Finalization of Recommendations on the Oversight of Genetic Testing

Andrea Ferreira-Gonzalez, Ph.D.
Chair, SACGHS Oversight Task Force
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Questions to Consider

In reviewing each recommendation, consider the following questions:

- Does the recommendation adequately address the identified problem?
- Is the wording of the recommendation satisfactory?

Chapter 6, Recommendation 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 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 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.

Chapter 6, Recommendation 1
(continued)

B. Conduct research and surveillance on how knowledge of analytic validity, clinical validity, clinical utility, and utilization can inform development of evidence-based clinical practice guidelines and 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.

Chapter 6, Recommendation 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, advisory committees to the Secretary of HHS (e.g., AHIC, ACHDGDNC), 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.

Chapter 6, Recommendation 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.

Chapter 6, Recommendation 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.

Chapter 6, Recommendation 4
(continued)

These efforts will require engaging providers and payers as well as providing incentives and protections in order to ensure participation in design and dissemination of tools, implementation of clinical decision support, and contribution of necessary data.

Chapter 6, Recommendation 5

Direct-to-consumer advertising of genetic tests and consumer-initiated genetic testing have the potential for adverse patient outcomes, social stigmatization, privacy concerns, 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, HRSA, 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, as well as protecting them from unanticipated and unwanted compromises in privacy that may lead to harm. Any additional oversight strategies that may be established should be balanced with the benefits that consumers may gain from wider access to genetic tests and potential cost savings.

Chapter 5, Recommendation 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:

Chapter 5, Recommendation 1
(continued)

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 and level of certainty required for different situations such as coverage, reimbursement, quality improvement, and clinical management.
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;

Chapter 5, Recommendation 1
(continued)

5. identify sources of data and mechanisms for making them usable for research, including the use of data from EMRs;
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.

Chapter 5, Recommendation 1
(continued)

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; and

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

Chapter 5, Recommendation 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:

Chapter 5, Recommendation 2

(continued)

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 for high priority tests and applications. Implementation of innovative approaches should be accompanied by careful evaluation to assess whether they enhance or hinder innovation, understanding effectiveness, and appropriate utilization.

Chapter 5, Recommendation 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:

Chapter 5, Recommendation 3
(continued)

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.

Chapter 5, Recommendation 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 and implementation 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 decision making.

Chapter 4, Recommendation 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:

Chapter 4, Recommendation 1
(continued)

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 cannot be achieved immediately. Consequently, the following actions should be taken:

1. CMS should require PT of all high complexity tests for which PT products are available. For tests without PT products, laboratories must use alternative assessment methods, as required under current CLIA regulations.

2. In order 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 support innovations in the way PT is performed such as through methodology-based processes.

Chapter 4, Recommendation 1
(continued)

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.

Chapter 4, Recommendation 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.

Chapter 4, Recommendation 2

(continued)

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). Such initiatives should be structured to encourage robust participation, for example and may a need to consider mechanisms for anonymous reporting and/or protections from liability to encourage information sharing among members.

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

Chapter 4, Recommendation 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. To gain a better understanding of the genetic tests being offered and to enhance the transparency of this field, SACGHS reviewed a number of proposals for a voluntary or mandatory test registry. Current CLIA regulations require nonwaived clinical laboratories to register with CMS and provide information that "describes the characteristics of the laboratory operation and the examinations and other test procedures performed by the laboratory." In light of this existing requirement, SACGHS recommends that:

CMS enhance the mandatory CLIA registration of nonwaived laboratories by augmenting the database of required laboratory information. Specifically,

Chapter 4, Recommendation 3
(continued)

1. The CMS-CLIA database should include or link to CMS information about laboratory sanctions.

2. The CMS-CLIA database should link to relevant FDA information such as product approval information.

3. A template created by FDA, based on prior work by the Secretary's Advisory Committee on Genetic Testing, should be used to capture additional data elements for all nonwaived tests. Before information in this template is required, CMS should consult with stakeholders to gather their perspectives on submitting additional data along with what is currently required by CMS for laboratories performing nonwaived tests and inclusion of this information in the CMS-CLIA database.

Chapter 4, Recommendation 3

(continued)

4. CMS should crosslink with the GeneTests Laboratory Directory, whose infrastructure is supported by the National Center for Biotechnology Information (NCBI). GeneTests could be enhanced to include additional data elements beyond those currently required by CLIA, such as information on clinical validity, and information from the Association for Molecular Pathology (AMP) on laboratories offering testing for somatic mutations. GeneTests/NCBI should receive sufficient funding to support this expanded scope.

5. All information in the CMS-CLIA database should be freely and easily available to the public. CMS should be assured of sufficient resources to accomplish this objective.

Chapter 4, Recommendation 3
(substitute version)

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 (LDTs) 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 address the information gaps. Since genetic tests are not unique from other laboratory tests for oversight purposes, the registry should include all LDTs. The Committee also discussed whether such a database should reside at CDC, CMS, or FDA. Based on its exploratory work, SACGHS concludes that the concept of a mandatory registry offers promise but recognizes that there are unresolved issues, including practical and legal questions, that require further analysis before a final decision can be made about how and where to implement the registry.

Chapter 4, Recommendation 3
(substitute version, continued)

In light of these unresolved issues, SACGHS recommends the following course of action:

A. CDC, in collaboration with CMS and FDA, should convene a stakeholders meeting by September 2008 to determine the data elements to be included in the test registry. CDC should cast a wide net for a broad stakeholder representation, including representatives from the private sector who can represent a role for public-private partnerships in developing a registry. CDC, through this stakeholders 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.

Chapter 4, Recommendation 3
(substitute version, continued)

B. HHS should perform the requisite legal analysis to determine what data elements, as determined by the CDC stakeholder group, can be required by CDC, CMS, and/or FDA. For example, if clinical validity is a required data element, the legal analysis should determine whether CDC, CMS, or FDA currently have the statutory authority to require reporting of this information for all LDTs. If these agencies do not currently have the necessary statutory authority, the legal analysis should identify specific statutory provisions that may be needed in order to effect a system of enhanced reporting requirements and statutory authority should be sought.

Chapter 4, Recommendation 3
(substitute version, continued)

C. HHS should appoint and fund a lead agency to develop and maintain the mandatory registry for LDTs. The lead agency should work collaboratively with its sister agencies to create a comprehensive registry and minimize duplicative collection of registry information. The lead agency should have qualified personnel who are experienced in developing and updating large databases in a timely and accurate manner.

D. 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 clinical validity data for these tests publicly available on laboratory websites.

Chapter 4, Recommendation 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 the review of 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. SACGHS, however, suggests that further analysis, deliberation, and consultation are needed to determine whether the appropriate weight has been apportioned to risks associated with the novelty and complexity of the testing platform and technology. SACGHS recommends that:

Chapter 4, Recommendation 4

(continued)

A. HHS convene relevant HHS agencies, including FDA, CMS, CDC, AHRQ, HRSA, and NIH, as well as stakeholders such as (but not limited to) laboratorians, clinicians, patient advocates, manufacturers, and pharmaceutical representatives, to provide further input into the development of a risk-based framework for the regulation of LDTs, including those offered directly to consumer. The risk-based framework should consider the intended use(s) of the LDT and likelihood of harm to patients or consumers if test results are inaccurate, susceptible to misinterpretation, or if tests are misapplied or extended beyond the proposed intended use.

Chapter 4, Recommendation 4

(continued)

B. For LDTs that will not be subject to FDA premarket 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 analytic and clinical validity of laboratory developed genetic tests. For infrequently performed LDTs, such as those for rare diseases, models such as the Collaboration, Education, and Test Translation (CETT) Program could be used to assess analytic and clinical validity.

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, for example, 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.

Chapter 4, Recommendation 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. The CLIA program has an array of enforcement actions available, but those actions cannot be imposed on uncertified laboratories. Instead, CMS must report the laboratory to the HHS Inspector General for action. Laboratories without CLIA certificates cannot be reimbursed by Medicare or Medicaid, but this restriction has no consequence for laboratories that perform direct-to-consumer testing. 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.

Chapter 4, Recommendation 5
(continued)

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.

Chapter 4, Recommendation 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, along with FDA's risk-based regulatory authority and regulatory processes should be expanded to encompass the full range of health-related genetic tests, including those offered directly to consumers. Relevant agencies (e.g., CMS, CDC, FDA, FTC) should collaborate in an effort to develop an appropriate definition of health-related genetic tests that FDA and CMS could use as a basis for expanding their scope.

Chapter 2, 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:

Chapter 2, Overarching Recommendation
(continued)

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.

Voting

Questions to consider in voting for the recommendations:

- Are thes recommendations the optimal way to address the opportunities and challenges identified in the report?
- Are these the recommendations that SACGHS should make to the Secretary?