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Submitted via e-mail to GTR@od.nih.gov

Dear Dr. Fomous,

The American Society for Clinical Pathology (ASCP) commends the National Institutes of Health (NIH) for convening a public meeting to scrutinize the issues surrounding the development of a Genetic Test Registry (GTR).

While ASCP supports the concept of the GTR, we believe that the NIH needs to coordinate with other government entities in establishing a reliable framework for oversight of the registry. We are concerned that the segregation among federal agencies, all of which have varying agendas regarding the regulation of genetic tests, would compromise the value and credibility of the GTR. The NIH, in partnership with the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ) should maintain the authority to remove the genetic test information in the registry if they have a reasonable concern that it provides insufficient clinical validity. There must be assurances that all genetic tests in the registry are clinically valid. This is necessary to ensure that patients gain access to quality advanced diagnostics which can be integrated into the practice of medicine. The ASCP Board of Directors recently approved a public policy statement (attached) with regards to laboratory developed tests (LDTs). While this policy statement examines the regulation of LDTs, ASCP believes that it shares a common goal with the NIH by asserting that diagnostic genetic tests should be of highest quality, reliability, and safety, and that each test should provide valid and useful information for clinical decision making.

In recent years, genetic tests have assumed a more pivotal role in medical decision-making. Therefore, the GTR could prove to be a necessary resource for doctors, industry, researchers and the public but only if it is a reliable source of information. However, ASCP is concerned that the increased utilization of genetic tests, their use outside of the physician-patient context, and their development by larger corporations without proper validation for intended use may put patients at risk for incorrect diagnosis and inappropriate treatment. The voluntary submission of data in the GTR with minimal or no regulation could encourage certain genetic test manufacturers to use the registry as a means to promote their services, whether or not the information they submitted is scientifically accurate. There must be assurances that genetic tests are clinically valid, performed correctly by competent laboratories, and the results communicated to patients by clinicians adequately trained to interpret these tests. ASCP supports strengthened oversight to ensure that genetic tests remain one of the key tools clinicians can use to answer increasingly complex questions regarding patient care.

ASCP believes that comparative effectiveness research (CER) is the best way to demonstrate the value of genetic tests for improving clinical outcomes. Unfortunately, many of the genetic tests being manufactured and utilized today are not associated with enhanced clinical outcomes. Often times, the issue becomes not which test is best, but how many tests can be performed within any given disease profile, despite their lack of clinical utility. As a result, treatment for patients is often inconsistent and based on professional experience rather than data-driven evidence. As a strong proponent of CER, we encourage the NIH to require genetic tests providers who submit their information in the GTR to provide peer-reviewed literature associated with their test.

Genetic tests are increasingly being integrated into standard practice for diagnosing and managing disease, predicting the risk of developing disease, and informing decisions about lifestyle and behavior. These tests are enabling improved prevention, treatment, and disease management for an array of common chronic conditions as well as rare genetic disorders. They have become indispensable tools in the practice of medicine. However, ASCP strongly believes that only high-quality, clinically and analytically valid genetic tests should be offered to patients. Therefore, we urge NIH to consider featuring a review process for every submission to the registry. In doing so, health care providers and patients can avoid being misled by the idea that each genetic test entered in the database is clinically valid just because it is an NIH mandated database.

The ASCP is a professional organization with over 130,000 members working as pathologists, residents and other physicians, pathologists' assistants, laboratory professionals, medical students and laboratory students. As a patient-centric organization, ASCP's mission is to protect patient safety while promoting advances in medicine. As the largest specialty society representing the field of pathology and laboratory medicine ASCP appreciates the opportunity to comment on the development of genetic testing registry. Please do not hesitate to contact me or

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Sincerely,

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American Society for Clinical Pathology

POLICY STATEMENT

REGULATION OF LABORATORY DEVELOPED TESTS (LDTS)

(POLICY NUMBER 10-02)

POLICY STATEMENT:

The American Society for Clinical Pathology (ASCP) believes that laboratory developed tests (LDTs), as with all diagnostic tests, should be of the highest quality, reliability, and safety, and that each test should provide valid and useful information for clinical decision-making.

BACKGROUND AND RATIONALE:

For years, the diagnostics industry, clinical laboratories, researchers and patient groups have debated the appropriate regulatory scheme for LDTs. LDTs play a vital role in health care and their potential impact on patient care will increase dramatically in the coming years. There must be assurances that LDTs, particularly high-risk LDTs, provide clinically relevant information to physicians and patients. Yet LDTs present some unique regulatory questions. How do regulators establish fair, concrete, predictable regulatory requirements for LDTs that will protect the public's health but not deter innovation or unduly hamper access to tests? ASCP believes that the regulatory oversight of LDTs should be under the purview of the appropriate federal agencies and an independent, neutral third party reviewer in a process unfettered by any conflicts of interest. ASCP supports a clearly defined risk-based regulatory scheme that carries provisions that permit appropriate and timely responsiveness in a public health crisis.

I. Introduction

A. Definition and Use of Laboratory Developed Tests

Laboratory developed tests (LDTs) are *in vitro* diagnostic tests that are developed, validated and used for in-house pathology and diagnostic purposes. LDTs are intended for use only by the laboratory entity where they are developed, unlike the majority of commercially marketed laboratory tests which are manufactured by medical device companies and sold to laboratories, hospitals or physicians' offices in interstate commerce, and must be cleared or approved by the Food and Drug Administration (FDA)

through either the premarket notification or pre-market approval (PMA) processes. Laboratories that develop these "in-house" diagnostic tests, either create the necessary reagents themselves or purchase reagents from outside vendors, and then develop their own proprietary test. These tests are never sold to other laboratories, hospitals or doctors, and therefore have not typically been subjected to FDA approval or clearance processes. FDA-approved commercially marketed tests that have been modified in any way by a laboratory are also considered to be LDTs and subject to the same regulations applied to all LDTs.

Because this very common definition for LDTs is also quite broad, it could potentially include a number of common diagnostic laboratory tests including microscopic examinations, microbiology culture and susceptibility tests, staining and examination of tissue sections, and blood cross-matching procedures. These tests are well established diagnostic laboratory tests with adequately demonstrated clinical validity and utility. Some of these tests may also be available as commercially marketed laboratory tests and therefore subject to the regulations governing that category. However, most LDTs are molecular genetic tests for which there is no commercial test available. The Clinical Laboratory Improvement Advisory Committee (CLIAC) Genetic Testing Good Laboratory Practices Workgroup describes these LDTs as encompassing "a broad range of laboratory tests performed to analyze DNA, RNA, chromosomes, proteins, and certain metabolites using biochemical, cytogenetic or molecular methods or a combination of these methods." These LDTs are used to detect heritable or acquired disease-related genotypes, mutations, or phenotypes for clinical purposes." [1]

B. Current Oversight Authority

Oversight of laboratory tests in the U.S. is provided by a still-evolving system that currently includes government agencies, health care payers, professional associations, and other stakeholders. With the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) and Clinical Laboratory Improvement Amendments (CLIA), the U.S. Congress established provisions for the oversight of various aspects of laboratory medicine.[2] Passage of the Medical Devices Amendments Act in 1976 granted the FDA jurisdiction over commercially distributed test kits as in-vitro diagnostic devices. The FDA claims the statute also grants them jurisdiction over the regulation of LDTs. However, the agency issued a draft guidance in 2006 announcing that, with the exception of a small subset of LDTs deemed to be "in vitro diagnostic multivariate index assays" (IVDMIAs), the agency would exercise enforcement discretion, reasoning that most LDTs were simple, low risk diagnostic tools that were well-characterized.[3] In addition, most LDTs were reliant upon various FDA-regulated individual components, either analyte specific reagents or general reagents, and the tests were performed in CLIA laboratories certified to conduct high complexity testing.[4]

II. Justification for Enhanced Regulatory Oversight

LDTs, initially used to diagnose rare diseases and conditions, were intended to be used within a single institution by physicians and pathologists actively engaged in their patients' care. In recent years, LDTs have become increasingly more complex, and their use has expanded to assess high-risk, but relatively common diseases and conditions. However, as LDTs have begun to assume a

more pivotal role in medical decision-making, they are more frequently being performed in geographically distant commercial laboratories instead of within the patient's health care setting under the supervision of a pathologist and treating clinician. In some instances, LDTs are being marketed directly to the patients. ASCP is concerned that due to the increased application of LDTs for genetic testing and personalized medicine, the use of LDTs outside of the physician-patient context, and the development of LDTs by larger corporations, that some LDTs may not have been properly validated for their intended use, putting patients at risk for missed diagnosis, wrong diagnosis, and inappropriate treatment.

For more than a decade, during a period of greatly accelerated advances in molecular pathology and increased growth of clinical applications of LDTs, various groups have examined the need for strengthening Federal oversight of genetic testing and testing laboratories. In 1997, the Task Force on Genetic Testing, convened jointly by the National Institutes of Health (NIH) and the U.S. Department of Energy (DOE), issued *Promoting Safe and Effective Genetic Testing in the United States*, which made several recommendations regarding the oversight of genetic tests and testing laboratories.[5] In its review of current practices at the time, the Task Force concluded that, "sometimes, genetic tests are introduced before they have been demonstrated to be safe, effective, and useful," and "there is no assurance that every laboratory performing genetic tests for clinical purposes meets high standards." The report also noted deficiencies in the informational materials available to help providers and patients interpret results. In this report, the Task Force recommended the development of a framework for ensuring that new tests meet criteria for safety and effectiveness before they are unconditionally released, thereby reducing the likelihood of premature clinical use.

Between 1998 and 2000, the Clinical Laboratory Improvement Advisory Committee (CLIAC) recommended the enhancement of regulations governing the quality of clinical laboratories generally and genetic testing laboratories specifically.[6] In 2000, the Centers for Disease Control and Prevention considered adding a genetic testing specialty under regulations of the Clinical Laboratory Improvement Act Amendments of 1988 (CLIA).[7] Later that same year, the Secretary's Advisory Committee on Genetic Testing (SACGT) issued *Enhancing the Oversight of Genetic Tests*, which concluded that additional oversight of genetic tests was warranted and should be achieved through new multifaceted and innovative oversight mechanisms.[8] SACGT also agreed with CLIAC that a genetics specialty should be added to CLIA. In 2003, the CLIA regulations were amended in several general ways, but the Centers for Medicare & Medicaid Services (CMS) did not proceed with adding a genetics specialty.[9]

In 2008, Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) published *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, an extensive report about the oversight roles of Federal, State, and private sector entities concerning the analytical and clinical validity of genetic tests, private sector responsibilities for clinical laboratory accreditation, standard setting, and the development of clinical practice guidelines for genetic testing. The Committee identified gaps in oversight in a number of areas, including, (1) the regulations governing clinical laboratory quality; (2) the oversight of the clinical validity of genetic tests; (3) the transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) 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. To help close the gaps in oversight related to clinical validity, which would help assure the appropriate use of laboratory tests, the Committee recommended that "the 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." [10]

While LDTs represent the leading edge of clinical testing being offered to patients today, and most have a solid record of advancing patient care safely and effectively, ASCP agrees that the time has come for the FDA to insert its regulatory authority over high risk LDTs. There must be assurances that these tests are clinically valid, performed correctly by competent laboratories, and the results communicated to patients by clinicians adequately trained to interpret them. ASCP supports strengthened oversight to ensure that LDTs remain one of the key tools clinicians can use to answer increasingly complex questions regarding patient care.

The FDA itself suggests that its policy of enforcement discretion may have disincentivized innovation by manufacturers who must seek FDA approval, yet it also acknowledges the dependence of innovation upon an appropriate oversight framework, particularly in areas such as genomics, genetic testing, and diagnostics for rare diseases, areas in which medicine is highly reliant upon LDTs. In the Agency's states that, "In these and other categories, it is important that FDA provide a reasonable, predictable, and consistent regulatory policy for ensuring the safety and effectiveness of LDTs and provide sufficient time for implementation. Therefore, enhanced regulation should encourage innovation, improve patient outcomes, strengthen patient confidence in the reliability of these products, and help reduce health care costs." [11]

III. Other Regulatory Models

As federal agencies seek to develop a new regulatory paradigm for LDTs, it will be important to adopt a global perspective. With the formation of multinational companies and global markets for their products, innovation in genomics clearly transcends national boundaries. International research is being conducted by such groups as the Human Genome Organisation (HUGO) and the Human Proteome Organisation (HUPO), and there are transnational regulation and standard setting initiatives underway by other organizations such as the International Conference on Harmonization (ICH) and the International Organization for Standardization (ISO).[12]

While the United States is home to more consumer genetic diagnostic companies than any other country, regulatory oversight of LDTs, particularly those marketed directly to consumers, is also under close scrutiny abroad. In Australia, Canada, and across Europe, a number of governmental committees and task forces have reviewed the oversight of genetic testing in their respective countries, and issued reports with similar conclusions: genetic tests should not enter clinical practice without thorough independent evaluation.

Achieving this universal goal would require addressing a number of regulatory deficiencies. While all of these countries employ a regulatory scheme based on risk classification, there are significant differences in how risk is defined and degree to which the regulation has been enforced. While LDTs in both Canada and the United States have generally not been subject to pre-market review procedures required of commercially marketed laboratory tests, there is more widespread support in Europe and Australia for a more consistent approach in private laboratories. However, in Europe, genetic tests, like nearly all diagnostic tests, are classified as

low-risk, and are therefore exempt from pre-market evaluation. Public sector laboratories in Europe are exempt from the European Union's In Vitro Diagnostics Directive, although an alternative mechanism for ensuring the clinical quality of LDTs occurs through professionally driven quality assessment schemes.

IV. Important Considerations in the Establishment of a New Regulatory Scheme

As federal agencies determine how best to assert their regulatory authority over high complexity LDTs, ASCP believes the following to be important considerations.

A. Regulating Bodies and Conflicts of Interest

The process to review the validation standards of LDTs must be unbiased and impartial, regardless of their risk stratification. It is imperative that there be no conflicts of interest or potential business relationships that would drive decision-making. Accrediting bodies should monitor the performance and quality of LDTs, but that role should be post-clearance, to avoid any conflicts of interest. The establishment of an independent, third party reviewer to develop and verify quality and accuracy of claims prior to review by FDA and the federal CLIA-regulating agencies would enhance the transparency of the process. This entity would be not-for-profit, non-governmental, non-accrediting, non-industry, and entirely neutral. Both public health and patient safety would be best served by implementing a centralized third party review system rather than a peer review model. In addition, strengthening federal government oversight through the FDA and CLIA processes is essential. This will require additional resources (e.g. staff and expertise), for both FDA and CLIA.

B. Risk-Based Regulation Scheme

While a risk-based approach to regulation is most logical, there must be clearly established guidelines regarding how the FDA will define which tests are subject to regulation. The criteria established by FDA should ensure that there will be minimal confusion and appropriate classification of LDTs. While high risk LDTs should fall under the purview of the FDA, lower risk LDTs, those not deemed to be "*in vitro* diagnostic multivariate assays" should continue to be regulated by CLIA. The development of an enhanced regulatory process of oversight should involve a combination of governmental and non-governmental organizations. The CLIA regulatory process must ensure that data is collected that substantiates claims of clinical validity.

C. Applying New Scheme to Existing LDTs

There must be assurances that all LDTs are clinically valid. However, the FDA should establish a regulatory framework that phases-in the requirements on those LDTs currently in use. This is necessary to ensure continued patient access to advanced diagnostics. For those LDTs that can demonstrate a history of current use, FDA should provide laboratories a reasonable period to demonstrate the clinical validity while at the same time allowing them to continue providing the assay for clinical purposes. Moreover, FDA should maintain the authority to suspend use of the test for diagnostic purposes if the Agency has a reasonable concern that it provides insufficient clinical validity. LDTs

that cannot demonstrate a history of current use should go through the regular approval process.

D. Phase-In Period for new LDTs

Specific requirements regarding premarket review and quality systems should be phased-in over time to help facilitate predictability and planning within the laboratory community and industry. Implementation in a step-wise fashion could first require compliance for high-risk tests, and later implement requirements for moderate and low-risk tests. An algorithm to prioritize FDA's processing of premarket approval applications should be developed. Among those factors that we suggest should be included in such an algorithm are test volumes, severity of the condition or disease being tested, and impact the test can have on the treatment of the patient.

E. Proficiency Testing

Proficiency testing (PT) should be required for all non-waived genetic laboratory tests for which PT products are available, and the ASCP recommends that the Department of Health and Human Services fund studies to evaluate alternative performance assessment methods, such as certification and test-based continuing education. A balanced approach will be essential to evaluate the reproducibility of these assays with a protocol that maintains the advantages of multi-site PT, but also addresses the risks of inter-laboratory variation.

F. Clinical Validity and Utility

Evaluation of LDTs, as with any other diagnostic laboratory test, should include the test's analytic and clinical validity. Clinical utility, however, remains a subjective standard dependent on how clinicians utilize assay results in managing patient treatment, and not on an objective quality inherent in the test method. Requiring proof of clinical utility as a pre-requisite for marketing of these assays might impede or even prevent patient access to them. A lengthy approval process that requires evidence of clinical utility might hinder the development of these assays, thus preventing researchers from implementing translational findings into clinical practice.

G. Impact of Lengthy Regulatory Processes

ASCP cautions that lengthy approval procedures could delay implementation of new tests, stifle innovation, increase development costs, and thus limit patient access to potentially beneficial assays. Low volume LDTs, such as those for rare genetic tests, could experience difficulty attaining approval because of the small populations that would be available for clinical trial testing. Moreover, smaller laboratories, particularly laboratories at academic medical centers that have historically been major sites of innovation for LDTs, could be forced to abandon this area of testing, precluding patients from cutting-edge therapeutics.

H. Emergency Use Authorization (EUA) Provision

The establishment of an Emergency Use Authorization (EUA) provision within the regulatory framework is recommended for protection of the public health in emergencies. Overly burdensome regulatory requirements could present significant risks to public health by increasing the time needed for assay development during pandemics and other emerging infectious disease scenarios. The EUA provision should focus on expediting the approval process for state and federal public health laboratories in times of crisis.

Conclusion

Laboratory developed tests or LDTs are increasingly being integrated into standard practice for diagnosing and managing disease, predicting the risk of developing disease, and informing decisions about lifestyle and behavior. These tests are enabling improved prevention, treatment, and disease management for an array of common chronic conditions such as cancer, heart disease, and diabetes, as well as rare genetic disorders. They have become indispensible tools in the practice of medicine. However, ASCP strongly believes that only high quality, clinically and analytically valid diagnostic laboratory tests should be offered to patients. As a patient-centric organization, ASCP's mission is to protect patient safety while promoting advances in medicine. At this early stage of the genetic diagnostic era, it is vital that federal agencies strike the right balance in asserting their authority over the regulation of laboratory developed tests. The regulatory infrastructure adopted must be sufficiently meticulous to safeguard the public without being so burdensome that it impedes the emerging technology.

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