

Creating a Genetic Testing Specialty Under CLIA: What Are We Waiting For?

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Introduction

Since the inception of the Human Genome Project in 1990, genetic testing has become an increasingly integral component in the diagnosis, treatment, management, and prevention of numerous diseases and conditions. Today, the number of genetic tests available is rising dramatically, with new tests entering the healthcare market every day. Information gained from genetic test results has a significant impact on medical decision-making. Incorrect genetic test results can lead to misdiagnosis, inappropriate and/or delayed treatment, anxiety, and, in rare cases, even death. While there are many diligent laboratories that comply with voluntary measures to ensure quality, the absence of oversight creates an environment in which poor performers can continue in the marketplace and bad actors can go undetected and uncensored. From the doctor and patient's perspective, moreover, the minimalist level of regulation makes it difficult to distinguish high quality from low quality laboratories. As the role of genetic testing in medicine continues to grow, so too does the urgent need to ensure that the genetic tests offered to the public are accurate and reliable and provide information relevant to a patient's current or future health status.

Laboratories that perform genetic testing for health-related purposes must be certified by CMS pursuant to the Clinical Laboratories Improvements Amendments of 1988 (CLIA). Congress enacted CLIA to ensure that clinical laboratories consistently perform tests in a valid and reliable manner. The stringency of CMS oversight under CLIA depends on the complexity of the test. "High complexity"

tests are generally grouped according to “specialty areas” and are subject to additional requirements to ensure safety. In particular, they are subject to specified “proficiency testing” standards, which require them to demonstrate their ability to accurately perform their tests. Under CLIA, clinical genetic tests are considered to be high complexity, but CLIA regulations do not contain a specialty area for molecular and biochemical genetic tests, and do not specify proficiency tests for them.

Beginning in the mid-1990s, key federal agencies began to take note of the growing use of genetic tests in clinical practice, and to raise concerns about the adequacy of oversight for both genetic tests and the laboratories that develop and perform them. In 1997, a joint task force of the National Institutes of Health (NIH) and the Department of Energy (DOE) issued several recommendations to improve the quality of genetic testing, including a recommendation for enhanced regulation of genetic testing laboratories.¹ Subsequently, an advisory committee to the Centers for Disease Control (CDC) recommended that the regulation of clinical laboratories be amended to include a genetic testing specialty area.

In May 2000, these recommendations were published in the Federal Register for public comment as a Notice of Intent (NOI), with the statement that the Centers for Medicare and Medicaid Services (CMS), an agency within the Department of Health and Human Service (HHS) would issue a proposed rule based on comments received.² The NOI noted that, along with the “tremendous potential for improving health and preventing disease, genetic testing can also do great harm” if errors occur in test selection, performance, or interpretation.³ The NOI cited literature pointing to errors or substandard practice in each of these categories.

The CDC received 57 comments in response to the NOI. The CDC reviewed these comments and, apparently finding them largely negative with respect to the recommendations, asked the advisory committee to further analyze the issues raised by the NOI and to suggest modifications. In February

2001 the advisory committee completed its report and recommended that the Department of Health and Human Services proceed with the development of a proposed rule to create a genetic testing specialty under CLIA.

Five years after the publication of the NOI, CMS has not proposed the creation of a genetic testing specialty. Neither the advisory committee's revised recommendations nor the proposed rule has been published. The record has gone virtually silent.

From the public's perspective, the process begun with much enthusiasm and sense of mission a decade ago has come to a grinding halt. Those who submitted comments five years ago have seen no further action by CDC or CMS regarding the creation of a genetic testing specialty, nor have they heard any rationale for the government's failure to proceed notwithstanding the recommendations of its own advisory committee.

The failure of CMS to proceed with the creation of a genetic testing specialty has meant federal oversight of genetic testing laboratories continues to be inadequate to ensure quality. Meanwhile, the number of new gene discoveries, commercially available genetic tests, and emerging genetic testing technologies continue to increase dramatically. The need to assure the American public that genetic testing is safe and reliable has never been more urgent. Thus, continued inaction by the government agencies responsible for public health and clinical laboratory quality is unacceptable. Is this inaction caused by the perception that comments to the NOI raised irresolvable concerns, or has the agency simply dropped the ball? In an effort to discern the reason for the delay, we reviewed the comments submitted to the agency to see whether there was an overall favorable or unfavorable reaction to the recommendations. As this White Paper describes, we found substantial support for the creation of a genetic testing specialty, with concerns regarding only a few of the recommendations.

Purpose

This paper reviews the comments submitted in response to the NOI and identifies areas of consensus as well as areas of concern and opposition. It finds that there was support for key recommendations in the NOI, and recommends that CMS issue a proposed rule that focuses on these key issues, while leaving aside those that were more controversial and arguably less central to ensuring laboratory quality. Before reviewing the comments, however, it is necessary to place the NOI within the overall history and purpose of CLIA and the regulation of laboratory tests more generally.

History

Concern about the quality of clinical laboratory testing arose long before the launch of the Human Genome Project. In response to widespread misreporting of Pap smear results, Congress enacted the Clinical Laboratory Improvement Amendments (CLIA) of 1988. In enacting CLIA, Congress gave CMS broad power to ensure that laboratories have the right facilities, personnel, and standards in place to ensure quality testing. Pursuant to CLIA, CMS established “specialty areas” for several types of testing, including (1) microbiology; (2) immunology; (3) chemistry; (4) hematology, and (5) pathology. The creation of a specialty area is a necessary step in the development of specific and tailored requirements for a particular category of testing, particularly testing that is complex to perform or interpret.

Perhaps because genetic testing was in its infancy at the time CLIA was enacted, CMS did not initially establish a genetic testing specialty. However, CLIA requires CMS to develop regulations to ensure the quality and safety of all clinical laboratory testing. To be sure, CLIA’s general requirements for laboratory quality, such as general obligations to have appropriately trained personnel, establish quality control procedures, and engage in proficiency testing, do apply to laboratories performing clinical genetic testing. However, the absence of a genetic testing specialty with specifically tailored

requirements for the now burgeoning genetic testing industry hampers the agency's ability to ascertain and ensure the quality of a laboratory's testing. In particular, the absence of a specialty has meant that there are no specific "proficiency tests" that laboratories must perform to show they can reliably get the "right answer" in performing a genetic test. Many laboratories do follow the proficiency testing programs established by professional organizations, but such programs are voluntary and, moreover, are available for only a small number of genetic tests.

Indeed, concerns that the general provisions of CLIA were inadequate to ensure the quality of genetic testing led to recommendations for the creation of a genetic testing specialty. In May 2000, the CDC published a NOI in the Federal Register requesting public comment on the recommendation to create a genetic specialty under CLIA. The NOI specifically requested feedback on:

- (1) The definition of genetic testing;
- (2) The role of the laboratory director in documenting clinical validity;
- (3) Who should be authorized to order a genetic test;
- (4) Whether the laboratory should be responsible for documenting a patient's informed consent;
- (5) Whether additional procedures are needed to protect patient confidentiality;
- (6) Whether more stringent personnel qualifications were needed to ensure genetic test quality; and
- (7) Whether the recommended additions to the general requirements for preanalytic, analytic, and postanalytic phases of testing were appropriate.

Review and Analysis of NOI Responses

The CDC received 57 responses to the NOI. Respondents included academic laboratories (20), professional organizations (18), state and federal government agencies (8), commercial laboratories (5), manufacturers/industry (5), trade organizations (2), and other miscellaneous groups or individuals (2).⁴

A. General Reaction to Creation of Genetic Testing Specialty:

The overwhelming majority of respondents (93%) supported the recommendation to create a genetic testing specialty for molecular and biochemical genetic tests as a means to promote their reliability, accuracy, and quality. Nine (out of the 57) respondents explicitly affirmed that the creation of a specialty would help ensure that genetic testing is of high quality, while 45 respondents appeared to accept the creation of a genetic specialty and focused their comments on other aspects of the NOI. The New York State Department of Health, which certifies all laboratories that test patient specimens from New York, and which is exempt from CLIA requirements because it's program is more stringent, supported CLIA's efforts to establish "appropriate quality control standards for the growing category of genetic testing."⁵ Only three respondents explicitly opposed the creation a genetic specialty, asserting that "genetic testing should not be regulated differently than other testing."⁶ Interestingly, none of objectors were clinical laboratories providing clinical genetic testing services to the public.⁷⁸

B. Definition/Categories of Genetic Tests

The NOI proposed definitions for two categories of genetic tests to be included under a new genetic testing specialty: (1) molecular and cytogenetic tests; and (2) biochemical genetic tests. It asked for comments on whether the proposed definitions (below) were appropriate, too broad, or too restrictive.

Molecular and cytogenetic tests: analysis performed on human DNA, RNA, and chromosomes to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Includes predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations.

Biochemical genetic tests: analysis of human proteins and certain metabolites, which is predominantly used to detect inborn errors of metabolism, heritable genotypes, or mutations for clinical purposes. Purposes include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. [Tests used primarily for other purposes, but may contribute to diagnosing a genetic disease (e.g., blood smear, certain serum chemistries), not covered by definition].

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the definitions needed further clarification and refinement. Some characterized the proposed definitions as “too broad” or “unclear.” Some opposed combining cytogenetic and molecular genetic testing under one heading, believing the two were distinct enough to warrant their own separate subcategories, and some were concerned that the inclusion of the word “phenotypes” was unnecessarily broad. A few groups specializing in HLA tissue matching for transplantation believed this type of testing should be exempt from the specialty entirely because they were adequately covered under existing rules and many of the new requirements would not be inapplicable. Several laboratories performing biochemical testing were concerned that the new rules would conflict with existing specialty areas under CLIA and that the proposed specialty would encompass more general tests whose indications do not fit under the realm of genetic disease prediction, diagnosis, or management.⁹

Based on review of these comments it would appear that concerns about the definition could be addressed if (1) the definition of a genetic test contained three distinct subcategories, molecular, cytogenetic, and biochemical; (2) specific exemptions to the new CLIA regulation were allowed for tests already subject to adequate regulation under other subspecialties;(3) more clarity were provided with respect to what constitutes a “genetic disease”; and (4) clarity is provided to distinguish when a test is “genetic” under CLIA if can be used both to determine genetic status and for other purposes (e.g., iron testing for diagnosing hemochromatosis, a genetic disorder, vs. iron testing for diagnosing anemia, which may not be genetic).

C. Role of Laboratory Director in Documenting Clinical Validity

Current CLIA regulations state that the director of a clinical laboratory must ensure that tests performed by the laboratory provide “quality laboratory services for all aspects of test performance” including preanalytic, analytic, and post-analytic phases of testing,¹⁰ and that the “test methodologies selected have the capability of providing the quality of results required for patient care.”¹¹ The regulations do not, however, explicitly require the laboratory to ensure that tests performed will provide information that is relevant to the current or future health status of a patient, i.e., that the tests are clinically valid. For many laboratory tests, long history of use by physicians has provided the needed link between test results and the clinical context; for example, it is now well accepted that a high white blood cell count may signify an infection or other disorder and that a high cholesterol level relates to increased risk of heart disease. Because information regarding genetic variation is so new and is developing so rapidly, the clinical significance of many of the mutations that can be detected through genetic testing may not yet be clear. Thus the NOI proposed a greater role for laboratory directors in assessing “clinical validity,” i.e., that the detection of a particular mutation has clinical relevance.

The NOI suggested the following requirements for clinical validation of genetic tests: (1) a positive confirmatory test must have a defined positive predictive value which can be communicated to the caregiver (2) clinical validity must be documented in 10 affected individuals when the disease incidence is greater than 1/10,000; and (3) predictive values should be defined in terms of ethnic populations, where applicable.

The NOI did not specify where the data used to establish clinical validity should come from (e.g. from research carried out by the laboratory itself or from data collected by others and reported in the scientific literature.) and, as a consequence, the issue of the laboratory director's role in documenting clinical validity was extremely contentious. Of the respondents, 23/57 (40%) argued that documentation of clinical validity was not required of laboratory directors overseeing other testing specialty areas and was beyond the scope of the laboratory and the laboratory director's responsibility. Among the dissenters, there was consensus that the laboratory director was responsible for documenting analytic validity, but that documenting clinical validity would be unduly burdensome. One commenter was concerned that the new regulation would impose an "FDA-like product submission that would stifle the development of new tests."¹² Other commenters did not categorically oppose a role for laboratory directors, but thought it should be limited to reviewing and documenting existing data published in the medical and scientific literature. New York State noted that its program "requires laboratories to submit documentation of established technical validity for review prior to offering patient testing for any in house developed assay for which there is no prior reference method."¹³

Some commenters were concerned about specific details regarding defining predictive value and documenting at least 10 positive controls, arguing that this was not possible in all cases, particularly for tests for rare diseases or for tests where the predictive value is either impossible to determine or has not

yet been determined. 7/57 (12%) of respondents agreed that there was a role for the laboratory director to document clinical validity and 27/57 (47%) had no comment.

While clearly the issue of the laboratory director's role in documenting clinical validity is contentious, some of the disagreement may be attributable to the lack of a clear understanding as to the meaning of clinical validity, what counts as documentation, and what is the definition of a "confirmatory test." Thus it is evident that more clarity is needed on this issue.

The comments submitted by New York State detailing their process for assessing new tests provided one possible model for assessing clinical validity. According to these comments:

The New York State Program requires laboratories to submit documentation of established technical validity for review prior to offering patient testing for any in-house developed assay for which there is no prior reference method. Materials submitted include such items as: a description of the scientific basis of the assay; the reagents and pre-analytic quality control for each critical reagent; the source and documentation of positive and negative control samples; the data from which sensitivity, specificity, accuracy and precision have been calculated; sample reports which must include any disclaimer regarding the limitation on available information regarding clinical validity; and a plan for collecting prospective clinical outcome data for future risk of positive and negative predictive values.¹⁴

D. Authorization to Order a Genetic Test

The NOI raised the concern that CLIA currently defers to State law regarding which individuals are authorized to order tests and that some states provide no guidance on this issue. While the basis for this concern was not explained, it presumably related to the risk of genetic tests being ordered inappropriately by those without adequate training or education. The NOI asked for comments regarding whether genetic testing is sufficiently different to require a new federal guideline to define who is authorized to order a genetic test.

Ten respondents (18%) answered yes to this question, while 18 (32%) answered no. About half of the comments either did not respond to this question or were equivocal. A few, notably genetics professional groups, wanted a federal guideline defining authorized persons to ensure that only licensed

professionals are able to order these tests. Others stated that variation in state laws is confusing and “some federal requirement needs to be established to define who is authorized to order a genetic test.”¹⁵ The main point expressed by those who opposed this suggestion was that the current CLIA regulations were adequate, i.e., individuals currently authorized to order other laboratory tests are qualified to order genetic tests and the authorization should continue to be determined by the individual states.

E. Informed Consent

The NOI asked for comments regarding whether the laboratory should be required to document that the patient’s informed consent has been obtained by an authorized person for certain genetic tests or types of tests (screening, diagnostic, carrier, or for presymptomatic susceptibility.) The failure to define the word “certain” led to much confusion. In the words of one commenter: “Wording such as this is fraught with ambiguity. . . . [w]hat does ‘certain’ genetic tests mean? Who decides which tests are the ‘certain’ ones?”¹⁶

By far, this recommendation generated the strongest opposition. An overwhelming majority of respondents 41/57 (72%) stated that the responsibility for obtaining patient informed consent rests with the provider ordering the test for the patient. Many stated that laboratories should be able to “presume consent was obtained” or use the test requisition form as a vehicle to document that consent was granted, e.g. a checkbox on the form. Not only was the requirement to obtain consent viewed as unduly burdensome, it was viewed as infeasible and potentially detrimental to quality testing. Some argued that specimen integrity might be compromised by the delay required to obtain or verify consent. Moreover, laboratories expressed the view that it was not their proper role to “police” physicians and other providers. “At some point during the testing process it seems appropriate to require that the physician have some small measure of responsibility.”¹⁷ Only 4/57 (7%) believed that the lab was the appropriate

place to regulate consent. Those who did not express an opinion 12/57 (21%) mainly represented professional or trade organizations that did not perform direct clinical laboratory testing.

F. Confidentiality

The issue of confidentiality was another hot topic. The NOI included recommendations that laboratories have a policy in place to protect the confidentiality of test results, and asked for comments regarding whether additional policies were necessary to enhance the confidentiality of certain genetic test information or if the current CLIA confidentiality policies were sufficient.

Fifty-one percent (29/57) of the respondents flatly opposed adding additional processes to enhance the confidentiality of genetic tests. One CMS employee who provided comments summed up the main theme of the comments: “All test results are confidential...genetic test results should be handled like any other test results in a confidential manner.”¹⁸ Some opponents also argued that even if additional measures were necessary, CLIA was not the appropriate vehicle to implement them. Twenty-four commenters (42%) did not take a position regarding confidentiality. Only four respondents (7%) expressly supported additional measures, with one expressing the view that “additional language to protect confidentiality” would be a good idea.¹⁹ Another stated that “more confidentiality would be good” but was not sure what specific provisions would be appropriate.²⁰ However, it should be noted that the NOI was published prior to the development and implementation of the Health Insurance Portability and Accountability Act (HIPAA) regulations regarding the privacy of medical information. These regulations, which were finalized in 2003, impose requirements for protecting the confidentiality of all identifiable health information, including genetic information.

G. Genetic Counseling

The NOI proposed that under the new genetic specialty, the clinical consultant’s qualifications and responsibilities expand to provide genetic counseling to the laboratory’s clients (care providers, patients,

individuals, etc.) and that board-certified genetic counselors be added to the category of clinical consultant. The NOI asked for comments on whether laboratories should be required to provide genetic counseling services.

There was very little support for this recommendation. More than half of the respondents flatly rejected the proposal. One commenter's response summarized the general dissent: "The primary role of the laboratory is to analyze patient specimens and to provide analytical results in an understandable format.... genetic counseling should remain the responsibility of the physicians and genetic counselors."²¹ Only three respondents appeared to favor the recommendations: one favored having a "documented relationship" with providers of genetic counseling services;²² another believed "someone associated with the laboratory be capable of providing genetic counseling";²³ and the third comment suggested that the clinical consultant should be required to fill this role. The remaining 39% of responders had no comment.

H. Preanalytic, Analytic, Postanalytic

The NOI included recommendations regarding preanalytic, analytic, and postanalytic phases of testing, addressing laboratory personnel requirements and responsibilities, reuse of tested samples, ordering of additional tests, the content of test requisitions, quality control and patient test management, analytic validation, clinical validation, proficiency testing, reporting requirements, and record and sample retention. The NOI asked for feedback on each of these areas. For some there were few comments or little controversy; we are highlighting ones that generated differences of opinion or appeared highly contentious.

a. New personnel requirements

The recommended changes to current personnel qualifications described in the NOI would increase the amount of training and experience in genetic testing required for the laboratory director, technical

supervisor, general supervisor, and clinical consultant. Twenty-five comments addressed these recommendations. On the whole, most commenters appeared to support the general concept of enhanced personnel requirements, but some disagreed with certain provisions relating to particular categories of personnel. In addition, a few commenters, including CAP, expressed concern that increasing the qualifications would lead to a shortage of trained personnel.

b. Reuse of patient samples

The NOI's recommendation that patient consent be required before a laboratory could re-use a patient specimen for the purpose of quality assurance and quality control (QA/QC) drew sharp criticism. Laboratories were concerned that the inability to reuse patient samples from which identifying information had been removed "would restrict the lab's ability to ensure test quality and improve testing."²⁴ Also, because many tests are used to detect rare mutations, requiring additional consent to re-use specimens would prevent laboratories from obtaining controls, i.e., samples against which compare test results. The lack of access to controls, particularly for rare diseases, would impede the laboratory goal of continued improvement and quality standards. There was consensus that de-identification of samples was a reasonable requirement to re-use samples, but that requiring consent under these circumstances was infeasible and unreasonable.

Conclusion

A review of the comments submitted in response to the NOI reveals that there was substantial support for the creation of a genetic testing specialty under CLIA in order to address the unique issues and complexities raised by genetic tests. Combining the support of the laboratories with the fact that a majority of the American public supports government regulation to ensure the safety and accuracy of genetic test results²⁵ only underscores the urgent need to revisit the issue of regulating genetic testing. Five years after the NOI was published, a genetic specialty has still not been created under CLIA. To

the extent that inaction results from perceived opposition to the issuance of a proposed rule, our review of the comments to the NOI indicate that the creation of a genetic testing specialty is achievable if the requirements focus on the key components needed to ensure quality. Key components include criteria for establishing analytic and clinical validity and requirements for proficiency testing. The more contentious issues, such as additional requirements for consent, confidentiality, and genetic counseling, should be set aside for the moment in the interest of ensuring that genetic tests are safe and accurate and provide information relevant to health care decision making. These additional requirements arguably would be beyond the appropriate role of clinical diagnostic laboratories and may well be better addressed through other means. When the responses are stripped of these issues, the comments suggest that any regulation must (1) clearly define “genetic testing” and include three subcategories: molecular, cytogenetic, and biochemical testing; (2) specify the tests exempt from the new CLIA regulations; (3) clearly outline if and when a test is considered “genetic”; and (4) provide clear guidance regarding the definition of clinical validity and the scope of the laboratory director’s duty to document it.

Federal regulation of genetic testing is widely supported and desperately needed to ensure the safety, accuracy, and reliability of genetic tests. Although many members of the public believe that the government already regulates the accuracy and reliability of genetic tests and, moreover, support this oversight role, there are serious gaps in the government’s oversight of genetic testing. Adequate oversight of the laboratories performing genetic tests is a key component of ensuring quality. Such oversight requires that the government take immediate steps to implement the long-promised regulations to establish a genetic testing specialty and thereby provide greater assurance that laboratories are providing accurate and reliable genetic tests to consumers.

Endnotes

¹ Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing (Neil A. Holtzman & Michael S. Watson eds., 1997).

² 65 Fed. Reg. 25928 (May 4, 2000).

³ Id. at 25929.

⁴ Comments were received from Abbot Laboratories, Inc., Academy of Clinical Laboratory Physicians and Scientists, Advanced Medical Technology Association, American Association of Bioanalysts, American Association of Blood Banks, American Association of Clinical Chemistry, American Clinical Laboratory Association, American College of Medical Genetics, American Medical Laboratories, Inc., American Society for Clinical Laboratory Science, American Society of Clinical Pathologists, American Society for Histocompatibility and Immunogenetics, American Society of Clinical Oncology, Association for Molecular Pathology, Association of Public Health Laboratories, Athena Diagnostics Inc., The Blood Center, Boston University School of Medicine, Bristol-Meyers Squibb Pharmaceutical Research Institute, Carolinas Medical Center, City of Hope National Medical Center, Clinical Immunology Society, Cornell Medical Center, Dianon Systems, College of American Pathologists, Columbia University, Eastern Virginia Medical School Cytogenetic Laboratory, Emory Genetics Laboratory, Genzyme Genetics, Johns Hopkins University Immunogenetics Laboratory, University of Kentucky Immuno-Molecular Laboratory, Lehigh Valley Hospital, Michael Malinowski, Natalie McIntosh, M.Sc., CGC, CGCC, MUSC Laboratory Services, Marshall University Clinical Laboratory Services Department, Mayo Clinic, University of Michigan Kellogg Eye Center, Medical College of Virginia Hospitals, National Credentialing Agency for Laboratory Personnel, National Society of Genetic Counselors, Neo Gen Screening, Orchid BioSciences, Inc., David Poynter, MSA, BS, MT(ASCP), Promega Corp., Pyrosequencing AB, Sacred Heart Medical Center, State of California Department of Health Services, State of New York Department of Health, State of Utah Department of Health, State of Washington Department of Health, University of Utah, and from individual Health Care Financing Administration personnel.

⁵ Comments of State of New York Department of Health (Wadsworth Center) (June 30, 2000).

⁶ Comments of Abbott Laboratories, Inc. (June 30, 2000).

⁷ Comments of Advanced Medical Technology Association (July 10, 2000) and ACLA (July 3, 2000).

⁸ Comments of Abbott Laboratories, Inc. (June 30, 2000).

⁹ Comments of the Blood Center (June 28, 2000).

¹⁰ 42 C.F.R. § 493.1445(e)(1).

¹¹ 42 C.F.R. § 493.1445(e)(3)(i).

¹² Comments of AdvaMed (July 10, 2000).

¹³ Id.

¹⁴ Comments of the State of New York Department of Health (June 30, 2000).

¹⁵ Comments of Francisca Lehr, Health Care Financing Administration (July 3, 2000).

¹⁶ Comments of Dianon Systems (June 29, 2000).

¹⁷ Comments of Dianon Systems (June 29, 2000).

¹⁸ Comments of Francisca Lehr, Health Care Financing Administration (July 3, 2000).

¹⁹ Comments of American Society for Clinical Laboratory Science (July 3, 2000).

²⁰ Comments of Marshall University (July 3, 2000).

²¹ Comments of Association of Molecular Pathologists (June 29, 2000).

²² Comments of American Society for Clinical Laboratory Science (June 29, 2000).

²³ Comments of American Association of Bioanalysts (June 29, 2000).

²⁴ Comments of American Association of Clinical Chemistry (June 22, 2000).

²⁵ Genetics and Public Policy Center, Reproductive Genetic Testing: What America Thinks (2004), available at www.dnapolicy.org.