



# **U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services**

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

**April 2008**

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Secretary's Advisory Committee on  
Genetics, Health, and Society  
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April 30, 2008

The Honorable Michael O. Leavitt  
Secretary of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

Dear Secretary Leavitt:

In March 2007, you charged the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) with investigating specific questions related to the adequacy and transparency of the current oversight system for genetic testing. In answer to this charge, we are pleased to submit our report on the *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*. The report, which is the culmination of nearly a year of extensive factfinding, analysis, expert consultation, outreach to the public, and deliberation by the Committee, highlights gaps in the oversight system for genetic testing and provides recommendations to maximize the benefits of genetic testing and minimize harms.

In carrying out its work, the Committee used a broad interpretation of oversight to include not only Federal and State governments and agencies, but also standard-setting organizations, knowledge-generating organizations, public and private sector health care payers, professional societies, health providers, patients, and consumers. The recommendations focus primarily on actions that the Committee strongly believes should be taken by the Department of Health and Human Services (HHS) and its agencies but also speak to the critical role of the private sector and the value of public-private partnerships in enhancing oversight.

The Committee identified gaps in five main areas: the regulations governing clinical laboratory quality; the oversight of the clinical validity of genetic tests; the transparency of genetic testing; the level of current knowledge about the clinical usefulness of genetic tests; and meeting the educational needs of health professionals, the public health community, patients, and consumers, along with providing tools to assist these groups with the interpretation and communication of genetic test results. We would like to highlight critical action steps identified in the report to address gaps in these five areas.

- To improve clinical laboratory quality, the Centers for Medicare & Medicaid Services should require proficiency testing (PT) of all nonwaived laboratory tests for which PT products are available, HHS should support innovations in the way PT is performed, and the Department should also ensure funding for the development of reference materials and methods for assay, analyte, and platform validation; quality control; performance assessment; and standardization.
- To help close the gaps in oversight related to clinical validity, which would help assure the appropriate use of laboratory tests, the Food and Drug Administration (FDA) should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current experience.

- To enhance the transparency of genetic testing and assist efforts in reviewing the clinical validity of laboratory tests, HHS should appoint and fund a lead agency to develop and maintain a mandatory, publicly available, Web-based registry for laboratory tests.
- To better understand the usefulness of genetic tests, HHS should create and fund a public-private partnership to evaluate the clinical utility of genetic tests, develop a research agenda to address gaps in knowledge, conduct public health surveillance to assess the health impact of genetic testing, and help advance the appropriate use of electronic health records as a resource for assessing clinical utility and quality of health care.
- To meet the educational needs of health professionals, public health workers, patients, and consumers, HHS should support efforts to identify education or training deficiencies in each of these groups and support research and development of effective clinical decision support systems. In addition, FDA should prepare a guidance document articulating the scope of its regulation of clinical decision support systems.

Although SACGHS was tasked to look at the oversight of genetic tests specifically, we concluded that the concerns associated with genetic testing generally do not differ from other complex laboratory tests. For this reason, and because it will be increasingly difficult to distinguish between genetic and other complex laboratory tests, we chose to apply a number of our recommendations to laboratory tests generally. Nonetheless, we recognize that implementing an expansion of Federal oversight of laboratory tests will require incremental steps and that, in this context, genetic tests should have the highest priority.

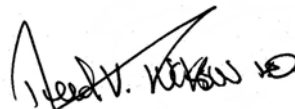
The Committee's recommendations identify very important steps that HHS can take to enhance the oversight of genetic tests, which are critical to the public health and the advancement of personalized health care. The Committee also highlights the complexity of the oversight system and urges enhanced interagency coordination of the activities associated with the oversight of genetic testing, including policy and resource development, education, regulation, and knowledge generation. Although challenging, we believe that implementation of these recommendations will help the Department fulfill its mission to improve the health and well-being of Americans.

We appreciated the opportunity to address this important topic and hope that our input will prove helpful to you and the Department. We stand ready and would welcome the opportunity to provide further advice on the implementation of these important and challenging initiatives.

Sincerely,



Steven Teutch, M.D., M.P.H.  
Current Chair, SACGHS



Reed V. Tuckson, M.D.  
Former Chair, SACGHS

# About SACGHS

The Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) was first chartered in 2002 by the Secretary of the U.S. Department 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
- 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, health care delivery, evidence-based practice, public health, behavioral sciences, social sciences, health services research, health policy, health disparities, ethics, economics, law, health care 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 of the views and perspectives of the general public.

Representatives of at least 19 Federal departments 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 Healthcare 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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- Gurvaneet Randhawa (Agency for Healthcare Research and Quality); Linda Bradley, Joe Boone, Marie Earley, Scott Grosse, Lisa Kalman, Muin Khoury, Ira Lubin, Joanne Mei (Centers for Disease Control and Prevention); Judy Yost (Centers for Medicare & Medicaid Services); Steven Gutman, Elizabeth Mansfield (Food and Drug Administration); Marie Mann (Health Resources and Services Administration); Tim O’Leary (Department of Veterans Affairs); Phyllis Frosst (National Institutes of Health (NIH)); Michael Amos (National Institute of Standards and Technology)

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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, 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 and specifically diagnose disease in individuals, families, and populations and then using this information to guide health care decisions. However, 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 from genetic tests, 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 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 the oversight of genetic testing as a priority area in 2004. After monitoring the issue for a couple of years, SACGHS began a concentrated effort in 2006 to assess the various systems of oversight that play a role in genetic testing. Like its predecessor—the Secretary's Advisory Committee on Genetic Testing—the overarching concern of SACGHS was the adequacy of the oversight system and whether there were gaps that could lead to harms in public health.

In March 2007, the Department of Health and Human Services (HHS) launched the Personalized Health Care 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.<sup>1</sup> 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 under way by SACGHS, the HHS 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 under way at the Federal level and encompasses all sectors of the health care system concerning oversight, including the Federal Government, State Governments, and the private sector. Refined during Committee discussion, the charge was to:

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<sup>1</sup> Department of Health and Human Services Web site: "Personalized Health Care: Goals." See <http://www.hhs.gov/myhealthcare/goals/index.html#Goal3>. Accessed on March 14, 2008.

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:

- What evidence of harm exists regarding genetic tests? Is that harm attributable to analytical 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?
- What distinguishes genetic tests from other laboratory tests for oversight purposes?
- What are the existing pathways that examine the analytical 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 (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 PT? Is the current level of PT 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?

Given the charge, 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 Committee came to appreciate that many of the issues subject to its review of genetic tests were similar to those of other complex laboratory tests. As such, the discussions and recommendations on the 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 could well be applied more broadly to improve the quality of all laboratory tests.

## 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 testing that range from the research and development of tests to the delivery and interpretation of tests results to guide health and lifestyle decisions. Depending on the aspect of testing, oversight is provided by Government agencies, health care payers, professional associations, or other groups; voluntarily by certain sectors; or not at all. Some aspects of oversight are quite specific to genetic testing, whereas 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 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 devices, which includes test kits and analyte-specific reagents (ASRs). ASRs can be antibodies, receptor proteins, nucleic acid sequences, or other biological or chemical reagents used to identify or quantify substances in biological specimens.<sup>2</sup> Until recently, FDA has not exercised its regulatory authority over LDTs; the Clinical Laboratory Improvement Amendments of 1988 (CLIA) are used to regulate the laboratories that develop LDTs.<sup>3</sup>

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, PT, quality assurance, and recordkeeping. CLIA requires a laboratory to verify and establish the analytical performance characteristics of tests offered by that laboratory. Although CMS provides guidance and resources to help laboratories achieve compliance, current regulations do not specify particular procedures or protocols. Rather, they require laboratories to ensure 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.<sup>4,5</sup>

At the State level, many agencies use CLIA requirements to regulate genetic testing laboratories. The States of New York and Washington, however, independently operate 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 preapproval prior to offering a genetic test in a clinical setting. As all laboratories that solicit and receive specimens from New York are subject to these clinical laboratory requirements,<sup>6</sup> an estimated 75 percent of all cytogenetic and genetic specimens tested in the United States are subject to this oversight.<sup>7</sup>

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<sup>2</sup> Gutman, S.I. *FDA's Role in the Regulation of In Vitro Diagnostic*. Presentation May 10, 2003. Food and Drug Administration, Center for Devices and Radiological Health, Office of In Vitro Device Evaluation and Safety. See <http://www.fda.gov/cdrh/oivd/presentations/051003-gutman-1.html>. Accessed on March 19, 2008.

<sup>3</sup> Centers for Medicare & Medicaid Services Web site. "Clinical Laboratory Improvement Amendments (CLIA)". See <http://www.cms.hhs.gov/clia>. Accessed on March 19, 2008.

<sup>4</sup> S.976: Genomics and Personalized Medicine Act of 2007. See [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_bills&docid=f:s976is.txt.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:s976is.txt.pdf). Accessed on March 20, 2008.

<sup>5</sup> S. 736: Laboratory Test Improvement Act. See [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_bills&docid=f:s736is.txt.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:s736is.txt.pdf). Accessed on March 20, 2008.

<sup>6</sup> Wadsworth Center, New York State Department of Health Web site. "Clinical Laboratory Evaluation Program." See <http://www.wadsworth.org/labcert/lep/lep.html>. Accessed on March 20, 2008.

<sup>7</sup> Willey, A.W. *New York State Laboratory Specific Assay Validation Review and Approval as Applied to Genetic Testing*. Presentation to SACGHS meeting March 26, 2007. See <http://www4.od.nih.gov/oba/sacghs/meetings/Mar2007/Mon%20pm%20-%20Willey.pdf>. Accessed on March 20, 2008.

Ensuring the analytical and clinical validity of genetic testing is paramount. Analytical validity refers to a test's ability to measure the analyte or 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 fully enforced under CLIA, as CMS does not have authority under CLIA to enforce clinical validity.<sup>8</sup> 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. Prospective data of a test's clinical validity, however, are 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 the sharing of information among laboratories.

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 PT unless they are testing a small subset of established analytes regulated under CLIA,<sup>9</sup> 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,<sup>10</sup> and it is considered to be the most rigorous form of performance assessment currently available. In principle, 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 public and private health care 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, and National Institutes of Health (NIH) have led to great strides in evidence development for genetic testing, a more coordinated approach for effectively translating genetic 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

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<sup>8</sup> Centers for Medicare & Medicaid Services Web site. "Clinical Laboratory Improvement Amendments (CLIA)." Op. cit.

<sup>9</sup> Centers for Disease Control and Prevention Web site. "Clinical Laboratory Improvement Amendments (CLIA), Subpart I – Proficiency Testing Program for Nonwaived Testing." See [http://wwwn.cdc.gov/clia/reggs/subpart\\_i.aspx](http://wwwn.cdc.gov/clia/reggs/subpart_i.aspx). Accessed on March 20, 2008.

<sup>10</sup> 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 Laboratory; Approved Guideline – 2<sup>nd</sup> Edition. GP27-A2, Vol. 27(8). Wayne, PA: Clinical and Laboratory Standards Institute. See <http://www.clsi.org/source/orders/free/gp27-a2.pdf>. Accessed on March 20, 2008.

<sup>11</sup> American College of Medical Genetics Website. "American College of Medical Genetics Practice Guidelines." See [http://www.acmg.net/AM/Template.cfm?Section=Practice\\_Guidelines&Template=/CM/HTMLDisplay.cfm&ContentID=2257](http://www.acmg.net/AM/Template.cfm?Section=Practice_Guidelines&Template=/CM/HTMLDisplay.cfm&ContentID=2257). Accessed on March 20, 2008

practitioners about the ordering of genetic tests and reporting of results.<sup>11</sup> Organizations such as the National Coalition for Health Professional Education in Genetics have engaged in efforts to enhance clinician understanding of genetic testing and its appropriate use.<sup>12</sup> Yet there are 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 health care 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 an alert warning consumers to be wary of claims made by at-home genetic tests.<sup>13</sup> 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 possible 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. Thus, there have been calls for more genetics professionals to help patients understand the health impact of their genetic information.<sup>14,15,16</sup>

## 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 improved 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 how it affects health outcomes. A related shortcoming is the dearth of educational programs for clinicians, practitioners, and health care professionals on how to deliver and interpret genetic information for patients. The translation of genetic tests into clinical practice will rely heavily on preanalytical and postanalytical clinical decision support and research into the impact of genetic information on health care delivery, outcomes, and costs.

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<sup>12</sup> National Coalition for Health Professional Education in Genetics Web site. “Contracts and Grants.” See <http://www.nchpeg.org/content.asp?dbsection=contracts#1>. Accessed on March 20, 2008.

<sup>13</sup> Federal Trade Commission Web site. “At-Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription.” See <http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm>. Accessed on March 20, 2008.

<sup>14</sup> Cooksey, J.A., Forte, G., Benkendorf, J., and Blitzer, M.G. (2005). The state of the medical geneticist workforce: findings of the 2003 survey of American Board of Medical Genetics certified geneticists. *Genetics in Medicine*. 7(6):439-443.

<sup>15</sup> Cooksey, J.A., Forte, G., Flanagan, P.A., Benkendorf, J., and Blitzer, M.G. (2006). The medical genetics workforce: an analysis of clinical geneticist subgroups. *Genetics in Medicine*. 8(10):603-614.

<sup>16</sup> Benkendorf, J. *The Medical Genetics Workforce: Getting to Where We Need to Be From Here*. Presentation to SACGHS meeting November 20, 2007. See <http://www4.od.nih.gov/oba/SACGHS/meetings/Nov2007/benkendorf.pdf>. Accessed on March 20, 2008.

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 continuous quality management and the maintenance of process standards for laboratories performing genetic testing. Emerging technologies continue to pose a significant challenge with regard to 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 establish how genetic testing affects health outcomes. The development of evidentiary standards, data sources, and evidence-based methods applicable to genetic testing can help establish clinical utility and guide the effective translation of genetic research into practice.
- **Education and guidance** for clinicians, laboratory personnel, and other health care 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 preanalytical and postanalytical phases of genetic testing is also needed.
- **Ongoing public health surveillance** such as surveys of patients, providers, and the general population are needed to monitor the uptake and use of genetic tests and the determinants of care.
- **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 establishing analytical validity, quality assurance, clinical validity, clinical utility, and education and guidance.

## Recommendations

### Overarching Recommendation

In keeping with his responsibility and commitment to protect and improve public health and as part of an effort to support the advancement of personalized health care, the HHS Secretary charged SACGHS to assess the adequacy of the U.S. system of oversight of genetic testing. After extensive factfinding, consultation, and analysis, the Committee found significant gaps in the U.S. system of oversight of genetic testing that can lead to harms. The Committee also identified novel opportunities that would enhance oversight. The Committee formulated recommendations that, if implemented and sufficiently supported, will close major gaps, enhance future oversight, help ensure public safety and health, and facilitate the realization of personalized health care. These steps are extraordinarily challenging, and they will require both swift action and sustained leadership by the HHS Secretary and coordinated efforts at the highest level within the administration of HHS.

### 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 by adding a genetic testing specialty under CLIA. Recently, CMS changed direction and is now addressing these gaps with a multifaceted action plan. SACGHS considered the CMS rationale and reviewed the CMS action plan. SACGHS also carefully considered the recommendations of prior groups as well as the perspectives of stakeholders that support the specialty. In the end, the Committee concluded 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 nonwaived 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 PT. PT is currently considered to be the most rigorous form of performance assessment. In principle, genetic tests and all other nonwaived laboratory tests should be required to undergo PT. However, such a goal cannot be achieved immediately. Consequently, the following actions should be taken:
- CMS should require PT of all nonwaived laboratory tests for which PT products are available. For tests without PT products, laboratories must use alternative assessment methods, as required under current CLIA regulations.
  - To promote the development of new PT products and facilitate performance assessment efforts, HHS should fund studies of the effectiveness of other types of performance assessment methods to determine whether they are as robust as PT and should support innovations in the way PT is performed, such as through methodology-based processes.
- 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 exempt from any hiring constraints imposed by or on CMS.
- 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 devoting public resources for genetic testing through the following actions:**
- A. In consultation with relevant agencies, HHS should ensure funding for the development and characterization of reference materials, methods, and samples (e.g., positive and negative controls and samples from different ethnic/geographic populations) for assay, analyte, and platform validation; for quality control and performance assessment; and for standardization.
- B. HHS should ensure 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, expand clinical reference sequence databases, and provide summary data on gene-disease associations to inform clinical validity assessments (e.g., RefSeqGene, HuGENet). Such initiatives should be structured to encourage robust participation; for example, there is a need to consider mechanisms for anonymous reporting and/or protections from liability to encourage information sharing among members.
- D. HHS should provide the necessary support for professional organizations to develop and disseminate additional standards and guidelines for applying genetic tests in clinical practice. CMS should work

with professional organizations to develop interpretative guidelines to enhance inspector training and laboratory compliance.

**3. The Committee is concerned by the gap in oversight related to clinical validity and believes that it is imperative to close this gap as expeditiously as possible. To this end, the Committee makes the following recommendations:**

- A. FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests.
- B. This step by FDA will require the commitment of significance resources to optimize the time and cost of review without compromising the quality of assessment.
- C. The Committee recommends that HHS convene a multistakeholder public and private sector group to determine the criteria for risk stratification and a process for systematically applying these criteria. This group should consider new and existing regulatory models and data sources (e.g., New York State Department of Health Clinical Laboratory Evaluation Program). The multistakeholder group should also explicitly address and eliminate duplicative oversight procedures.
- D. To expedite and facilitate the review process, the Committee recommends the establishment of a mandatory test registry as noted in the following recommendation.

**4. There are considerable information gaps about the number and identity of laboratories performing genetic tests and the specific genetic tests being performed. To gain a better understanding of the genetic tests being offered as laboratory-developed tests and to enhance the transparency in this field, SACGHS reviewed proposals for a voluntary or mandatory test registry and considered the benefits and burdens of each type of system. The Committee decided that a mandatory, publicly available, Web-based registry that is well staffed to maintain an accurate and current database would offer the best approach to addressing these information gaps in the availability of tests and their analytical and clinical validity. Since genetic tests are not different from other laboratory tests for oversight purposes, the registry should include all laboratory tests. The Committee also discussed whether such a database should reside at CDC, CMS, or FDA, but recognized that unresolved issues, including practical and legal questions, require further analysis before a final decision can be made about how and where to implement the registry. In concluding that a mandatory registry should be established, SACGHS recommends the following course of action:**

- A. HHS should appoint and fund a lead agency to develop and maintain the mandatory registry for laboratory tests. The lead agency should work collaboratively with its sister agencies to create a comprehensive registry and minimize duplicative collection of registry information. For this purpose, the lead agency should be staffed with qualified personnel who are experienced in developing and updating large databases in a timely and accurate manner.
- B. The lead agency, in collaboration with its sister agencies, should convene a stakeholders meeting by September 2008 to determine the data elements associated with analytical validity, clinical validity, clinical utility, and accessibility that should be included in the test registry. The lead agency should cast a wide net for broad stakeholder representation, including individuals from the private sector who can represent a role for public-private partnerships in developing a registry. The lead agency, through this stakeholder effort, should assess the level of effort, as well as the burden on the laboratory and the impact on other key stakeholders such as patients, physicians, and payers, necessary to obtain each data element, including linking to reliable sources of existing information.



C. While awaiting completion of the above processes, HHS should use short-term voluntary approaches such as incentivizing laboratories to register with GeneTests and encouraging laboratories to make their test menus and analytical and clinical validity data for these tests publicly available on laboratory Web sites.

**5. Factfinding by SACGHS also identified gaps in the enforcement of existing regulations. For example, the CLIA program has an array of enforcement actions available, but those actions cannot be directly imposed on uncertified laboratories. Instead, CMS must report the laboratory to the HHS Inspector General for action. Neither Medicare nor Medicaid can reimburse laboratories without CLIA certificates, but this restriction has no consequence for laboratories that perform direct-to-consumer testing. To address enforcement gaps, SACGHS recommends the following actions:**

- A. To prevent laboratories from performing tests without appropriate CLIA certification, CMS should establish and exercise its regulatory authority to take direct enforcement actions against laboratories that perform 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 laboratory tests, including direct-to-consumer tests.

**6. SACGHS is concerned about certain types of health-related tests that are marketed directly to consumers and apparently fall outside the scope of CLIA. Some nutrigenomic tests (e.g., a test for caffeine metabolism) and tests that determine the gender of a fetus are examples of health-related tests that skirt 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. Direct-to-consumer marketing of laboratory tests and consumer-initiated testing have the potential for adverse patient outcomes, social stigmatization, privacy concerns, and cost implications for the health care system. SACGHS recommends that:**

CLIA regulations and, if necessary, CLIA’s statutory authority, along with FDA’s risk-based regulatory authority and regulatory processes, should be expanded to encompass the full range of health-related tests, including those offered directly to consumers. Relevant Federal agencies (e.g., CMS, CDC, FDA, and FTC) should collaborate to develop an appropriate definition of health-related tests that FDA and CMS could use as a basis for expanding their scope. Additionally, these Federal agencies, including the HHS Office for Civil Rights, along with other State agencies and consumer groups should propose strategies to protect consumers from potential harm and from unanticipated and unwanted compromises in privacy that may lead to harm. Additional oversight strategies that might be established should be balanced against the benefits that consumers may gain from wider access to genetic tests and potential cost savings.

## 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 the clinical utility of genetic testing. There are 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, there has been insufficient analysis of the standard of evidence on which the clinical utility of genetic tests should be evaluated and on which evidence-based methods applicable to genetic testing should be 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:

- Identify major evidentiary needs
- Establish evidentiary standards and level of certainty required for different situations such as coverage, reimbursement, quality improvement, and clinical management
- Establish priorities for research and development
- 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
- Identify sources of data and mechanisms for making them usable for research, including the use of data from electronic medical records
- Recommend additional studies to assess clinical effectiveness
- Achieve consensus on minimal evidence criteria to facilitate the conduct of focused, quick-turnaround systematic reviews
- Increase the number of systematic evidence reviews and make recommendations based on their results
- Facilitate the development and dissemination of evidence-based clinical practice guidelines and clinical decision support tools for genetic/genomic tests
- Establish priorities for implementation in routine clinical practice
- Publish the results of these assessments or otherwise make them available to the public via a designated HHS or other publicly supported Web site (e.g., GeneTests)

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

- 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
- Disseminate these findings to the public via a designated HHS or other publicly supported Web site (e.g., GeneTests)

**2. Health care 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:**

Because the issues identified by SACGHS in the *Coverage and Reimbursement of Genetic Tests and Services* report are still current, the Committee urges HHS to act on the report's recommendations. In addition, public and private health care payers, in collaboration with relevant groups such as test developers and clinical laboratorians, should develop mechanisms, such as coverage with evidence development or phased reimbursement, to facilitate the collection of clinical utility evidence for high-priority tests and applications. Implementation of innovative approaches should be accompanied by careful evaluation to assess whether they enhance or hinder innovation, the understanding of effectiveness, and appropriate utilization.

- 3. The value of genetic tests to patients is realized only when they are used appropriately. Quality improvement processes are needed to ensure 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 recommendation:**

HHS should conduct public health surveillance to assess health outcomes (or appropriate surrogate outcomes), practice measures (including appropriate utilization), and the public health impact of genetic testing. Information should be linked to quality improvement practices that affect patient outcomes and the provision of health care services. 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 genetic testing.

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

HHS should ensure the coordination and implementation of efforts—including the deliberations of SACGHS; the American Health Information Community (AHIC) and/or its successors; and other 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 enhance the quality of decisionmaking.

### **Communication and Decision Support**

- 1. There are documented deficiencies in genetic knowledge in all relevant stakeholder groups. In addition to the creation of the SACGHS education task force, SACGHS recommends the following strategies to address these deficiencies:**

- A. HHS should work with all relevant government agencies and interested private parties to identify and address deficiencies in knowledge about appropriate genetic and genomic test applications in practice and to educate key groups such as health care practitioners, public health workers, public and private payers, and consumers of health care. These educational efforts should take into account differences in language, culture, ethnicity, and perspectives on health and disability as well as issues of medical literacy, access to electronic information sources such as the Internet, and deficiencies in public infrastructures (e.g., libraries) that can affect the use and understanding of genetic information.

B. Based on increased research regarding analytical validity, clinical validity, and clinical utility, sufficient resources should be provided to translate this knowledge into evidence-based clinical practice guidelines that enhance the quality of clinical health care and public health care outcomes.

- 2. Although FDA has asserted its authority over clinical decision support systems, the extent to which the Agency intends to regulate such systems is not clear. Given that clinical decision support systems will be necessary to communicate information appropriately in the preanalytical and postanalytical periods and given that 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, advisory committees to the HHS Secretary (e.g., AHIC and the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children), and stakeholders to gather perspectives on the appropriate regulatory framework for clinical decision support systems in light of changing health care delivery and health care data collection systems. As part of this process, FDA should prepare a guidance document articulating the basis of its authority to regulate clinical decision support systems as well as its rationale for 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 close these gaps and enhance the quality of patient care. SACGHS recommends that:**

HHS allocate resources to AHRQ, CDC, NIH, and the Health Resources and Services Administration to design and support programmatic and research efforts to encourage the 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. HHS also should address current inadequacies in the clinical information needed for test interpretation. These efforts will require engaging health care providers and payers as well as providing incentives and protections to ensure their participation in the design and dissemination of tools, the implementation of clinical decision support, and the contribution of necessary data.