



September 8, 2009

Agency for Healthcare Research and Quality  
540 Gaither Road  
Rockville, MD 20850

Re: Comments on Technology Assessment Program Draft Report: *Quality, Regulation and Clinical Utility of Laboratory-developed Tests*

Dear Sir or Madam:

The American Clinical Laboratory Association (ACLA) is submitting these comments regarding the draft report, *Quality, Regulation and Clinical Utility of Laboratory-developed Tests*, issued by the Technology Assessment Program at the Agency for Healthcare Research and Quality (AHRQ) (the “Draft Report”).<sup>1</sup> ACLA is an association representing clinical laboratories throughout the United States, including local, regional, and national laboratories. ACLA helps promote public awareness about the value of laboratory services in preventing illness, diagnosing disease, assisting in the selection of appropriate medical treatment, and monitoring medical treatment. Many ACLA members create and perform a variety of laboratory-developed molecular tests (LDMTs) and have been in the forefront of this rapidly developing and promising area. As a result, ACLA members have a strong interest in, and extensive experience concerning, the issues discussed in the Draft Report.

## I. Overarching Recommendations

ACLA supports AHRQ’s efforts to fulfill the request from the Coverage and Analysis Group of the Centers for Medicare and Medicaid Services (CMS) for a summary of the available scientific evidence on the quality of LDMTs. LDMTs are instrumental to the welfare and treatment of patients and play a critical role in medical and clinical decision-making. These tests are well-established and well-accepted in the medical community. LDMTs are especially important in ensuring that medical innovations can be incorporated quickly and effectively into patient care services and in providing treatment guidance for patients with rare diseases or in other situations in which, for any number of reasons, either there are no tests with Food and Drug Administration (FDA) approval or clearance, or existing FDA-approved or -cleared tests are not adequate to meet emerging clinical needs. These benefits for patients and the reliability of LDMTs are well-documented, and, as such, we commend AHRQ’s identification of several important scientific resources regarding LDMTs and its discussion of these issues in the Draft Report.

However, one of ACLA’s primary concerns with the Draft Report is its failure to reference a number of extremely important resources that should have some bearing on the report’s conclusions. These resources include the Centers for Disease Control and Prevention’s

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<sup>1</sup> AHRQ, *Quality, Regulation and Clinical Utility of Laboratory-developed Tests* (the “Draft Report”) (July 24, 2009), available at <http://www.ahrq.gov/clinic/ta/labststqrcut/labststqrcut.pdf>.

(CDC) June 2009 Morbidity and Mortality Weekly Report (MMWR) article, entitled “Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions” (the “June 2009 MMWR”),<sup>2</sup> and the Organisation for Economic Co-Operation and Development (OECD) report, “OECD Guidelines for Quality Assurance in Molecular Genetic Testing.”<sup>3</sup> These reports provide significant insights into the current LDMT regulatory scheme, including valuable information on the quality of LDMTs and existing processes for establishing the analytical validity, clinical validity, and clinical utility of these tests. As such, these reports are directly relevant to the issues addressed in the Draft Report, and ACLA recommends that AHRQ reference these reports and incorporate their findings throughout the Draft Report where appropriate.

Another of ACLA’s overarching recommendations is that the term “home brew test” be deleted entirely from this Draft Report<sup>4</sup> (other than where it is used solely to identify a search term used by AHRQ in its research for the report).<sup>5</sup> This term does not accurately communicate the significant professional expertise and diligence performed by the laboratory in developing these tests, and the mere fact of its prevalent use in the past does not warrant continued reference to it. The terms “laboratory-developed tests” (or “LDTs”) and “in-house tests” more accurately and objectively describe the subject matter.

Our other recommendations relate generally to overbroad or inaccurate statements in the Draft Report and to discussions that we believe should be expanded or clarified. Below in this letter, we present these recommendations in a chapter-by-chapter format, identifying the specific portions of the Draft Report with which we have concerns and suggesting appropriate modifications. ACLA appreciates the opportunity to submit comments on the Draft Report and would welcome the chance to be of further assistance to AHRQ during its process of reviewing comments on the Draft Report and preparing the final version of this report, including by meeting to discuss these issues further or providing additional written information if that would be useful. Furthermore, given the significance of the omitted references (mentioned above) and the inaccuracies in the Draft Report (discussed herein)—especially the false representation of LDMTs as lacking analytical validity, clinical validity, and clinical utility and the misleading absence of explanations of the extent to which the existing regulatory scheme addresses clinical validity, in particular—ACLA strongly encourages AHRQ to release a revised version of the Draft Report to the public for comment after incorporating the edits suggested below (and others received through the public comment process).

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<sup>2</sup> CDC, “Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions” (the “June 2009 MMWR”), *Morbidity and Mortality Weekly Report*, Recommendations and Reports, Vol. 58, No. RR-6 (June 12, 2009), available at <http://www.cdc.gov/mmwr/PDF/rr/rr5806.pdf>.

<sup>3</sup> OECD, “OECD Guidelines for Quality Assurance in Molecular Genetic Testing” (2007), available at <http://www.oecd.org/dataoecd/43/6/38839788.pdf> (setting forth principles and best practices for quality assurance in molecular genetic testing for clinical purposes).

<sup>4</sup> Draft Report, 1 (“the quality of laboratory-developed (‘home brew’ or ‘in-house’) molecular tests”), 19 (“it has been marketed since 2004 as a ‘home brew’ assay”), 182 (“Home-brew qualitative PCR assays performed better than commercial quantitative assays”).

<sup>5</sup> *Id.* at 87 (“home brew” listed as a topic-specific search term), 90 (“home brew,” “home-brew,” and “homebrew” listed as part of a search statement).

## II. Comments on the Introduction

### A. FDA Jurisdiction over LDMTs

The Draft Report states that “LDMTs are not actively regulated by the FDA, although the Agency claims its jurisdiction over such tests.”<sup>6</sup> ACLA would like to point out as an initial matter that there currently is an unresolved legal question about whether FDA in fact has the authority to exercise oversight responsibility over LDTs, including LDMTs. The Washington Legal Foundation (WLF) raised this issue in a Citizen Petition it filed with FDA on September 28, 2006, arguing that, pursuant to the Clinical Laboratory Improvement Amendments of 1988 (CLIA), CMS—not FDA—has the authority to regulate LDTs offered only to health care professionals.<sup>7</sup> ACLA supports the positions articulated in the WLF Citizen Petition regarding the primacy of CMS’ authority over LDTs. Genentech, Inc. also raised the issue of FDA authority over LDTs, albeit from the opposing perspective, in a Citizen Petition it filed with FDA on December 9, 2008.<sup>8</sup> ACLA disagrees with Genentech’s view on this issue and a variety of other issues raised in the Genentech Citizen Petition and, as such, submitted a response to the Genentech Citizen Petition in February 2009.<sup>9</sup> As of the date of these comments on the Draft Report, FDA has not yet substantively responded to either the WLF or the Genentech Citizen Petition.

As we explained in our response to the Genentech Citizen Petition, ACLA believes that there is a significant question as to whether or not FDA has the legal authority to exercise oversight responsibility over LDTs because LDTs neither constitute “medical devices” nor are they distributed commercially in interstate commerce—both requirements for FDA jurisdiction under the Federal Food, Drug, and Cosmetic Act (FFDCA).<sup>10</sup> First, the components of LDT processes are not marketed as kits or test systems, and they are not physically distributed or delivered outside the laboratory. Instead, laboratories provide written reports of the results to the ordering physicians after the laboratories have performed the tests within their laboratories. Thus, clinical laboratories that develop and perform LDTs are selling *services* to outside entities; they are not selling any identifiable *medical device*. We emphasize here the differences between the medical devices typically regulated by FDA and the services that are usually considered to be regulated under CLIA.

Moreover, even if LDT services were somehow considered “medical devices,” they still would not qualify for FDA oversight pursuant to FDA’s legal mandate under the FFDCA to regulate products intended for introduction into interstate commerce.<sup>11</sup> Laboratories performing these tests are engaged in a process that does not involve any sale or distribution of a medical

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<sup>6</sup> *Id.* at 2.

<sup>7</sup> WLF Citizen Petition (filed Sept. 28, 2006), [available at http://www.fda.gov/ohrms/dockets/dockets/06p0402/06p-0402-cp00001-01-vol1.pdf](http://www.fda.gov/ohrms/dockets/dockets/06p0402/06p-0402-cp00001-01-vol1.pdf).

<sup>8</sup> Genentech Citizen Petition (filed Dec. 9, 2008), Document ID: FDA-2008-P-0638-001, [available at http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-P-0638](http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-P-0638).

<sup>9</sup> ACLA Comment to Genentech Citizen Petition (filed Feb. 18, 2009), Document ID: FDA-2008-P-0638-0006.1, [available at http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064808607b6](http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064808607b6).

<sup>10</sup> 21 U.S.C. § 301, *et seq.*

<sup>11</sup> *See, e.g., U.S. v. Prigmore*, 243 F.3d 1, 4 (1st Cir. 2001).

device to a third party. For these reasons, we believe FDA would be acting outside its legal authority if it sought to oversee LDTs. Further, we think it is important that a revised version of the Draft Report acknowledge this issue as an unresolved legal question, rather than noting only FDA's claim of jurisdiction over LDTs.

It is also worth noting that despite the questionable validity of FDA's claim of jurisdiction over LDTs, FDA has issued several warning letters to laboratories conducting LDTs in recent years, alleging that such tests are devices subject to FDA premarket clearance or approval. In several cases, LDMTs have been withdrawn or kept from the market in response to such warning letters. In that sense, it is somewhat misleading to state, as the Draft Report does, that LDMTs are currently not actively regulated by FDA.<sup>12</sup> The Draft Report should acknowledge that FDA has been actively exercising its claimed jurisdiction over LDTs through these warning letters on a case-by-case basis, further complicating the regulatory framework for LDTs.

## **B. Clinical Utility of LDMTs**

The Draft Report states: "While no consensus has been reached on any of the currently proposed analytic frameworks for the evaluation of genetic tests, the experts in the field generally agree that such evaluation should cover several key components, including the tests' analytical validity, clinical validity, and *clinical utility*."<sup>13</sup> As a general matter, ACLA agrees that it is important for LDMTs to be analytically valid, clinically valid, and clinically useful. However, with regard to clinical utility, it is imperative to recognize that (1) many definitions of "clinical utility" exist, some of which are more appropriate than others to the evaluation of LDMTs, and (2) clinical utility, as understood under the most common definitions, is a more subjective standard than either analytical validity or clinical validity because it depends upon how physicians integrate the test into their clinical decision-making as a practical matter, rather than on the objectively verifiable quality of the laboratory test alone. Therefore, while clinical utility (if properly defined in the context of LDMTs) is certainly important for patient care, its differences from both analytical validity and clinical validity are important and should not be overlooked.

With respect to the definition of "clinical utility," we emphasize that there is no standard, agreed-upon definition of this term. While the Draft Report defines "clinical utility" as "the usefulness of the test and the value of information to medical practice" and explains further that "[i]f a test has utility, it means that the results of the test can be used to pursue effective treatment or provide other concrete benefit," this is not the only available definition of the term.<sup>14</sup> For instance, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative, established by the National Office of Public Health Genomics at the CDC, defines "clinical utility" as the balance of benefits and harms associated with the use of the test in practice, including improvement in measurable clinical outcomes and usefulness or added

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<sup>12</sup> Draft Report, 2.

<sup>13</sup> Id. at 5 (emphasis added).

<sup>14</sup> Id.

value in clinical management and decision-making compared to not using the test.<sup>15</sup> OECD defines “clinical utility” as “the anticipated effect(s) of the clinical use of the test result, including on health outcomes, recognizing that a variety of factors influence this outcome.”<sup>16</sup> According to the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS), “clinical utility represents a balance between health-related benefits and the harms that can ensue from a genetic test. . . . In general, the benefits and harms of genetic testing should be compared with the best alternative to genetic testing.”<sup>17</sup>

This is not intended to be an exhaustive list of the existing definitions of “clinical utility.” Rather, by showing the variety of definitions of this term, the above discussion is meant to demonstrate that general statements about an LDMT’s clinical utility (or lack thereof) must be understood in the context of the particular definition of “clinical utility” being used by the person making the statement. Accordingly, when the Draft Report discusses the scientific literature’s conclusions about the clinical utility of particular LDMTs or of LDMTs on the whole, it should take care to identify which definition of “clinical utility” is behind the conclusion. Without a widely-accepted definition of “clinical utility,” it is unfair and misleading to simply say that any given test lacks clinical utility without specifying the particular criteria of clinical utility being considered.

In addition, it is essential to understand that appropriate definitions of “clinical utility” take into account the variety of factors bearing on a test’s usefulness in patient care—not just the test’s cost-effectiveness (as some proposed definitions do). We also underscore that clinical utility is not equivalent to clinical outcomes. That is, clinical utility refers to the likelihood that a test will provide information to guide future actions—not whether it will result in improved outcomes—since the latter is the result of many factors (e.g., the patient’s prognosis, the presence of comorbidities, the patient’s compliance with a treatment regimen) that have nothing to do with how well the test is helping physicians identify the treatment(s) most likely to be effective for particular patients.

With respect to a laboratory’s ability to demonstrate the clinical utility of its tests, it is critical to recognize that determinations of clinical utility (on the most common definitions of the term, which consider whether a test guides treatment decisions and is successful, with success being measured in different ways) depend upon how physicians use the tests in advising patients. This circumstance should be contrasted to clinical *validity*, however, whereby a test is proven to be useful for a particular, clinically relevant purpose (e.g., the test identifies a biomarker that is, in fact, a predictor of cancer). Thus, clinical validity demonstrates that a test is clinically useful for a particular disease or treatment and, as such, can be objectively shown. Clinical utility, in contrast, is a more subjective determination that reflects how physicians utilize the test and

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<sup>15</sup> See EGAPP Working Group, “The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group,” *Genetics in Medicine*, Vol. 11, No. 1 (Jan. 2009).

<sup>16</sup> OECD, “OECD Guidelines for Quality Assurance in Molecular Genetic Testing” (2007), 31, [available at http://www.oecd.org/dataoecd/43/6/38839788.pdf](http://www.oecd.org/dataoecd/43/6/38839788.pdf).

<sup>17</sup> SACGHS, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* (the “SACGHS Report”) (Apr. 2008), 115-116, [available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS\\_oversight\\_report.pdf](http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf).

integrate it into their decision-making processes. This distinction between the relative subjectivity of clinical utility, on the one hand, and the relative objectivity of clinical validity (and analytical validity), on the other hand, should be explained in the Draft Report.

### C. FDA Oversight of *In Vitro* Diagnostic Multivariate Index Assays

According to the Draft Report, “LDMTs, with the exception of in-vitro diagnostic multivariate index assays (IVDMIA)s, are not actively regulated by the FDA.”<sup>18</sup> This statement should be revised to clarify that, while FDA has issued a draft guidance document relating to the agency’s plans to begin regulating IVDMIA)s (the “IVDMIA Draft Guidance”), to date FDA has not finalized this guidance.<sup>19</sup> In fact, FDA itself stated the following in the IVDMIA Draft Guidance: “This draft guidance, *when finalized*, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.”<sup>20</sup> In a few other places in the Draft Report, the IVDMIA Draft Guidance is accurately referred to as a draft—not a final—document.<sup>21</sup> For consistency and accuracy, all references in the Draft Report to the IVDMIA Draft Guidance or to the regulatory status of IVDMIA)s should make it clear that FDA oversight of these devices has not yet been implemented or articulated in a final guidance document.

### D. Scope of CLIA’s Regulatory Framework

The Draft Report indicates that “under the current CLIA framework, only the analytic validity of the test is assessed, while the clinical validity and clinical utility of the test are not.”<sup>22</sup> While it is true that CLIA addresses the analytical validity of tests, it is not true that CLIA does not address clinical validity and clinical utility; in fact, CLIA addresses all three concepts. As a preliminary matter, we note that the CLIA statute does not require CMS to enforce requirements related only to analytical validity but rather states more broadly that “[t]he Secretary [of the Department of Health and Human Services (HHS)] shall issue standards to assure consistent performance by laboratories issued a certificate under this section of *valid* and reliable laboratory examinations and other procedures.”<sup>23</sup> In fact, there are provisions in the CLIA regulations designed to address clinical validity and clinical utility, as discussed below in this section.

Further, Congress clearly intended CLIA to be the controlling mechanism for regulating laboratory testing services, as it expressly stated when enacting CLIA that “the current system offers a patchwork of inconsistent and overlapping standards that leaves some laboratories trying

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<sup>18</sup> Draft Report, 5.

<sup>19</sup> FDA, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* (the “IVDMIA Draft Guidance”) (July 26, 2007), [available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf).

<sup>20</sup> *Id.* at 3 (emphasis added).

<sup>21</sup> *See, e.g.*, Draft Report, 42 (“On July 26, 2007, FDA published a draft guidance document on IVDMIA)s for industry, clinical laboratories, and the FDA staff”), 59 (“Draft Guidance for Industry, Clinical Laboratories, and FDA Staff – In Vitro Diagnostic Multivariate Index Assays (IVDMIA)s”).

<sup>22</sup> *Id.* at 5.

<sup>23</sup> 42 U.S.C. § 263a(f)(1) (emphasis added).

to comply with multiple layers of regulation.”<sup>24</sup> Similarly, Congress expressed its intent for CLIA to serve as a comprehensive quality control and regulation system for laboratories by noting that “[t]he Clinical Laboratory Improvement Amendments of 1988 . . . resolve concerns that have been raised about deficiencies in the Clinical Laboratory Improvement Amendments of 1967. The legislation intended to strengthen federal oversight of clinical laboratories to assure that the test results are accurate and reliable.”<sup>25</sup> Thus, it is critical to recognize that CLIA constitutes a comprehensive regulatory scheme that governs nearly every aspect of a laboratory’s testing performance and that, as a result, CLIA addresses clinical validity and clinical utility as well as analytical validity.

### 1. CLIA’s Role in Ensuring Clinical Validity of LDMTs

With regard to clinical validity, the applicable CLIA regulation provides that the laboratory director of a high complexity laboratory—currently the only type of laboratory at which genetic testing may be performed—is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures, to record and report test results promptly, accurately, and proficiently, and to assure compliance with the applicable regulations.<sup>26</sup> More specifically, the regulation explicitly requires the laboratory director “[t]o ensure that [t]he test methodologies selected have the capability of providing the quality of results required for patient care.”<sup>27</sup> Implicit in this responsibility is the clear regulatory imperative to choose medically relevant test methodologies that have an effective clinical purpose, since otherwise those methodologies could not be said to be “required for patient care.”<sup>28</sup>

In addition, CLIA requires that the laboratory director must meet stringent qualification standards<sup>29</sup> and also must ensure that the laboratory engages qualified personnel (who must meet separate qualification standards in the regulations<sup>30</sup>) to develop and perform tests.<sup>31</sup> That, along with the other CLIA requirements, is designed to ensure ongoing quality in the performance of testing. CLIA also requires the laboratory to have a clinical consultant who “must be qualified to consult with and render opinions to the laboratory’s clients concerning the diagnosis, treatment and management of patient care.”<sup>32</sup> The responsibilities of the clinical consultant are to provide information about the “appropriateness of the testing ordered and interpretation of the test results.”<sup>33</sup> Furthermore, CLIA makes the laboratory director responsible for ensuring that the ordering physician can properly interpret results by requiring the laboratory to include pertinent

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<sup>24</sup> S. REP. NO. 561, 100<sup>TH</sup> CONG., 2D SESS. 3-4 (1988); H. REP. NO. 899, 100<sup>TH</sup> CONG., 2D SESS. 11 (1988).

<sup>25</sup> H. REP. NO. 899, 100<sup>TH</sup> CONG., 2D SESS. 8 (1988).

<sup>26</sup> See 42 C.F.R. § 493.1445.

<sup>27</sup> 42 C.F.R. § 493.1445(e)(3)(i).

<sup>28</sup> Id.

<sup>29</sup> See 42 C.F.R. § 493.1443.

<sup>30</sup> See 42 C.F.R. §§ 493.1449 (qualification standards for technical supervisors), 493.1455 (qualification standards for clinical consultants), 493.1461 (qualification standards for general supervisors), 493.1489 (qualification standards for testing personnel).

<sup>31</sup> 42 C.F.R. § 493.1445.

<sup>32</sup> 42 C.F.R. § 493.1455.

<sup>33</sup> 42 C.F.R. § 493.1457.

interpretive information in the reports and to make consultation available to its clients regarding the quality of the test results and their interpretation.<sup>34</sup> The CLIA regulations, thus, require that a test have both clinical validity and transparency by requiring the laboratory director to select clinically relevant tests and provide clinical interpretation for those tests. The Draft Report should be revised to accurately describe CLIA as addressing the clinical validity of LDMTs.

We also note that the College of American Pathologists (CAP), which has been authorized by CMS to accredit laboratories as meeting CLIA requirements, provides mechanisms in its Laboratory Accreditation Program for assuring the clinical validity of LDMTs.<sup>35</sup> For example, CAP expects laboratories to demonstrate how the tests they offer have been clinically validated.<sup>36</sup> CAP-accredited laboratories that fail to make such demonstrations are subject to loss of accreditation or other sanctions. Currently, roughly 6,000 laboratories in the United States are CAP-accredited, and 23,000 laboratories are enrolled in the CAP proficiency testing (PT) programs.<sup>37</sup>

Further, up to 75 percent of all genetic testing performed in the United States is subject to oversight by the State of New York.<sup>38</sup> New York State carefully examines the clinical validation of new tests. More specifically, laboratories must receive approval from the New York Department of Health (DOH) prior to performing LDMTs on specimens from New York residents. Such approval requires that the laboratory submit complete documentation of, among other things, the following: the testing methods, including “[a] description of the assay, assay principle and clinical validity”; the references, including “[c]opies of pertinent literature references that describe the scientific basis and clinical utility of the assay”; and the initial validation protocol and data, including “[c]linical validity, data regarding the degree to which a result or variant predicts a disease state.”<sup>39</sup> In addition to the CLIA regulations cited above that require clinical validation of LDMTs, the oversight from CAP and the New York DOH that occurs in practice results in a substantial amount of review of the clinical validity of LDMTs, which is quite different from the complete lack of independent review suggested by the Draft Report; the Draft Report should mention these additional layers of oversight of LDMTs’ clinical validity.

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<sup>34</sup> 42 C.F.R. § 493.1445(e)(8), (9).

<sup>35</sup> See, CAP, *Laboratory Accreditation Manual* (July 2007), available at [http://www.cap.org/apps/docs/laboratory\\_accreditation/standards/lapmanual\\_0707.pdf](http://www.cap.org/apps/docs/laboratory_accreditation/standards/lapmanual_0707.pdf).

<sup>36</sup> To evaluate the sufficiency of the documentation for the performance characteristics of an LDT, CAP “determines whether clinical performance characteristics of each assay are documented, using either literature citations or a summary of internal study results, and whether final reports include an appropriate summary of the methods, the loci or mutations tested, the analytical interpretation, the clinical interpretation (if appropriate), and a summary statement, signed by the laboratory director or designee, that documents the review of validation studies and approval of the test for clinical use.” SACGHS, SACGHS Report, 105.

<sup>37</sup> CAP Fact Sheet, available at [http://www.cap.org/apps/cap.portal?\\_nfpb=true&cntvwrPtl.actionOverride=%2Fportlet%2FcontentViewer%2Fshow&\\_windowLabel=cntvwrPtl&cntvwrPtl%7BactionForm.contentReference%7D=media\\_resources%2Ffactsheet.html&\\_state=maximized&\\_pageLabel=cntvwr](http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl.actionOverride=%2Fportlet%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl&cntvwrPtl%7BactionForm.contentReference%7D=media_resources%2Ffactsheet.html&_state=maximized&_pageLabel=cntvwr) (last visited Aug. 26, 2009).

<sup>38</sup> SACGHS, SACGHS Report, 36.

<sup>39</sup> New York DOH, “Clinical Laboratory Evaluation Program Submission Guidelines for Test Approval” (rev. July 2008), 4, 5.

Of note, CLIA's role in ensuring clinical validity is also addressed in the June 2009 MMWR, issued by the CDC on June 12, 2009. One section of this report, entitled "Documentation of information on clinical validity," states that "[f]or tests of high complexity, such as molecular genetic tests, laboratory directors and technical supervisors are responsible for ensuring that the testing method is appropriate for the clinical use of the test results and can provide the quality of results needed for patient care."<sup>40</sup> This section also notes that "[d]ocumentation of available clinical validity information helps laboratories that perform molecular genetic testing to fulfill their responsibilities for consulting with health-care professionals and other users of laboratory services."<sup>41</sup> Both of these statements express the view that CLIA is responsible for ensuring the clinical validity of LDMTs.

Further, this section of the June 2009 MMWR identifies the following as "[l]aboratory responsibilities for clinical validity":

- "Documenting information regarding clinical validity (including clinical sensitivity, clinical specificity, positive predictive value, and negative predictive value) of all genetic tests the laboratory performs from available information sources (e.g., published studies and professional practice guidelines);
- Providing clinical validity information to users of laboratory services before tests are selected and specimens submitted;
- Establishing clinical sensitivity, clinical specificity, and predictive values on the basis of internal study results [if clinical validity information is not available from published sources];
- Documenting whether the clinical claims in the references or information sources used can be reproduced in the laboratory and providing this information to users, including indicating test limitations in all test reports;
- Informing users of changes in clinical validity values as a result of knowledge advancement; and
- Specifying that the responsibilities of the laboratory director and technical supervisor include ensuring appropriate documentation and reporting of clinical validity information for molecular genetic tests performed by the laboratory."<sup>42</sup>

As such, the June 2009 MMWR clearly indicates that laboratories should, pursuant to their existing CLIA requirements, ensure that the LDMTs they perform are clinically valid. In addition, it notes that the recommendations in the June 2009 MMWR are consistent with the voluntary professional practice and accreditation guidelines for molecular genetic testing of the American College of Medical Genetics, the Clinical Laboratory and Standards Institute, and

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<sup>40</sup> CDC, June 2009 MMWR, 14.

<sup>41</sup> Id.

<sup>42</sup> Id.

CAP.<sup>43</sup> As we mentioned at the outset of these comments, one of our overarching recommendations is that the June 2009 MMWR be referenced and discussed where appropriate in the Draft Report; the revised discussion of CLIA's role in ensuring the clinical validity of LDMTs would be one suitable and important place to discuss the June 2009 MMWR.

## **2. CLIA's Role in Ensuring Clinical Utility of LDMTs**

In addition to ensuring that LDMTs are clinically valid, CLIA is responsible for ensuring that LDMTs are clinically useful. As noted above with regard to clinical validity, the applicable CLIA regulation requires the laboratory director of a high complexity laboratory "[t]o ensure that [t]he test methodologies selected have the capability of providing the quality of test results required for patient care."<sup>44</sup> Tests can have the capability of providing the quality of results required for patient care only if they are clinically relevant for the patient population being tested and only if they are clinically useful for medical decision-making. Therefore, under the existing CLIA regulations, the determination of whether an LDMT has sufficient clinical utility to be offered is one that should be made by the laboratory director in the exercise of his or her professional judgment, as part of his or her responsibility under CLIA to ensure that selected test methodologies are capable of "providing the quality of test results required for patient care."<sup>45</sup> The Draft Report should be revised to include an accurate representation of CLIA's role in ensuring the clinical utility of LDMTs.

Also, as mentioned above, 75 percent of LDMTs are subject to oversight from New York State,<sup>46</sup> which obligates the laboratories offering these tests to submit to the New York DOH, prior to performing their tests on specimens from New York residents, "[c]opies of pertinent literature references that describe the scientific basis and clinical utility of the assay."<sup>47</sup> This additional layer of oversight from New York State supplements the requirements for laboratory directors under the CLIA regulations through which CLIA ensures the clinical utility of LDMTs, and the Draft Report should be amended to mention this important aspect of New York State oversight of LDMTs' clinical utility.

### **III. Comments on Chapter 2: How Is Analytic Validity Established for Laboratory-Developed Molecular Tests?**

#### **A. Clinical Validity of LDMTs**

The Draft Report states that "New York State Clinical Laboratory Standards of Practice guidelines on validation also state that laboratories must establish performance specifications for accuracy, precision, reportable range, reference intervals, analytical sensitivity and specificity, and other applicable performance characteristics" and further notes that "[v]alidation studies

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<sup>43</sup> Id.

<sup>44</sup> 42 C.F.R. § 493.1445(e)(3)(i).

<sup>45</sup> Id.

<sup>46</sup> SACGHS, SACGHS Report, 36.

<sup>47</sup> New York DOH, "Clinical Laboratory Evaluation Program Submission Guidelines for Test Approval" (rev. July 2008), 5.

must be submitted to New York State and approved before the test may be commercially offered for use on samples submitted from New York State.”<sup>48</sup> These statements are accurate but incomplete because the Draft Report fails to state explicitly that New York also requires laboratories to submit information on the clinical validity of their LDMTs as part of this approval process. As explained above in Section II.D.1., the New York DOH requires laboratories offering LDMTs to provide, in their requests for approval to offer these tests, “clinical validity, data regarding the degree to which a result or variant predicts a disease state.”<sup>49</sup> Because the degree to which clinical validity of LDMTs is established under the current regulatory system is a key issue in the Draft Report, the discussion of the New York State requirements should be amended to state explicitly that New York requires this information on LDMTs’ clinical validity. This revision is important not only because the Draft Report’s failure to mention the New York DOH’s requirement to submit information on clinical validity makes this discussion somewhat misleading, but also because such a high proportion (i.e., over 75 percent) of genetic tests, including LDMTs, are subject to the New York clinical validity requirement.<sup>50</sup>

### **B. Analytical Validity of Oncotype DX**

When evaluating the establishment of analytical validity for LDMTs, the Draft Report identifies several specific LDMTs and discusses the validation studies of these tests. With regard to *Oncotype Dx*, developed by Genomic Health, Inc., the Draft Report cites one systematic review of the analytical and clinical validity of three molecular tests used for risk stratification of patients with breast cancer, which was performed by the Johns Hopkins Evidence-based Practice Center (EPC) under contract to AHRQ.<sup>51</sup> The Draft Report also notes that Genomic Health’s website lists five published studies used in the development of *Oncotype DX* and that, in addition, Genomic Health published one analytical validation study and two clinical validation studies after the development of the assay.<sup>52</sup> It is unclear to which specific studies the Draft Report is referring as the Genomic Health website lists five reports on platform technology and assay development and three clinical validation studies.

Importantly, the section of the Draft Report addressing the analytical validity of *Oncotype DX* does not refer to the detailed summary of data supporting the analytical validity of the assay set out in the Johns Hopkins EPC Report: “Evidence about the analytic validity of *Oncotype DX* is available from two technical studies, Cronin *et al.*, 2004, and Cronin *et al.*, 2007, and from several clinical reports. Information about the overall success rate of the assay was documented in 9 studies (Chang, 2007, Cobliegh, 2005, Esteva, 2005, Gianni, 2005, Habel, 2006,

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<sup>48</sup> Draft Report, 12.

<sup>49</sup> New York DOH, “Clinical Laboratory Evaluation Program Submission Guidelines for Test Approval” (rev. July 2008), 5.

<sup>50</sup> SACGHS, SACGHS Report, 33.

<sup>51</sup> Draft Report, 18. The Draft Report also makes reference here to a systematic review of clinical validity, authored by Lyman *et al.*, that reviewed *Oncotype DX*, but notes that the following chapter (i.e., Chapter 3) of the Draft Report addresses clinical validity. *Id.* at 19.

<sup>52</sup> *Id.*

Mina, 2006, Oratz, in press, Paik, 2004, and Paik, 2006).”<sup>53</sup> This evidence base included three studies on assay variability and reproducibility, two studies on technical and operational aspects of analytical validity, and eight studies that compared gene expression measurements of specific individual genes (ER, progesterone receptor (PR), HER-2) to measurements of the corresponding proteins produced by those genes as obtained by other techniques, in particular immunohistochemistry (IHC). It is puzzling that the Draft Report does not refer to this substantial evidence base since the Johns Hopkins EPC Report is mentioned in this section of the Draft Report.

Because there are such a large number of analytical validation studies of *Oncotype DX*—in marked contrast to the Draft Report’s general assertion that “very few validation studies of in-house developed or commercially available molecular tests have ever been published”<sup>54</sup>—the Draft Report’s discussion of the analytical validation of *Oncotype DX* should be revised to mention the evidence base supporting the analytical validation of this assay. ACLA understands that Genomic Health is submitting its own comments on the Draft Report, but we wanted to raise this issue here nonetheless because we think it is important.

#### **IV. Comments on Chapter 3: What Processes Have Been Developed for Examining Clinical Validity and Clinical Utility of Molecular Tests?**

##### **A. Clinical Validity of LDMTs**

Chapter 3 of the Draft Report discusses the processes that have been developed for examining the clinical validity and clinical utility of LDMTs. In particular, the Draft Report notes that AHRQ “examined systematic reviews that reported on test characteristics, such as sensitivity, specificity, predictive values, and likelihood ratios,” when drafting the portions of Chapter 3 dealing with clinical validity.<sup>55</sup> However, this chapter fails to discuss laboratories’ obligations under CLIA to ensure and document the clinical validity of their LDMTs. As noted above in Section II.D.1., the June 2009 MMWR—which this chapter (like the rest of the Draft Report) overlooks—underscores laboratory directors’ and technical supervisors’ responsibilities under the CLIA regulations to “ensur[e] that [t]he testing method is appropriate for the clinical use of the test results and can provide the quality of results needed for patient care,” as well as laboratories’ responsibility to document “available clinical validation information,” such as “published studies and professional practice guidelines,” “internal study results,” and information on “whether the clinical claims in the references or information sources can be reproduced in the laboratory.”<sup>56</sup> The discussion of clinical validity in the June 2009 MMWR found in the section of that document titled “Documentation of information on clinical validity” makes the critical points that the clinical validity of LDMTs can and should be documented by laboratories under CLIA, and this discussion should be added to the Draft Report.

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<sup>53</sup> Marchionni L, Wilson RF, Marinopoulos SS, Wolff AC, Parmigiani G, Bass EB, Goodman SN, “Impact of gene expression profiling tests on breast cancer outcomes” (prepared by The Johns Hopkins University EPC), AHRQ Publication No. 08-E002 (Evidence report/technology assessment, no. 160) (Jan. 2008).

<sup>54</sup> Draft Report, 18.

<sup>55</sup> *Id.* at 21.

<sup>56</sup> CDC, June 2009 MMWR, 14.

In addition, the Draft Report should highlight the implications of the existing CLIA regulations that impose these documentation requirements on laboratories<sup>57</sup> and that require laboratories to have a clinical consultant,<sup>58</sup> since compliance with these regulations ensures that laboratories must make clinical validation information available to customers and CMS (or its agents) upon request and be able to explain this information to customers. Importantly, these regulations do not require laboratories to publish the results of their clinical validation activities in journals or on their websites, for instance, but do require laboratories to obtain and maintain this information. Therefore, the fact that a literature survey of the sort conducted by AHRQ (i.e., one surveying published articles and company websites) did not identify comprehensive information supporting LDMTs' clinical validity does not support the conclusion that such information does not exist in support of these tests' clinical validity.

Further, though AHRQ “consulted systematic reviews that evaluated clinical validity and/or clinical utility of various molecular tests,”<sup>59</sup> the Draft Report fails to mention a critical study authored by Richard Simon and published in the October 2005 issue of the *Journal of Clinical Oncology*.<sup>60</sup> This study, “Roadmap for Developing and Validating Therapeutically Relevant Genomic Classifiers,” contains detailed descriptions of laboratories' internal validation methods, which they use during the development of an LDMT to verify the potential usefulness of the test, and of external validation studies, which independent third parties conduct after an LDMT has been developed to evaluate whether the use of the test “for therapeutic decision making in a defined clinical context results in patient benefit.”<sup>61</sup> The Draft Report should be revised to include a discussion of the internal and external validation methods identified in Richard Simon's study and to reference this important study.

## **B. Clinical Validity of *Oncotype DX***

In its assessment of the clinical validity of LDMTs, the Draft Report discusses several different LDMTs and the clinical validation studies evaluating them. Regarding *Oncotype DX*, the Draft Report mentions the two clinical validation studies conducted by Genomic Health after the development of the assay, the ongoing TAILORx trial, sponsored by the National Cancer

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<sup>57</sup> See 42 C.F.R. §§ 493.1253(c), 493.1291 (requiring documentation of activities related to establishment and verification of various performance specifications and provision of this and other information, upon request, to laboratory clients); 493.1236 (requiring documentation of all PT evaluation and verification activities); 493.1239 (requiring documentation of all general laboratory systems quality assessment activities); 493.1249(c), 493.1289(c), 493.1299(c) (requiring documentation of preanalytic, analytic, and postanalytic system assessment activities); 493.1773(d) (requiring provision, upon request, of information needed by CMS or its agent to evaluate laboratory compliance with CLIA). The Draft Report mentions some of these documentation requirements in Chapter 4 in the section titled “Transparency of Data Used to Support Test Performance,” but the report fails to identify the significance of these requirements to CLIA's role in regulating the clinical validity of LDMTs. See Draft Report, 39.

<sup>58</sup> 42 C.F.R. § 493.1457(d) (requiring the clinical consultant to “[e]nsure that consultation is available and communicated to the laboratory's clients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions”).

<sup>59</sup> Draft Report, 21.

<sup>60</sup> Richard Simon, “Roadmap for Developing and Validating Therapeutically Relevant Genomic Classifiers,” *Journal of Clinical Oncology*, Vol. 23, No. 29 (Oct. 10, 2005).

<sup>61</sup> *Id.* at 4, 8.

Institute, which the Draft Report incorrectly characterizes as designed to clinically validate *Oncotype DX*, and the Johns Hopkins EPC study of the analytical and clinical validity, and impact on clinical decision-making, of three gene expression-based tests, including *Oncotype DX*.<sup>62</sup> However, as noted above, the Draft Report fails to mention several published, evidence-based assessments by clinical oncology professionals and payers which address the clinical validity and usefulness of *Oncotype DX*.

For instance, the “American Society of Clinical Oncology [(ASCO)] 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer” draws the following conclusion:

In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the *Oncotype DX* assay can be used to predict the risk of recurrence in patients treated with tamoxifen. *Oncotype DX* may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present [2007] to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the ‘Rotterdam Signature,’ and the Breast Cancer Gene Expression Ratio are under investigation.<sup>63</sup>

The National Comprehensive Cancer Network’s (NCCN) 2009 “NCCN Clinical Practice Guidelines in Oncology Breast Cancer” guideline concludes that *Oncotype DX* is “an option when evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features or >1cm, or node negative, hormone receptor-positive, and HER2-negative.”<sup>64</sup> In addition, in 2007, the BlueCross BlueShield Association’s (BCBSA) Technology Evaluation Center (TEC) concluded that use of *Oncotype DX* to inform decision-making about adjuvant chemotherapy meets the BCBSA TEC criteria for women with estrogen receptor-positive, lymph node-negative tumors who have been treated with tamoxifen.<sup>65</sup>

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<sup>62</sup> Draft Report, 23, 28.

<sup>63</sup> Harris L, Fritsche H, Mennel R, “American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer,” *Journal of Clinical Oncology*, Vol. 25, No. 33 (Nov. 20, 2007), available at <http://jco.ascopubs.org/cgi/reprint/JCO.2007.14.2364v1.pdf>.

<sup>64</sup> NCCN, “NCCN Clinical Practice Guidelines in Oncology Breast Cancer,” V.1 (2009). NCCN category of evidence and consensus 2B states: “The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).” *Id.*

<sup>65</sup> BCBSA TEC, “Gene Expression Profiling of Breast Cancer to Select Women for Adjuvant Chemotherapy,” Assessment Program, Vol. 22, No. 13 (Apr. 2008), available at [http://www.bcbs.com/blueresources/tec/vols/22/22\\_13.pdf](http://www.bcbs.com/blueresources/tec/vols/22/22_13.pdf). The BCBSA TEC criteria are: (1) The technology must have final approval from the appropriate governmental regulatory bodies; (2) The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; (3) The technology must improve the net

Beyond these systematic reviews, there have been published data on the impact of *Oncotype DX* on clinical decision-making in a practice setting. Oratz, *et al.* reported the results of a retrospective analysis of 74 patients from a community-based oncology practice with ER-positive, lymph node-negative, stage I or II breast cancer in whom *Oncotype DX* Recurrence Scores were obtained. The investigators found that knowledge of the Recurrence Score changed clinicians' treatment recommendations for 21 percent of patients and changed eventual treatment in 25 percent of patients. The decision to change from hormone therapy to chemotherapy ( $\pm$ hormone therapy) was generally associated with high Recurrence Score; the decision to change from chemotherapy to hormone therapy was generally associated with low Recurrence Score.<sup>66</sup>

Accordingly, ACLA recommends that the Draft Report's discussion of the clinical validity of *Oncotype DX* be revised to include references to the ASCO and NCCN guidelines, the BCBSA assessment, and the Oratz, *et al.* report on use in clinical management. In addition, we note that the purpose of the TAILORx trial is not to clinically validate *Oncotype DX*. Rather, the principal objectives of the trial are to:

1. Compare the disease-free survival of women with previously resected axillary-node negative breast cancer with an *Oncotype DX* Recurrence Score (ODRS) of 11-25 treated with adjuvant combination chemotherapy and hormonal therapy versus adjuvant hormonal therapy alone;
2. Compare the distant recurrence-free interval, recurrence-free interval, and overall survival of patients with an ODRS of 11-25 treated with these regimens; and
3. Create a tissue and specimen bank that includes formalin-fixed, paraffin-embedded tumor specimens, tissue microarrays, plasma, and DNA obtained from peripheral blood of patients enrolled in this trial.<sup>67</sup>

The investigators who designed this trial accept that the assay has been validated and use its results in determining clinical management under the trial. The Draft Report should be revised to ensure that the TAILORx trial is portrayed accurately.

### C. Analytical Validity and Clinical Validity of LDMTs

According to the Draft Report, "for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established."<sup>68</sup> This statement is incorrect because, as discussed above, analytical validity is a central component of CLIA, and the comprehensive CLIA regulatory scheme also addresses clinical validity (and clinical utility).

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health outcome; (4) The technology must be as beneficial as any established alternatives; and (5) The improvement must be attainable outside the investigational settings. *Id.*

<sup>66</sup> Oratz R, Paul D, Cohn AL, Sedlacek, SM, "Impact of a Commercial Reference Laboratory Test Recurrence Score on Decision Making in Early-Stage Breast Cancer," *Journal of Oncology Practice*, Vol. 3, No. 4 (July 2007).

<sup>67</sup> National Cancer Institute, "Phase III Randomized Study of Adjuvant Combination Chemotherapy and Hormonal Therapy Versus Adjuvant Hormonal Therapy Alone in Women With Previously Resected Axillary Node-Negative Breast Cancer With Various Levels of Risk for Recurrence (TAILORx Trial)" (rev. Sept. 2, 2009), [available at http://www.cancer.gov/clinicaltrials/ECOG-PACCT-1#Objectives\\_CDR0000472066](http://www.cancer.gov/clinicaltrials/ECOG-PACCT-1#Objectives_CDR0000472066).

<sup>68</sup> Draft Report, 25.

We discuss this support for LDMTs' analytical validity and clinical validity in more detail below.

### **1. Analytical Validity**

With respect to analytical validity, one of the principal purposes of CLIA is to ensure that laboratories establish the analytical validity of their tests. As mentioned above in Section II.D.1., the CLIA statute requires the Secretary of HHS to “issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations and other procedures.”<sup>69</sup> While we explained above that CLIA is not limited to ensuring analytical validity, but rather also has responsibility to ensure clinical validity and clinical utility, the statute's requirement regarding “valid and reliable laboratory examinations” certainly encompasses analytical validity.<sup>70</sup>

The applicable implementing regulation, likewise, requires laboratories to verify or establish certain performance specifications of tests before reporting patient results based on them.<sup>71</sup> More specifically, this regulation requires that before reporting patient test results, all laboratories using unmodified, FDA-cleared or -approved tests must demonstrate accuracy, precision, and reportable ranges of test results for the test systems (meeting performance specifications comparable to those established by the tests' manufacturers), and must verify that the manufacturers' reference intervals are appropriate for the laboratories' patient populations.<sup>72</sup> Further, this regulation requires laboratories that modify FDA-cleared or -approved tests, that use LDTs, or that use test systems for which the manufacturers do not provide performance specifications, to establish the following performance characteristics before reporting patient test results: accuracy; precision; analytical sensitivity; analytical specificity to include interfering substances; reportable range of test results for the test system; reference intervals (normal values); and any other performance characteristic required for test performance.<sup>73</sup> Accordingly, CLIA is designed to ensure that LDMTs are analytically valid.

If the statement in the Draft Report is rooted in the concern that the supporting data for an LDMT's analytical validity is often collected and maintained by the laboratory that conducts the test, rather than by an outside party, then this concern should be clearly identified—since a concern about potential bias in existing data is not equivalent to a total absence of supporting scientific information. Moreover, although laboratories often collect and maintain their own data on their tests' analytical validity, the CLIA regulations regarding validation, described immediately above, and the CLIA survey and inspection system are designed to verify the quality of laboratories' procedures for obtaining information on analytical validity (among other things), so there is a layer of outside review of analytical validity. The Draft Report should be revised to reflect these existing methods used by laboratories under CLIA to establish analytical validity.

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<sup>69</sup> 42 U.S.C. § 263a(f)(1).

<sup>70</sup> Id.

<sup>71</sup> 42 C.F.R. § 493.1253.

<sup>72</sup> 42 C.F.R. § 493.1253(b)(1).

<sup>73</sup> 42 C.F.R. § 493.1253(b)(2).

## 2. Clinical Validity

With respect to clinical validity, we again emphasize that CLIA was enacted in order to ensure the validity of laboratory examinations—which encompasses clinical validity as well as analytical validity.<sup>74</sup> Thus, if the Draft Report’s conclusion regarding the lack of clinical validity for many LDMTs stems from skepticism about CLIA’s ability to accomplish its statutory purposes, then this underlying issue should be clearly articulated. ACLA does not believe that CLIA is so flawed as to warrant such skepticism (though we do support specific methods of strengthening CLIA<sup>75</sup>), but if that is the concern motivating the Draft Report’s conclusion that many LDMTs lack clinical validity, then it is imperative that this concern be identified so it can be evaluated properly. If this conclusion arises, rather, from the instances in which clinical validity is not published in peer-reviewed literature, then the source of the concern should likewise be identified. Importantly, such a concern does not support the conclusion that clinical validity is not established, since the internal validation processes used by laboratories to establish clinical validity under CLIA are well-developed (as described in detail in the June 2009 MMWR) and since there are also external validation methods in place, namely under CAP’s Laboratory Accreditation Program and the New York DOH’s approval process for laboratories offering LDMTs.<sup>76</sup> The Draft Report should be modified to identify these methods of clinically validating LDMTs under CLIA, CAP, and the New York State review process.

Moreover, some studies have found no measurable difference in quality between LDMTs and FDA-approved or -cleared tests, thus demonstrating that FDA approval or clearance is not necessary—or even sufficient—for ensuring the availability of high-quality tests.<sup>77</sup> In fact, a number of LDMTs that are not FDA-approved or -cleared are well-established as standards of care in practice guidelines issued by major professional groups and are reducing wasteful expenditures attributable to population-wide treatment approaches that these tests are rendering obsolete—a good example being the tests involved in the evaluation of children with developmental delay/mental retardation. The standard of care for this evaluation is to conduct Fragile X Syndrome testing (since Fragile X Syndrome is one cause of mental retardation) and chromosome analysis (to identify other causes of mental retardation).<sup>78</sup> LDMTs are available for both chromosome analysis and Fragile X testing and are widely used. For Fragile X Syndrome testing, there is one research-use-only assay available, but no FDA-approved or -cleared tests are

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<sup>74</sup> See 42 U.S.C. § 263a (f)(1).

<sup>75</sup> See ACLA Comments on IVDMA Draft Guidance (filed Dec. 11, 2007), available at [http://www.clinical-labs.org/documents/ACLACommentstoFDAonIVDMARevisedDraftGuidance\\_000.pdf](http://www.clinical-labs.org/documents/ACLACommentstoFDAonIVDMARevisedDraftGuidance_000.pdf).

<sup>76</sup> We discuss these internal and external processes for establishing LDMTs’ clinical validity above in Section II.D.1. of this letter. See CDC, June 2009 MMWR, 14; CAP *Laboratory Accreditation Manual* (July 2007), available at [http://www.cap.org/apps/docs/laboratory\\_accreditation/standards/lapmanual\\_0707.pdf](http://www.cap.org/apps/docs/laboratory_accreditation/standards/lapmanual_0707.pdf); New York DOH, “Clinical Laboratory Evaluation Program Submission Guidelines for Test Approval” (rev. July 2008), 4, 5.

<sup>77</sup> See, e.g., EGAPP Study (evaluating the analytical validity, clinical validity, and clinical utility of two LDMTs—Genomic Health’s *OncoType DX* and Quest Laboratories’ Breast Cancer Gene Expression Ratio Assay—and one FDA-cleared test, Agendia’s *MammaPrint Test*).

<sup>78</sup> See Stephanie Sherman, Beth A. Pletcher, and Deborah A. Driscoll, “Fragile X syndrome: Diagnostic and carrier testing,” American College of Medical Genetics, *Genetics in Medicine*, Vol. 7, No. 8 (Oct. 2005). See also Robert A. Saul and Jack C. Tarleton, “*FMRI*-Related Disorders,” *GeneReviews* (updated Aug. 5, 2008), available at <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fragilex>.

available for use in diagnostic procedures. There are, however, a number of LDMTs well-established for use in Fragile X Syndrome testing, as documented in one recent study coordinated by the CDC and the Association for Molecular Pathology.<sup>79</sup> ACLA recommends that the Draft Report be revised to mention that LDMTs are already considered standard of care in many areas, without FDA approval or clearance, given that this fact provides significant support for these tests' clinical validity.

## V. Comments on Chapter 4: How Does CLIA Regulate Molecular Testing?

### A. Clinical Validity Under CLIA

Chapter 4 of the Draft Report, which addresses how CLIA regulates molecular testing, highlights many important aspects of the CLIA regulatory scheme, such as CLIA surveys, quality control requirements, and PT.<sup>80</sup> However, the chapter fails to mention CLIA's responsibility for ensuring clinical validity. As explained above in Section II.D.1., the applicable CLIA regulation currently requires the laboratory director to ensure that the test methodologies selected have the capability of providing the quality of results required for patient care,<sup>81</sup> which ultimately requires the laboratory director to assure that all tests offered by the laboratory are clinically relevant for the patient population being tested (i.e., are clinically valid). Also discussed above in Section II.D.1., laboratories are required under CLIA to document evidence of clinical validity. Chapter 4 of the Draft Report should be revised to discuss these responsibilities of laboratory directors and laboratories for ensuring clinical validity under CLIA and to make reference to the June 2009 MMWR, which describes these responsibilities in more detail.

### B. Specialties and Subspecialties Under CLIA

The Draft Report states, “[c]urrently, there is no CLIA specialty or subspecialty set for molecular or biochemical genetic testing. Therefore, there are no specific personnel, quality control, or proficiency-testing requirements for molecular tests.”<sup>82</sup> This statement is misleading for a few reasons. For one, molecular tests can be classified under other specialties, so while there is no genetic testing category that includes these tests exclusively, molecular tests and associated personnel, quality control, and PT requirements are covered by other specialties.<sup>83</sup> Moreover, two years ago CMS determined that it was unnecessary at that time to create a new “genetic testing specialty or specific proficiency testing standards for genetic tests under CLIA” because the agency believed that it could “more effectively oversee genetic testing under existing

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<sup>79</sup> Jean Amos Wilson, *et al.*, “Consensus Characterization of 16 *FMRI* Reference Materials: A Consortium Study,” *Journal of Molecular Diagnostics*, Vol. 10, No. 1 (Jan. 2008). This study compared the performance of several laboratories using their LDMTs to evaluate the same set of reference materials, as well as the National Institute of Standards and Technologies' standard reference materials, and found that all of these assays performed well. *Id.*

<sup>80</sup> *See* Draft Report, 44-51.

<sup>81</sup> 42 C.F.R. § 493.1445(e)(3)(i).

<sup>82</sup> Draft Report, 35.

<sup>83</sup> While there are no external PT programs available for most LDMTs, CLIA still requires laboratories offering these tests to establish procedures for verifying the accuracy of their tests, as discussed below in Section VIII of this letter. *See* 42 C.F.R. § 493.1236.

regulations and infrastructure.”<sup>84</sup> CMS pointed out that, as an initial matter, “neither the statute nor the CLIA regulations affirmatively require that all moderate and high complexity tests fall within a specialty area.”<sup>85</sup> However, CMS also noted that “CLIA also imposes requirements for personnel qualifications and quality testing responsibility for certain required positions . . . for laboratories performing high complexity testing (42 CFR §§ 493.1441 through 493.1495)” and that “[t]he vast majority of genetic tests are categorized as high complexity at this time, including all genetic tests that are laboratory-developed.”<sup>86</sup> Further, CMS highlighted the fact that “[t]he testing personnel that perform [LDMTs] must meet the more stringent, high complexity CLIA personnel requirements” and that laboratories performing these tests “must retain the additional required position of a general supervisor, who is responsible for day-to-day operations . . . regardless of whether the personnel conducting the testing are in a specialty area or not.”<sup>87</sup> The Draft Report should be revised to clarify that LDMTs can be classified within existing specialties that have specific personnel, quality control, and PT requirements and that these tests will be subject to CLIA’s personnel qualifications and quality testing standards for high complexity laboratories even if they are not separately classified into a specialty or subspecialty.

### **C. Handling of Complaints or Unexpected Events**

The Draft Report’s discussion of how complaints are handled under CLIA could be improved in a few important ways.<sup>88</sup> First, this discussion should explain that the information regarding alleged laboratory deficiencies that is collected and analyzed by laboratories as part of their failure investigations can and should be used for root cause analysis.<sup>89</sup> In addition, this section of the Draft Report should indicate whether it is referring to complaints due to inadequate methods (i.e., the use of LDMTs versus FDA-approved or -cleared tests) or to issues with laboratory processes, sample collection techniques, or clinical information. It should also define or describe what is meant by “unexpected events.” These clarifications would make this section of the Draft Report more informative and useful.

## **VI. Comments on Chapter 5: What FDA Guidance Has Been Issued Pertaining to Oversight of Laboratory-Developed Molecular Testing?**

### **A. Special Control Documents**

Chapter 5 of the Draft Report, which is intended to discuss the FDA guidance that has been issued relating to oversight of LDMTs, identifies only the IVDMA Draft Guidance and the analyte specific reagent final guidance<sup>90</sup> as the directly relevant guidance documents. As such,

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<sup>84</sup> CMS, Letter from Dennis G. Smith to Kathy Hudson (Aug. 15, 2007), 8, [available at http://www.dnapolicy.org/resources/CMSresponse8.15.07.pdf](http://www.dnapolicy.org/resources/CMSresponse8.15.07.pdf).

<sup>85</sup> *Id.* at 5.

<sup>86</sup> *Id.* at 7.

<sup>87</sup> *Id.* at 5, 7.

<sup>88</sup> *See* Draft Report, 39-40.

<sup>89</sup> *See* 42 C.F.R. § 493.1233 (requiring investigations of complaints, when appropriate, and documentation of all complaints and problems reported to the laboratory).

<sup>90</sup> FDA, *Guidance for Industry and FDA Staff Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions* (Sept. 14, 2007), [available at](#)

the Draft Report ignores FDA's Special Controls guidance documents, some of which also contain important information and guidance for manufacturers.<sup>91</sup> As such, a discussion of these Special Controls guidance documents should be added to Chapter 5 of the Draft Report.

## **B. IVDMIA Draft Guidance**

The Draft Report accurately notes that on page 42 that “[o]n July 26, 2007, FDA published a draft guidance document on IVDMIA for industry, clinical laboratories, and the FDA staff.”<sup>92</sup> However, on the previous page, the Draft Report simply refers to the IVDMIA Draft Guidance as one of “two FDA guidance documents relevant to . . . LDMTs.”<sup>93</sup> To ensure that readers are aware that the IVDMIA Draft Guidance has not yet been finalized, this should be clarified on page 41, and, in addition, an explicit statement to the effect that FDA has not yet finalized this draft guidance document should be added to the discussion on page 42.

## **VII. Comments on Chapter 6: What is the Role of Other Federal Agencies in Regulating Marketing Claims Regarding the Clinical Validity and Utility of Laboratory-Developed Tests Not Currently Being Actively Regulated by FDA?**

Chapter 6 of the Draft Report addresses the roles of FDA and the Federal Trade Commission (FTC) in the oversight of marketing claims relating to the clinical validity and clinical utility of LDMTs, noting that “[n]o other government agencies were identified that may play a role in such regulation.”<sup>94</sup> As such, CMS under its CLIA authority is not mentioned as having a role in regulating marketing claims of LDMTs' clinical validity and utility. While we agree that CMS is not and does not need to be actively involved in the regulation of these marketing claims, we believe it is imperative to recognize the FTC's jurisdiction and expertise in this area and to avoid concluding or implying that FDA's existing jurisdiction over labeling and advertising of restricted devices and over labeling of non-restricted devices should be extended to cover advertising of non-restricted devices as well. The FTC is fully equipped to oversee the advertising claims of unrestricted LDMTs, as the agency has demonstrated in its recent heightened enforcement over claims made by laboratories offering direct-to-consumer (DTC)

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<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071269.pdf>

<sup>91</sup> See, e.g., FDA, “Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System (Mar. 10, 2005), [available at](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071085.pdf)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071085.pdf>; FDA, “Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Nucleic Acid Amplification Assay for the Detection of Enterovirus RNA” (Jan. 2, 2009), [available at](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092761.pdf)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092761.pdf>; FDA, “Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 and 2 Serological Assays” (Apr. 3, 2007), [available at](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071036.pdf)

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071036.pdf>

<sup>92</sup> Draft Report, 42.

<sup>93</sup> *Id.* at 41.

<sup>94</sup> *Id.* at 44.

testing.<sup>95</sup> Given the FTC's jurisdiction over unrestricted LDMTs' advertising claims and its recently-demonstrated ability to regulate these claims effectively, it is appropriate for CMS not to serve in an oversight role in this area.

It is important to point out that to the extent that the term "marketing" is used to refer to laboratories' references to scientific literature supporting the use of its tests, these references do not need to be subject to FDA or FTC review because they do not constitute "marketing" as traditionally defined. These types of references to analytical and clinical validation studies used by the laboratory in developing an LDMT, or to other scientific evidence the laboratory has used to determine that an LDMT has clinical utility, differ from the labeling and advertising claims typically considered to be "marketing." Such references simply describe the scientific—and objectively proven—basis for the test; they do not constitute "marketing" in the usual sense that this term is used. We note that the United States Circuit Court for the District of Columbia has already determined in another context that drug manufacturers have the First Amendment right to distribute such information.<sup>96</sup> Moreover, these references to scientific literature supporting the validity and usefulness of LDMTs are largely self-regulating due to the fact that many of these scientific publications are subject to peer review.

#### **VIII. Comments on Chapter 7: How Is Proficiency Testing Accomplished for Molecular Tests?**

The Draft Report explains that CLIA requires laboratories to enroll in PT programs for their tests and that "[f]or tests with no available formal testing program (e.g., most molecular tests) laboratories are still required to participate in some equivalent activity such as exchanges of materials with other laboratories."<sup>97</sup> The Draft Report further notes that "[c]ontrols preferably have been validated against a primary standard, but for molecular testing this may not be possible" and that "[o]ur interviews with the experts and representatives from the CLIA program and the three accreditation organizations did not provide sufficient information for us to make an estimation of the extent to which laboratories exchange samples voluntarily for PTs."<sup>98</sup> Importantly, while validation of controls against a primary standard is preferable, it is, in fact, extremely rare—even for common analytes—and, as such, the unavailability of primary standards is not a circumstance unique to molecular testing. Further, with its limited discussion of the efforts of laboratories offering LDMTs to regulate the quality of these tests through standardization practices, the Draft Report fails to provide a fair assessment of the standardization requirements applicable to laboratories conducting LDMTs.

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<sup>95</sup> See, e.g., FTC, "At-Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription," *FTC Facts for Consumers* (July 2006), available at <http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.pdf> (advising consumers about the risks of DTC genetic tests and discouraging uncritical reliance on the marketing claims made by the manufacturers of DTC genetic tests); SACGHS, Letter from SACGHS Chair Reed Tuckson to Secretary Michael Leavitt (Feb. 8, 2006), available at [http://oba.od.nih.gov/oba/sacghs/reports/DTC\\_letter\\_to\\_Sec\\_02\\_08\\_2006.pdf](http://oba.od.nih.gov/oba/sacghs/reports/DTC_letter_to_Sec_02_08_2006.pdf) (highlighting the inter-agency work group, composed of staff from the FTC, FDA, CDC, and National Institutes of Health, that was formed to help assess the scientific accuracy of claims made by companies advertising genetic tests on the internet).

<sup>96</sup> *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

<sup>97</sup> Draft Report, 49.

<sup>98</sup> *Id.* at 47, 48.

It is true that there are no external PT programs available for most LDMTs and that, as such, laboratories offering these tests must establish their own procedures to verify the accuracy of their tests.<sup>99</sup> However, the Draft Report does not convey the significance and reliability of these laboratory procedures. It is critical to recognize that CLIA, like any comprehensive regulatory structure, contains a certain amount of self-regulation under which the regulated entities must follow specific requirements and document their compliance with them. This does not mean that there is no external review of laboratories' compliance, though, since CLIA also contains inspection and survey requirements under which laboratories' documentation is reviewed and noncompliant laboratories are subject to sanctions. This combination of self-regulation and oversight is not unique to CLIA and is effective in ensuring that LDMTs for which there are no approved PT programs are still verified regularly through other appropriate means.

#### **IX. Comments on Chapter 8: What Guidelines and Standards Exist for Laboratories Conducting Molecular Testing?**

Table 10, "Summary of Guidelines and Standards for Laboratories Performing Molecular Tests," contains a variety of useful information about several clinical practice guidelines and published standards for laboratories offering LDMTs.<sup>100</sup> We note, however, that the Table is dated March 24, 2009, which is prior to the release of the June 2009 MMWR—a very important resource that, as we noted at the outset of these comments, should be incorporated throughout the Draft Report where appropriate. One place the June 2009 MMWR should be added to the Draft Report is in Table 10.

#### **X. Comments on the Epilogue**

In summarizing its discussion of CLIA's regulation of LDMTs, the Draft Report states, "under the CLIA program, laboratories are not obligated to provide evidence to support the clinical validity or utility of the LDMTs that they offer to the public."<sup>101</sup> This statement is both incorrect and internally inconsistent with statements made elsewhere in the Draft Report. Firstly, CLIA does require laboratories to provide evidence of the clinical validity and clinical utility of their tests, as described in more detail above in Section II.D. of this letter. Specifically, the CLIA regulations require a high complexity laboratory's clinical consultant to provide information about the "appropriateness of the testing ordered and interpretation of the test results"<sup>102</sup> and its laboratory director "[t]o ensure that [t]he test methodologies selected have the capability of providing the quality of test results required for patient care."<sup>103</sup> The applicable regulation also makes the laboratory director responsible for ensuring that the ordering physician can properly interpret results by requiring the laboratory to include pertinent interpretive information in the reports and to make consultation available to its clients regarding the quality

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<sup>99</sup> 42 C.F.R. § 493.1236.

<sup>100</sup> Draft Report, 58-68.

<sup>101</sup> *Id.* at 70.

<sup>102</sup> 42 C.F.R. § 493.1457.

<sup>103</sup> 42 C.F.R. § 493.1445(e)(3)(i).

of the test results and their interpretation.<sup>104</sup> Moreover, the Draft Report itself identifies several requirements in the CLIA regulations regarding the transparency of data supporting a laboratory's test performance.<sup>105</sup> The Draft Report should be revised to accurately describe CLIA as addressing the clinical validity and clinical utility of LDMTs.

## **XI. Conclusion**

Laboratories offering LDMTs have already produced dramatic improvements in patient care, and they have tremendous potential to continue translating medical advancements into services that can be used in clinical decision-making. As such, it is critical that information published regarding LDMTs' analytical validity, clinical validity, and clinical utility be as accurate and complete as possible to encourage the continued availability of these important patient care services. To that end, we have provided these comments seeking revisions to various portions of the Draft Report. As noted at the outset, we strongly encourage AHRQ to release a revised version of the Draft Report to the public for comment after incorporating comments received on this version of the report. We greatly appreciate the opportunity to submit our comments and would be happy to provide additional information or to discuss our views further with AHRQ if that would be useful. Thank you for your consideration.

Sincerely,

Alan Mertz, President

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<sup>104</sup> 42 C.F.R. § 493.1445(e)(8), (9).

<sup>105</sup> Draft Report, 39 (citing 42 C.F.R. §§ 493.1253(c), 493.1249(c), 493.1289(c), 493.1299(c), 493.1773(d)).