAP checklists in their pathology reports for each site and specimen.[596] CDC is currently exploring whether synoptic reporting of genetic and genomic test results could result in similar improvements in patient care.[597]

NonGenetic Laboratories

As the volume of genetic and genomic tests grows, it is anticipated that many of these tests may move into the general clinical laboratory. This trend is already evident with the rapid detection of infectious agents using DNA-based technology. While not quantified, some molecular genetic tests for human mutations (e.g., factor V Leiden and other thrombophilic polymorphisms, hemochromatosis due to C282Y) are being performed in general clinical laboratories. Emerging pharmacogenomic tests that will be used to choose the most appropriate medications and doses for patients may require a turnaround time that is unachievable by a reference laboratory, thus promulgating testing at or near the point of care. Finally, an increasing number commercial test kits have been FDA-cleared/approved, making these tests financially attractive to nongenetic laboratories, because there would be no costs associated with test development. Some authors have raised concerns about the impact on the quality of testing. While this concern has primarily been focused on analytic validity,[598] it could be argued that if there is a lack of clinical genetic expertise to inform interpretation and reporting, this will have a tremendous clinical impact even if the testing is analytically valid. Currently, there are no published data that allow assessment of the magnitude of this problem.

Point-of-Care Genetic Testing

At the present time, molecular genetic testing is not being performed at the point of care, with the exception of some DNA-based tests that are used in studying the epidemiology of infectious diseases. Several authors, however, have noted that point-of-care testing may well emerge in the near future.[599,600] This type of testing may be required in situations such as pharmacogenomic testing, where dosing decisions may not be able to wait for the sample to be sent to a referral laboratory with its attendant turnaround time. In the setting of a clinical trial, genotyping of the common variants of CYP2C9 and VKORC1 was completed with a median turnaround time of 48 minutes, which allowed this information to be used to inform the initial dose of coumadin in patients initiating anticoagulation.[601] All of the problems noted in this report regarding validity and utility will likely be amplified if point-of-care testing becomes commonplace.[602]

Impact of Direct-to-Consumer Advertising

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[596] Amin MB (2006). Key issues in reporting common cancer specimen findings using the College of American Pathologists cancer protcols. *Arch Pathol Lab Med*. 230(3):284-6.

[597] CDC. Reporting DNA-Based Genetic Test Results Applicable to Heritable Conditions and/or Markers of Drug Metabolism: The Clinical Laboratory Report as a Decision-Support Tool. Available at http://www.cdc.gov/od/pgo/funding/CI07-709.htm.%20, Accessed on August 9, 2007.

[598] Strom C.M. (2005) Mutation detection, interpretation, and applications in the clinical laboratory setting. *Mutation Research*. 573:160-7.

[599] Fortina P., Surrey S., Kricka L.J. (2002) Molecular diagnostics: hurdles for clinical implementation. *Trends in Molecular Medicine*. 8:264-6.

[600] Trent R.J., Yu B., Caramins M. (2004) Challenges for clinical genetic DNA testing. *Expert Review of Molecular Diagnostics*. 4:201-8.

[601] Couma-Gen (2007) Available at http://clinicaltrials.gov/ct/show/NCT00334464;jsessionid=1B6C6035A24A8C808FCAF2C58E9952B1?order=39. Accessed June 19, 2007.

[602] Fortina P., Surrey S., Kricka L.J. (2002) Molecular diagnostics: hurdles for clinical implementation. *Trends in Molecular Medicine*. 8:264-6.

As noted previously, laboratories are increasingly marketing directly to the consumer to encourage testing. While the impact of these campaigns is difficult to define at present,[603,604] this practice has attracted the attention of both the Government and organized medicine. SACGHS has encouraged collaboration of Federal agencies on the regulation of advertisements for genetic tests marketed directly to consumers and the impact of DTC marketing of these tests. An investigation of companies offering nutrigenetic testing directly to consumers by the U. S. Government Accountability Office (GAO) concluded that the information provided by these companies "misleads consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers."[605] The FTC also issued a consumer alert warning consumers to be "wary of claims about the benefits these products supposedly offer."[606] This concern led ACOG, represented by the Massachusetts delegation to the AMA's House of Delegations, to submit a resolution on the subject of direct-to-consumer genetic testing. This resolution took the form of a directive to take action that Stated, "…that our American Medical Association study the issue of direct to consumer advertising of genetics tests and the provision of genetics testing to patients on the Internet or other vehicles not directly involving the patient's physician, taking into consideration appropriate mechanisms to regulate this practice."[607]

There is currently no requirement that test providers disclose information to support claims about the accuracy and validity of testing and no central or uniform mechanism for providing this information in an accessible format to patients and providers.

An information management technique that is showing promise in complex medical conditions is known as shared decisionmaking. Shared medical decisionmaking is an attempt to balance the tension between evidence-based guidance and respecting patient choice.[608] The principles involved in shared decisionmaking are: [609]

- Shared decisionmaking involves at least two (often many more) participants, as a minimum, the doctor and the patient;
- Both parties take steps to participate in the process of decisionmaking;
- Information sharing is a prerequisite to sharing of the decisionmaking; and
- A decision is made and both parties agree to it.

An extensive review of existing decision aids by the Cochrane Collaboration demonstrated that decision aids are consistently superior to usual care in increasing knowledge and patient satisfaction while decreasing decisional conflict.[610] Elwyn et al. note that genetic counseling already embraces many of the

[603] Centers for Disease Control and Prevention (CDC). (2004) Genetic testing for breast and ovarian cancer susceptibility: evaluating direct-to-consumer marketing--Atlanta, Denver, Raleigh-Durham, and Seattle, 2003. *MMWR Morbidity and Mortality Weekly Report*. 53:603-6.

[604] Mouchawar J., Hensley-Alford S., Laurion S., Ellis J., Kulchak-Rahm A., Finucane M.L., Meenan R., Axell L., Pollack R., Ritzwoller D. (2005) Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally-occurring experiment. *Genetics in Medicine*. 7:191-7.

[605] GAO. (2006) see http://www.gao.gov/new.items/d06977t.pdf Accessed June 25, 2007.

[606] FTC. (2006) see http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm. Accessed June 25, 2007.

[607] AMA (2007) HOUSE OF DELEGATES Resolution: 522(A-07)

[608] Elwyn G., Gray, J., Clarke A. (1999) Shared decisionmaking and non-directiveness in genetic counseling. *Journal of Medical Genetics* 37:135-138.

[609] Ibid.

[610] O'Connor AM, Stacey D, Rovner D, Holmes-Rovner M, Tetroe J, Llewellyn-Thomas H, Entwistle V, Rostom A, Fiset V, Barry M, Jones J. (2003) Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. (2):CD001431.

concepts of shared decisionmaking.[611] The only applications of shared decisionmaking in genetic care were published by the Nijmegen group and involved decisions about breast surgery or cancer surveillance in known BRCA1 and BRCA2 carriers.[612,613] There are no published reports of this approach being used in the decision to undergo genetic testing.

Given the growing role of consumers in shared decisionmaking and the ability of consumers to assess some genetic tests without healthcare provider intervention, there is a greater need to ensure that information about tests is complete and reliable, otherwise appropriate use and interpretation of the tests cannot be assured.

Patient Access to Expertise

The only area of genetic testing where there may be consistent patient access to genetics expertise is in the State-based newborn screening (NBS) programs. Most NBS programs have been mandated by State law for more than 30 years and are funded by user fees.[614,615] The user fees allow the programs to pay for consultations with genetics providers or other subspecialists when a newborn receives a positive NBS test result.[616] This type of guaranteed payment model allows patients to access genetics expertise at least up to the diagnosis of the disorder. Some NBS programs go further by subsidizing treatment and follow-up services, such as nutritional and clinical consultations.[617] One of the reasons that NBS has been successful is that the Federal Government has been active in providing funding and technical assistance to the NBS programs, community-based support services, and primary care provider communities. For example, the Health Resources and Services Administration (HRSA) Genetics Services Branch (GSB) funds many technical assistance, education, and follow-up activities related to NBS, such as the National Newborn Screening and Genetics Resource Center,[618] the National Coordinating Center for the Genetics and Newborn Screening Regional Genetics Collaborative Groups,[619]; Sickle Cell Disease Community-Based Projects,[620] and partnerships with the American Academy of Pediatrics and National Conference of State Legislatures. Within the past three years, the HRSA GSB has created an Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children to address issues surrounding harmonization of NBS across the Nation and develop criteria to help determine which new disorders should be added to the NBS panel.[621]

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[611] Elwyn G., Gray, J., Clarke A. (1999) Shared decisionmaking and non-directiveness in genetic counseling. *Journal of Medical Genetics* 37:135-138.

[612] Stalmeier PF, Unic IJ, Verhoef LC, Van Daal WA. (1999) Evaluation of a shared decisionmaking program for women suspected to have a genetic predisposition to breast cancer: preliminary results. *Med Decis Making.* 19:230-41.

[613] Unic I, Stalmeier PF, Verhoef LC, van Daal WA. (1998) Assessment of the time-tradeoff values for prophylactic mastectomy of women with a suspected genetic predisposition to breast cancer. *Med Decis Making.* 18:268-77.

[614] National Newborn Screening and Genetics Resource Center. National Newborn Screening Status Report. August 3, 2007. Available at http://genes-r-us.uthscsa.edu/nbsdisorders.pdf. Accessed on August 9, 2007.

[615] National Newborn Screening and Genetics Resource Center. Summation of Fees Charged for Newborn Screening in the U.S. in 2007. Available at http://www2.uthscsa.edu/nnsis/. Accessed on August 9, 2007.

[616] Johnson K, et al (2006). Financing State newborn screening programs: Sources and uses of funds. *Pediatrics*. 117(5): S270-S279.

[617] Ibid.

[618] National Newborn Screening and Genetics Resource C enter. Available at http://genes-r-us.uthscsa.edu/. Accessed on August 1, 2007.

[619] National Coordinating Center for the Genetics and Newborn Screening Regional Collaborative Groups. Available at http://www.nccrcg.org/. Accessed on August 1, 2007.

[620] Sickle Cell Disease Association of America. Sickle Cell and Newborn Screening Program. Available at http://www.sicklecelldisease.net/index.html. Accessed on August 1, 2007.

[621] HRSA MCHB. Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Available at http://mchb.hrsa.gov/programs/genetics/committee/default.htm. Accessed on August 1, 2007.

Unfortunately, other areas of genetics do not share the same broad access to services as NBS. As described earlier in this section, there is a small number of formally trained genetic service providers in the country. Most health care in the country is provided by primary care providers who have little, if any, training in genetics. Besides the small number of genetic service providers, the SACGHS Coverage and Reimbursement report concluded that patients' access to genetic services may be limited by their health insurer or a genetics providers' lack of reimbursement for services. The report also noted that families in rural areas may not have access to genetics professionals or may have to travel long distances for an appointment.[622] The SACGHS report, *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges* States that the role of genetics professionals is important to help interpret pharmacogenomics testing information, since many doctors do not possess the training to correctly interpret it. The report also finds, however, that many other support systems besides the availability of genetics professionals must be put in place to help primary care providers understand the criteria for testing, information to be discussed with the patient, interpretation of the test result, and use of the result for patient care.[623] To date, no research has been done to determine whether the proposed support systems would result in appropriate use of pharmacogenomic tests. Some initial studies using telephonic access to genetic expertise (telegenetics) establish that this is technically feasible and may be equivalent to face-to-face counseling in some circumstances.[624,625,626] Additional studies are needed to determine if this is a viable solution to rural access, although this approach will not address the genetic provider shortage as outlined in previous sections.

Role of Professional Societies

Professional societies have played and will continue to play an important role in defining standards of practice. In addition to defining training to become eligible for specialty status and (where appropriate) board certification, professional societies are increasingly engaged in the production of professional practice guidelines to improve and standardize clinical care. "Practice guidelines" are systematically developed Statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.[627]

Professional societies, including ACMG, ACOG, the American Society of Clinical Oncologists Association of Public Health Laboratories, and the National Society of Genetic Counselors have actively developed and promoted guidelines regarding a variety of genetic tests. Dissemination of these guidelines has occurred through the societies' journals, websites, and a variety of other educational venues. It is anticipated that the number of guidelines will continue to increase.

While important, guidelines in and of themselves are not sufficient to optimize medical practice,[628] as evidenced in this country by studies that show that only 50 percent of patients receive recommended

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[622] SACGHS. Report on Coverage and Reimbursement of Genetic Tests and Services. February 2006. Available at http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf. Accessed on July 31, 2007.

[623] SACGHS. *Realizing the Promise of Pharmacogenomics: Opportunities and Challenges.* 2008.

[624] Gattas M.R., MacMillan J.C., Meinecke I., Loane M., Wootton R. (2001) Telemedicine and clinical genetics: establishing a successful service. *Journal of Telemedicine and Telecare.* 7 Suppl 2:68-70.

[625] Lea D.H., Johnson J.L., Ellingwood S., Allan W., Patel A., Smith R. (2005) Telegenetics in Maine: Successful clinical and educational service delivery model developed from a 3-year pilot project. *Genetics in Medicine* 7(1):21-27.

[626] Stalker H.J., Wilson R., McCune H., Gonzalez J., Moffett M., Zori R.T. (2006) Telegenetic medicine: improved access to services in an underserved area. *Journal of Telemedicine and Telecare.* 12(4):182-185.

[627] Beghi E., Citterio A., Cornelio F., Filippini G., Grilli R., Liberati A. (1998)
Practice guidelines: a more rational approach to diagnosis and treatment and a more effective use of health care resources. *Italian Journal of Neurologic Science*. 19:120-3.

[628] Lomas J., Anderson G.M., Domnick-Pierre K., Vayda E., Enkin M.W., Hannah W.J. (1989) Do practice guidelines guide practice? The effect of a consensus Statement on the practice of physicians. *New England Journal of Medicine*. 321:1306-11.

preventive care.[629] In acute care situations, only 70 percent of patients are receiving recommended care, while 30 percent receive treatments that are contraindicated.[630] Even worse, in patients with chronic illness, only 60 percent receive recommended treatments and 20 percent receive contraindicated treatments.[631] The reasons for these findings are many and will not be recapitulated here. There is no reason to believe that this situation will be any different with regard to genetic tests. As noted by Giardiello et al. 20 percent of the APC gene tests in their study cohort were ordered inappropriately.[632] Grover et al. reported that of 75 patients who met the Bethesda criteria for familial risk of colorectal cancer, only 13 (17 percent) were subsequently referred by gastroenterologists for genetic counseling, despite guidelines that recommended this action.[633] One study by Rohlfs et al. that measured compliance with recommended testing for the IVS-8 poly(T) variant in the CFTR gene showed no difference in testing behavior before and after the guideline was issued.[634] While it is tempting to dismiss this finding as a problem of practitioners who have inadequate training in genetics, a study by Andersson et al. demonstrates significant deficiencies in compliance with guidelines for genetic test reporting in CFTR and factor V Leiden.[635]

Another issue is that guidelines are not in and of themselves subject to any type of enforcement. As noted in Chapter 2, the tort system may use compliance or noncompliance with guidelines to bolster a malpractice claim or defense. The tort system, however, may have less to do with breaching an appropriate standard of medical practice and more to do with disruption of the provider-patient relationship. In short, doctors with fewer medical errors but who have a poor bedside manner are more likely to be sued than doctors that maintain good provider-patient relationships but do not provide a high quality of care.[636,637] Some authors even contend that the focus on malpractice may have a negative effect on efforts to reduce error and enhance safety.[638]

Another way that compliance to guidelines might be encouraged is through reimbursement mechanisms. The role of third-party payers will be explored in more detail below, but the emergence of so-called "pay for performance" initiatives that tie reimbursement to compliance with evidence-based medical practice may elevate the role guidelines will play in directing medical practice. Conceptually, this makes sense, but there is little empirical evidence at present to allow conclusions to be drawn regarding the impact of

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[629] Schuster M.A., McGlynn E.A., Brook R.H. (1998) How good is the quality of health care in the United States? *Milbank Quarterly* 76:517-63.

[630] Ibid.

[631] Ibid.

[632] Giardiello F.M., Brensinger J.D., Petersen G.M., Luce M.C., Hylind L.M., Bacon J.A., Booker S.V., Parker R.D., Hamilton S.R. (1997) The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *New England Journal of Medicine.* 336:823-7.

[633] Grover S., Stoffel E.M., Bussone L., Tschoegl E., Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. (2004) *Clinical Gastroenterology and Hepatology* 2:813-19.

[634] Rohlfs E.M., Weinblatt V.J., Treat K.J., Sugarman E.A. (2004) Analysis of 3208 cystic fibrosis prenatal diagnoses: impact of carrier screening guidelines on distribution of indications for CFTR mutation and IVS-8 poly(T) analyses. *Genetics in Medicine.* 6:400-4.

[635] Andersson H.C., Krousel-Wood M.A., Jackson K.E., Rice J., Lubin I.M. (2002)
Medical genetic test reporting for cystic fibrosis (deltaF508) and factor V
Leiden in North American laboratories. *Genetics in Medicine.* 4:324-7.

[636] Studdert DM, Thomas EJ, Burstin HR, Zbar BI, Orav EJ, Brennan TA. (2000) Negligent care and malpractice claiming behavior in Utah and Colorado. *Med Care*. 38:250-260.

[637] Localio AR, Lawthers AG, Brennan TA, Laird NM, Hebert LE, Peterson LM, Newhouse JP, Weiler PC, Hiatt HH. (1991) Relation between malpractice claims and adverse events due to negligence. Results of the Harvard Medical Practice Study III. *N Engl J Med* 325:245-251.

[638] Pawlson LG, O'Kane ME. (2004) Malpractice prevention, patient safety, and quality of care: a critical linkage. *Am J Manag Care* 10:281-284.

pay-for-performance on improvements in medical care.[639] There are no studies in the literature that examine pay-for-performance in the context of genetic or genomic testing guidelines.

In conclusion, professional societies will continue to play a critical role in the development and maintenance of guidelines for appropriate use of genetic tests, but publication of these guidelines is insufficient to impact use of tests in the clinical setting. Potential solutions to this dilemma are discussed below.

Role of Third-Party Payers

While payers are not traditionally considered to have a role in oversight, access to tests and interventions in the United States is dependent in part on whether insurers will pay for the test or intervention. Insurers make determinations regarding medical necessity (i.e., will the test or intervention lead to benefit for the patient) and experimental/investigational status (i.e., is there sufficient evidence in the literature to support a test or intervention as being a standard of care, or at least well-accepted in clinical practice). In addition, the definition of benefits explicitly States what the insurer will and will not cover. If a benefit excludes coverage of genetic tests (a situation that is encountered not infrequently) it does not matter if the test is medically necessary and no longer investigational—it is not covered by the insurer. A full discussion of the implications of third-party reimbursement for genetic and genomic tests is outside the scope of this document and has been addressed in a separate report.[640]

There is, however, one specific aspect that is relevant to address in this report. In order for third parties to make determinations of medical necessity and experimental/investigational status, it is necessary for them to perform technology assessments. Most of these groups lack specific genetic expertise. As a result, assessment of new genetic tests is challenging.[641,642] This is a critical issue, as it has been shown in this report that there is no current independent oversight of most genetic and genomic tests. This lack of expertise can potentially lead to harms, both from the denial of reimbursement for a test of proven clinical benefit and from access to a test of dubious utility. Ramsey et al. have proposed an evidence-based approach for payers to use when evaluating new tests.[643] Gudgeon et al. have adapted the ACCE model for use as a standardized way for payers and others to perform a rapid technology assessment of emerging genetic tests.[644,645]

The barriers to accessing genetics professionals will most likely increase as genetic testing becomes more readily available for diagnosis, predictive testing, and pharmacogenomics. Strategies using the development of practice guidelines, new technology to provide services, and the training of primary care

[639] Petersen LA, Woodard LD, Urech T, Daw C, Sookanan S. (2006) Does pay-for-performance improve the quality of health care? *Ann Intern Med*. 145:265-272.

[640] SACGHS. Report on Coverage and Reimbursement of Genetic Tests and Services. February 2006. Available at http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf. Accessed on July 31, 2007.

[641] Logue L.J. (2003) Genetic testing coverage and reimbursement: a provider's dilemma. *Clinical Leadership & Management Review*. 17:346-50.

[642] Gudgeon J.M., McClain M.R., Palomaki G.E., Williams M.S. (2007) Rapid-ACCE: Experience with a rapid and structured approach for evaluating gene-based testing. *Genetics in Medicine*.9(7):473-478.

[643] Ramsey S.D., Veenstra D.L., Garrison L.P., Carlson R., Billings P., Carlson J., Sullivan S.D. (2006) Toward evidence-based assessment for coverage and reimbursement of laboratory-based diagnostic and genetic tests. *American Journal of Managed Care*. 12:197-202.

[644] Gudgeon J.M., McClain M.R., Palomaki G.E., Williams M.S. (2007) Rapid-ACCE: Experience with a rapid and structured approach for evaluating gene-based testing. *Genetics in Medicine*.9(7):473-478.

[645] National Office of Public Health Genomics, CDC. ACCE Model System for Collecting, Analyzing and Disseminating Information on Genetic Tests. see: http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm. Accessed June 19, 2007.

providers will be needed to increase access for families to accurate information before and after genetic testing.

Communication of Test Results

Electronic health records (EHRs) are increasingly promoted as a tool to improve the quality and consistency of patient care.[646] There are two primary reasons for this: the dramatic increase in the amount and complexity of medical information, and the recognition that a team approach to patient care results in better outcomes.[647] Use of an EHR has been shown to be directly related to prevention of errors and improved care.[648,649] It has also been shown that patients who understand their conditions and partner with their practitioners in making healthcare decisions are better able to manage these illnesses. Use of a patient-centered health information system, sometimes referred to as a Personalized Health Record (PHR), has been shown to have a positive impact.[650] While much has been promised by the EHR and the PHR, some authors debate how well the current evidence base supports the implementation of electronic records systems.[651] It is also a reality that implementation of electronic records systems in the United States is slow. As of 2005, only 24 percent of physicians had an EHR in the ambulatory setting and only 5 percent of hospitals were using Computerized Order Entry Systems (CPOEs).[652]

Role of the Electronic Health Record

The recognition of the need for EHRs has led to a number of initiatives to promote use of the capabilities of electronic health records. One of the four "leaps" in hospital quality and safety is implementation of Computerized Order Entry Systems.[653] The Institute of Medicine has identified information technology, including medical informatics, as a priority area of study to improve the quality of the U.S. healthcare system.[654] Research in medical informatics is being sponsored by AHRQ.[655] Other countries are also exploring national, integrated EHRs.[656]

The mounting evidence is enough that in the United States, the Secretary of HHS launched the American Health Information Community (AHIC).[657] AHIC is a Federal advisory body, chartered in 2005, to make recommendations to the Secretary on how to accelerate the development and adoption of health information technology. AHIC was formed by the Secretary to help advance efforts to achieve President Bush's goal for most Americans to have access to secure EHRs by 2014. There are 10 workgroups of the AHIC, including the Personalized Medicine Workgroup (PMW) formed October 31, 2006. PMW is

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[646] Shortliffe E.H. (1999) The evolution of electronic medical records. *Academic Medicine*. 74:414-9.
[647] Dove J.T. (2005) The electronic health record--the time is now. *American Heart Hospital Journal*. 3:193-200.
[648] Balas E.A. (2001) Information Systems Can Prevent Errors and Improve Quality. *Journal of the American Medical Informatics Association*. 8:398-9.
[649] Miller R.H., Sim I. (2004) Physicians' use of electronic medical records: Barriers and solutions. *Health Affairs*. 23:116-126.
[650] Gustafson D.H., Hawkins R., Boberg E., Pingree S., Serlin R.E., Graziano F., Chan C.L. (1999) Impact of a patient-centered, computer-based health information/support system. *American Journal of Preventive Medicine*. 1999 16:1-9.
[651] Clamp S., Keen J. (2007) Electronic health records: is the evidence base any use? *Medical Informatics and the Internet in Medicine*. 32:5-10.
[652] Jha A.K., Ferris T.G., Donelan K., DesRoches C., Shields A., Rosenbaum S., Blumenthal D. (2006) How common are electronic health records in the United States? A summary of the evidence. *Health Affairs (Millwood)*. 25:w496-507.
[653] Leapfrog Group Fact Sheet. See http://www.leapfroggroup.org/about_us/leapfrog-factsheet. Accessed June 14, 2007.
[654] Chassin M., Galvin R., and National Roundtable on Health Care Quality. Statement on Quality of Care—the urgent need to improve health care quality. Washington, D.C.: Institute of Medicine, Sept. 16, 1998.
[655] AHRQ (2002) Medical Informatics for better and safer health care. See http://www.ahrq.gov/data/informatics/informatria.htm Accessed June 14, 2007.
[656] Alvarez R. (2004) The electronic health record: a leap forward in patient safety. *Health care Papers*. 5:33-6.
[657] American Health Information Community. (http://www.hhs.gov/healthit/community/background/) Accessed on June 12, 2007.

charged with determining how health information technology (HIT) can be used for the development of standards for interoperable integration of genomic test information into personal e-health records. Personalized health care begins with HIT and the EHR. As the Secretary Stated at an AHIC meeting on September 12, 2006, "…genomics will play an increasingly larger role in medicine, and now is the time to figure out how best to incorporate genetic information into e-health records, before multiple nonstandard approaches take hold." Part of the proposed charge of PMW aims to "encourage the incorporation of interoperable, clinically useful genetic laboratory test data and analytical tools into electronic health records to support clinical decisionmaking for the healthcare provider and patient." This charge has been broadened by the workgroup to include family history, given its importance in the ordering and interpretation of genetic and genomic tests.[658] It seems clear that EHRs and informatic applications will be critical in realizing the maximum benefit from genetic and genomic tests.

Representation of Genetic and Genomic Test Results

The use of computerized systems to capture and deliver genetic test results to the provider can help detect procedural errors in the laboratory and reduce communication errors between the laboratory and provider. Eventually, the adoption of EHR systems can also help ensure that genetic test results are appropriately, consistently, and continuously utilized in the delivery of patient care. The EHR is significantly more than an electronic replacement for patient charts and printed reports. It is an interactive system in which transactions, such as medication orders, can be evaluated using context-specific algorithms to assess whether a decision is appropriate for a particular patient. Inappropriate decisions can be intercepted before a patient is harmed. EHR systems can also automatically identify and address gaps in patient data and enact activities that address these gaps. In the context of genetic testing, for example, an abnormal clotting result might trigger an automated order for a panel of genetic tests related to inherited clotting disorders, but could also prevent the practitioner from ordering clotting protein levels as these results are not informative in the context of an acute clotting event.[659]

Three components of the EHR are particularly relevant for this discussion: the Laboratory Information System (LIS), the Electronic Chart, and the Computer Physician Order Entry (CPOE) system. The LIS is utilized within the diagnostic laboratory to manage workflow, document results, and support the reporting (electronic or manual) of the results to the ordering provider. Much information captured in an LIS is not provided to the ordering clinician such as details related to the extraction of nucleic acid from the patient specimen. Currently, most genetic test findings are stored in long textual reports and are thus of limited value to both clinical decision support system and for queries. Among the most common approaches to documenting genetic test findings is the use of off-the-shelf database systems or the use of an anatomic pathology reporting system. Some high-volume, low-complexity genetic test findings are captured using clinical pathology systems such as factor V Leiden results. Anatomic pathology and clinical pathology systems are generally capable of electronically transmitting the genetic test report to an electronic chart or generating a printed or faxed report. Some LIS suppliers now offer modules designed specifically to support the capture of discrete genetic test findings, optimized to support genetic testing workflow. At the present time, the challenge of representing genomic test results from multiplex platforms is unsolved for the most part. The impact on patient management of these deficiencies is unknown at present.

Results review has also been identified as a key issue in adoption of the EHR.[660] Most EHR systems offer an electronic chart that provides a computer viewable summary of clinically significant information

[658] AHIC Personalized Health care Workgroup. (http://www.hhs.gov/healthit/ahic/health care/) Accessed on June 12, 2007.
[659] Hoffman MA. (2007) The genome-enabled electronic medical record. *J Biomed Inform.* 40:44-46.
[660] Wilbright W.A., Marier R., Abrams A., Smith L., Tran D., Thriffiley A., Butler M.K., Rigamer E., Williams C., Post R. (2005) Building a results review system: a critical first step in transitioning from paper medical records. *American Medical Informatics Association Annual Symposium Proceedings.* 2005:819-23.

about the patient. Electronic Charts may present a variety of views to the clinician and combine the ability to view discrete results with the ability to open online versions of a clinical report. LIS systems and Electronic Charts can either be fully integrated, if developed by the same supplier, or interfaced, generally using Health Language 7 (HL7) messages.[661] Electronic integration (whether direct or via an interface) is important, as it provides the means to synchronize updates or corrections in real time between the laboratory and the provider, a key safety advantage over paper-based reporting methodologies. The degree to which current EHR systems are able to integrate genetic test results is unknown. It has been indicated, however, that this degree of functionality is absent from most commercial EHRs, which limits the ability to perform the safety functions inherent in supporting the highest quality of patient care. While some high volume genetic referral laboratories with fully functional LIS systems that are HL7 enabled have been unable to integrate results into their own EHRs,[662] some other commercial products are able to present discrete genetic findings in an electronic chart, sending these test results from LIS system to EHR.[663]

In a CPOE system, discrete results integrated into an EHR allow for electronically captured clinical decisions to be evaluated. For example, medication orders may be evaluated using "If-Then" logic based on a patient's age, gender, known allergies, or on their genetic test results. A patient with a known variant of their CYP2C9 gene may, by default, be treated with a different dose of warfarin than a patient with a "wild-type" CYP2C9 genotype. The CPOE system can also be configured to prompt the ordering practitioner to provide pre-analytic information that is necessary for interpretation of the test result. Additionally, a CPOE system could prevent a practitioner from re-ordering a genetic test that had been performed previously, given that the result will not change over time. An internal survey at Intermountain Health care (unpublished data) has revealed a large number of duplicate tests for factor V Leiden were not necessary. The impact of CPOE systems to improve ordering of genetic tests has not been studied. It can also be seen that practitioners in different health systems will not have access to results, given the lack of interoperability of systems. This problem is certainly not limited to genetic test ordering and is one of several factors that led to the creation of AHIC.

Communication to Support Genetic Testing in the EHR

In its most basic iteration, the EHR can simply represent an electronic version of the paper medical record. While this approach has some advantages (access to appropriate healthcare workers without transporting a paper chart, improved ability to find information, lower risk of losing information) it does not support most of the goals outlined above. Representation of genetic and genomic test results as scanned images or free text does not address the critical issue of how to communicate these results effectively. Perhaps more importantly, an EHR that does not support transactions, such as CPOE for laboratory tests, misses the opportunity to collect patient specific information in the pre-analytic phase, which is crucial for proper interpretation of the test result. To realize the full potential of genetic and genomic tests requires the use of clinical decision support.

Role of the Personal Health Record

The Personal Health Record (PHR) is a consumer viewable version of the EHR.[664] Generally utilized through either web-based access or kiosks, the PHR allows consumers (patients) to conduct activities

[661] HL7. http://www.hl7.org. Accessed June 22, 2007.
[662] Ullman-Cullere personal communication.
[663] Hoffman, personal communication.
[664] Haux R. (2006) Health information systems - past, present, future. *International Journal of Medical Informatics.* 75:268-81.

such as managing their appointments, updating prescription refills, and viewing laboratory results. With respect to genetic test result findings, the last activity raises a number of process concerns:

- PHR systems should be configurable to limit whether certain laboratory results, including genetic test results, can be viewed by the consumer until required transactions, such as a genetic counseling consultation, have occurred.

- PHR systems often integrate with general web search capabilities. With respect to genetic testing, tools that promote the use of clinically appropriate requisitioning of genetic tests should be promoted.

- PHR systems are often based on groups determined by insurance coverage. Parents can often access laboratory results for their minor children. When a genetic test result is provided and that test has been performed for multiple family members, informed consumers may be able to draw conclusions about the paternity of their children.

There has been no systematic study of genetic test reporting in the PHR environment.

Risk Stratification and Clinical Decision Support

As suggested above, a key part of the value of electronic capture and communication of genetic test results is the opportunity to apply automated algorithms to discrete data in order to evaluate the appropriateness of clinical processes for a patient. Discretely stored genetic test results can also be applied to algorithms that perform automatic risk stratification. For example, cystic fibrosis screening results can be combined with discrete documentation capturing patient response to questions about family history, ethnicity and other information necessary to make a complete assessment of residual risk. These computations can be performed by the system, limiting the risk of human error or inconsistency in determining the risk assessment.

Clinical decision support provides value both within the care delivery setting (e.g., through recommending useful orders) or in the laboratory setting. LIS systems can be configured to intercept and flag values that fall above or below expected reference ranges. For genetic testing, these automated capabilities can be very useful in flagging cases that require further review before delivering the results to the ordering physician, as discussed in more detail below.

Clinical Decision Support

As noted in the Introduction to this chapter, clinical decision support refers broadly to providing clinicians and/or patients with clinical knowledge and patient-related information, intelligently filtered, or presented at appropriate times, to enhance patient care.[665] Clinical decision support can be passive or active. Passive decision support occurs when a system facilitates access to relevant patient data or clinical knowledge for interpretation by the physician, while active decision support implies some higher level of information processing or inference.[666] In the traditional laboratory setting, a reference to the normal value ranges that accompany a laboratory report can be considered passive decision support, while calling the physician with a critical value on a result is active decision support (at its most simplistic). To

[665] Adapted from Teich J.M., Osheroff J.A., Pifer E.A., Sittig D.F., Jenders R.A.; The CDS Expert Review Panel . (2005) Clinical decision support in electronic prescribing: recommendations and an action plan: report of the joint clinical decision support workgroup. *Journal of the American Medical Informatics Association*. 12:365-76.

[666] Elson R.B., Connelly D.P. (1995) Computerized decision support systems in primary care. *Primary Care*. 22:365-84.

illustrate the difference, consider a patient presenting with an acute asthmatic attack. The patient is experiencing air hunger, has a respiratory rate of 50 breaths per minute with retractions and decreased air movement. A blood gas is obtained and the $PaCO_2$ is 40 mm Hg. Passive decision support provides a reference range for $PaCO_2$ of 35-45 mm Hg. The passive information tells the physician that the result is in the normal range. An experienced physician knows that even though the result is in the normal range, it is not normal for the clinical presentation. This patient is experiencing incipient respiratory failure. If this result was assumed to be normal by the physician, the gravity of the situation could be missed and the patient could suffer injury and death. In contrast, were an active decision support system built for this scenario, it would use rules to capture relevant data about the diagnosis and patient parameters, so that when the result returned, it would generate an urgent message to the care team indicating that the patient was at risk for respiratory failure and, depending on its sophistication could suggest possible interventions.

Passive Decision Support

Pre-analytic phase. An example of a passive decision support tool is an order sheet, whether paper or electronic, that requires the ordering practitioner to fill in certain data elements necessary to interpret the test. In the case of maternal serum screening, information would need to be provided about gestational age, diabetic status, single vs. multiple gestation, and maternal weight, so that the analyte values can be compared against the appropriate reference ranges. The quality of the information provided has a measurable impact on the performance of the test.[667] Patient-specific factors, such as ethnicity, have such a large impact on test interpretation that they are referenced in professional society guidelines for genetic testing of cystic fibrosis[668] and breast/ovarian cancer.[669] The problem with this type of system is that if the practitioner does not have access to the form, does not complete all the information, or enters erroneous information, the test interpretation will either be delayed or inaccurate. Human intervention is required to catch and remedy the error. For example, if inaccurate data entry led to an interpretation of an increased risk for Down syndrome and the error was not caught, the patient would be offered an invasive diagnostic procedure (amniocentesis) with risk for pregnancy loss secondary to the procedure. To date, the degree to which the lack of collection of data in the pre-analytic phase impacts interpretation of genetic test results has not been studied.

Post-analytic phase. One approach to improving the interpretation of the test result is to embed educational resources with the result. This approach allows practitioners to access relevant material with a single click without navigating away from the patient record. This "just-in-time" educational approach facilitates rapid access to context-specific material that can answer questions that arise. State newborn screening programs have used just-in-time education (through the use of information sheets and contact with professionals to aid in management) for primary care providers for decades with great success.[670] Since most of the disorders detected are very rare, primary care providers appreciate the information when they have a patient who potentially has the disorder. With HRSA funding, the ACMG and AAP have jointly developed "ACT sheets" for primary care providers to provide this type of just-in-time information for newborn screening.[671] There is some evidence to suggest that this may be the most

[667] Benn P.A., Borgida A., Horne D., Briganti S., Collins R., Rodis J.F. (1997) Down syndrome and neural tube defect screening: the value of using gestational age by ultrasonography. *American Journal of Obstetrics and Gynecology*. 176:1056-61.
[668] ACMG CF (2001) http://www.acmg.net/resources/policies/pol-005.asp Accessed June 19, 2007.
[669] ACMG BRCA. (1996) http://www.acmg.net/resources/policies/pol-002.asp Accessed June 19, 2007.
[670] e.g., California Newborn Screening Program. GeneHelp Resource Center. Available at http://www.dhs.ca.gov/pcfh/gdb/html/NBS/GeneHelpResCenter.htm. Accessed on August 9, 2007.
[671] ACMG. Newborn Screening ACT Sheets and Confirmatory Algorithms. Available at http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm. Accessed on August 9, 2007.

effective way to promote the practice of evidence-based medicine.[672] Just-in-time patient education has also been shown to be effective even for patients with low literacy facing complex medical issues.[673] For State newborn screening programs, just-in-time patient education has been used quite successfully. HRSA has funded several projects over the past several decades to develop just-in-time patient education that is culturally competent and community-based.[674,675,676] Sickle cell disease and trait is an example of an area that has extensive patient educational materials.[677] Just-in-time education has been used to deliver information on genetics and genomics at the point of care for practitioners and patients[678,679,680] including one project specifically focused on education relevant to genetic test results.[681] The latter study found that nearly half of the respondents were unfamiliar with some aspect of the result report. They confirmed the usefulness of the program as an educational tool at the point of care. At present, most EHRs do not support this capability, which could lead to suboptimal care.

Active Decision Support

Pre-analytic phase. The concept of active decision support in the laboratory to support collection of pre-analytic information and assist in test interpretation dates to the late 1970s, with extant examples presented in the literature as early as 1982.[682] Even then, the main limitation identified was the lack of key clinical information.[683] This limitation not only hindered interpretation of the ordered test result, but missed the opportunity to suggest a more appropriate test to answer the clinical question for which the test was actually ordered. This problem has been recognized even with tests for common disorders.[684] This variability seems to be related to individual physician characteristics.[685] These results led to the conclusion that if electronic knowledge support could be applied during the ordering phase of testing, one

[672] Slawson D.C., Shaughnessy A.F. (2005) Teaching evidence-based medicine: should we be teaching information management instead? *Academic Medicine*. 80:685-9.

[673] Jibaja-Weiss M.L., Volk R.J., Friedman L.C., Granchi T.S., Neff N.E., Spann S.J., Robinson E.K., Aoki N., Robert Beck J. (2006) Preliminary testing of a just-in-time, user-defined values clarification exercise to aid lower literate women in making informed breast cancer treatment decisions. *Health Expectations*. 9:218-31.

[674] HRSA. HRSA Awards $1.9 Million to Improve Treatment of Sickle Cell Disease. September 29, 2006. Available at http://newsroom.hrsa.gov/NewsBriefs/2006/sickle-cell-treatment.htm. Accessed on August 17, 2007.

[675] HRSA. HRSA Awards More Than $4.4 Million in Grants to Enhance Services for Newborns with Sickle Cell Disease and Improve Women's Health. November 13, 2002. Available at http://newsroom.hrsa.gov/releases/2002releases/sicklecell.htm. Accessed on August 17, 2007.

[676] HRSA. HRSA Awards $3.6 Million to Improve State Sickle Cell Disease and Newborn Screening Programs. October 3, 2003. Available at http://newsroom.hrsa.gov/releases/2003/sicklecell.htm. Accessed on August 17, 2007.

[677] For example, ACMG. Newborn Screening ACT Sheet: Sickle Cell Anemia. Available at http://www.acmg.net/resources/policies/ACT/ACT-sheet_HBSC_FSC_4-18-06.pdf. Accessed on August 17, 2007.

[678] Green M.J., Peterson S.K., Baker M.W., Harper G.R., Friedman L.C., Rubinstein W.S., Mauger D.T. (2004) Effect of a computer-based decision aid on knowledge, perceptions, and intentions about genetic testing for breast cancer susceptibility: a randomized controlled trial. *Journal of the American Medical Association*. 292:442-52.

[679] Kaihoi B., Petersen C., Bolander M.E. (2005) Providing "just-in-time" medical genomics information for patient care. *American Medical Informatics Association Annual Symposium Proceedings*. 1003.

[680] Del Fiol G., Williams M.S., Maram N., Rocha R.A., Wood G.M., Mitchell J.A. (2006) Integrating genetics information resources with an EHR. *American Medical Informatics Association Annual Symposium Proceedings*. 904.

[681] Goos L.M., Silverman I., Steele L., Stockley T., Ray P.N. (2004) Providing information at the point of care: educational diagnostic reports from a genetic testing service provider. *clinical Leadership & Mangement Review*. 18:11-24.

[682] McNeely M.D. (2002) The use of expert systems for improving test use and enhancing the accuracy of diagnosis. *Clinics in Laboratory Medicine*. 22:515-28.

[683] Ibid.

[684] van Walraven C., Naylor C.D. (1998) Do we know what inappropriate laboratory utilization is? A systematic review of laboratory clinical audits. *Journal of the American Medical Association*. 280:550-8.

[685] Malcolm L., Wright L., Seers M., Davies L., Guthrie J. (2000) Laboratory expenditure in Pegasus Medical Group: a comparison of high and low users of laboratory tests with academics. *New Zealand Medical Journal*. 113:79-81.

could influence use, optimize test ordering, and gain the critical clinical information needed to enhance test interpretation.[686]

While the development of expert systems is complex, it has been demonstrated that even with common clinical conditions and tests, implementation of a system can decrease the cost of testing while improving the diagnostic accuracy.[687,688] The complexity and the frequent requirement for patient information in the pre-analytic phase in order to interpret the results of a genetic test has led to calls for closer relationships between clinicians, patients, and laboratories.[689] Despite the demonstration of the role active decision support can play to solve this issue, there are no published examples of active clinical decision support being implemented in the pre-analytic phase, although an operating example of a CPOE system that supports genomic testing for neuropsychiatric medications at Cincinnati Children's Hospital was presented at the 2007 NCHPEG meeting.[690] This gap has been noted by the Collaboration, Education and Test Translation (CETT) program. At the 2007 spring meeting, a presentation by Lisa Forman outlined the challenges of collecting patient data and linking this data with the test sample and result.[691] As noted above, this could harm patient well-being and waste scarce medical resources on inappropriate or duplicate tests. McPherson presents several genetic testing scenarios that illustrate these concepts.[692] This problem, however, has not been systematically studied at present.

Post-analytic phase. As noted above, there is ample documentation of the challenges faced by practitioners attempting to interpret the results of genetic tests with resultant negative impacts on patient care. As with the pre-analytic phase, the proposed solution at the present time is to produce clearer written reports, supplemented by genetic professionals associated with the laboratory that are available for consultation.[693,694] In the laboratory setting, there is evidence that active decision support can facilitate appropriate interpretation of results.[695,696.697] Again, there are no published examples of such a system being used to facilitate the interpretation by the clinician of genetic or genomic tests. The Couma-Gen trial used an algorithm to combine patient characteristics such as age, gender, weight, and medications with genomic data to determine the starting dose of coumadin for patients initiating anticoagulation.[698] While the results of the trial are still being analyzed, the active decision support algorithm that supplied

[686] McNeely M.D. (2002) The use of expert systems for improving test use and enhancing the accuracy of diagnosis. *Clinics in Laboratory Medicine*. 22:515-28.

[687] Smith B.J., McNeely M.D. (1999) The influence of an expert system for test ordering and interpretation on laboratory investigations. *Clinical Chemistry*. 45:1168-75.

[688] van Wijk M.A., van der Lei J., Mosseveld M., Bohnen A.M., van Bemmel J.H. (2001) Assessment of decision support for blood test ordering in primary care. a randomized trial. *Annals of Internal Medicine*. 134:274-81.

[689] Quillin J.M., Jackson-Cook C., Bodurtha J. (2003) The link between providers and patients: how laboratories can ensure quality results with genetic testing. *Clinical Leadership & Management Review*. 17:351-7.

[690] Glauser T. (2007) http://www.nchpeg.org/downloads/annual_mtg_2007_agenda.doc Accessed June 19, 2007.

[691] CETT 2007. http://www.cettprogram.org/documents/CETT_Meeting_Database_NCBI_March_2007.pdf Accessed June 19, 2007.

[692] McPherson E. (2006) Genetic diagnosis and testing in clinical practice. *Clinical Medicine & Research*. 4:123-9.

[693] McGovern M.M., Benach M., Zinberg R. (2003A) Interaction of genetic counselors with molecular genetic testing laboratories:implications for non-geneticist health care providers. *American Journal of Medical Genetics Part A*. 119:297-301.

[694] Quillin J.M., Jackson-Cook C., Bodurtha J. (2003) The link between providers and patients: how laboratories can ensure quality results with genetic testing. *Clinical Leadership & Management Review*. 17:351-7.

[695] Van Lente F., Castellani W., Chou D., Matzen R.N., Galen R.S. (1986) Application of the EXPERT consultation system to accelerated laboratory testing and interpretation. *Clinical Chemistry*. 32:1719-25.

[696] Trendelenburg C., Colhoun O., Wormek A., Massey K.L. (1998) Knowledge-based test result in interpretation in laboratory medicine. *Clinica Chimica Acta*. 278:229-42.

[697] Smith B.J., McNeely M.D. (1999) The influence of an expert system for test ordering and interpretation on laboratory investigations. *Clinical Chemistry*. 45:1168-75.

[698] Couma-Gen (2007) http://clinicaltrials.gov/ct/show/NCT00334464;jsessionid=1B6C6035A24A8C808FCAF2C58E9952B1?order=39 Accessed June 19, 2007.

the dose to the Doctor of Pharmacy performed well and was well accepted by the practitioners. The necessary components of a system, including whether it should reside in the EHR or the LIS, as well what factors are necessary to maximize acceptance and use by clinicians, remain to be elucidated. The role, and indeed the question of whether there should be a role, for the PHR in active decision support for interpretation of test results is unknown.

One additional point with regard to the EHR needs to be addressed. This issue involves how the capture of outcomes data can improve knowledge and ultimately improve the care of patients. In a study by van Wijk et al.,[699] the authors noted that 61 percent of practitioners were not in compliance with the expert system's recommendation. In nearly two-thirds of these cases, there were deficiencies in the underlying guidelines. Capture of the noncompliant orders led to improvement in construction of the guideline. This issue is critically important in the case of genetic and genomic tests, where complete knowledge is rarely present at the time of test introduction. The CETT program's data collection process is designed to capture information that can be used to increase knowledge about ultra-rare genetic disorders.[700] Several genetic referral laboratories routinely store variants of unknown significance and periodically reevaluate these in light of new knowledge and increased experience.[701] HRSA is currently funding the development of model data structures and electronic systems to collect long-term follow-up data on children who have disorders detected via newborn screening.[702] This type of research would not be possible without electronic systems. How to implement such a system, where the data should be kept, who should access to the data, and under what circumstances it should be used are problems that await a solution. The lack of such systems could delay integration of new knowledge into clinical care resulting in harm to patients. Recognition of these problems has led to the establishment of two programs within the AHRQ: Centers for Education and Research on Therapeutics (CERT)[703] and Developing Evidence to Inform Decision on Effectiveness (DEcIDE).[704] For a more complete discussion of the potential value of this type of system in healthcare (although not specific to genetic applications), see Detmer, 2003 or Etheredge, 2007.[705,706]

Finally, FDA's revised draft guidance on IVDMIAs has implications for regulation and oversight of clinical decision support.[707] The guidance:

1. Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., "classification," "score," "index,"), that is intended for use in the

[699] van Wijk M.A., van der Lei J., Mosseveld M., Bohnen A.M., van Bemmel J.H. (2001) Assessment of decision support for blood test ordering in primary care. a randomized trial. *Annals of Internal Medicine*. 134:274-81.

[700] CETT 2007. http://www.cettprogram.org/documents/CETT_Meeting_Database_NCBI_March_2007.pdf Accessed June 19, 2007.

[701] Chenevix-Trench G., Healey S., Lakhani S., Waring P., Cummings M., Brinkworth R., Deffenbaugh A.M., Burbidge L.A., Pruss D., Judkins T., Scholl T., Bekessy A., Marsh A., Lovelock P., Wong M., Tesoriero A., Renard H., Southey M., Hopper J.L., Yannoukakos K., Brown M., Easton D., Tavtigian S.V., Goldgar D., Spurdle A.B.; kConFab Investigators. (2006) Genetic and histopathologic evaluation of BRCA1 and BRCA2 DNA sequence variants of unknown clinical significance. *Cancer Research*. 66:2019-27.

[702] HRSA MCHB. Minutes of May 17-18, 2007 Meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Available at http://mchb.hrsa.gov/programs/genetics/committee/final-10th-minutes.htm#_Toc168809630. Accessed on August 1, 2007.

[703] Centers for Education and Research on Therapeutics. Available at http://www.ahrq.gov/clinic/certsovr.htm. Accessed on July 26, 2007.

[704] AHRQ. Developing Evidence to Inform Decision on Effectiveness. Available at http://effectivehealthcare.ahrq.gov/aboutUs/index.cfm. Accessed on July 26, 2007.

[705] Detmer D.E. (2003) Building the national health information infrastructure for personal health, health care services, public health, and research. *BMC Medical Informatics and Decisionmaking*. 3:1.

[706] Etheredge L.M. (2007) A rapid-learning health system. *Health Affairs (Millwood).* 26:w107-18.

[707] Draft Guidance for Industry, Clinical Laboratories, and FDA Staff. In Vitro Diagnostic Multivariate Index Assays. http://www.fda.gov/cdrh/oivd/guidance/1610.html. Last accessed July 26, 2007.

diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, and

2. Provides a result whose derivation is nontransparent and cannot be independently derived or verified by the end user.

Specific examples are used to illustrate what the FDA considers to be within and outside of its scope of regulation. As previously discussed in Chapter 3, the FDA considers, "A device that integrates a patient's age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition" as an IVDMIA subject to its regulation. The pharmacogenomic dosing of warfarin could fall under this regulation if FDA interprets this method as predicting risk or diagnosing a condition. To further complicate the issue, however, the FDA outlines that clinical decision support tools that analyze stored clinical information to, create disease registries, summarize patient-specific information in an integrated report, and/or track a patient's treatment or disease outcome "[do] not represent a unique interpretation function but rather summarizes standard interpretation of individual variables that clinicians could do themselves." In the case of warfarin dosing, if a clinician uses an available dosing algorithm that incorporates the results of the CYP2C9 and VKORC1 tests done by a referral laboratory with clinical information supplied by the clinician, it is unclear if it would be considered an IVDMIA and subject to regulation as a device. Presumably, if all of these functions were integrated within the testing laboratory and a warfarin dose was returned to the clinician as a result, this would clearly meet the definition of an IVDMIA. At what point, however, does the assembly of disparate information within an EHR, independent of the testing laboratory, constitute an IVDMIA? Harm could potentially result from overzealous application of regulation, by inhibiting the development and implementation of clinical decision support needed to empower clinicians to use the results of genetic tests. On the other hand, potential harm could also result from insufficient scrutiny of devices whose clinical utility is not well understood, leading to inappropriate application of the test in a clinical setting.

The prevailing standard is the use of Arden syntax,[708] a formalized representation of CDS logic modules. Often, CDS logic is deployed as a local configuration within the EHR system and is not generally considered to be new software development. An analogy is the use of macros within a commercial spreadsheet system – each user of the system is free to implement local macros that satisfy their particular goals. Often provider organizations that implement local CDS logic create a local review committee that approves the clinical logic and confirms that appropriate validation of the CDS has been performed. While the FDA provides general guidance on the validation of clinical software,[709] to the best of this Committee's knowledge, there are no guidelines describing a formal process for the adoption and validation of local CDS configurations.

Communicating Genetic Test Results: Implications for the Consumer

Patients and families need accurate, accessible, and complete information about genetic tests in order to make informed healthcare decisions. Three factors make the availability of high quality information about testing particularly important. First, patients are taking a greater interest in and responsibility for managing their health. Second, as discussed above, primary care providers may not have sufficient training or expertise to offer high quality genetic testing information and services. Third, the increasing marketing and sale of genetic tests directly to consumers mean that testing services can be accessed by the patient themselves without the involvement of a healthcare provider.

[708] Arden Syntax Mission and Charter. Available at http://www.hl7.org/Special/committees/Arden/index.cfm#Mission . Accessed on September 25, 2007

[709] General Principles of Software Validation; Final Guidance for Industry and FDA Staff http://www.fda.gov/cdrh/comp/guidance/938.html. Last accessed September 7, 2007.

There is a rich and extensive history of social science research on the public's attitudes toward genetic research, the clinical application of genetics and genetic testing, and the social and policy issues emerging from advances in our understanding of the human genome. Numerous studies have also detailed patient understanding, preferences, and information and support needs of specific patient populations. These studies have been undertaken to inform the design of research studies and clinical practices. For example, researchers have sought to understand attitudes towards genetic testing, factors that affect perceptions of risk, decisionmaking of at-risk and healthy individuals about whether to obtain a specific genetic test,[710,711,712,713,714,715,716,717,718] models of informed consent,[719,720,721,722] modes of education and communication,[723] the psychological impact of testing,[724,725726,727,728,729] and the like. Some of these studies focused on racial and ethnic differences in attitudes toward uptake and impacts of genetic testing or participation in genetics research.[730,731,732,733,734,735,736]

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[710] Metcalfe K, Liede A, Trinkaus M, Hanna D, Narod SA. 2000 An evaluation of needs of female BRCA1 and BRCA2 carriers undergoing genetic counseling. *J Med Gen* 37:866-874.

[711] Eccles DM, Evans DG, Mackay J. 2000 Guidelines for a genetic riskbased approach to advising women with a family history of breast cancer. *J Med Gen* 37:203-109.

[712] Vernon SW, Gritz ER, Peterson SK, Perz CA, Marani S, Amos CI, Baile WF. 1999. Intention to learn results of genetic testing for hereditary colon cancer. *Cancer Epidemiol Biomarkers Prev*;8(4 Pt 2):353-60.

[713] Codori AM, Petersen GM, Miglioretti DL, Larkin EK, Bushey MT, Young C, Brensinger JD, Johnson K, Bacon JA, Booker SV. 1999. Attitudes toward colon cancer gene testing: factors predicting test uptake. *Cancer Epidemiol Biomarkers Prev*;8(4 Pt 2):345-51.

[714] Lerman C, Seay J, Balshem A, Audrain J. 1995. Interest in genetic testing among first-degree relatives of breast cancer patients. *Am J Med Genet*;57(3):385-92.

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[722] Andrews LB. 1997 Compromised consent: deficiencies in the consent process for genetic testing. *J Am Med Womens Assoc*;52(1):39-42, 44.

[723] Green MJ, Fost N. 1997 An interactive computer program for educating and counseling patients about genetic susceptibility to breast cancer. *J Cancer Educ*;12(4):204-8.

[724] Lerman, C et al. 1996. BRACA1 testing in families with hereditary breast-ovarian cancer: A prospective study of patient decisionmaking and outcomes. *JAMA*;275(24), 1885-1892.

[725] Lerman et al 1998. What you don't know can hurt you: Adverse psychologic effects in member of BRCA1-linked and BRCA2-linked families who decline genetic testing. *J. Clin Oncol* ;16(5), 1650-1654

[726] Audrain J, Schwartz MD, Lerman C, Hughes C, Peshkin BN, Biesecker B. 1997. Psychological distress in women seeking genetic counseling for breast-ovarian cancer risk: the contributions of personality and appraisal. *Ann Behav Med*;19(4):370-7.

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[728] Codori AM. 1997. Psychological opportunities and hazards in predictive genetic testing for cancer risk. *Gastroenterol Clin North Am;* 26(1):19-39. Review.

[729] Codori AM, Slavney PR, Young C, Miglioretti DL, Brandt J. 1997. Predictors of psychological adjustment to genetic testing for Huntington's disease. Health Psychol.;16(1):36-50.

[730] Mittman IS, Secundy MG. 1998. A national dialogue on genetics and minority issues. *Community Genet*;1(3):190-200.

There are a number of publicly available sources of information and support about genetic conditions and genetic testing,[737,738,739,740,741] as well as informational materials provided by individual clinics, State programs, disease-specific support groups, and laboratories. Not all of these resources are designed to provide information at a patient level. In addition, a motivated patient would encounter difficulties in accessing and understanding relevant articles in the medical literature because many are available only with a subscription and the articles themselves use highly technical language and complex statistical analyses. Some patient and professional groups are now advocating for open access to these resources. As an example, the Genetic Alliance recently announced opening of The National Consumer Center for Genetics Resources and Services funded by a cooperative agreement between HHS, HRSA, and the Genetic Services Branch of the Maternal and Child Health Bureau.[742] The major purpose of this 5-year, $500,000 a year special project is to mitigate the substantial information and resource deficit for consumers of genetic services.

Various studies have assessed the accuracy, completeness, and readability of patient information about genetic tests. For example, a study of materials on the genetic risk of breast cancer found that the images and text were not sufficiently clear.[743] Another study of education materials about genetic testing found that most materials did not contain essential information about the purpose or accuracy of the test.[744] In addition, materials frequently fail to discuss the social and psychological implications of testing.

Several efforts to develop and assess genetic testing information materials have identified key issues about testing that should be included in patient materials.[745] A study in Europe[746] used the following key issues in evaluating information materials about genetic testing and found substantial omissions in the materials reviewed.

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[731] Duran DG. 1998. Lack of Hispanics' involvement in research -- is it Hispanics or scientists? *Community Genet*;1(3):183-9.
[732] Jaeger AS, Goode EL, Boyle JM. 1997. Attitudes and opinions towards genetic testing among US Hispanics. *Am J Hum Genet*;61(4):A221.
[733] Durfy SJ, Bowen DJ, McTiernan A, Sporleder J, Burke W. 1999. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in western Washington. *Cancer Epidemiol Biomarkers Prev*;8(4 Pt 2):369-75.
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[736] Hughes C, Gomez-Caminero A, Benkendorf J, Kerner J, Isaacs C, Barter J, Lerman C. 1997. Ethnic differences in knowledge and attitudes about BRCA1 testing in women at increased risk. *Patient Educ Couns*;32(1-2):51-62.
[737] Online Mendelian Inheritance in Man (OMIM) see http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM Accessed June 25, 2007.
[738] GeneTests see http://www.genetests.org/ Accessed June 25, 2007.
[739] Genetics Home Reference (GHR) see http://www.ghr.nlm.nih.gov/ Accessed June 25, 2007.
[740] Genetic Alliance see http://www.geneticalliance.org/ Accessed June 25, 2007.
[741] National Organization of Rare Diseases (NORD) see http://www.rarediseases.org/. Accessed June 25, 2007.
[742] http://www.tmcnet.com/usubmit/2007/09/05/2914707.htm. Last accessed September 7, 2007.
[743] Thompson Hs, Wahl E. Fatone A, Brown K, Kwate NO, Valdimarsdottir H. 2004 Enhancing the readability of materials describing genetic risk for breast cancer. *Cancer Control*; 11: 245-253.
[744] Cho MK, Arruda M, Hotlzman NA. 1997 Education material about genetic test; does it provide key information for patients and practitioners? *Am J Med Genet*; 73:314-320.
[745] Shepperd S, Farndon P, Grainge V et al: 2006 DISCERN-Genetics:quality criteria for information on genetic testing. *Eur J Hum Genet*; 14: 1179-1188.
[746] Lewis C, Mehta P, Kent A, Skirton H, Coviello D. 2007 An assessment of written patient information provided at the genetic clinic and relating to genetic testing in seven European countries. *Eur J Hum Genet*. June 13 [Epub ahead of print].

1. Background and effect of condition
2. Treatment and management
3. Heredity and risk
4. Patient rights
5. Type of test
6. Accuracy of test
7. What happens after the test
8. Shared decisionmaking
9. Psychosocial consequences
10. Consequences for family members
11. Benefits and risks
12. Date and sources
13. Additional support and information

An earlier study in the United States concluded that most materials did not contain basic information about the purpose or accuracy of the test.

When discussing the role of the consumer and genetic testing, the focus has generally been on either patients/families/disease-specific support groups or the general public. If one represents these two "communities" as the ends of a spectrum, it is clear that there may be other self-identified communities that reside between these two ends. These could include racial/ethnic communities, culturally defined groups, and those with disabilities. Some work has been done to define some of these communities and explore their attitudes and beliefs about genetics.

Ethnic, racial, and cultural minorities, many of whom are new immigrants, face the greatest barriers to understanding pre- and postgenetic testing information. Many studies already document the language, cultural, and socioeconomic barriers that prevent these minority populations from accessing and using healthcare information and services.[747,748,749,750,751,752,753,754,755,756,757] The greatest barrier to accessing and understanding health information for minority populations has universally been identified as the lack of English proficiency. According to the 2000 U.S. Census data, over 50 percent of Hispanics, Chinese, and Vietnamese do not speak English.[758] The lack of English proficiency and the other documented barriers

[747] Yu, SM et al (2006). *Parental English proficiency and children's health service access*. Am J Public Health, 96(8), 1449-55.
[748] Davidson, JA et al (2007). *Cardiovascular disease prevention and care in Latino and Hispanic subjects.* Endocr Pract, 13(1), 77-85.
[749] Ngo-Metzger, O et al (2003). *Linguistic and cultural barriers to care.* J Gen Intern Med, 18(1), 44-52.
[750] Kelly, PA, Haidet, P (2007). *Physician overestimation of patient literacy: a potential source of health care disparities.* Patient Educ Couns, 66(1), 119-22.
[751] Safeer RS et al (2006). *The impact of health literacy on cardiovascular disease.* Vasc Health Risk Management, 2(4), 457-64.
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[756] Nguyen, GT and Bowman, MA (2007). *Culture, language, and health literacy: communicating about health with Asians and Pacific Islanders.* Fam Med, 39(3), 195-200.
[757] Ka'opua, LS et al (2004). *Increasing participation in cancer research: insights from Native Hawaiian women in medically underserved communities.* Pac Health Dialog, 11(2), 170-5.
[758] Shin, HB and Bruno, R (2002). *Language use and English-speaking ability*, CK2BR-29, U.S. Census Bureau.

to accessing and understanding basic health information does not bode well for minority populations' ability to take advantage of the complexities of genetic test results to improve health outcomes.

Qureshi and Kai did a review of the literature to assess the use of genomic medicine for minority populations. They found that effective communication with appropriate translations and interpretations in the context of the ethnic, racial, or cultural groups was the biggest challenge facing the introduction of genomic medicine to minority groups.[759] The importance of appropriate translation of health information was also reported by Ngo-Metzger et al.[760] Ngo-Metzger conducted focus groups in Boston with Chinese and Vietnamese patients with limited English skills to assess their general health information needs. The patients reported that the use of professional interpreters that are gender-concordant, rather than family members, was very important to them. Given that genetic information may affect the family member who is translating the information, Qureshi and Kai also found that the use of professional interpreters to help non-English speaking minority patients should be the preferred practice by healthcare providers if the provider can not communicate in the patient's language.[761]

Most studies about genetic testing in minority populations has centered around genetic testing for cancer risk assessment. Several studies have shown that the uptake of cancer susceptibility genetic tests is lower in African American, Hispanic, Asian, and Native American populations than the Caucasian population.[762,763,764] The African American and Native American populations expressed more anxiety about the use of genetic information for adverse actions, such as discrimination.[765,766,767] Interestingly, Catz et al. found that Hispanic and Asian patients reported more difficulty accessing the services because of language and cultural barriers rather than any fear of adverse actions.[768] For Asian Americans, one major identified cultural barrier was the inability of Western doctors to respect and incorporate the patients' beliefs about traditional Asian medicine and practices into their care.[769] Given the difficulties that minority groups face in accessing, understanding, and using genetic tests and information, it is important that pre- and post-educational materials also be made available in languages other than English. It is not enough to just translate the English information directly, but an effort must be made to translate the information within the context of the culture of the minority group to optimize the use of the information by the patient. It is also important to ensure that professional translators are available, especially if the genetic test or information may affect a family member who had come with the patient to translate.

Whatever strategy is developed to provide pre- and post-genetic testing information to patients must include additional effort and funding to make the information and materials culturally, ethnically, and

[759] Qureshi, M and Kai, J (2005) *Genomic Medicine for Underserved Minority Populations in Family Medicine.* Am Fam Physician, 72(3), 386--7
[760] Ngo-Metzger, O et al (2003). *Linguistic and cultural barriers to care.* J Gen Intern Med, 18(1), 44-52.
[761] Qureshi, M and Kai, J (2005) *Genomic Medicine for Underserved Minority Populations in Family Medicine.* Am Fam Physician, 72(3), 386--7
[762] Armstrong, K et al (2005). *Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer.* JAMA, 13;293(14), 1729-36
[763] Hall, MJ and Olopade, OI (2006). *Disparities in genetic testing: thinking outside the BRCA box.* J Clin Oncol. 12;24(14), 2197-203.
[764] Peters, N et al (2004). *The association between race and attitudes about predictive genetic testing.* Cancer Epidemiol Biomarkers Prev. 13(3), 361-5
[765] Ibid.
[766] Armstrong, K et al (2005). *Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer.* JAMA, 13;293(14), 1729-36
[767] Catz, DS et al (2005). *Attitudes about genetics in underserved, culturally diverse populations.* Community Genet, 8(3), 161-72.
[768] Ibid..
[769] Ngo-Metzger, O et al (2003). *Linguistic and cultural barriers to care.* J Gen Intern Med, 18(1), 44-52.

racially appropriate. These efforts would help assure that minority groups will have some hope in overcoming the barriers to access and use appropriate genetic tests and information to improve their health outcome. Additionally, healthcare providers must receive further training to help them provide the genetic information within their patients' cultural and lifestyle beliefs to optimize the use of the genetic information.

Gaps in Clinical Decision Support

- There significant gaps in the communication of information required for interpretation of test results. During the pre-analytic phase, gaps include limited information about how practitioners order genetic tests, an inability of laboratories to collect the clinical information necessary for test interpretation, and insufficient data concerning how family information is obtained and used to support clinical decisionmaking about test ordering and results reporting.

- Concerning the interpretation and use of test results, there is limited information about how practitioners interpret them and about the collection and use of patient and family information to support them, a lack of guidance for interpreting complex genomic tests, an inconsistent approach to clinically validating and communicating information about variants of unknown significance, insufficient data on how practitioners account for variations in laboratory methodologies in applying results to decisionmaking, no studies that examine how practitioners are using genomic information to inform care or how genomic information is combined with other information in clinical decisionmaking, and logistical issues that create barriers the to transfer of information to and from laboratories.

- There are no studies on the incorporation of guideline recommendations into laboratory practice or the impact of implementation on the laboratory and end-user. Practitioners are unfamiliar with guidelines for appropriate use of genetic tests and there is a lack of appropriate mechanisms to communicate guidelines for testing at the time of test ordering. Processes have not been implemented and evaluated to support practitioners in the use of genetic /genomic test information. Publication of care guidelines is insufficient to alter patterns of care delivery and guidelines are not enforceable. There are no data on the role active clinical decision support can play in driving appropriate utilization of genetic/genomic tests and results, on practitioner use and acceptance of active clinical decision support for genetic/genomic tests, or the role of active clinical decision support in the personal health record.

- There is inadequate didactic and practical genetic education in practitioner training programs, resulting in an inadequately educated provider system. Other deficiencies include a lack of resources on genetic/genomic tests, a lack of educational materials designed to help patients use genetic/genomic test results, and a lack of knowledge concerning how practitioners use available resources to answer questions about genetic/genomic tests and the role of just-in-time education to support best practice. Data are needed on electronic information resources, including the number of practitioners using available online genetic resources and the accuracy and accessibility of genetic information in commonly used electronic resources.

- There is a lack of reimbursement for the laboratory-employed or contracted genetic professionals that provide support to patients and practitioners regarding genetic tests and a lack of data on whether these genetic professionals improve the ordering and interpretation of genetic tests. Conversely, there are no data on whether the lack of these professionals adversely impacts the ordering and interpretation of genetic tests. There is a lack of access to providers with genetic

expertise and a lack of genetic expertise in groups that perform technology assessment of emerging genetic/genomic tests.

- In the area of research and translation, there is a lack of on ongoing data collection to refine knowledge after a test is clinically available and a lack of integration of new knowledge into decision support to improve care.

- There is a lack of studies that compare multiplex genomic assays to other approaches to stratify risk and that determine the impact of point-of-care testing.

- There are gaps in CLIA and gaps in the oversight of clinical validation.

- Numerous gaps exist related to electronic and personal health records. There is limited deployment, utilization, and functionality of HER systems in general. The representation of genetic test results and multiplex genomic results in EHRs is now in development, but current coding systems are inadequate for this purpose. The impact of this deficiency on patient care is unknown. There are no data on representing genetic/genomic test results in the personal health record and no data on the role of computerized order entry in ensuring appropriate utilization of genetic/genomic tests. There is a lack of interoperability between systems and barriers to data sharing. For example, widely used versions of HL-7 (versions 2.7 and lower) require updating to support transmission of genetic and genomic test findings. There is also a lack of communication between public and private data repositories, a lack of an accepted and consistent process for local review and approval of CDS logic by affected providers, and a lack of clarity concerning how FDA will choose to regulate CDS systems that are not integrated within the testing laboratory for genetic and genomic tests.

Evidence of Harms and Potential Harms

There is a lack of studies that quantify actual harm to patients, families, practitioners, and the healthcare system. The following harms have at least some documentation in the literature:

- Practitioners unfamiliar with guidelines about the indications for conducting a genetic test may order tests inappropriately. Practitioners are less likely to order a test if it is labeled as a genetic test.

- There is misinterpretation of tests based on limited or inaccurate clinical information and because of inadequate or confusing reports.

- Practitioners are not adequately prepared to use test information to treat patients appropriately, and practice guidelines are insufficient to ensure appropriate care.

- There is a lack of patient access to expertise.

- The lack of adequate electronic health records impacts patient safety, although the genetic contribution is unknown.

- Duplicate genetic and genomic testing wastes limited resources.

- Direct-to-consumer advertising misleads consumers with claims that are unproven and ambiguous.

The following harms are not documented in the literature, but are nonetheless plausible:

- Tests could be misinterpreted because of limited or inaccurate clinical information, because the patient ordered the test, or because of an inadequate or confusing report. Inappropriate attribution of causality could lead to diagnostic and therapeutic interventions that are not indicated. Conversely, incorrect assignment of a variant as "benign" could lead to beneficial interventions not being offered. It could be incorrectly inferred that data obtained from retrospective studies will define the appropriate application in clinical settings in the absence of prospective trials.

- There is a lack of available educational materials designed to help patients use genetic/genomic test results and harms could also result if patients do not understand their conditions. In addition, a lack of discussion about psychological and social implications of testing could result in harms.

- The lack of adequate electronic health records creates an inability to collect data and integrate new knowledge to improve patient care in a timely fashion, which could result in sub-optimal patient care. Text-based reports limit the ability to implement practice guidelines to support active clinical decision support.

- The lack of specific codes for genetic and genomic tests also hinders electronic support for appropriate care, as could an inability to communicate critical between a Laboratory Information System and EHRs.

- Uncertainty about the FDA's role in regulating CDS systems for genetic/genomic tests that are not integrated within the testing laboratory could result in harms.

- The use of systems that do not support current regulatory requirements (e.g., HIPAA) risks release of personal health information.

Recommendations

1) There are documented deficiencies in genetic knowledge in all relevant stakeholder groups. Since current strategies are inadequate to address these deficiencies:

   HHS should work with all relevant Governmental agencies and interested private parties to identify and address deficiencies in genetic knowledge and education of three key groups in particular: healthcare practitioners, public health workers, and consumers. These educational efforts should take into account the differences in language, culture, ethnicity, and perspectives on disability that can affect the use and understanding of genetic information.

2) Although FDA has asserted its authority over clinical decisions support systems, the extent to which the agency intends to regulate such systems is not clear. Given that clinical decisions support systems will be necessary to communicate information appropriately in the pre- and post-analytic period and because these systems contain elements that involve the practice of medicine, clarification of the nature and scope of FDA oversight of such support systems is critical. SACGHS recommends that:

   FDA should engage with other relevant Federal agencies, working groups (e.g., AHIC), and stakeholders to gather perspectives on the appropriate regulatory framework for clinical decision support systems in light of the changing healthcare delivery and healthcare data collection

systems. FDA should then prepare a guidance document articulating the basis of its authority to regulate clinical decision support systems as well as its rationale and approach to such regulation, explaining in particular which features of the system constitute a device.

3) The need for genetic expertise to support best genetic testing practices has been identified as an essential element for the provision and interpretation of appropriate genetic tests. Access to genetic expertise could be addressed in part by solving problems in the reimbursement of genetic tests and services. SACGHS recommends that:

   HHS act on the recommendations in the 2006 SACGHS *Coverage and Reimbursement of Genetic Tests and Services* report.

4) There are extensive gaps in knowledge about genetic tests and their impact on patient care. Prioritizing activities under the authority of HHS would help to close these gaps and enhance the quality of patient care. SACGHS recommends that:

   HHS allocate resources to AHRQ, CDC, HRSA, and NIH to design and support programmatic and research efforts in order to:

   1. encourage development and assist in the evaluation and dissemination of tools, particularly computerized tools, for clinical decision support in the ordering, interpretation and application of genetic tests; and

   2. address current inadequacies in clinical information needed for test interpretation.

5) Direct-to-consumer advertising of genetic tests and consumer-initiated genetic testing have the potential for adverse patient outcomes and cost implications for the healthcare system. There is a gap in knowledge concerning the extent of this impact. SACGHS recommends an examination of these issues:

   HHS should step up its efforts through collaborations among relevant Federal agencies (e.g., FDA, CDC, NIH, and FTC), States, and consumer groups to assess the implications of direct-to-consumer advertising and consumer-initiated genetic testing, and as necessary, propose strategies to protect consumers from potential harm. Any additional oversight strategies that may be established should be attentive to cost and access issues that might prevent consumers from gaining benefits of wider access to genetic tests.

Chapter 7
Conclusion

The Secretary of Health and Human Services charged SACGHS with determining whether there is evidence of harms related to genetic testing due to gaps in the complex systems that conduct oversight and, if so, whether they are attributable to issues of analytic validity, clinical validity, and/or clinical utility. The charge also called upon SACGHS to consider how identified gaps in the system could be rectified. To make these determinations, the Committee examined the roles of public and private entities that have responsibility for oversight, the resources available to them, and, where relevant, the regulations that govern them.

Through an extensive review of the literature, input from expert consultants, and deliberation through frequent teleconferences and face-to-face meetings, SACGHS has reached the conclusion that there are significant gaps in oversight that can lead to harms. These include:

- Inadequacies in CLIA's current requirements for proficiency testing (PT);
- The need for additional training of CLIA's laboratory inspectors;
- Lack of enforcement of existing regulations concerning non-CLIA certified laboratories;
- The need for increased monitoring and enforcement against laboratories and companies that make false and misleading claims about genetic tests;
- Inadequate information and transparency on the number and type of genetic tests being used in clinical and public health practice;
- Lack of clarity about FDA's role in regulating laboratory tests (LDTs);
- Gaps in the extent to which analytical validity, clinical validity, and clinical utility can be assured for some genetic tests and inadequate processes for conducting such assessments;
- The need for an assessment of the scope, purpose, accuracy, and validity of certain health-related tests that currently fall outside of CLIA's authority, but are marketed directly to consumers;
- Gaps in knowledge about the potential for direct-to-consumer advertising and consumer-initiated genetic testing to lead to adverse patient outcomes and expense to the healthcare system;
- The need to assess the impact of genetic testing on patient care and public health and identify opportunities for improving their utility;
- Deficiencies in genetic knowledge by practitioners, public health workers, and consumers;
- The need to evaluate the regulatory framework for clinical decision support systems in light of changing healthcare delivery and data collection systems; and,
- The need for appropriate coverage and reimbursement of genetic tests and services.

The Committee's recommendations emphasize the importance of enforcing existing regulations more than the need for additional regulation. They urge HHS and other relevant Federal agencies to strengthen their enforcement actions against non-CLIA-certified laboratories that perform genetic tests for clinical purposes and recommend strengthened enforcement efforts against laboratories and companies that make false and misleading claims about genetic tests.

In lieu of adding a genetic testing specialty under CLIA, CMS is implementing a multi-faceted action plan designed to address the gaps that fall within their purview. SACGHS reviewed CMS's plan and agrees that gaps can be addressed without the creation of a genetic testing specialty. However, the Committee found inadequacies in CLIA's requirements for proficiency testing. To support and augment the CMS action plan, SACGHS recommends that HHS fund studies of the effectiveness of other types of performance assessment methods to determine whether they are as robust as PT. CMS should update its list of regulated analytes to include genetic tests for which PT products are available and HHS should

develop incentives for PT providers to expand PT products for those tests. SACGHS also found that that there is a need for additional training of CLIA laboratory inspectors and recommends that experts be used to train them in the practical application of CLIA requirements.

The recommendations also promote new and enhanced partnerships between the Federal Government and the private sector, for example, to bring more resources and expertise to bear on the assessment of laboratory developed tests that are not reviewed by FDA and to develop incentives for the registration of genetic tests. The significant knowledge gaps identified concerning clinical validity and clinical utility could likewise be addressed through public/private partnerships.

In the Committee's view, HHS should conduct public health surveillance to assess the appropriate utilization and public health impact of genetic testing, act on the recommendations in the SACGHS *Coverage and Reimbursement of Genetic Tests and Services* report, advance the use of interoperable electronic health records, and work with other Government agencies and private entities to address deficiencies in genetic knowledge by healthcare providers, public health workers, and consumers.

Research and programmatic efforts are recommended to close the extensive gaps that exist in knowledge regarding genetic tests and their impact on patient care. Funding for AHRQ, CDC, HRSA, and NIH is needed to support the development of evidence and the dissemination of guidelines on evidence-based practice for genetic/genomic tests, assist in the evaluation and dissemination of computerized tools for clinical decision support related to genetic tests, and address inadequacies in the clinical information needed for test interpretation.

SACGHS concludes that expanded efforts are needed to prevent laboratories from performing genetic tests without appropriate CLIA certification and that HHS should explore mechanisms for developing new authorities and resources that will enable CMS to strengthen its enforcement efforts against laboratories that perform genetic tests for clinical purposes without proper CLIA certification. In addition, appropriate Federal agencies should strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about genetic tests.

Because of the importance of clinical decision support systems in the pre- and post-analytic periods, clarification of the nature and scope of FDA oversight of these systems is critical. FDA should engage with other relevant Federal agencies, working groups (e.g., AHIC), and stakeholders to gather perspectives on the appropriate regulatory framework for clinical decision support systems in light of the changing healthcare delivery and healthcare data collection systems. FDA should then prepare a guidance document articulating the basis of its authority to regulate clinical decision support systems.

The Committee also highlights the complexity of the oversight system and calls for enhanced interagency coordination of the activities associated with the oversight of genetic testing, including policy and resource development, education, regulation, and knowledge generation.

The Committee hopes that this report and recommendations will be useful to the Secretary in leading HHS efforts to maximize the benefits of genetic testing in the United States and the important role they play and will continue to play in achieving personalized health care.

APPENDIX A

To be Added in the Final Draft

APPENDIX B

GENETIC TECHNOLOGY RESOURCES

Regulation and Guidance

Centers for Medicare & Medicaid Services, Clinical Laboratory Improvement Amendments (CLIA): http://www.cms.hhs.gov/clia/01_overview.asp ?
The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA).

Clinical and Laboratory Standards Institute: Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline—Second Edition (2006):
http://www.clsi.org/source/orders/index.cfm?section=SALES&SKU=MM01A2E
The document provides guidance for the use of molecular biological techniques for clinical detection of heritable mutations associated with genetic disease.

Food and Drug Administration (FDA) Office of In Vitro Diagnostics Web Information Page:
www.fda.gov/cdrh/oivd
This site contains a guidance database, database with cleared or approved FDA submissions, and up-to-date news on FDA regulatory activities.

Chromosome Databases

Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER):
http://www.sanger.ac.uk/PostGenomics/decipher
The DECIPHER database of submicroscopic chromosomal imbalance collects clinical information about chromosomal microdeletions/duplications/insertions, translocations and inversions.

European Cytogenetics Association Register of Unbalanced Chromosome Aberrations:
http://www.ECARUCA.net
This database provides cytogenetic and clinical information on rare chromosomal disorders, including microdeletions and microduplications.

National Center for Biotechnology Information, Cancer Chromosomes database:
http://www.ncbi.nlm.nih.gov/sites/entrez?db=cancerchromosomes
A resource that combines three databases: the NCI/NCBI SKY/M-FISH and CGH Database, the NCI Mitelman Database of Chromosome Aberrations in Cancer, and the NCI Recurrent Aberrations in Cancer.

Sequence Variation Databases

Catalog of Somatic Mutations in Cancer (COSMIC): http://www.sanger.ac.uk/genetics/CGP/cosmic/
Mutation data and associated information is extracted from the primary literature and entered into the COSMIC database, which can be queried by tissue, histology or gene.

Database of Genomic Variants: http://projects.tcag.ca/variation/
This database provides a curated catalogue of structural variation in the human genome.

Human Gene Mutation Database (HGMD): http://www.hgmd.cf.ac.uk/ac/index.php
HGMD collates known (published) gene lesions responsible for human inherited disease. The database includes mutations within the coding regions, splicing and regulatory regions of human nuclear genes; somatic mutations and mutations in the mitochondrial genome are not included.

International HapMap Project: http://www.hapmap.org/index.html.en
HapMap is an international partnership to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals.

National Center for Biotechnology Information, Database of Single Nucleotide Polymorphisms (dbSNP): http://www.ncbi.nlm.nih.gov/projects/SNP/
dbSNP is a central repository for both single base nucleotide substitutions and short deletion and insertion polymorphisms.

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB): http://www.pharmgkb.org/
PharmGKB curates information that establishes knowledge about the relationships among drugs, diseases and genes, including their variations and gene products.

Sorting Intolerant from Tolerant (SIFT): http://blocks.fhcrc.org/sift/SIFT.html
SIFT predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids. SIFT can be applied to naturally occurring nonsynonymous polymorphisms and laboratory-induced missense mutations. Given a protein sequence, SIFT will return predictions for what amino acid substitutions will affect protein function.

University of California Santa Cruz (UCSC) Genome Browser: http://genome.ucsc.edu/cgi-bin/hgGateway
This resource provides a rapid and reliable display of any requested portion of genomes at any scale, together with dozens of aligned annotation tracks (e.g., known genes, predicted genes, ESTs, mRNAs, CpG islands, assembly gaps and coverage, and chromosomal bands).

WayStation—locus-specific databases: http://www.centralmutations.org/Lsdb.php
This resource provides a central point for the submission and collection of human genetic variation data.

Gene Expression Databases

miRBase: http://microrna.sanger.ac.uk/
This database contains all published microRNA (miRNA) sequences, genomic locations, and associated annotation and predicted miRNA targets genes. It also provides a service for assigning official names for novel miRNA genes prior to publication of their discovery.

Oncomine database: http://www.oncomine.org
A product for online cancer gene expression analysis dedicated to the academic and non-profit research community.

Disease-Related Genetic Databases

GeneTests: http://www.genetests.org/
This resource provides current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling.

Genetic Association Database (GAD): http://geneticassociationdb.nih.gov/
GAD is an archive of human genetic association studies of complex diseases and disorders that allow users to identify medically relevant polymorphism from the large volume of polymorphism and mutational data, in the context of standardized nomenclature.

Genomics and Disease Prevention Information System (GDPInfo):
http://apps.nccd.cdc.gov/Genomics/GDPQueryTool/default.asp
GDPInfo provides access to information and resources for guiding public health research, policy, and practice on using genetic information to improve health and prevent disease.

Human Genome Epidemiology Network (HuGeNet): http://www.cdc.gov/genomics/hugenet/default.htm
Human Genome Epidemiology Network, or HuGENet™ is a global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health & prevent disease.

National Center for Biotechnology Information, Database of Genotype and Phenotype (dbGAP):
http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap
dbGAP archives results from studies that have investigated the interaction of genotype and phenotype, such as genome-wide association studies, medical sequencing, molecular diagnostic assays, as well as association between genotype and non-clinical traits.

Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
OMIM is a curated catalog of human genes and genetic disorders.

Genetic Test Review Programs

Collaboration, Education, and Test Translation Program: http://www.cettprogram.org/
The CETT Program facilitates the translation of genetic tests from the research setting to Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories through collaborations among clinicians, laboratories, researchers, and disease-specific advocacy groups.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP):
http://www.cdc.gov/genomics/gtesting/EGAPP/about.htm
EGAPP is a pilot project initiated by the CDC National Office of Public Health Genomics in the fall of 2004. The project's goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice.

U.S. Preventive Services Task Force (USPSTF): http://www.ahrq.gov/clinic/uspstfix.htm
The USPSTF conducts rigorous, impartial assessments of the scientific evidence for the effectiveness of a broad range of clinical preventive services, including screening, counseling, and preventive medications. It makes recommendations about which preventive services should be incorporated routinely into primary medical care and for which populations; and identify a research agenda for clinical preventive care.

Appendix C

Table 1: CAP Products for Proficiency Testing

ACMG/CAP Cytogenetics CY CY

product_u	mail_c	enrollment	Domestic	International
CY	A	314	231	83
CY	B	319	236	83
CY	C	319	236	83

ACMG/CAP Fluorescence In Situ Hybridization – Constitutional and Hematologic Disorders CYF

product_u	mail_c	enrollment	Domestic	International
CYF	A	*344	219	125
CYF	B	264	225	39

ACMG/CAP Fluorescence In Situ Hybridization – Breast Cancer (HER2 Gene Amplification) CYH

product_u	mail_c	enrollment	Domestic	International
CYH	A	253	218	35
CYH	B	257	222	35

ACMG/CAP Fluorescence In Situ Hybridization – Urothelial Carcinoma CY

product_u	mail_c	enrollment	Domestic	International
CYI	A	108	108	0

ACMG/CAP FISH for Paraffin Embedded Tissue

product_u	mail_c	enrollment	Domestic	International
CYP	A	93	82	11
CYJ	A	59	54	5
CYK	A	38	36	2
CYKX	A	5	4	1
CYL	A	58	53	5
CYLX	A	14	10	4

* Labs that were enrolled in CYG & CYF in 2006 were autoconverted to 2 CYF modules for 2007

ACMG/CAP Biochemical Genetics BGL

product_u	mail_c	enrollment	Domestic	International
BGL	A	110	85	25
BGL	B	113	88	25

ACMG/CAP Molecular Genetics MGL1, MGL2, MGL3, MGL4

product_u	mail_c	enrollment	Domestic	International
MGL1	A	370	350	20
MGL1	B	379	359	20
MGL2	A	212	192	20

MGL2	B	214	194	20
MGL3	A	39	33	6
MGL3	B	41	35	6
MGL4	A	31	27	4
MGL4	B	32	28	4

Molecular Oncology MO, MO2, MO3

product_u	mail_c	enrollment	Domestic	International
MO	A	78	63	15
MO	B	76	61	15
MO2	A	80	69	11
MO2	B	80	69	11
MO3	A	102	87	15
MO3	B	103	88	15

In Situ Hybridization ISH

product_u	mail_c	enrollment	Domestic	International
ISH	A	105	94	11
ISH	B	111	98	13

Minimal Residual Disease MRD

product_u	mail_c	enrollment	Domestic	International
MRD	A	90	65	25
MRD	B	95	69	26

Proficiency Testing Monitoring by the CAP Laboratory Accreditation Program

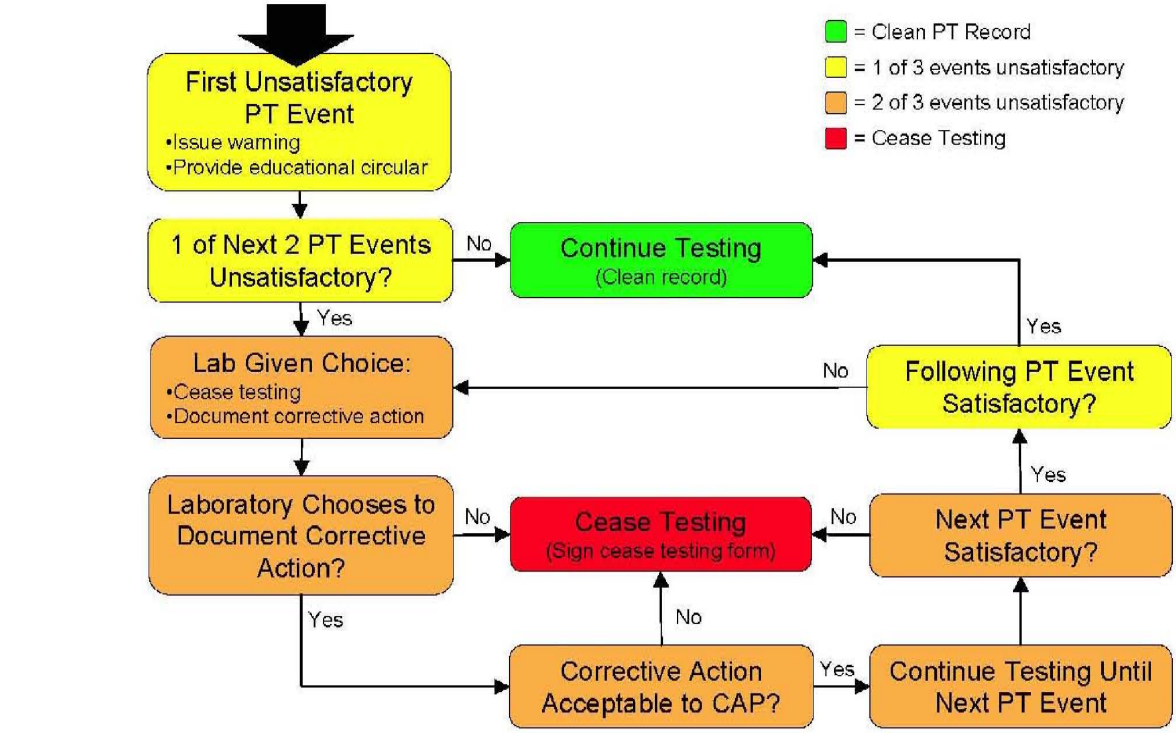

Figure I

2006 MGL PT Performance

Analyte	2006A correct	2006A total	2006A correct	2006B correct	2006B total	2006B correct		2006 A+B Correct
FVL	778	784	0.992	831	834	0.996		0.994
FVL interp	782	786	0.995	833	835	0.998		0.996
PT	758	764	0.992	789	798	0.989		0.990
PT Interp	756	765	0.988	799	808	0.989		0.989
MTHFR	454	458	0.991	476	482	0.988		0.989
MTHFR Interp	424	457	0.928	472	491	0.961		0.945
FMR1	223	229	0.974	256	260	0.985		0.980
FMR Status	245	246	0.996	261	265	0.985		0.990
FMR Interp	247	247	1.000	262	267	0.981		0.990
PW Interp	169	170	0.994	178	180	0.989		0.991
HH	337	339	0.994	348	348	1.000		0.997
HH Interp	319	338	0.944	341	343	0.994		0.969
DMD	21	21	1.000	21	24	0.875		0.933
Hb S/C	72	72	1.000	72	75	0.960		0.980
HB S/C Interp	72	72	1.000	72	75	0.960		0.980

Table 2

CY Analytes	Reporting Year	No. Acceptable *	Cumulative **	Percent
Karyotype Nomenclature	2002	692	865	80.00%
Karyotype Nomenclature	2003	281	402	69.90%
Karyotype Nomenclature	2004	2067	2230	92.69%
Karyotype Nomenclature	2005	3186	3300	96.55%
Karyotype Nomenclature	2006	2991	3407	87.79%
Modal Chromosome Number	2002	47	48	97.92%
Modal Chromosome Number	2003	49	56	87.50%
Modal Chromosome Number	2004	2126	2148	98.98%
Modal Chromosome Number	2005	3270	3300	99.09%
Modal Chromosome Number	2006	3179	3407	93.31%
Molecular Pathology & Genetics	2004	8526	8847	96.37%
Molecular Pathology & Genetics	2005	12311	12929	95.22%
Molecular Pathology & Genetics	2006	8207	8815	93.10%
Recognition of Abnormalities	2002	211	241	87.55%
Recognition of Abnormalities	2003	145	187	77.54%
Recognition of Abnormalities	2004	2041	2178	93.71%
Recognition of Abnormalities	2005	3229	3300	97.85%
Recognition of Abnormalities	2006	3056	3407	89.70%
Sex Chromosome Designation	2002	37	38	97.37%
Sex Chromosome Designation	2003	25	32	78.13%
Sex Chromosome Designation	2004	2126	2148	98.98%
Sex Chromosome Designation	2005	3270	3300	99.09%
Sex Chromosome Designation	2006	3184	3407	93.45%

*Total number of challenges with acceptable grade.
**Total number of challenges reported both acceptable and unacceptable.

Table 3

CAP PT Performance (2002-2006)

Appendix D

Guidelines and Standards for Molecular Diagnostics Testing

Organization	Guideline or Standard	Address
Clinical and Laboratory Standards Institute	**MM1-A2** Molecular Diagnostic Methods for Genetic Diseases **MM2-A2** Immunoglobulin and T-Cell Receptor Gene Rearrangement Assays **MM5-A** Nucleic Acid Amplification Assays for Molecular Hematology **MM7-A** Fluorescence in Situ Hybridization Methods for Medical Genetics **MM9-A** Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine **MM12-A** Diagnostic Nucleic Acid Microarrays **MM13-A** Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods **MM14-A** Proficiency Testing for Molecular Methods **MM16-A** Use of External RNA Controls in Gene Expression Arrays **MM17-P** Validation and Verification of Multiplex Nucleic Acid Assays	Wayne, PA http://www.clsi.org/AM/Template.cfm?Section=Standards_Development
ACMG	Standards and guidelines for clinical genetic laboratories: Policy Statements Prenatal Interphase Fluorescence In Situ Hybridization ACMG Position Statement on Multiple Marker Screening in Women 35 and Older Fragile X Syndrome: Diagnostic and Carrier Testing Technical standards and guidelines for Fragile X: The first in a serious of disease specific supplements to the standards and guidelines for clinical genetics laboratories of the American College of Medical Genetics Statement on Storage and Use of Genetic Materials Statement on Multiple Marker Screening in Pregnant Women Statement on Use of Apolipoprotein E Testing for Alzheimer Disease Diagnostic Testing for Prader-Willi and Angelman Syndromes: Statement on Population Screening for BRCA-1 Mutation in Ashkenazi Jewish Women Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines Principles of Screening: Report of The Subcommittee on Screening of the American College of Medical Genetics Clinical Practice Committee Position Statement on Carrier Testing for Canavan Disease Cystic fibrosis carrier screening, laboratory standards and guidelines for population based Cystic Fibrosis Carrier Screening Genetic testing for colon cancer: a joint statement of the American College of Medical Genetics and the American Society of Human Genetics Consensus Statement on Factor V Leiden Mutation Testing Technical and clinical assessment in fluorescent of situ hybridization: an ACMG/ASHG position statement. Technical considerations ACMG recommendations for standard interpretation of sequence variations American College of Medical Genetics statement on diagnostic testing for	ABMG/ABGC/ ACMG, Administrative office, 9650 Rockville Pike, Bethesda. MD 20814-3998 www.acmg.net

	uniparental disomy	
ASHI	Standards for Molecular Histocompatibility and Immunogenetic Testing	ASHI PO Box 15804 Lenexa, KS 66285-5804
NIH-DOE	Task Force on Genetic Testing-Promoting Safe and Effective	www.nhgri.nih.gov/Policyandpublicaffairs/Elsi/tfgentest
FDA	Guidance for industry in the manufacture and clinical evaluation of in vitro tests to detect in vitro nucleic acid sequences of HIV-1-Draft Guidance for industry and/or FDA reviewers staff-Premarket approval applications for assays pertaining to Hepatitis C virus (HCV) that are indicated for diagnosis or monitoring of HCV infection or associated disease-Draft Guidance Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material Guidance for Industry and FDA Staff Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays Guidance for Industry and FDA Staff - Pharmacogenetic Tests and Genetic Tests for Heritable Markers Guidance for Industry and FDA Staff -Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Quality Control Material for Cystic Fibrosis Nucleic Acid Assays Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: CFTR Gene Mutation Detection Systems Class II Special Controls Guidance Document: RNA Preanalytical Systems	www.fda.gov/cber/gdlns/nashiv.pdf www.fda.gov/cdrh/ode/1353pdf http://www.fda.gov/cdrh/oivd/guidance/2231.html http://www.fda.gov/cdrh/oivd/guidance/1590.html http://www.fda.gov/cdrh/oivd/guidance/1610.html http://www.fda.gov/cdrh/oivd/guidance/1549.html http://www.fda.gov/cdrh/oivd/guidance/1551.html http://www.fda.gov/cdrh/oivd/guidance/1627.html http://www.fda.gov/cdrh/oivd/guidance/1614.html http://www.fda.gov/cdrh/oivd/guidance/1564.html http://www.fda.gov/cdrh/oivd/guidance/1563.html http://www.fda.g

	(RNA Collection, Stabilization and Purification Systems for RT-PCR used in Molecular Diagnostic Testing) Guidance for Industry and FDA Staff -Class II Special Controls Guidance Document: Automated Fluorescence in situ Hybridization (FISH) Enumeration Systems **Guidance for Industry and FDA Staff -Class II Special Controls Guidance Document:** **Factor V Leiden DNA Mutation Detection Systems**	ov/cdrh/oivd/guidance/1550.html http://www.fda.gov/cdrh/oivd/guidance/1236.html
AMP	Recommendations for in-house development and operation of molecular diagnostic tests.	www.ampweb.org
Technical Working Group on DNA Analysis Methods	Guidelines for a Quality Assurance Program for DNA Analysis	Crime Laboratory Digest (1991) 18:44-75