Project Name:		Quality, Regulation and Clinical Utility of Laboratory-developed Tests	
Project ID:		LABC0707	
Disposition of Comments			
Table 2: Public Review Comments			
Reviewer Name[2]	**Reviewer Affiliation[3]**	**Reviewer Comments**	**Author Response**
David Mongillo	American Clinical Laboratory Association	Section I: CDC June 2009 MMWR article, Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions is an relevant document, but was not incorporated in the draft report.	This reference was published after we had submitted the draft report to AHRQ. We agree with the reviewer that this reference is an important document. Therefore, we have added the reference to the revised report and incorporated the findings from the reference as appropriate.
David Mongillo	American Clinical Laboratory Association	Section I: OECD Guidelines for Quality Assurance in Molecular Genetic Testing is an relevant document and its findings should be incorporated throughout the report where appropriate.	The OECE Guideline mentioned by the reviewer was referred to in the draft report and its findings have been incorporated as appropriate.
David Mongillo	American Clinical Laboratory Association	Section I: The term, home brew test, should be deleted entirely from this Draft Report.	In the report, we generally use the term LDMT. however, given that the term has been and is still being used in some discussions about LDTs, we believe it is still appropriate to mention the term at the beginning of the report or to cite the term if it was used in the included references.
David Mongillo	American Clinical Laboratory Association	Section II, A: FDA's claim on jurisdiction over LDMTs is debatable	Throughout the report, we only state that FDA "claims" its jurisdiction over LDTs. We believe that this statement is accurate regardless of the citizen petitions mentioned by the reviewer. We also believe that the statement is appropriate for the paragraph. The key point we make in the paragraph is that FDA has not actively exercised the "claimed" jurisdiction over LDTs.
David Mongillo	American Clinical Laboratory Association	Section II, B: The Draft Report defines "clinical utility" as "the usefulness of the test and the value of information to medical practice" and explains further that "if a test has utility, it means that the results of the test can be used to pursue effective treatment or provide other concrete benefit." However, there are multiple definitions of "clinical utility." 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.	We had also identified the multiple definitions of "clinical utility". The definition we used in the report was taken from the CDC's ACCE project. It is a widely used definition of clinical utility in the discussion of genetic tests. We used this definition because we believe it is essential for patients or providers to know whether a LDMT provides valuable information to decision making and leads to effective treatment. We do not believe that the use of the ACCE definition of "clinical utility" would mislead the readers.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo	American Clinical Laboratory Association	Section II, C: The section on FDA's role in future IVDMIAs oversights should be further clarified.	We agree with the reviewer and added the following sentences in the relevant section: "Note that the FDA's IVDMIA Draft Guidance is not a finalized document. As such, this draft guidance only represents FDA's current thinking on this topic. FDA's oversight of these devices has not yet been implemented or articulated in a final guidance document."
David Mongillo	American Clinical Laboratory Association	Section II, D: 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." 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.	We removed the content that caused the reviewer's concern. We also added discussions about the roles of laboratory directors, clinical consultants, CAP and the NYS CLEP program in ensuring clinical validity or utility under the CLIA framework.
David Mongillo	American Clinical Laboratory Association	Section III, A: The report did not state that New York requires laboratories to submit information on the clinical validity of their LDMTs as part of this approval process.	We added a section in chapter 4 to discuss the NYS CLEP program, including its review of clinical validity data in the regulation process.
David Mongillo	American Clinical Laboratory Association	Section III, B: Analytical Validity of Oncotype DX	We appreciate the reviewer's attention to detail. However, although the studies the reviewer cites are highly relevant to discussions of the Oncotype assay, they are not, strictly speaking, about analytical validity. Some of the cited studies are about development of the assay, and the rest are about establishing the clinical validity and utility of the assay. Indeed, the company, Genomic Health Inc., lists these studies on their webpage under the headings "assay development" or "clinical validity". See attached file for our evaluation of the studies.
David Mongillo	American Clinical Laboratory Association	Section IV, A: Chapter 3 fails to discuss laboratories' obligations under CLIA to ensure and document the clinical validity of their LDMTs.	As the reviewer suggested, we added relevant content discussing laboratories' obligations under CLIA to ensure and document the clinical validity of their LDMTs. However, we added this information to Chapter 4, where the CLIA regulations are discussed, instead of in Chapter 3.
David Mongillo	American Clinical Laboratory Association	Section IV, A: Though AHRQ "consulted systematic reviews that evaluated clinical validity and/or clinical utility of various molecular tests," 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.	We thank the reviewer for bringing the Simon article to our attention. However, given the limited time allowed for the project, AHRQ and ECRI Institute agreed to focus on the evidence from systematic reviews (refer to the method section in the Chapter). Simon's 2005 article is a narrative review and does not meet the inclusion criteria.
David Mongillo	American Clinical Laboratory Association	Section IV, B: Clinical Validity of Oncotype DX	The two reports--one by the American Society of Clinical Oncology and the other by the National Comprehensive Cancer Network-- that the reviewer mentions are now briefly summarized in Table 36 of the report. Likewise, the Blue Cross Blue Shield TEC report titled "Gene Expression Profiling of Breast Cancer to Select Women for Adjuvant Chemotherapy" was published after the draft of this report was posted. The Tec report is now summarized in chapter 3.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo	American Clinical Laboratory Association	Section IV, C: According to the Draft Report, for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established.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.	We removed the statement in chapter 3 that had caused the reviewer's concern.
David Mongillo	American Clinical Laboratory Association	Section IV, C: According to the Draft Report, for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established. 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. 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), 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. The Draft Report should be modified to identify these methods of clinically validating LDMTs under CLIA, CAP, and the New York State review process.	We removed the statement in chapter 3 that had caused the reviewer's concern.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo (Continued)	American Clinical Laboratory Association (Continued)	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. 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). LMDTs 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 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. 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.	
David Mongillo	American Clinical Laboratory Association	Section V, A: Chapter 4 fails to mention CLIA's responsibility for ensuring clinical validity.	In the revised report, we enhance the content regarding the mechanisms within the CLIA regulation framework that potentially helps to ensure the clinical validity of molecular tests. For example, in Chapter 4, add content discussing the role of laboratory directors, accreditation organizations such as CAP, and exempted State such as New York in evaluating analytic validity.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo	American Clinical Laboratory Association	Section V, B: The Draft Report states, currently, 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. 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.	To respond to this comment, we quote a paragraph from the revised report: "Molecular tests are not listed in Subpart I, therefore laboratories are not required to participate in a formal PT program for molecular tests (however, an accredited laboratory may still be required by the accreditation organization to participate in the available PT programs). Under CLIA, a subspecialty of clinical cytogenetics is established under the cytology specialty but this subspecialty is limited to chromosomal analysis and does not include molecular tests.(87) Although laboratories can choose to enroll in other specialties (e.g., pathology), they are not required to do so. Meanwhile, no PT programs are mandated for the pathology specialty (except for the subspecialty of cytology, which is limited to gynecologic examinations) or for the clinical cytogenetics subspecialty under current regulations." We believe this statement is accurate and should not mislead readers.
David Mongillo	American Clinical Laboratory Association	Section V, C: The Draft Report's discussion of how complaints are handled under CLIA could be improved in a few important ways. 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. 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.	Based on the comment, we removed the term "unexpected events". However, we did not add other content that the reviewer recommended. We believe that we define "complaint" concisely and clearly in the report. As it is stated, "a complaint against a laboratory is an allegation that could result in citing noncompliance with any of the CLIA requirements".
David Mongillo	American Clinical Laboratory Association	Section VI, A: The Draft Report ignores FDA's Special Controls guidance documents, some of which also contain important information and guidance for manufacturers. As such, a discussion of these Special Controls guidance documents should be added to Chapter 5 of the Draft Report.	Given the main purpose of the report, we still consider it appropriate to focus the discussion on the two documents that are more relevant to laboratory-developed tests (i.e., the guidance for ASRs and the draft guidance for IVDMIAs), although we also cataloged other FDA guidance documents related to genetic testing.
David Mongillo	American Clinical Laboratory Association	Section VI, B: On page 41, the Draft Report simply refers to the IVDMIA Draft Guidance as one of "two FDA guidance documents relevant to . . . LDMTs." 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.	We revised the relevant content as suggested by the reviewer. Now, the two sentences read as: "We identified two FDA guidance documents relevant to laboratory-developed molecular tests (LDMTs). These two documents—one guidance for analyte specific reagents (ASRs) and draft guidance for in-vitro diagnostic multivariate index assays (IVDMIAs)—address the oversight of laboratory-developed tests (LDTs) and are applicable to LDMTs." We also revised the section about IVDMIA draft guidance (see our response above).

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo	American Clinical Laboratory Association	Section VII, per chapter 7: 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) testing. 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. 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	In this chapter, we simply described how FDA and FTC split up the responsibilities in regulating marketing claims regarding LDMTs. We did not conclude or imply by any means 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. Neither did we conclude, imply or suggest that CMS should serve any oversight role in marketing claims. Given the main purpose of the report (i.e., horizon scanning), we believe our current description of FDA and FTC's roles in overseeing marketing claims is accurate and appropriate. We also believe that we had defined the meaning of "marketing" quite clearly in the chapter. Here is the relevant quotation from the current report: "Regulation of marketing claims regarding the clinical performance of medical devices involves oversight of both labeling and advertising. Device labeling covers a broad category of materials including brochures, mailings, journal reprints if distributed by (or on behalf of) a company, sales materials, package inserts, and immediate package label. Advertising is not defined in the Food, Drug and Cosmetic Act. However, the Center for Drug Evaluation and Research of FDA has a technical definition of advertisement, which includes all ads in published journals and magazines, other periodicals and broadcast ads".
David Mongillo	American Clinical Laboratory Association	Section VIII: 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. 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.	The quality assurance mechanisms that the reviewer mentioned (such as alternative methods to validate LDMTs' analytical performance, laboratory documentation procedures, and external surveys required by CLIA) are currently covered in Chapter 4 of the report. It would be inappropriate for the report to speculate about the reliability of these laboratory procedures.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
David Mongillo	American Clinical Laboratory Association	Section IX: 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. 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.	See our previous comment about the MMWR report. We have added the report to Table 10.
David Mongillo	American Clinical Laboratory Association	Section X: 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." 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" 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." 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 of the test results and their interpretation. Moreover, the Draft Report itself identifies several requirements in the CLIA regulations regarding the transparency of data supporting a laboratory's test performance. The Draft Report should be revised to accurately describe CLIA as addressing the clinical validity and clinical utility of LDMTs.	We revised the relevant sections as suggested by the reviewer. Also see our previous response regarding this matter.
Mary Steele Williams	Association for Molecular Pathology	Repeatedly, the report draws conclusions and makes inferences without knowledge of extant regulations concerning the responsibilities of laboratory directors, without reference to available proficiency testing programs, without review of available proficiency testing data for many molecular tests, some of which have been in place for years. We strongly recommend the inclusion of laboratory professionals who are familiar with and operating under current regulatory guidelines for molecular LDTs.	We disagree with the reviewer's opinion on the PT matter. While proficiency tests are available for some molecular tests, only some laboratories (e.g., those accredited through CAP) are required to participate in such tests. As we currently state in the report, "Molecular tests are not listed in Subpart I, therefore laboratories are not required to participate in a formal PT program for molecular tests (however, an accredited laboratory may still be required by the accreditation organization to participate in the available PT programs)." We believe this statement is accurate and appropriate.
Mary Steele Williams	Association for Molecular Pathology	The report focuses on molecular LDTs but the title suggests a more broad report on all LDTs. We recommend that the title of the report reflect this distinction.	We agree with the reviewer on this comment and revised title of the report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	Most diagnostic tests, particularly most molecular tests, have their origins as LDTs. One such example is HIV viral load testing. Whether or not LDTs become commercial products depends primarily on demand, market size and intellectual property licensing issues. If LDTs were not as readily available as they are now, diagnosis of a many cancers, infectious diseases and genetic conditions would not be available to patients. Certainly, the rapid response in initiating the development of diagnostic tests for many emerging infectious agents would not be possible but for LDTs. A prime example of this is the role that LDTs played in the novel H1N1 outbreak earlier this year. The adaptation and validation of available molecular tests for Influenza allowed community molecular diagnostics laboratories to perform accurate and specific diagnoses for the new influenza strain, and markedly reduced the workload on the public health laboratory network. The one assay advancement by FDA under Emergency Use Authorization (EUA) was restricted to authorized public health laboratories. The only recourse to clinical laboratories throughout the entire 12 week episode was the use of laboratory developed tests for influenza. Indeed, in the coming months, the majority of novel H1N1 diagnoses in this country will be made in clinical laboratories using LDTs. To not recognize this is a failure to understand and appreciate the important contributions LDTs make to the advancement of medical science and clinical practice.	We acknowledge the significant role that LDMTs play in patient care and disease prevention. This acknowledgement is reflected in the revised Epilogue of the report.
Mary Steele Williams	Association for Molecular Pathology	This report attempts to compile and review all of the information on LDTs currently available for the Medicare population (>65 years old) including tests available, laboratories providing tests, regulations (CLIA, FDA, and others), proficiency testing available, etc. Unfortunately the review has relied entirely on peer-reviewed journal publications, which is not an optimal source for this topic since test validations are rarely published (see below, comment regarding page 18). Input from laboratory professionals and their organizations would have led to a much more comprehensive report. It is noted that consultations with FDA were conducted to enhance the report. We recommend a similar approach with laboratory professionals and their organizations. The membership of AMP could possibly be a great resource to fill this gap.	The methodology of the report was determined and mutually agreed by ECRI Institute and AHRQ with the input from ECRI's internal staff and external experts who are associated with professional organizations such as AMP. To identify the information, we used peer-reviewed literature as well as other sources such as the AMP test directory, FDA, CLIA program, and New York State CLEP. Regardless of all these efforts, there is a possibility that we might have missed important information in the draft report. That is why this public commenting process is crucial to the success of the report. As always, we are willing to take any constructive suggestions. We are confident that, with the help from peer reviewers and the public reviewers, we are able to capture significant flaws in the draft report and make the final report much better. In the revised report, we added a section in chapter 4 to discuss the roles of professional organizations such as AMP within the CLIA framework.
Mary Steele Williams	Association for Molecular Pathology	There are inconsistencies in the report. For example, on the one hand the report appears to exclude heritable diseases, and on the other cites guidelines from the American College of Medical Genetics (ACMG), which are specifically directed toward heritable disease testing. The authors are also not clear about the applicability of published validations for various types of molecular assays. For example, the report appears to generalize information from articles on quantitative infectious disease testing or tuberculosis (TB) to the whole of molecular diagnostics.	While tests for heritable diseases are out of the scope of the report, we believe the guidelines from the American College of Medical Genetics (ACMG) may still be interesting to the key users of the report (such as CMS). In the report, we reviewed systematic reviews on quantitative infectious disease testing or tuberculosis (TB) but did not generalize information from these studies to the whole of molecular diagnostics.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	The report does not comment on controversial aspects nor does it provide any recommendations or conclusions concerning the oversight, quality and utility of LDTs. We recommend that these areas be addressed.	This report is a horizon scanning report. Its goal is to collect information for the decision makers who commissioned this report. The authors of the report are not charged with making recommendations. Meanwhile, some controversies surrounding quality and regulation of LDMTs are indeed discussed in various sections of the report (e.g., Introduction and Epilogue).
Mary Steele Williams	Association for Molecular Pathology	We recommend that this report use standardized nomenclature for genes and genomic variations as documented by the HUGO Gene Nomenclature Committee and Human Genome Variation Society).	We took the suggestion from the reviewer and made revisions accordingly.
Mary Steele Williams	Association for Molecular Pathology	While we are appreciative of the utility the report found in the AMP Test Directory, it should be emphasized that the Test Directory was developed not primarily as directory of clinical molecular laboratory testing services, but as a resource for AMP members who, as experts in the investigation of disease at the molecular level, are frequently at the forefront in developing novel diagnostic test. The Directory was instituted as a vehicle for exchange of information and collaboration in order to promote standardization among laboratories and to promote development of uniform high quality proficiency for often very esoteric tests. In the report's tables it can be seen that many of the molecular LFTs are truly for esoteric diseases and the vast majority are offered by no more than two or three laboratories. The report would be greatly enhanced in recognizing the esoteric nature of many molecular tests, the evolutionary course of novel diagnostic medical tests from the research bench to the clinical laboratory, the contributions of clinician scientists and molecular pathologists, and the role AMP and the AMP Test Directory play in the development of LDTs as high quality clinical tests.	Given the limited time and resources for the project, as well as the dynamic nature of the molecular testing field, it is impossible for the report to catalogue all LDMTs currently available for clinical use (which had never been the goal of the project). For this report, we intended to capture major categories of LDMTs clinically available for the Medicare over-65-year-old population, particularly the tests offered by the key laboratories specified in the AHRQ Statement of Work (SOW). For this purpose, we consider the AMP test directory an appropriate source for LDMTs. While we were aware that the AMP Test Directory was developed not primarily as directory of clinical molecular laboratory testing services, this source did provide more information about the tests and the laboratories offering these tests than other sources (such as Genetests.org). In addition, we did not entirely depend on the AMP directory. We also used other sources to identify relevant LDMTs that were not covered by the AMP directory (see the methods section of Chapter 1).
Mary Steele Williams	Association for Molecular Pathology	Introduction: There is a statement in the introduction that experts agree that clinical utility should be included in the validation process of a laboratory test. AMP does not agree with this, nor does FDA require such. Consideration of clinical utility is intrinsic to the assessment of clinical validity by the Medical Director, but clinical utility is fully understood only when experience with laboratory tests is progressively gained over time.	We revised the sentence that caused the concern. Now it reads: "While no consensus has been reached on any of the currently proposed analytic frameworks for the evaluation of genetic tests, many experts in the field argue that such evaluation should cover several key components, including the tests' analytic validity, clinical validity, and clinical utility"
Mary Steele Williams	Association for Molecular Pathology	On page 6 (Question 5) the Food and Drug Administration (FDA) is incorrectly referred to as the Federal Drug Administration.	The typo was corrected.
Mary Steele Williams	Association for Molecular Pathology	Page 4: The authors may want to include array-based karyotyping methodologies, such as array Comparative Genomic Hybridization (aCGH) or SNP arrays. Although currently these methods are primarily used in the diagnosis of inherited conditions in pediatric patients, this technology is now in the early phase of use for diagnosis of oncologic disorders.	The Introduction section is not intended to cover all methodologies that have been developed for genetic testing. Instead, it only focuses on the most commonly used technologies at this time. Therefore, we did not discuss some newer technologies such as array-based karyotyping methodologies.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	Page 5: The authors discuss that clinical validity and clinical utility of any given assay are not assessed by CLIA. However, under CLIA, the medical director of the laboratory must approve the clinical validity of any LDT; CLIA inspectors are expected to assess whether and how well a laboratory director is performing the validity assessment.	The terms “clinical validity” and “clinical utility” are not explicitly mentioned in the CLIA regulations. Although some requirements in the CLIA regulations might be interpreted by some stakeholders as the mechanisms to ensure clinical validity or utility of tests, these requirements do not specify what types of data are appropriate for establishing clinical relevance of the tests, where the data should come from (e.g. from research carried out by the laboratory itself or from data reported in peer-reviewed literature), and how the data should be synthesized to reach conclusions. Based on the reviewer's comments, we have added a section in Chapter 4 to discuss the potential roles of laboratory directors and CLIA inspectors in assessing clinical relevance of the tests.
Mary Steele Williams	Association for Molecular Pathology	Page 5:The authors state that laboratories do not have to participate in proficiency testing. This is an over-reaching statement as none of the currently regulated analytes are molecular tests. Laboratories are in fact required to perform alternative assessment (AA) twice a year. For molecular assays, proficiency testing for a large number of tests is offered by the College of American Pathologists (CAP). The CAP establishes proficiency testing (PT) whenever there are a sufficient number of participants to justify it. In fact, the greatest obstacle to more widespread proficiency testing is the lack of control materials and the lack of economic feasibility of establishing PT for assays performed by only small numbers of laboratories. The CAP has recently established a mechanism to assist in such instances through its Sample Exchange Registry Service, in which the CAP coordinates sample exchanges between laboratories for relatively rare diseases, and for esoteric analytes for which formal proficiency testing is not yet established. As noted above, the AMP Test Directory was also instituted for this purpose.	We were aware of the obstacles to creating official PT programs. We were also aware that none of the currently regulated analytes are molecular tests. However, our statement that "laboratories are not required to participate in a formal CLIA-approved proficiency testing program" is factually accurate. Meanwhile, following that sentence, we did pointed out that laboratories are required to perform alternative assessment (AA) twice a year. Note that we have revised the paragraph to address some of the comments from other reviewers. The relevant section now reads as follows:" Meanwhile, unlike most of the other tests of moderate or high complexity, molecular tests do not have a CLIA-designated specialty or sub-specialty of their own. No formal CLIA-approved proficiency testing (PT) programs (i.e., external test quality control programs) have been established for molecular tests. Laboratories are currently required to use alternative methods to validate the analytical performance of molecular tests prior to offering them to patients (e.g., through a sample split program or an unofficial PT program). It is still unclear whether the alternative validation methods are as effective as a formal proficiency testing program in detecting potential quality problems.
Mary Steele Williams	Association for Molecular Pathology	Page 13: Typo: AMCG, should be ACMG.	The typo was corrected.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	Page 14: Dimech et al. recommend at least 100 positive and 100 negative samples be tested. This may not be possible in rare disorders, though the authors do indicate that a minimum of 20 positives should be tested. Sample size is a statistical measurement and should be treated as such. The number of samples used in a validation determines its statistical power, which is a measure of how much confidence can be placed on the results of the validation. Therefore, validation sample size is ultimately one of the most important factors in determining the analytical utility of the test. Unfortunately, definitive guidelines defining specific sample sizes cannot realistically be given as the requirement is so dependent on a wide range of factors including the nature and performance of the test, critical parameters, how the test will be used in practice and the confidence level required for clinical utility. The report also does not describe the option of a tiered risk assessment strategy with corresponding levels of comparative statistical analysis requirements which would reflect more stringent criteria for high risk testing. A large number of tools for determining sample size given certain input criteria (e.g. confidence interval) are freely available on the internet (e.g. www.statpages.org/Power#, accessed in August, 2009).	We agree with the reviewer that statistical power calculations could, in theory, be used to decide upon an appropriate sample size. In practice this does not seem to be the case.
Mary Steele Williams	Association for Molecular Pathology	Page 16: "Analytical specificity" refers to 2 concepts (below). However, the authors only discuss cross reactivity (number 2 below). 1. The ability of a test to give a normal (negative) result in specimens without the mutation or analyte being tested. Specificity = True negative / (True negative + False positive) 2. Also used to refer to the ability of a test to detect the analyte without cross-reacting with other substances	We are aware that the term "analytical specificity" has been used differently by different authors. In this report, "analytical specificity" is defined as "the ability of a test to measure the target substance when potentially interfering or cross-reacting substances are present in the specimen."
Mary Steele Williams	Association for Molecular Pathology	Page 18: The authors discuss that very few validation studies have been published, but do not address why. It is important to recognize that very few journals will accept validation studies as an article for publication. An accurate depiction would be that most laboratories do not publish their validations, so that there is little published evidence of validation of individual assays. One reason for this is that assay validation is deemed a routine professional activity. Most assays that are published in the literature are in some way novel.	The reviewer agreed with us on that very few validation studies have been published. We decided not to revise the sentence as the reviewer suggested, since the reviewer did not provide appropriate references for the speculated reasons that few validation studies have been published.
Mary Steele Williams	Association for Molecular Pathology	Page 18: The authors discuss a validation published by the Wadsworth Center. When discussing sensitivity and specificity, it should be clarified whether the discussion pertains to analytical or clinical sensitivity and specificity.	We rechecked the section mentioned in this comment and still believe the section is clear as written. Given that Chapter 2 is focused on analytic validity, our discussion clearly pertains analytic sensitivity and specificity.
Mary Steele Williams	Association for Molecular Pathology	Page 20: CYP2C9 is not in the Roche CYP450 Amplichip assay.	This typological error has been corrected.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	Page 25: Challenges in Assessing Clinical Utility of Molecular Tests This paragraph is inaccurate and conflicts with later discussions about CLIA requirements to establish analytic validity, and does not acknowledge CAP's Laboratory Accreditation Program (LAP). As discussed above, the lack of published validation data does not mean that "for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established." All CLIA regulated laboratories need to establish analytical and clinical validity. This information is available at each laboratory and is reviewed during inspections to maintain accreditation by CMS, CAP, JCAHO and other organizations. As mentioned above, it appears that the authors did not consult with laboratory professionals who could have pointed to appropriate sources of information. Given that this is report is an evidence-based review, we recommend removal or revision of this comment.	We revised the paragraph to make the content consistent throughout the report. The revised paragraph reads as follows: "The major challenge in assessing clinical utility is lack of studies that directly correlate test results with clinical outcomes. RCTs, particularly effectiveness RCTs, are rarely available. Other study designs, such as case series (single group designs) are prone to various internal validity issues. As a result, evaluation of clinical utility often involves inference based on the evidence for the analytic validity and clinical validity of the test. However, evaluation of analytic and clinical validity itself is also challenging (see our previous discussion)."
Mary Steele Williams	Association for Molecular Pathology	Page 26: It is unclear whether the authors are discussing analytical or clinical sensitivity and specificity.	In chapter 3, we focus on the properties of clinical validity, which include clinical sensitivity and specificity. We provide our definition of clinical validity in the beginning of the chapter. Analytical validity is discussed in chapter 2 of the report.
Mary Steele Williams	Association for Molecular Pathology	Page 28: The abbreviation ESBC should be spelled out	We have spelled out the abbreviation for ESBO, which indicates early stage breast cancer.
Mary Steele Williams	Association for Molecular Pathology	Page 38: Proficiency testing: see comment above (page 5)	See response above
Mary Steele Williams	Association for Molecular Pathology	Page 38 "Clinical validity" see comment above (page 5)	See response above
Mary Steele Williams	Association for Molecular Pathology	Chapter 5: Some FDA special control documents that could apply to molecular assays were omitted (such as those for multiplex instrumentation, and replacement reagent).	As suggested, three FDA guidance documents were added to the revised report.
Mary Steele Williams	Association for Molecular Pathology	Page 41: Note that the ASR guidance was updated in 2007.	We are not clear about this comment. The ASR guidance cited in in the report was indeed published in September 2007.
Mary Steele Williams	Association for Molecular Pathology	Chapter 6: The report states that the FDA and FTC do not have clearly defined internet promotion as labeling or advertising, but warning and/or untitled letters have in fact pointed to FDA's conclusion that labeling also can include websites and use of literature.	As of November 2009, the FDA still does not formally define internet promotion as labeling or advertising. According to Federal Register (vol. 74, no. 181 [September 21, 2009], pp. 48083-48088.), in November 2009, the agency would hold a public hearing on the promotion of drugs and medical devices on the Internet and other new media tools. Our search did not identify any decisions made by the FDA following this public hearing.
Mary Steele Williams	Association for Molecular Pathology	Page 48: The CDC has had annual meetings, often adjoining the AMP annual meeting, since 2003.	The statement in the text indicates the two meetings in 2003 and 2004 led to the development of the Genetic Testing Materials Coordination Program; other annual meetings of the CDC may occur but are not relevant to the sentence as written.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Mary Steele Williams	Association for Molecular Pathology	Page 48-49: This section states that the AMP currently facilitates sample exchanges among laboratories across North America for molecular testing and that a manuscript describing results from the sample exchanges is currently being drafted. This is an inaccurate statement that should be corrected, the systematic sample exchange is facilitated by the CAP and the used reference is not one of the AMP publications. AMP has performed sample exchange studies for specific molecular tests when it believes such a study would be useful to the molecular pathology community. When AMP conducts such studies, it can include laboratories outside of North America. AMP publications regarding sample exchanges and QC of molecular testing can be found at: http://www.amp.org/ (members section) and can be provided upon request.	We have removed the inaccurate statement.
Mary Steele Williams	Association for Molecular Pathology	Page 49: All molecular tests are non-regulated analytes. See proficiency testing comments above (page 5).	Revision has been made based on the comment. Also see responses above.
Mary Steele Williams	Association for Molecular Pathology	Page 71: Please note that EGAPP (Evaluation of Genomic Applications in Practice and Prevention) has focused primarily on genetic-related testing; not necessarily on molecular infectious disease testing.	This report is not narrowly focused on molecular infectious disease testing, rather it is about molecular testing for various clinical applications. We are aware that EGAPP has a focus on genetic-related testing. We believe that the discussion of the EGAPP effort in the Epilogue is directly relevant to the subject of this report (i.e., molecular LDTs).
Mary Steele Williams	Association for Molecular Pathology	The implication that the NY State model should be emulated is concerning. Laboratorians who have experienced this process know its strengths and limitations and its potential to impede patient care via administrative delays. More specifically, to our knowledge there are no data confirming that the NY State process results in better results and better patient care outcomes for NYS-reviewed LDTs versus those in non-NYS labs that are CAP-accredited.	In our discussion, we did not suggest that NYS-reviewed LDTs have better results than those non-NYS-reviewed tests. We stated that the experience of NY CLEP "should certainly provide some valuable lessons in how the oversight of LDMTs might be accomplished and what resources would be necessary to do so on a national scale".
Naomi Aronson	Blue Cross and Blue Shield Association	We suggest the following edits after reference 61, with an additional sentence: In general, the benefits and harms of a molecular test should be compared to those using the best alternative test to assess additional incremental benefits and harms of a molecular test. Alternatively, the incremental benefits and harms of using a molecular test should be compared to those using no test at all if that is the current standard of care.	Revision has been made as the reviewer suggested.
Naomi Aronson	Blue Cross and Blue Shield Association	In paragraph 2 (page 24), the last sentence has been edited by us to read: Patient outcomes refer to endpoints such as mortality and quality of life, i.e. clinical results that can be perceived by and that matter to the patient.	Revision has been made as the reviewer suggested.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Naomi Aronson	Blue Cross and Blue Shield Association	In paragraph 4, the authors state: "The impact of an intervention on patient outcomes is typically measured using randomized controlled trials (RCTs)." We believe that this statement is insufficient. High quality comparative evidence is best obtained using randomized controlled trials (RCTs) and may be appropriate in high risk and large population/public health scenarios. However, prospective RCTs designed to evaluate molecular tests are not always necessary. Depending on the clinical scenario, already completed RCTs designed to answer other clinical research questions but with banked samples and known outcomes may also be appropriate to evaluate particular molecular tests. In some cases an indirect chain of evidence may be constructed to link evidence of the clinical validity of the molecular test to already existing evidence of clinical utility. If the intent of the test is diagnosis, and treatment in the case of a true positive is established, then evaluation of clinical validity is likely to be sufficient. The message should be that RCTs represent best quality evidence, not the only acceptable evidence.	In general, we agree with the reviewer's view on clinical utility evaluation. However, we don't think the reviewer's view is contradictory to what we currently express in the paragraph (i.e., "The impact of interventions that occur as a consequence of a molecular test is particularly important in assessing clinical utility. The impact of an intervention on patient outcomes is ideally measured using randomized controlled trials."). Besides, in the revised report, we added the following sentences in a paragraph on the same page: " ..."evaluation of clinical utility often involves inference based on the evidence for the analytic validity and clinical validity of the test. However, evaluation of analytic and clinical validity itself is also challenging (see our previous discussion)." We believe that this revision echoes the reviewer's view.
Naomi Aronson	Blue Cross and Blue Shield Association	In the (one-paragraph) subsection "Challenges in Assessing Clinical Utility of Molecular Tests, " the following edits and additions are offered. Analytical and clinical validity of molecular tests are important prerequisites for assessing clinical utility. However, for most molecular tests, especially laboratory-developed tests, any data on analytical and clinical validity have not been clearly established.(61) are not publicly accessible unless published in peer-reviewed journals (rare). In contrast, FDA-approved commercially marketed lab test kits are accompanied by a kit insert that summarizes the analytical and clinical validity data submitted for approval; FDA Decision Summaries are publicly available via the FDA website and contain a summary of submitted data; kit inserts are often available on the company website. However, few molecular tests have been submitted for FDA approval.	The paragraph was revised based on the comment.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Naomi Aronson	Blue Cross and Blue Shield Association	The sentence that originally followed reference 61 in this subsection should be changed to read as follows to render it accurate: "In addition to lack of studies of analytic and clinical validity and utility, another challenge in assessing clinical utility is lack of studies that correlate test results with clinical outcomes." As it stands, this statement is inaccurate. "studies that correlate test results with clinical outcomes" is clinical validity!!! Clinical validity describes (i.e. statistically correlates or associates) the relationship between test result and any clinical outcome of interest. Clinical utility asks a COMPARATIVE question i.e. Do you improve patient outcomes if you manage patients using the test results compared to when you manage patients without the test results? -- The language in the report only confuses the reader and could be interpreted as supporting the viewpoint that there is no need to establish the clinical utility of molecular tests. Please clarify the language here and also in the Epilogue.	Revision has been made based on the comment.
Roger D. Klein	BloodCenter of Wisconsin/Medical College of Wisconsin	1) The report makes a highly objectionable statement on page 25: "Analytical and clinical validity of molecular tests are important prerequisites for assessing clinical utility. However, for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established." I believe that this statement is downright false, and that there is no evidence whatsoever to support it.	The statement that caused the concern was removed. The paragraph was also revised to reflect our current view on the issue.
Roger D. Klein	BloodCenter of Wisconsin/Medical College of Wisconsin	2) There are a number of other inconsistencies in the report. For example, on the one hand the report appears to exclude heritable diseases, and on the other repeatedly cites guidelines, proficiency testing, etc. for example from ACMG, that are directed toward inherited disorders. Further, the report confuses the applicability of published validations for various types of unrelated molecular assays, attempting, for example, to generalize articles directed toward quantitative infectious disease testing or TB to the whole of molecular diagnostics.	Per comment on the guidelines and PT testing for heritable diseases, we believe this information is interesting to the key users of the report (such as CMS) although heritable diseases are outside of the scope of the report.
Roger D. Klein	BloodCenter of Wisconsin/Medical College of Wisconsin	3) Further, the report gives insufficient attention to the CLIA personnel (director, technical and clinical consultant) requirements and their role in ensuring laboratory quality, prominently ignoring the "clinical consultant" requirement that squarely addresses clinical validity	See our previous comments. We have revised the report to reflect the roles of CAP, AMP, the CLIA personnel (director, technical and clinical consultant) in ensuring laboratory quality. Changes have been made throughout the report in this regard.
Roger D. Klein	BloodCenter of Wisconsin/Medical College of Wisconsin	4) There is insufficient emphasis on the CAP requirements for proficiency testing as part of the LAP.	See our previous comments. We have revised the report to reflect the roles of CAP in ensuring laboratory quality, including CAP sponsored PT programs.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Steve Shak	GENOMIC HEALTH, INC	The reviewer made two overarching comments regarding the oversight of LDMTs (refer to the original document): "There are two takeaway conclusions from this report with which we agree strongly…"	We did not identify a specific point for responding here, although we generally agreed with the reviewer's two comments.
Steve Shak	GENOMIC HEALTH, INC	The following change needs to be made on Oncotype DX® assay: p. 19: "Although the Oncotype DX® assay may fall into the . . .(IVDMIA) class . . ." [Replacing "falls into."]	Revision has been made as the reviewer suggested.
Steve Shak	GENOMIC HEALTH, INC	p. 19: Reference #41 in the draft report is the Genomic Health website address. That reference information should stay in the report. However, it is important to distinguish and reference the clinical validity and clinical utility studies done, and their endpoints or conclusions reached and reported in peer-reviewed publications. This is not now accomplished by including only the existing references #40 (to the Lyman et al overview of developmental work) and #42 (to the Cronin et al reprise of the validation studies).	We appreciate the reviewer's viewpoint; however, the section in question doesn't discuss clinical validity or utility at all; it is entirely focused on analytical validity. All published studies on the analytical validity of Oncotype are referenced in this section. The reference to the website is provided as a sort of introduction to the subject, a way to get additional information if the reader should choose to do so.
Steve Shak	GENOMIC HEALTH, INC	The following text needs to be added to make the report more current and complete: On the company's Web site, Genomic Health lists published studies on the development and validation of the Oncotype DX® assay. (Retain ref. #41) The primary clinical validation study – using NSABP-14 tumor samples - was published in 2004. This study showed that the 21-gene assay could predict the likelihood of disease recurrence in estrogen-receptor positive (ER+) node negative (N-) patients. Additional studies that establish the clinical validity and clinical utility (proven patient benefits from chemopredictive endpoints) using NSABP-20 and Kaiser samples were published in 2006. , Since these early clinical validation and clinical utility studies were reported, Oncotype DX® also has been validated for chemopredictive use in patients with node positive (N+) disease.	We have indicated in this section that published studies on the development and validation of the Oncotype DX assay are available on the Genomic Health website.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Steve Shak	GENOMIC HEALTH, INC	p.24: The following text is offered to correct misinformation now in the draft report (two paragraphs): Paragraph 1: The Oncotype DX® assay (Genomic Health, Inc., Redwood City, CA), described in Chapter 2, is used to assess prognosis and guide choice of adjuvant therapy in breast cancer patients (hormonal therapy alone versus hormonal therapy plus chemotherapy) – for women and men. As noted previously, developmental studies, clinical validation studies, and clinical utility studies are available through the Genomic Health Web site. (Ref. #41) Paragraph 2: The National Cancer Institute (NCI) is sponsoring an on-going clinical trial that began in 2006 to evaluate the effect of adjuvant chemotherapy on disease-free survival in women with "Mid-Range" Oncotype DX® Recurrence Scores®. The study is planned to enroll about 10,000 breast cancer patients and assess recurrence and mortality outcomes for 20 years. (Trial Assigning Individualized Options for Treatment/TAILORx) The study employs the Oncotype DX® test as a proven technology and is not designed to validate the Oncotype DX® Breast Cancer Assay. The principal objectives of the trial are: A. To determine whether hormonal therapy alone is not inferior to hormonal therapy plus chemotherapy in women whose tumors meet established clinical guidelines for adjuvant chemotherapy and whose Oncotype DX® Recurrence Score® test results are in the "uncertain chemotherapy benefit" category as set by study investigators (Recurrence Score® results from 11 to 25). The primary study endpoint is disease-free survival. Other co-primary endpoints include distant recurrence-free interval, recurrence-free interval, and overall survival. B. To create a tissue and specimen bank for patients enrolled in this trial, including formalin-fixed, paraffin-embedded tumor specimens, tissue microarrays, plasma, and DNA obtained from peripheral blood – a resource critical for future studies on emerging cancer tests.	We have corrected the text as the reviewer suggests.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	In the general comments section, the review provided their opinions about how LDMTs "should" be regulated.	While we respect the reviewer's opinions, these opinions could not be cited as evidence in this horizon scan report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	While we acknowledge that the report is focused on assessment of CLIA regulations, we note a spectrum of FDA regulations that are not referenced in the report and are key aspects of the FDA review process for diagnostic tests that are useful for considering in review of the current regulation of diagnostic testing. We concur with the report that analytical and clinical validity information is important for tests that are made available to the public. In addition to assessment of clinical validity, FDA oversight includes premarket review, Good Manufacturing Practices, labeling regulations, corrections and removals, medical device reporting for adverse events, and a number of other requirements found in the FD&C Act. In addition, there may be Special Controls that FDA has established for a device. These are essential attributes of FDA oversight to support the safety and effectiveness of devices.	The chapter is intended to focus on the FDA guidance specifically pertaining to oversight of LDMTs. The other FDA regulations that the reviewer specified are relevant to LDMTs, as well as to any other medical devices regulated by FDA. While we agree those regulations play an important role in ensuring the safety of FDA-regulated technologies, we only focus on the FDA guidance specifically pertaining to LDMTs. In the methods section of the chapter, we added relevant content to make our intention clearer.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 1: Not all molecular tests are molecular genetic tests. Interchangeable use of these terms is inaccurate and creates confusion in other parts of the report. Furthermore, the focus of the report appears to be molecular tests, not genetic molecular tests. Therefore, it is unclear why the reference to the definition of molecular genetic test recommended by the Genetic Work Group of the Clinical Laboratory Improvement Advisory Committee is referenced. Remove reference to molecular genetic testing and reference to interchangeable use of the terms “molecular test” and “molecular genetic test.” Add the following definition: “Lab developed molecular tests are available that measure DNA, RNA, chromosomes and proteins. Detection of these analytes spans from nucleic or amino acid base sequence up to the level of whole chromosomes. Molecular tests can evaluate both somatic and germline mutations as well as levels of gene expression or proteins in normal or pathologic cells and tissues.”	The requester of this horizon scan report (CMS/AHRQ) and ECRI Institute mutually agreed that protein-based testing is out of the scope of the report. Therefore, the definition provided by the reviewer does not fit this report. As we had clarified with the report requester, the main focus of the report is on DNA- or RNA-based testing. The definition of genetic molecular test that is currently used in the report appropriately meets the need of the requester. We used "molecular test" and "molecular genetic test" interchangeably to make the report less cumbersome. We believe that, since we had defined the terms explicitly at the beginning, the terms should not confuse the readers of the report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 1: the scope of the molecular tests in this document is confusing. It would be more understandable if the scope was defined in terms of what molecular lab-developed tests (molecular LDT is the more common term, not LDMT) are in scope and which ones are out of scope based on intended use/indication and applicability to the Medicare population rather than grouping tests in scope based on technology used to detect the analyte or type of analyte measured (e.g. reference to pathogen testing as within scope). Add the following in place of the current language regarding scope: "In accordance with the objectives for this project, we confine our analysis to nucleic acid based molecular tests of potential clinical relevance to the Medicare over-65-year-old population performed with a variety of detection methodologies/ technologies that measure human or pathogen DNA or RNA for the purposes of: Diagnosis in symptomatic individuals Prognostic indicators Therapy response monitoring Therapy selection or drug dosage selection." Use the more commonly recognized terminology "molecular lab-developed tests or molecular LDT" in the document rather than "lab-developed molecular test or LDMT."	We defined the scope of the report mainly to meet the needs of the report's requester, CMS. That is why the report is primarily focused on LDMTs applicable to the Medicare over-65-year-old population. We mentioned pathogen testing separately in the report because we want to make it clearer that testing of both human and pathogen DNA and RNA are within the scope of the report since the definition of molecular test recommended by the Clinical Laboratory Improvement Advisory Committee only covers testing on human DNA or RNA. As we had confirmed with CMS, the agency is interested in both human and pathogen LDMTs. Neither "molecular lab-developed tests" (molecular LDT) or "lab-developed molecular test" (LDMT) is a part of standardized nomenclature system. We believe that we defined LDMT clearly at the beginning of the report and that it should not cause confusion among the readers of the report.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 2: Replace "a useful tool" with "potentially useful aid."	Revision has been made as the reviewer suggested.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 3: We would suggest to add a discussion of different intended uses of test results generated by LDTs and how they apply or do not apply to the Medicare population.	In the Introduction section of the report, we briefly mentioned tests for various clinical applications such as tests used for diagnostic purposes in symptomatic individuals, tests used as prognostic indicators, tests used to monitor response to therapy, and tests used to choose therapies for a known disease entity or used to adjust medication dosing. We do not feel it is necessary to further expand the discussion in the Introduction section, since many of the clinical applications of the tests are discussed in the following chapters.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 4: Replace "inheritable" with "heritable." The correct term is "heritable", not "inheritable."	Revision has been made as the reviewer suggested.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 4,5: Replace “genetic tests,” with “molecular lab-developed tests,” before “ the experts in the field generally agree . . ..” Similarly, replace “genetic tests” with “molecular lab-developed tests” before “in the U.S. is provided by a still-evolving system that current includes. . ..” Similar to a previous comment, interchangeable use of these terms is confusing and the discussion referenced is not limited to genetic tests.	On page 4, we changed the term to "molecular tests". On page 5, we changed the term to "genetic or other laboratory tests", which include molecular test. Also see our previous responses on the terminology matter.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 5,24: The draft report used different definitions of "clinical utility" on pages 5 and 24. Recommend a consistent definition of “clinical utility” be used, and AHRQ consider adopting the definition used by the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS). This definition is very similar to the definition found on page 5 of the draft report.	We agreed with the reviewer that there should be a consistency in defining the term. We changed the definition on page 24 so that it is in line with the one on page 5.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 5: Reference other reports/projects regarding genetic testing (i.e. CLIAC, ISO 15189, Organization for Economic Cooperation and Development, Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report ‘Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions’	We cite references as we see appropriate.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 7, 8: Roche Diagnostics should be removed from the list. Roche is not a service laboratory. We also note that the list of laboratories does not appear to be comprehensive.	Roche Diagnostics is one of the laboratories identified in the Statement of Work (SOW) as relevant sources for this report. However, we agreed with the reviewer that Roche is not a service laboratory and therefore removed the lab from the report.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	page 8: Replace “FDA-approved” with “FDA-approved or cleared” before “commercial kit . . ..”, “full testing systems. . ..”, “commercially available tests. . ..”, and “molecular tests.” Commercial kits can be FDA-cleared or approved. Only class III devices are approved (under a Premarket Approval Application). Class I/II non-exempt devices are cleared.	Revision has been made as the reviewer suggested.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 8: Remove “FDA-approved” before “analyte specific reagents . . ..” Most analyte specific reagents do not require approval or clearance, although they are subject to the general control provisions to assure safety and effectiveness of these devices.	We changed the wording to "FDA-cleared analyte specific reagents". In the section, we specifically talk about FDA-cleared ASR.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	page 13: Chapter 2/ Results/Accuracy/ Accuracy in Comparison to Reference Methods. This section is inaccurate. The lab is responsible for these data and having them available for a CLIA audit. Only New York State requires that the data be submitted to its Department of Health, as mentioned in later sections of the Tech Assessment. Replace “report” with “establish and verify.”	We are unclear about which specific sentences or paragraphs this reviewer was referring to. In the sections, we did not discuss whether a lab is required to submit the data to CLIA or NYS for review.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	page 13: Replace the terms “reference standard” and “reference standard test” with “reference method” or “measurement procedure” in this subsection.	Revision has been made as the reviewer suggested.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 14: Replace “repeatability” with “within day or run reproducibility.” The term “repeatability” is no longer commonly used and has been deleted from standards use such as in Clinical and Laboratory Standards Institute documents (CLSI).	We decided to keep the term "repeatability" since it is still used in some discussions and literature.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 15 (reference 27) cites a link to the CLSI website (harmonized terminology Database). Cite CLSI and not WHO as the source of the linearity definition.	The link has already been provided in the reference list of the draft report. In the revised report, we cited CLSI and not WHO as the source of the linearity definition.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	page 20, Add “ CYP2D6” before “in December 2004 . . ..” The AmpliChip CYP450 Test was cleared under two 510(k)s (one for CYP2D6 and a second for CYP2C19).	Revision has been made as the reviewer suggested.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 25: We suggest referencing the technical limitations of lab testing for infectious disease. The microbiology community has noted more significant limitations for culture than a validated NAA method. Add a statement such as the following to this section: ”The use of molecular techniques in infectious disease testing is gaining acceptance, often as the best method for detection of the infectious agent. However, there are two issues that must be kept in mind when nucleic acid amplification (NAA) is used: 1. Infectivity or virulence of an infectious agent might not correlate directly with the presence or concentration of nucleic acid. 2. “remnant” DNA or RNA from the infectious agent might still be detectable when the clinical symptoms have resolved or were not present at all (sub-clinical).”	We did not made suggested addition. The section the reviewer refer to is intended to be focused on the evidence from existing systematic reviews. The suggested addition does not fit into the section.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	page 25: Include additional examples of systemic reviews that evaluated the clinical validity of infectious disease tests. This section cites seven systematic reviews of infectious disease tests that evaluated clinical validity. Six of these were for TB and one for Lyme Disease. There are numerous publications that cite the clinical validity and clinical utility of tests for HBV, HCV, HIV, HPV and C. trachomatis and N. gonorrhoeae, including Treatment Guidelines and Consensus Standards. We suggest that such additional publications should be included for improved accuracy.	Given the limited time allowed for the project, AHRQ and ECRI Institute agreed to focus on the evidence from systematic reviews (refer to the method section in the Chapter).

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 33: The three CLIA test complexity categories are not based on potential risk to public health. Corrected language is offered to reflect the three CLIA complexity categories. Remove "based on its potential risk to public health" before "three CLIA complexity categories. . .." After "CLIA complexity categories, replace remainder of the sentence so that it correctly reads: "FDA has assumed primary responsibility for assigning each test to one of the three CLIA complexity categories, of which two are based on ease of use and the training needs for successful operation. ("Moderate complexity" is deemed sufficiently simple to be successfully preformed by operators with a high school education; "high complexity" must be performed by operators with at least two years of college training. There are other laboratory supervisory requirements for these two categories, as well.) The third category, Waived Tests, are defined as simple laboratory examinations and procedures . . .."	we made the following changes to make the statement more accurate and appropriate for the section: We removed "based on its potential risk to public health" before "three CLIA complexity categories. . ..". We also added a reference at the end of the paragraph for those who are interested in detailed FDA criteria for test categorization (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124208.htm).
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 37 (Table 3): This relevant section of the CLIA regulation regarding Control Procedures was absent from Table 3. The table should note that molecular assays are addressed in the CLIA Regulations in Sec. 493.1256 (v), which states: "Each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting the inhibition."	We made changes as suggested by the reviewer.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 39-40: Define "unexpected events." We are not aware of this term being used in either CLIA or QSR. We appreciate clarification. If it is meant as Adverse Events that require MDR reports for IVD manufacturers and for users (if an incident is believed to be associated with a death), this should be specified.	We deleted the term "unexpected events".
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 43: Include a comprehensive list of FDA special controls guidance documents. Appropriate examples include: "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. "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.	The first guidance mentioned has already been included in the table. The second guidance mentioned had not been published when we completed the search for the draft report. But we added this guidance in the revised report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 47: Replace “validated” with “the same” before “samples to participating laboratories . . ..” Samples are not validated in the sense that ‘validate’ is used in the QSR. In fact, these samples are stable and uniform in their vials or other ‘package’ (such as a slide or tissue sample), with only approximately known concentrations for quantitative tests. The labs report back results are either compared to the group mean or to the result that is derived from use of a (rare) reference method. Comparison from one lab to the other is the generally accepted metric of conformity, if there is not a reference method available.	We modified the text based on this comment.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 47: Add a discussion on criteria for acceptance of the control material to evaluate laboratory performance. The materials are qualified under the CLIA regulations to judge performance if the percent agreement among all labs reporting results is below 80%. We suggest inclusion of this discussion as the criteria is an important element that indicates the care that must be taken to prepare these samples.	The criteria for acceptance of the control materials have been described in detail in some of the references cited in the "control material" section of the report. Therefore, we decided not to add an additional section to discuss those criteria.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 47: Distinguish primary standards (assumed to contain “truth” for detecting a component or to verify a measurement system for quantification) with material used in proficiency testing. These concepts cannot be mixed. The latter materials need to be stable and consistent, but do not constitute world-recognized primary standards. These are both important concepts, but they are not interchangeable. Very few controls are “validated” against a primary standard– even for common, routinely measured analytes— this is reserved for calibrators, when a primary standard is available.	We modified the text based on this comment.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 54: This section should provide additional, up-to-date published studies as may be available. We note that the assessment references two published studies that report the use of FDA-approved commercially available tests reduced variability in results in comparison to the use of non-approved or cleared tests along with other referenced studies. While we acknowledge that there may be limited available data, we suggest inclusion of additional, up-to-date published studies to enhance the report content.	We have included all the studies that met the inclusion criteria of the report (please refer to the methods section of Chapter 7 for the study inclusion criteria). We have updated the report with new studies meeting the inclusion criteria.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Page 69: Include discussion regarding the elements required by New York State for pre-approval of LDTs. Mention is made of pre-approval of LDTs by NY State. No discussion is provided as to the elements that NY requires in the submission. More detail would be helpful as to the prime elements of such submissions in order to gain approval.	In the revised report, a section about NYT CLEP program was added in Chapter 4.
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Table 25: Include the Roche Molecular Systems, Inc COBAS®AmpliPrep/COBAS®AMPLICOR®	We have updated the FDA tables to include tests that have been FDA cleared as of December, 2009.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Table 25: HCV Test, version 2.0 in the HCV qualitative detection section.	See above response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Table 25: Include the Roche Molecular Systems, Inc. COBAS® AmpliPrep/COBAS® TaqMan® HCV Test in the HCV quantitation section.	See above response
Khatereh Calleja	the Advanced Medical Technology Association (AdvaMed)	Table 25: Include the Roche Molecular Systems Inc. COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test in the HIV Quantitation section.	See above response
Ann Willey	NYS DOH	The report states it will exclude consideration of molecular tests for "tissue typing" and "screening for inherited diseases of metabolism" however it then includes HLA typing, screening for mutations associated with cystic fibrosis, and AneuVysion for prenatal detection of chromosmal aneuploidy in table 16 of Appendix B. This inconsistency should be corrected or clarified	These tests have been removed from Table 26 of Appendix B.
Ann Willey	NYS DOH	Statements about FDA oversight of ASRs are inaccurate. The agency does not review the individual reagents but only the general manufacturing practices of the manufacturer. This distinction is important to the end user laboratory as the quality control of these reagents has not actually been reviewed, but only inferred from the overall "quality" of the manufacturer. ASRs are not "FDA approved."	Revisions have been made based on this comment.
Ann Willey	NYS DOH	Not all manufacturers of reagents used in LDT development are subject to FDA oversight. Many manufacturers label materials as RUO's under the misunderstanding that this will exempt them from such oversight. Many laboratories purchase these RUO materials without realizing the lack of available reagent quality control puts an additional burden on the laboratory to establish these parameters prior to using the reagents in any LDT.	We are aware that not all manufacturers of reagents used in LDT development are subject to FDA oversight. But in the specific section, we particularly refer to FDA-cleared ASRs.
Ann Willey	NYS DOH	Page 7 of the introduction incorrectly refers to the FDA as the Federal Drug Administration.	We have corrected the typo
Ann Willey	NYS DOH	Although it is true that by definition each LDT is unique to the developing laboratory, to the extent that multiple labs use the same manufacturer's product, ASR or IVDMIA, and all follow the general methods offered by that manufacturer with the package inserts to detect the same analytical target in the same specimen matrix for the same clinical population and purpose...these are probably not different assays. Therefore the magnitude of the numbers may be an overstatement .	While we agree that some of the LDTs catalogued in the report might be similar to each other, these LDTs still need to be counted separately since the labs determine the protocols independently for the tests and don't market the test to other labs.
Ann Willey	NYS DOH	CLIA does require labs to validate LDTs, however the lab need not "report these parameters" to anyone prior to offering the test, except as they are included in routine elements of the test report.	We agreed with the reviewer. This view is reflected in the revised report.
Ann Willey	NYS DOH	Check for typos of various acronyms (e.g. AMCG rather than ACMG page 2, Chapter 2	We have corrected the typo

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Ann Willey	NYS DOH	The numbers of specimens required for LDT validation suggested by Dimech (n=1000)would rarely if ever be encountered in the current procedures for most human genome molecular tests. For inherited aberrations numbers studied generally range below 20 normals and often unfortunately include no known positive cases due the rarity or lack of access to such materials	The text already comments that they have alternative suggestions for rare disorders.
Ann Willey	NYS DOH	The lack of published LDT validation studies is to be expected as many of these tests are considered proprietary by the developing laboratory.	This view is reflected in the revised report.
Ann Willey	NYS DOH	The cited validation study for the Parkinson's disease test at the Wadsworth Center should more accurately be considered as a research effort to establish the feasibility of using a particular genetic marker for such assessments. It was not done in a clinical lab for purposes of validating a clinical test. The numbers of specimens tested is far beyond the capability of most clinical labs in developing a single gene molecular assay.	We agree the number of specimens is far beyond the capacity of most labs. The design of the study does however establish the validity of the Taqman assay to detect the mutation.
Ann Willey	NYS DOH	Under the CLIA system it is not always the state Department of Health that performs the contracted surveys of the certificate of compliance laboratories. It may be other regulatory agencies without link to the health department.	We changed the wording from "State Department of Health" to "State surveyor".
Ann Willey	NYS DOH	The CLIA category of cytogenetics includes FISH assays although none of the published standards are directly relevant to the performance of these molecular assays.	Our current report does not have any statement contradictory to this comment.
Ann Willey	NYS DOH	Chapter 5 page 1 paragraph 4 microarrays not microassays	We have corrected the typo
Ann Willey	NYS DOH	Chapter 7 page 3 error in table 7 entries	The comment is not specific enough. We are not clear what error the reviewer refer to.
Ann Willey	NYS DOH	Laboratory exchange programs may encounter issues of patient consent and confidentiality depending on state specific genetic testing legislation	We agree with the reviewer's viewpoint.
Ann Willey	NYS DOH	Chapter 8 table 10 NYSDOH clinical laboratory reference system includes materials for all of the listed categories except clinical utility	Correction was made based on the comment
Penny Keller	CMS CLIA	Page 5: Comment: Some of the "technical problems" that are listed for the molecular testing process such as 1) specimen contamination, 2) presence of interfering inhibitors in specimen, and 3) lack of consistency in test results, are also problems that can occur with other laboratory tests not only specific to molecular.	We revised the sentence based on the comment. Now it reads as follows: "As we discuss in Chapters 2, 3 and 7, many technical problems may occur in the complex molecular testing processes, such as flawed probe, primer, or array design."
Penny Keller	CMS CLIA	Page 13: Edited text for clarification with CLIA language (edited text in italics and underlined): The CLIA language for reg. Sec. 493.1253 does not specifically state that "laboratories performing tests not cleared by the FDA report these parameters prior to offering the test to the public," instead this regulation addresses "establishing these parameters prior to offering the test to the public."	We revised the sentence based on the comment. Now it reads as follows: "The CLIA regulations require laboratories to establish these parameters prior to offering the test to the public (Sec. 493.1253)."

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Penny Keller	CMS CLIA	Page 34: Comment: Laboratories do not receive COA from the accreditation organization; they receive it from CMS after the accreditation organization has confirmed a laboratories' accreditation status.	We revised the sentence based on the comment. Now, the sentence reads as follows "A laboratory that performs nonwaived (moderate and/or high complexity) testing can also apply for a COA in lieu of COC if the laboratory is accredited by one of the six accreditation organizations approved by CMS."
Penny Keller	CMS CLIA	Page 34: Edited text for clarification with CLIA language (edited text in italics and underlined): Edit 1: "A laboratory that performs nonwaived (moderate and/or high complexity) testing can obtain a COA in lieu of COC by virtue of accreditation by one of the six accreditation organizations approved by CMS." Edit2: "These two states have CLIA-approved laboratory programs and conduct inspections using standards equal to or more stringent than CLIA's."	Edit 1: see the response above. Edit 2: we revised the paragraph, it now reads as follows" Section 353(p) of the Public Health Service Act provides for the exemption of laboratories from the requirements of CLIA when the State in which they are located has requirements equal to or more stringent than those of CLIA. Currently, two States—Washington and New York—have CLIA-exempt status (New York has a partial exemption [i.e., the exemption applies to certain types of laboratories as determined by the state])."
Penny Keller	CMS CLIA	Page 37: Comment: Clarification is needed with the following statement s: that "review of regulations did not identify any molecular test-specific QC requirements in the current CLIA regulations." Section 493.1256 particularly describes in detail the requirements for quality control procedures and makes specific reference to "laboratory developed ("in-house") tests as a subset of tests." First, CLIA regulation Sec. 493.1253 only lists "in-house methods as an example among many non-FDA approved test systems. It makes no further reference to this type of test in the regulation language. Second, CLIA reg. Sec 493.1256(d) does address quality control for molecular tests, such as extraction and amplification control procedures .	Based on the comment, we removed the following statements: 1) "our review of regulations did not identify any molecular test-specific QC requirements in the current CLIA regulation"; 2) "and makes specific reference to laboratory-developed ("in house") tests as a subset of tests "not subject to FDA clearance or approval". We also add relevant content from Sec 493.1256(d) into the paragraph.
Penny Keller	CMS CLIA	Page 37: Table 3, bullet # 3, Comment: Should reference the specific CLIA regulation, "Sec. 493.1253(b)(2)," for the performance characteristics.	Revision has been made based on the comment.
Penny Keller	CMS CLIA	Page 38: Comment: It is not due to the absence of a specialty or subspecialty that molecular testing is not required to undergo proficiency testing; rather, it is the fact that the analytes are not listed in Subpart I. This situation is not unique to molecular tests; of the thousands of analytes tested in laboratories, 83 require CMS-approved proficiency testing. The remainder undergo twice-yearly accuracy assessment.	Revision has been made based on the comment. The sentence now reads as follows: "Molecular tests are not listed in Subpart I, therefore laboratories are not required to participate in a formal PT program for molecular tests."
Penny Keller	CMS CLIA	Page 38: Edited text for clarification with CLIA language (edited text in italics and underlined): Edit 1: "Under CLIA, each laboratory performing nonwaived testing (including molecular test) must enroll in one CMS-approved proficiency testing (PT) program for each specialty, subspecialty, and analyte specified in Subpart I of the CLIA regulations." Edit 2: "Molecular tests are not listed in Subpart I, therefore laboratories are not required to participate in a formal PT program for molecular tests."	Revision has been made based on the comment.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Penny Keller	CMS CLIA	Page 39: Bullet #3, CMS makes available disclosure of CLIA routine inspection results. 493.571(b) applies only to those states with licensure programs. Results of surveys performed by State Agencies in all other states are disclosable to the public.	Bullet #3 is a quote from the CLIA regulations, Sec. 493.1773 (d). The statement regarding Sec. 493.571 (b) is also a direct quote from the regulation. Therefore, we believe that they are accurate statements about the CLIA regulations.
Penny Keller	CMS CLIA	Page 45: Edit: These two states have CLIA-approved laboratory programs and conduct laboratory inspections using standards equal to or more stringent than CLIA.	Revisions have been made based on this comment.
Penny Keller	CMS CLIA	Page 49: Comment: The term "regulated test" applies only to regulation in terms of CMS-approved proficiency testing. While it is true that the tests are not regulated in terms of proficiency testing, these tests are, in fact, regulated in all other areas of CLIA requirements--Quality Control, Personnel, Facilities, Inspections, and Enforcement.	The sentence that may have caused the confusion was revised. Now, the sentence reads as follows: "Under CLIA, each laboratory performing nonwaived testing (including molecular tests) must enroll in one CMS-approved proficiency testing (PT) program for each specialty, subspecialty, and analyte specified in Subpart I of the CLIA regulations."
Penny Keller	CMS CLIA	Page 49: Edited text for clarification with CLIA language (edited text in italics and underlined): "CLIA requires that laboratories participate in a proficiency testing program for every test listed in Subpart I."	The sentence was revised. See the previous response.
Penny Keller	CMS CLIA	Page 50: Comment: "A laboratory that correctly tests 80% or more of the samples is graded as 'acceptable'. The first unsatisfactory performance on a proficiency testing survey is referred to as a CLIA Action 1." The use of the term "CLIA Action" may be misleading since these PT programs are not CMS-approved programs under CLIA. Also, these are NOT CLIA actions for the purpose of molecular testing.	We have changed the language in the report to reflect the current CAP wording.
Jeff Voigt	None	ECRI Institute note: Mr. Jeff Voigt in his two-page comment discussed how clinical utility should be defined and what types of studies should be designed to evaluate clinical utility. He did not make specific recommendations or requests to us about what revisions need to be made to the report.	We appreciate Mr. Jeff Voigt's insight about the clinical utility issues. My Voigt's opinions were fully considered by ECRI Institute in revising the report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Joseph Eyer	Coalition for 21st Century Medicine	1. Scope of the Technology Assessment Report. The Draft TA, offers a synthesis of evidence on the quality of LDMTs, primarily from review articles. It does not involve primary research on LDMT quality, and it is limited by the scope and timeliness of the sources used. The authors generally have provided fair and complete reports of the evidence and statements in the source materials. However, primary sources and more current sources may provide more complete evidence of analytical and clinical validity and clinical usefulness, especially when considering the evidence supporting individual tests mentioned in the report. We understand that sponsors of individual tests as well as organizations, such as the American Clinical Laboratory Association ("ACLA"), have submitted comments presenting the evidence supporting the validity and usefulness of specific tests. Although we do not reprise that evidence here, we encourage the authors of the Draft TA to consider carefully such comments and the evidence referenced therein.	As we all know, there is a overwhelmingly large volume of literature that has been generated for over a thousand molecular tests. Obviously, the limited time and resources for this project does not allow us to pursue the thousands of original studies for these many molecular tests. Given that the main goal of this Horizon Scan report is to collect information to reflect the overall landscape of the LDMT area, we believe that the methodology that we used for this project is appropriate.
Joseph Eyer	Coalition for 21st Century Medicine	2. FDA Draft IVDMIA Guidance. It is important to understand that the FDA's Guidance for Industry, Clinical Laboratories and FDA Staff, In Vitro Diagnostic Multivariate Index Assays (July 2007), is a draft guidance document that has not been finalized by the agency. Several times the Draft TA refers to the draft guidance as final or as a "rule" (see e.g., Draft TA p. 42 referring to the "FDA Guidance" and "proposed rules"). Moreover, even when finalized, guidance documents represent current agency thinking on a particular topic, but are not legally binding in the same manner as a statute or regulation. Consistent with the principles outlined above, the Coalition maintains that FDA oversight of advanced diagnostics must carefully balance patient safety with continued innovation and patient access. We agree that there is a role for FDA in strengthening oversight of LDMTs, but we also believe, as the Draft TA discusses in detail, that current regulations under the Clinical Laboratory Improvement Amendments ("CLIA") are effective in requiring laboratories to follow rigorous quality control standards designed to ensure the precision, accuracy, analytical validity and other performance characteristics of LDMTs. (42. C.F.R.: 493.1253(b)).	Based on the comment, we revised the section about the FDA's draft IVDMIA guidance.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Joseph Eyer	Coalition for 21st Century Medicine	3. Clinical Validity. Chapter 4 of the Draft TA notes that the authors "did not identify any requirements in the CLIA regulations (including relevant guidance published by CMS) for laboratories to submit data to support claims regarding clinical performance." (Draft TA p. 38). The Coalition understands that some believe that CLIA regulations address only analytical performance (does the test measure what it is purported to measure) and do not cover clinical validity (accuracy at predicting a clinical condition or predisposition) or clinical utility (value of the information to patient management). This is of significant concern to some who argue that failure to ensure clinical validity or utility is a short falling of CLIA, particularly with regard to complex LDMTs. The Coalition does not believe, however, that this is an accurate reading of the CLIA regulations. As the Draft TA correctly identifies, CLIA regulations require that laboratories validate clinical tests for their intended uses before patient use.* In the context of LDMTs, if the result reported by the laboratory is the product of a computational algorithm, then CLIA would require that the laboratory establish performance characteristics for that result. If the result is a predictive score, then CLIA would require clinical validation of such score.	We revised the statements that had caused the reviewer's concern. See our previous response on this matter.
Joseph Eyer	Coalition for 21st Century Medicine	Beyond the requirement for establishing performance specifications "including clinical validation when inherent in the reportable result" other provisions under CLIA also pertain to the clinical validity and clinical utility of laboratory testing. CLIA regulations require that the laboratory director "ensure that reports of test results include pertinent information required for interpretation" and that "consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions." (42 C.F.R.: 493.1407(e)(8), (9)). Laboratories are also required to have a clinical consultant who, among other things, must be available to assist the laboratory's clients in "ensuring that appropriate tests are ordered to meet the clinical expectations." (42 C.F.R.: 493.1419(b)). These regulations show that a comprehensive framework exists to assure that clinical testing is relevant to patient management.	Chapter 4 was revised based on the comment. The regulatory requirements mentioned in this comment were incorporated to the revised report. Also see our previous responses on this matter.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Joseph Eyer	Coalition for 21st Century Medicine	4. Coverage & Reimbursement. We understand that the Coverage and Analysis Group at the Centers for Medicare & Medicaid Services ("CMS") requested this Draft TA from AHRQ as a "horizon scan to summarize the available scientific evidence on the quality of laboratory-developed molecular tests." (Draft TA p. 1). Presumably, the Draft TA will be used by CMS to inform coverage and reimbursement decisions for LDMTs, an area of critical concern to the Coalition. As we have repeatedly emphasized in this document, advanced diagnostic tests, including LDMTs, are the cornerstone of personalized medicine. With the information that these tests provide, physicians are better able to assess whether an individual patient is or is not likely to benefit from "established" population-wide patterns of treating his or her disease or condition. Yet, patient access to these vital technologies is hindered because of complex and outmoded access and payment policies. The Coalition believes that the current reimbursement system does not recognize the value of diagnostics. Coding, coverage and payment do not encourage innovation, and savings which accrue from use of diagnostics are not credited. The Coalition looks forward to working with CMS to rectify these concerns.	This comment was directed to CMS and is beyond what the authors of the report can address.
Andrea Bennett	American Society for Clinical Pathology	ASCP agrees that evaluation of laboratory developed molecular tests, as with any other diagnostic test, should include the test's analytic and clinical validity. ASCP would like to note that the assessment report failed to include reference to CLIA's role in ensuring clinical validity, addressed in the June 2009 MMWR. In this report, CLIA charges laboratory directors and technical supervisors with the responsibility for ensuring that test methods are both appropriate for the intended clinical application and provide quality results.	The reference mentioned was published after we had submitted the draft report to AHRQ. We have added the reference to the revised report. See our previous comment about the MMWR report.
Andrea Bennett	American Society for Clinical Pathology	With regard to clinical utility, ASCP cautions that it 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. ASCP is has been concerned that requiring proof of clinical utility as a pre-requisite for marketing of these assays might impede or even prevent patient access to them. The nature of these molecular assays allow for nimble clinical intervention utilizing the latest published research. A lengthy approval process that requires evidence of clinical utility might hinder the development of these assays, preventing American researchers from implementing translational findings into clinical practice. Lengthy approvals may also prompt smaller laboratories to abandon this area of testing and large corporations to outsource the clinical implementation of these progressive diagnostic assays overseas, precluding Americans access to progressive therapeutic	This comment was directed to regulators and policy makers of LDMTs and is beyond what the authors of the report can address.
M J Finley Austin	Roche	First, we note that the report does not emphasize the fact that there is no mechanism to verify whether the practices described in the report are being consistently applied by labs. We suggest the summary section acknowledge this limitation.	We are not clear about what "practices" this reviewer referred to. Therefore, no action was taken based on this comment.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
M J Finley Austin	Roche	Second, for purposes of this report, AHRQ adopted the definition of molecular genetic tests recommended by the Genetic Work Group of the Clinical Laboratory Improvement Advisory Committee (CLIAC). However, not all molecular tests are molecular genetic tests and these terms should not be used interchangeably. We suggest the report clarify that the concerns addressed apply to all molecular LDTs, not just genetic tests, and that AHRQ review and revise the scope and definition of this report to ensure consistency and accuracy. We recommend AHRQ define the scope of "molecular" LDTs and then clarify which ones are out of scope based on the test's intended use or indication and applicability to the Medicare population. Such an approach would be more straightforward than grouping tests based on the technology used to detect the analyte or on the type of analyte measured.	As we responded previously, the definition of genetic molecular test that is currently used in the report appropriately meets the need of the requester of this Horizon Scan report. We used "molecular test" and "molecular genetic test" interchangeably to make the report less cumbersome. We believe that, since we had defined the terms explicitly at the beginning, the terms should not confuse the readers of the report.
M J Finley Austin	Roche	Roche Diagnostics is not a service lab and should not be included in the list beginning on page 7.	Roche Diagnostics is removed from the section based on the comment. Also refer to our previous response on the matter.
M J Finley Austin	Roche	Roche Diagnostics does not offer a lab developed test for yeast identification via PCR sequencing as identified in Table 6, Appendix B.	We have excluded Roche Diagnostics from Table 16.
M J Finley Austin	Roche	On page 8, only Class III devices are "approved" by the Food and Drug Administration (FDA). Class I and II devices are "cleared" by the agency. This language should also be changed in Table 6, p. 139.	The language has been changed based on the comment.
M J Finley Austin	Roche	On page 25, in the discussion of Systematic Reviews, the section cites seven systematic reviews of infectious disease tests evaluated for clinical validity; however, six of these were for TB and one for Lyme disease. We suggest other examples should be included, for example, there are numerous publications citing the clinical validity and clinical utility of tests for HBV, HCV, HIV, HPV, C. trachomatis, and N. gonorrhoeae.	Given the limited time allowed for the project, AHRQ and ECRI Institute agreed to focus on the evidence from systematic reviews (refer to the method section in the Chapter).
M J Finley Austin	Roche	Several Roche tests have been omitted from the tables of FDA approved molecular tests: o Page 139 - in the HCV qualitative detection section, the Roche Molecular Systems, Inc. COBAS®AmpliPrep/COBAS®AMPLICOR® o Page 139, under the HCV Test, version 2.0 and, in the HCV quantitation section, include the Roche Molecular Systems, Inc. COBAS® AmpliPrep/COBAS® TaqMan® HCV Test. o Page 140,in the HIV Quantitation section include the Roche Molecular Systems Inc. COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test. o Page 140, in the HBV/HCV/HIV for blood donations section include the COBAS® TaqScreen MPX Test for use on the cobas s 201 system.	We have updated the FDA tables to include the tests that have been FDA cleared as of December, 2009, which includes the tests that the reviewer mentions.
Barbara Goldsmith	American Association for Clinical Chemistry	In general, the ECRI Institute Evidence-based Practice Center document provides a comprehensive description of the scope and availability of LDMTs for the Medicare population and the current level of federal and private sector oversight in this area.	We thank the reviewer for the general evaluation of the report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Barbara Goldsmith	American Association for Clinical Chemistry	The TA frequently mentions that there isn't a separate specialty or subspecialty for genetic testing (GT) under CLIA'88 and that proficiency testing is not required for LDMTs. We suggest that ECRI include CMS's rationale for not creating a specific genetic testing category. For example, when CMS announced in 2007 that it would not create a GT specialty, it listed a number of reasons for its decision, including: 1)New GT standards for this fast evolving field would be outdated by the time they were implemented; 2) LDMTs are already subject to the most stringent standards under the CLIA'88 regulation; and 3) Requiring PT would not increase the number of laboratories conducting PT on LDMTs, since (as of 2007) there were only 16 proficiency tests available for more than 1,000 different genetic tests.	Revision has been made based on the comment. Some of the suggested content was added to the revised report as appropriate.
Barbara Goldsmith	American Association for Clinical Chemistry	Also, it should be noted that CMS is currently working on a proposed rule that would require PT for genetic tests, when available, and developing alternative mechanisms for assessing GT. AACC also suggests that AHRQ include information on the Centers for Disease Control and Prevention's (CDC's) ongoing education efforts in this area, such as its good laboratory practices document for molecular genetic testing that was published in the June 2009 MMWR. We believe this will give a more balanced accounting of government actions and activities in this area.	We have not included the proposed rules into this horizon scan report, since the detail of the rules is still under discussion. The MMWR 06/2009 report published by CMC was included in the revised report. Also see our previous comments regarding the MMWR report.
Barbara Goldsmith	American Association for Clinical Chemistry	The report also cites the New York State Clinical Laboratory Evaluation Program (CLEP) on a number of occasions, implying that it may serve as a potential model for federal oversight of LDMTs. In the Epilogue, ECRI adds that the New York State program may provide "valuable lessons in how the oversight of LDMT's might be accomplished and what resources would be necessary to do so on a national scale." We concur. AACC suggests that ECRI include a brief section within the TA that describes the New York program, its experiences, and initial results, particularly in regards to improving the quality of testing and its impact on test innovation. AACC also recommends that ECRI solicit and include feedback from the laboratories participating in the CLEP program.	As suggested, we added a section to briefly describe the New York CLEP program. We believe the peer-review and public commenting process for this Horizon Scan is part of the process to solicit and include feedback from the laboratories participating in the CLEP program.
Barbara Goldsmith	American Association for Clinical Chemistry	The TA also questions the quality of data used to demonstrate the analytic and clinical validity of LDMTs. We believe this characterization is a broad overstatement. Although we acknowledge there is a need for improving how clinical validity is established for some tests, we do not believe there is widespread problem in demonstrating the analytic validity of LDMTs.	We are unclear about which specific sections or paragraphs this reviewer was referring to. But note that we have made many revisions throughout the report, which may have resolved the concerns of this reviewer.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Barbara Goldsmith	American Association for Clinical Chemistry	We are also concerned that these assertions imply a lack of adequate oversight in this area. This is incorrect. All laboratories performing LDMTs must demonstrate the analytic validity of these tests and quite often the clinical validity as well. For example, 1) The CLIA'88 standards require laboratories performing LDMTs document the analytic validity of these tests and make that information available to inspectors. 2) The College of American Pathologists, one of the leading accrediting bodies in this area, requires laboratories in their Laboratory Accreditation Program to demonstrate the analytic validity of these tests as well as document how they are clinically validated. 3) The New York State program, which covers 75 percent of all LDMTs performed in the United States, requires laboratories to demonstrate that a test is clinically validated prior to being introduced.	We revised the report based on the comment. Sections discussing the potential role of CAP and NYS CLEP in ensuring LDMT quality were added.
Barbara Goldsmith	American Association for Clinical Chemistry	We recommend that ECRI gather more data from CMS, CAP and New York and reassess and revise its global characterization of the analytic and clinical validity of LDMTs. Further, we suggest that ECRI give greater acknowledgement within in the report to the ongoing efforts of public and private sector organizations to improve and document the quality of LDMTs . AACC will continue working with these entities to improve the quality of patient testing.	Revision has been made as the reviewer suggested. See our previous responses.
Not specified	College of American Pathologists	The College believes the report does not accurately represent the quality and regulation of laboratory developed tests and our commentary will discuss the reports glaring omission of the important role accreditation plays in ensuring quality of LDTs by requiring proficiency testing, analytical and clinical validation. Furthermore, 77 of the labs listed are CAP accredited and therefore must meet requirements that are more stringent than CLIA. CAP accredited laboratories exceed the quality standards established by CLIA including the assessment of clinical validity of molecular LDTs and participation in proficiency testing .	Revision has been made as the reviewer suggested. See our previous responses.
Not specified	College of American Pathologists	There are a number of inaccuracies and misconceptions in the introduction to the report that are of concern. The College is concerned with the report's inference that only CLIA-regulated tests lack review of their clinical utility, which is a mischaracterization; neither FDA nor CMS regulatory mechanisms were designed to assess clinical utility. The introduction also suggests that alternative assessments may be less effective than formal proficiency testing; there is no evidence to support this statement.	We disagree with the first half of the comment. In the Introduction section, we did not mention or imply that FDA assesses clinical utility. However, we have revised the statement regarding alternative assessments that had concerned the reviewer.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Not specified	College of American Pathologists	While reviewing the CLIA regulatory requirements for molecular LDT, the report fails to discuss the important role accreditation plays in laboratory oversight. CMS may a deem a laboratory to meet all applicable CLIA program requirements through accreditation by a private nonprofit accreditation program (that is, grant deemed status) or may exempt from CLIA program requirements all State licensed or approved laboratories in a State that has a State licensure program established by law, if the following conditions are met: the requirements of the accreditation organization or State licensure program are equal to, or more stringent than, the CLIA condition level requirement [42 CFR 493.551 (a)(1)]. As noted above, the LAP requirements are more stringent than CLIA in overseeing these laboratories.	In the draft report, we have described that a laboratory can choose to have a COC or COA to comply with the CLIA regulation. In the revised report, we added a section to further discuss the potential role of accreditation organizations including CAP in ensuring LDMT quality under the CLIA framework.
Not specified	College of American Pathologists	A report on the quality and regulation of molecular LDTS that fails to discuss the role of the CAP's program in assuring the quality of laboratories and the tests they offer, when a majority of the labs investigated are CAP accredited, will provide an inaccurate picture of the true quality of molecular LDTs.	See our previous comment. A section was added in the revised report to further discuss the potential role of accreditation organizations including CAP in ensuring LDMT quality under the CLIA framework.
Not specified	College of American Pathologists	The report asserts that "analytical and clinical validity of molecular tests are important prerequisites for assessing clinical utility. However, for most molecular tests, especially laboratory-developed tests, the analytical and clinical validity have not been clearly established." This statement is incorrect. Studies on LDTs may not be published however every lab is required to establish the analytic validity of the tests offered and every lab accredited by CAP is required to establish clinical validity of the molecular tests offered. A CAP accredited laboratory is required to have documentation of clinical validation available for inspectors.	The statement that caused the concern was removed. The paragraph was also revised to reflect our current view on the issue.
Not specified	College of American Pathologists	the College believes the report gives short shrift to the CLIA personnel (director, technical and clinical consultant) requirements and their role in ensuring laboratory quality, prominently ignoring the "clinical consultant" requirement that squarely addresses clinical validity. CLIA certified high complexity testing labs are required to provide clinical consultation to their clients as described in 42 CFR 493.1457: "The clinical consultant must--(a) Be available to provide consultation to the laboratory's clients; (b) Be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations; (c) Ensure that reports of test results include pertinent information required for specific patient interpretation; and (d) Ensure 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 ."	We added a section in Chapter 4 to discuss the CLIA regulations mentioned by the reviewer. See our previous response regarding this matter.

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Not specified	College of American Pathologists	the report evinces a fundamental misunderstanding of pathologists' clinical activities, which are largely professional in nature, and are not intended to generate publishable work. Clearly laboratories are required to establish the analytic performance characteristics of every test offered. The clinical consultant is clearly responsible for assuring that test results include pertinent information required for specific patient interpretation and for assuring that clients are assisted in test ordering to meet clinical expectations. Tests are commonly implemented based on published data from the literature, where analytic and clinical validity and to some extent clinical utility are found.	We disagree with the comment. In the report, we did not discuss pathologists' activities one way or the other. Per the role of clinical consultants in ensuring clinical relevance of the tests, see our previous response regarding the matter.
Not specified	College of American Pathologists	The College believes the quality of LDTs has been well documented by many years of continuous use. As previously mentioned CAP's Laboratory Accreditation Program ensures the quality of LDTs and modified FDA kits through the inspection process by the Molecular Pathology Checklist and related Checklists. To ensure laboratory performance, the College has a specialty inspectors list for molecular diagnostics, and defined criteria have been established. Inspectors are reviewed for qualifications in the four main areas of molecular testing, infectious disease, hematology/hematopathology, solid tumors, and heritable diseases, and selected on this basis. The College also believes that proficiency testing is a valuable means to monitor laboratory performance. Proficiency testing is an integral part of the CAP laboratory accreditation program which includes alternative assessment. The College disagrees with the report?s assertion that alternative assessments may be less effective than formal proficiency testing; there is no evidence to support this statement and further study is needed. The CAP establishes PT whenever there are a sufficient number of participants to justify it. In fact, the greatest obstacle to more widespread proficiency testing is the lack of control materials and the lack of economic feasibility of establishing PT for assays performed by small numbers of laboratories.	Per the comment on the potential role of CAP in ensuring laboratory performance, see our previous response regarding the matter. Per the comparison of PT program and alternative validation methods, also refer to our previous response on the matter.
Not specified	College of American Pathologists	There are a number of other inconsistencies in the report which we cannot fully document given the short turn around time for comments. For example, on the one hand the report appears to exclude heritable diseases from its scope, yet cites guidelines in Chapter 3 on clinical validation that are directed toward heritable disorders. It confuses the applicability of published validations for various types of molecular assays, attempting, for example, to generalize articles directed toward quantitative infectious disease testing or TB to the whole of molecular diagnostics. The anecdotal approach to this topic appears inappropriate as there is great variability in the targets, platforms, and uses of LDMTs. It would be more appropriate to consult/confer/partner with organizations such as the CAP to develop criteria, standards, and guidelines for clinical validity and utility.	Although test for heritable conditions is beyond the scope of the report, some of the references and guidelines for heritable condition testing (particularly those regarding molecular methods) may still be relevant to this report therefore are included into this report. Per the comment regarding the methodology used for the report, we still consider the methodology as appropriate, given the limited timeframe for the report.

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Not specified	College of American Pathologists	In Chapter 5, the report does not make a distinction between FDA regulations and guidance documents, nor does it distinguish between finalized documents and draft documents. The report does not make it clear that the draft FDA guidance on IVDMIA has not been finalized. The report also incorrectly referred to the IVDMIA draft guidance as a proposed rule. Guidance documents are not binding on the agency or the public (see www.fda.gov).	For Chapter 5, we were explicitly asked by the commissioner of the report to address the question "What FDA guidance has been issued pertaining to oversight of laboratory-developed molecular testing?" We believe we addressed the question exactly as requested. Per the comment on the FDA draft guidance on IVDMIA, see our previous response regarding this matter.
Not specified	College of American Pathologists	In Table 10, the standards covered by the CAP LAP Molecular Pathologist Checklist are not portrayed accurately. The checklist covers every area listed with the exception of Clinical Utility; the table should have an "X" under Testing Techniques, Testing Samples, Testing validation and verification, Proficiency testing, Sensitivity and Specificity, and results interpretation and reporting. The CAP website contains guidelines on reporting for Molecular Pathology.	Revision has been made as the reviewer suggested.
Not specified	College of American Pathologists	The report's assessment of guidelines and standards for laboratories conducting molecular testing is incomplete. For example, the report does not mention the College of American Pathologists (CAP) guidelines for Clinical Laboratory Reports in Molecular Pathology .	The relevant guidelines published by CAP have been included in Table 10
Richard Chapell	Merck & Co., Inc	We were surprised to observe that this report was released under the Evidence-based Practice Center logo and labeled a Technology Assessment Report. This report is not a formal systematic review and, as such, was not prepared with the expertise and systematic methodology for which the Evidence-based Practice Centers (EPCs) have become so well known. While we do not question the need for or the utility of horizon scans, to release them under the EPC logo or to claim that they are true technology assessments could diminish the reputation of the EPC program and the concept of technology assessment. We strongly suggest that the final report be issued without the EPC logo and labeled as something other than a Technology Assessment. We suggest "Horizon Scan" as an alternative designation.	This comment is beyond what the authors of the report could address. We would like to have AHRQ/CMS to evaluate the comment and determine the appropriate action to take.
Richard Chapell	Merck & Co., Inc	On page ii, the EPC discloses that one of the investigators has an affiliation related to the material, but fails to disclose that another investigator holds several patents on genes that are the target of laboratory-developed tests. The resulting financial interest should be acknowledged.	We appreciate the reviewer pointing out our oversight. In 1990 - 1992 while an undergraduate student at Massachusetts Institute of Technology (MIT), Dr. Wendy Bruening worked as a member of the team that discovered the Wilms' tumor suppressor gene (WT1). While she does receive royalties from MIT related to the patent filed by the university for the gene sequence, she has no control over uses of the gene sequence, and no conflict with the material in this report.
Richard Chapell	Merck & Co., Inc	Given the complexity of the material, steps should be taken to make the document more reader-friendly. A bulleted list of Key Points at the start of each chapter would increase accessibility. More diagrams would also be helpful. For example, flow charts depicting the process for assessing test validity or obtaining FDA approval would increase reader comprehension.	The authors of the report have made a great effort to make the report reader-friendly. Tables, charts, and bullet points that were mentioned in the comment are extensively used in the report.

Reviewer Name[2]	Reviewer Affiliation[3]	Reviewer Comments	Author Response
Richard Chapell	Merck & Co., Inc	CLIA regulations and guidances are complex legal documents, yet none of the investigators involved in preparing the report appear to have any legal training. This does not lend confidence in the accuracy of the discussions, particularly when reading sentences like "We did not identify any requirements in the CLIA regulations (including relevant guidance published by CMS) for laboratories to submit data to support claims regarding clinical performance (clinical validity or clinical utility)." Please insert a discussion of the qualifications of the investigators to offer their interpretations of matters of law. If AHRQ is not able to state that the opinions offered are legally sound, then please insert a disclaimer to that effect. A thorough legal review of the role of CMS and FDA on regulation of laboratory-developed tests would be a useful follow-up to the current document.	Per the statement the reviewer quoted from the report, the reviewer did not judge the statement as not accurate. So no action was deemed necessary to be taken by the authors. As of now, the authors of the report still consider that statement as accurate within the context of the paragraph. The draft report had been reviewed by experienced experts in the field including regulators from CLIA, FDA, and NYS, as well as by public reviewers who may have legal training. The authors of the report have taken serious steps to address every issue that had been raised by the reviewers or reviewers including the reviewer from Merck. We would appreciate it if Merck could explicitly express its evaluation of any statement that we made (e.g., whether it is accurate). Otherwise, no serious actions could be taken on the authors' side.
Richard Chapell	Merck & Co., Inc	In the discussion of CLIA regulations, please include a statement describing the changes made for the 2003 update. A key observation of the document that does not appear to be sufficiently stressed is that regulations have not developed apace with technology. Please consider adding a statement to that effect in the epilog to the document.	The information that was provided in the draft report is the reflection of the current status of the CLIA regulations, including the changes made since 2003. We don't deem it necessary to further describe the changes made for the 2003 update. Per the comment that CLIA "regulation have not developed apace with technology", we consider it as the reviewer's subjective evaluation. We do not a need to add that statement to the epilogue of the report.
Richard Chapell	Merck & Co., Inc	In addition, a section discussing gaps in the current regulations would be very informative. As the document points out, molecular tests are of limited use because there is no reference standard. However, such tests can determine patient therapy and are conducted in CLIA-certified labs. How will CMS continue to certify such labs in the absence of reference standards?	We have discussed the potentials gaps in the current regulations in various sections of the report, including Introduction, Epilogue, Chapters, 2, 3, 4, 6, and 7. We do not see the need to add another section to discuss these potential gaps.
Richard Chapell	Merck & Co., Inc	While limiting the document to the population of interest to CMS may be reasonable, given that CMS is funding the document, it remains a considerable limitation. Please consider adding "for patients over age 65" or "among the Medicare population" to the title of the document to acknowledge this.	The title was determined by AHRQ/CMS under the contract. The authors do not have the liberty to change the title. We leave that judgment AHRQ/CMS.
Richard Chapell	Merck & Co., Inc	We note that ECRI institute utilized interviews in addition to the standard literature search in preparing the document. As the topic does not lend itself to standard methodology, this innovation is well justified. However, the Methods section should include a full listing of interviewees as well as some explanation of why they were chosen. Ideally, a full transcript of each interview would be included in the appendix. Individuals who were approached but declined to be interviewed should also be listed. For example, the EPC interviewed Steve Gutman. While he is certainly a knowledgeable source, he is no longer at the FDA. The report should state whether his opinions reflect current thinking at the FDA.	We interviewed one CLIA staff member and one FDA staff member. Their names were identified in the Methods sections of Chapters 4 and 5, respectively. Dr. Steve Gutman was with FDA when he was interviewed. They were chosen for the interviews because they were key personal in the two regulatory agencies as well as technical experts on the subject. The main purpose of the interviews is to verify that the results of our search of the regulations and guidance documents were accurate, current, and thorough.