Project Name:	Quality, Regulation and Clinical Utility of Laboratory-developed Tests	
Project ID:	LABC0707	
Disposition of Comments		
Table 1: Invited Peer Reviewer Comments[1]		
Reviewer	**Reviewer Comments**	**Author Response**
Peer Reviewer 1	This Report is comprehensive and well done. I have tracked recommended corrections and rewordings from my perspective.	We appreciate the reviewer's comments and suggestions.
Peer Reviewer 1	Page 5: tracked edits in the third paragraph	We rewrote the paragraph based on this and other reviewers' comments. The tracked edits are no longer relevant.
Peer Reviewer 1	Page 12-13: tracked edits in the third paragraph	We accepted the tracked edit.
Peer Reviewer 1	Page 14: gene names/symbols are italicized and use correct nomenclature as found on genenames.org	We accepted the reviewer's suggestion and have made the changes throughout the file.
Peer Reviewer 1	Page 14-15: tracked edits	We accepted the tracked edits.
Peer Reviewer 1	Page 15: This section (Duration of Study) was omitted as it seems to confuse quality control with assay validation.	We concur with the reviewer and have deleted the section.
Peer Reviewer 1	Page 16: tracked edits	We did not accept the tracked edits in the section, "Analytical Specificity," because making the changes would render the sentence incorrect. We accepted other tracked edits the reviewer made on this page.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 1	Page 17: tracked edits	We did not accept the tracked edits in lines 9 and 10 because we cannot verify if other manufacturers offer the product the reviewer mentioned. We did not accept the tracked edits in line 22 because the reference was specifically about PCR. We did not accept the tracked edits in line 24 because the CAP Web site barely mentions this topic. We accepted other tracked edits on this page.
Peer Reviewer 1	Page 18-19: tracked edits	We accepted the tracked edits.
Peer Reviewer 1	Page 20: tracked edits	We did not accept the tracked edits in lines 9, 10, and 32 because making the changes would render the sentence incorrect. We accepted other tracked edits on this page.
Peer Reviewer 1	Page 23-24: tracked edits	We rewrote the relevant sections and, as a result, the tracked edits are no longer relevant.
Peer Reviewer 1	Page 25: tracked edits	We rewrote the relevant section, "Challenges in Assessing Clinical Utility of Molecular Tests." As a result, the tracked edit in the section is no longer relevant. We did not accept the tracked edits in lines 5 from the bottom of the page because making the changes would render the sentence incorrect. We accepted other tracked edits on this page.
Peer Reviewer 1	Page 26-29: tracked edits	We did not accept the tracked edits in the second paragraph on page 28. The paragraph cited the findings of an AHRQ evidence report. But the changes suggested by the reviewer are not among the findings of the report. We accepted or rejected other tracked edits (mostly stylistic changes) on the four pages as we thought appropriate.
Peer Reviewer 1	Page 29: LIPA is not a drug metabolism test; please clarify if "or resistance" should be added here.	Based on the comment, we have changed the title of the section to "Tests for Predicting Drug Reactions."
Peer Reviewer 1	Page 30-31: tracked edits	We did not remove the sentence on Page 31 as the reviewer suggested because we deem the sentence to be relevant to the discussion. We accepted other tracked edits on the two pages.
Peer Reviewer 1	Page 35: tracked edits	We accepted the tracked edits.
Peer Reviewer 1	Page 38: tracked edits	We accepted some suggested changes on the page. Since we rewrote some paragraphs based on this or other reviewers' comments, most tracked edits are no longer relevant.

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Peer Reviewer 1	Page 39: tracked edits	We did not add the paragraph as the reviewer suggested because the content of the paragraph does not fit in the section "Visibility of Test Claims (Labeling)." We accepted other tracked edits on this page.
Peer Reviewer 1	Page 40: tracked edits	Based on other reviewers' comments, we changed the title of the section to “Handling of Complaints,” which makes the sentence that this reviewer added no longer appropriate.
Peer Reviewer 1	Page 41: tracked edits	We accepted the tracked edits.
Peer Reviewer 1	Page 44: tracked edits	We did not move the sentence as the reviewer suggested because we deemed the sentence to fit better in the current paragraph.
Peer Reviewer 1	Page 46: please specify which experts	Revision has been made based on the reviewer comment.
Peer Reviewer 1	Page 46: tracked edits	We accepted the tracked edits.
Peer Reviewer 1	Page 47: tracked edits	We did not accept the paragraph that the reviewer added because the content of the paragraph does not fit in the section, "Control Materials." We did not either change the title of the section to add the paragraph as the reviewer suggested. We also rejected other tracked edits on this page either because making the changes would render the sentences incorrect or because those suggested changes were simply about writing style.
Peer Reviewer 1	Page 47: update Tables 5 & 6 with additional 36 articles listed in the PubMed file at http://www.ncbi.nlm.nih.gov.libproxy.lib.unc.edu/sites/myncbi/collections/public/141B8-V_XHRqAZYm7Chqnf25e/	We evaluated the 36 articles mentioned in this comment. These articles either have already been included in the report, or fail to meet the inclusion criteria for the report (see our comments on each of these articles on the separately attached document). As a result, we did not add these studies to the tables.
Peer Reviewer 1	Page 48: "update this number based on table 5 and 6 updates"	Please see prior comment. No change is necessary.
Peer Reviewer 1	Page 48: is this now QCMD? After updating this table, tally the total # of pubs in the last row.	Yes, EQUAL turned into QCMD in 2007/2008. We note this on Page 62 under the descriptions of programs in Europe. Based on the comment, we added additional footnotes to the tables.
Peer Reviewer 1	Page 48: tracked edits	We did not accept the tracked edits in the last line of the page because making the change would make the sentence incorrect. However, we accepted other tracked edits on the page.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 1	Page 49: Tracked edits and comments on the section, "To What Extent do Laboratories Exchange Samples Voluntarily for the Purpose of Proficiency Testing?	We rewrote the section. The comments and tracked edits are no longer relevant.
Peer Reviewer 1	Page 49: Other tracked edits	We did not accept the tracked edits in the first line of the page because making the change would render the sentence incorrect. We did not accept the tracked edits in Table 7 because the information that the reviewer suggested should be deleted is important to the readers of this report. We accepted other tracked edits on the page.
Peer Reviewer 1	Page 50: Tracked edits and comments on checking the facts regarding the MGL survey and the CAP website	Revisions have been made as we thought appropriate. We believe that the information about the 2005 survey was available on the CAP Web site at the time the original draft report was written. We were unable to locate this information in 2010.
Peer Reviewer 1	Page 51: tracked edits	We did not add the sentence as the reviewer suggested because that content is out of the scope of the report . We did not accept most other tracked edits on the page (except for a grammatical change that we accepted) because making those changes would render those sentences incorrect.
Peer Reviewer 1	Page 52: tracked edits	We accepted the tracked edits in the first paragraph. We did not accepted the tracked edits in the last paragraph because the added sentence only reflects the speculation of the reviewer.
Peer Reviewer 1	Page 53: The comment on EQUAL and QCMD	We revised the note for Table 8. The relevant section reads now as follows: "EQUAL-European Union Quality Control Concerted Action (now referred to as the Quality Control for Molecular Diagnostics, or QCMD)."
Peer Reviewer 1	Page 56: tracked edits	We did not accept the tracked edits on the page because making the change would render the sentence incorrect.
Peer Reviewer 1	Page 59: add the CDC/MMWR report from June 2009, CAP Reporting Recommendation (Gulley ML, APLM 2007), the CAP Validation Recommendation (Jennings L, APLMN 2009), AMP recommendation for in house development... (Am J Clin Pathol 11:449, 1999)	We added three of the four references the reviewer suggested to Table 10. We searched PubMed and the Website of Am J Clin Pathol for the fourth reference using the exact information the reviewer provided (i.e., “AMP recommendation for in house development... [Am J Clin Pathol 11:449, 1999]”), but did not identify the reference. As a result, we were unable to add this reference.
Peer Reviewer 1	Page 65: tracked edits	We accepted most of the tracked edits on the page except for the new title the reviewer suggested for a reference. We checked the reference and confirmed that the title we used is accurate.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 1	Page 69: reference 163 is a clsi document so perhaps this is a typo?	The typo has been corrected. The CLSI document is now listed separately in a row in Table 10.
Peer Reviewer 1	Page 70: tracked edits	We rewrote the first paragraph. We did not accept the tracked edits in the second paragraph because the original wording better captures the essence of the SACGHS report.
Peer Reviewer 1	Page 71: many laboratorians consider the CAP to be the single most effective organization for setting and enforcing standards supporting quality molecular test services	We have revised the text based on this comment. We have also added a section to Chapter 4 to discuss the role of CAP and other accreditation organizations under the CLIA framework.
Peer Reviewer 1	Page 71: tracked edits	We rewrote the first paragraph (see the previous response) and the third paragraph based on the comments from this and other reviewers. The tracked edits are no longer relevant. We accepted other tracked edits on the page.
Peer Reviewer 1	Page 72: tracked edits	We did not accept the opinion-based changes that the reviewer made on this page since the reviewer did not provide any supporting references.
Peer Reviewer 1	Page 96: consider estimating the number of tests on GeneTests and, even though not included on this table, refine the number in the text from 1442 to an even more realistic estimate of the total number of molecular tests	Table 11 is to provide molecular test information available from the AMP test directory. The information from GeneTests is not applicable to the table. In addition, there is no reliable way to judge whether one estimate is more “realistic” than another.
Peer Reviewer 1	Page 97: since the info in the AMP test directory is copyrighted, should you mention here that info in Table 12 may not be shared without permission of AMP?	The information provided in Table 12 was collected by the ECRI Institute project team from multiple sources including the AMP Web site (refer to the methods section of Chapter 1). AMP did not raise any copyright issues in its written comments on the draft report.
Peer Reviewer 1	Page 193: Tracked edits	We did not accept the tracked edits because we checked the reference and confirmed that the title we used is accurate.
Peer Reviewer 2	Thank you for the opportunity to review this document. The technology assessment Quality, Regulation, and Clinical Utility of Laboratory-developed Tests is well written and well organized. It provides a helpful summary of the strengths and weaknesses of regulations for molecular testing.	We appreciate the reviewer's comment.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 2	Page 2, 3rd paragraph in the section “Overview of molecular testing technology,” 3rd sentence: use official gene symbols (as assigned by the HUGO Gene Nomenclature Committee, http://www.genenames.org/). The official gene symbol for HER2 is ERBB2. The sentence could be revised as follows: For example, molecular tests to detect the ERBB2 gene (also known as HER2) have gained acceptance…	Revision has been made as the reviewer suggested.
Peer Reviewer 2	Page 12, 2nd line from bottom of page: remove the hyphen from “clinically-oriented.”	The typo has been corrected.
Peer Reviewer 2	Page 13, 2nd paragraph in the section “Accuracy,” last sentence in this paragraph: is “AMCG” supposed to be “ACMG”?	The typo has been corrected.
Peer Reviewer 2	Page 13, last paragraph on the page: change “their” to “its,” i.e., One laboratory published the results of its attempt to validate their its in-house PCR assay by following this approach.	Revision has been made as the reviewer suggested.
Peer Reviewer 2	p. 14, 1st sentence, consider the following edits: The laboratory compared the results of its HER2/neu assay to four …	Revision has been made as the reviewer suggested.
Peer Reviewer 2	Page 14, paragraph for the section “Types of samples tested,” last sentence: consider rephrasing the sentence as follows: In its 2008 report on the U.S. system of oversight of genetic testing, SACGHS recommended that …	Revision has been made as the reviewer suggested.
Peer Reviewer 2	Page 16, section on “Analytic sensitivity”: the definition is correct for quantitative measurements but consider expanding the definition to also address qualitative measurements (e.g., detection of a particular genetic variant).	We revised the definition of "analytic sensitivity" on Page 16. The sentence now reads as follows: "For quantitative tests, analytic sensitivity, also referred to as the lower limit of detection, is defined as the smallest quantity of a substance that can be reliably detected or quantified." For qualitative tests, we use the term "analytic accuracy" (which is also defined in the chapter) to measure how well the tests can detect the analytes.
Peer Reviewer 2	Page 49, 1st paragraph in the section “What organizations or programs are implementing proficiency testing programs…”, end of the paragraph: in addition to referring to chapter 5 of the TA, perhaps also cite CLIA regulation 42 CFR 493.1236(c).	Revision has been made as the reviewer suggested.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 2	Page 69, 4th paragraph, insert a “c” in “Barak” (i.e., Barack).	The typo has been corrected.
Peer Reviewer 3	The entire report would significantly benefit from an in depth and critical review and rewrite. The report reflects a lack of understanding of established clinical laboratory regulations and practices about molecular testing. There are conclusions and statements through out the document that do not reflect the current legislation or practices. These statements create serious concerns about the credibility of this report.	The comment is too general for us to take any specific actions.
Peer Reviewer 3	The authors should consult with professional organization, practicing laboratory directors who are familiar with this type of testing as they did with FDA personnel.	In preparing the draft report, we consulted multiple internal or external experts who were associated with professional organizations or had laboratory management experiences. These experts' opinions had been incorporated into the draft report.
Peer Reviewer 3	The title does not match the statement of work. The statement of the work and the overall report focuses on MOLECULAR laboratory-developed tests (LDTs) and not overall LDTs. I recommend that the title of the report reflect this distinction.	We agree with the reviewer and have changed the title of the report.
Peer Reviewer 3	There is a need to elaborate about the significant benefits of LDTs in the diagnosis and management of this patient population. There is no mentioned in the document as to how this LDT are originated and why they are still being used.	We disagree with the reviewer on the comment. We believe that the overview of laboratory-developed molecular tests (LDMTs) that we provide is concise, but adequate for readers to comprehend the potential benefits of LDMTs.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 3	Page 4 The reports attempts to provide a list and review of all LMDTs available for the Medicare population but the process taken to catalogue these test is not valid as the AMP test directory is only offered to AMP members and was not develop for this purpose. There is no sufficient description in the directory to determine the type of test and how many different test are even offer by the same laboratory.	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).
Peer Reviewer 3	Page 5 statement about CLIA specialty needs to be further elaborated to reflect why CMS decided to move forward with the creation of the Genetic subspecialty under CLIA. The statement regarding proficiency testing is inaccurate. Even thought there are a number of different specialties under CLIA, PT testing is only required for the 83 regulated analytes. For the rest of the testing, laboratory are required to performed alternative assessment. The alternative assessment is not only for the validation phase but is performed in an ongoing basis.	The paragraph has been revised based on this and other comments.
Peer Reviewer 3	Chapter 1: Methods: Unfortunately the reports has heavily rely on peer-reviewed literature to identify these tests but this is not an appropriate approach as many laboratories do not published this type of work.	We disagree with the reviewer on the comment. As we described in the Methods section of Chapter 1, we searched multiple sources to identify relevant tests, including peer-reviewed literature, the AMP test directory, and the Web sites of GENDIA, Gentests and multiple commercial laboratories.
Peer Reviewer 3	The report also rely on the AMP test directory and as already mentioned this directory is only available to AMP members and has not been develop for this goal.	Refer to our previous response on this matter.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 3	The report lists a number of laboratories that offer testing that reflect the scope of the statement of work but they have listed a very limited number of laboratories and have even included an IVD manufacturer (Roche Diagnostics is not a CLIA laboratory, do you mean LabCorp?).	As we previously responded, there is no practical way to catalogue all LDMTs that are currently available for clinical use (which was not the original goal of the report). We believe that the tests provided by the 95 laboratories that have been cataloged in this report are an appropriate representation of the field. However, we agree with the reviewer that Roche is not a CLIA laboratory and have removed Roche's tests from the LDMT list.
Peer Reviewer 3	Page 5 – The report discusses that clinical validity and clinical utility of any given assay are not assessed by CLIA. A review of the CDC MMWR on Good laboratory practices for molecular genetic testing will further elaborate on the current practices with regards to : a. Documentation regarding clinical validity (including, as applicable, clinical sensitivity, clinical specificity, positive predictive value and negative predictive value) of the genetic tests the laboratory performs from available information sources, such as literature references and professional practice guidelines. b. Establish clinical sensitivity, clinical specificity, and predictive values based on internal study results, if information regarding clinical validity is not available from published references.	The CDC MMWR report mentioned by the reviewer was published after we had submitted the draft report. We agree with the reviewer that the CDC report is an important reference for this horizon scan report and have added it to the revised report. The findings and opinions of the CDC report have been incorporated in the revised report as appropriate.
Peer Reviewer 3	Page 16 – Analytical sensitivity: The report only discusses limit of detection and failed to acknowledge that this actually refers to two different measurements such as the ability of a test to detect a mutation or disease when that mutation/disease is present and also used to refer to the lower limit of detection for the analyte of interest.	Revision has been made based on the comment.
Peer Reviewer 3	Page 20 – CYP2C9 is not in the Roche CYP450 Amplichip kit.	What we meant is gene CYP2C19. The typo has been corrected.

Reviewer	Reviewer Comments	Author Response
Peer Reviewer 3	Page 25 the reports reads: “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 extremely concerning as there is no data to substantiate it. Although for clinical utility rigorous data is often incomplete, this overstates to reflect that MLDT are not validated.	The sentence that caused the concern has been removed. The whole paragraph has also been revised to reflect our current view on the issue.
Peer Reviewer 3	Page 26 – It is not clear what is being discussed here, analytical or clinical sensitivity and specificity.	Clinical sensitivity and specificity (i.e., diagnostic accuracy) are being discussed here.
Peer Reviewer 3	Page 38 – Proficiency testing – see comment above	See our previous response.
Peer Reviewer 3	Page 38 – Clinical validity – see comment above.	See our previous response.
Peer Reviewer 3	A critical review and reference to the CDC MMWR “Best practices for molecular genetic testing” is highly recommended	See our previous response on the CDC report.