Project Name: Update on Genetic Tests Currently Available for Clinical Use in Common Cancers
Project ID: GEND0511

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	The goal of this report is to provide a comprehensive listing of available genetic tests for adult cancers. Given the virtual explosion in the availability of genetic and genomic tests together with the fact that one of the areas of largest growth is the developmental of genetic and genomic tests for cancer, it is surprising that just 44 new tests were identified in the two years since the previous version of the report. Indeed, upon review, it became clear that a number of tests had not been identified with the search strategies used. This is perhaps understandable given that no comprehensive central repository for genetic and genomic tests for cancer currently exists. However, the authors are encouraged to refine their search strategies and include a more comprehensive list of commercial diagnostic laboratories in their searches in order to maximize identification of new tests. Further suggestions are provided under "Methods".	Thank you. We have added additionally suggested genetic tests. While we strive to provide a comprehensive list of genetic tests, our methodology is based on grey literature searching, which currently is a limitation to achieve this goal. Therefore, we rely heavily on the input of experts' and manufacturers' input during peer and public review process.
2	General	I have followed the Technology Assessment Reports on genetic tests for common cancer and non-cancer diseases. These reports have provided useful information on horizon scanning and follow-up on implementation of emerging genetic/genomic tests with availability in the US. This is an extremely useful process, and has demonstrated value to review groups (e.g., CMS, EGAPP, BCBSA TEC, AHRQ) in selecting topics, as well as to payers/health care organizations looking to the future. As the Genetic Testing Registry develops, it may be useful to consider how these two processes can complement each other in terms of the	Thank you.

		information collected and presented.	
3	General	The report summarizes a great deal of relevant information. It would be more user-friendly as an HTML document with live hyperlinks, rather than PDF. Because cancer genetic testing is such a rapidly evolving field, it might be preferable to update this report yearly. Although the report cites our previous work on the GAPP Finder (ref 4), it does not mention that this website continues to be updated regularly or provide the URL (http://www.hugenavigator.net/GAPPKB/topicFinder.do). Because the GAPP Finder focuses on emerging genetic tests, it provides complementary information to this report and to the NIH Genetic Test Registry (GTR).	We have added this information to the discussion.
1	Executive Summary	No comments	None
2	Executive Summary	Clear and succinct summary.	Thank you.
3	Executive Summary	The Executive Summary is too long—hardly a summary, it repeats much of the content of the report.	We have minimized the repetition.
1	Introduction/Background:	No comments	None
2	Introduction/Background:	Provides clear rationale, discussion of somatic mutations in cancer, information on commissioning, as well as the information to be gathered and how it will be used. While I feel this is probably adequate for this Technology Assessment, it may be useful to new readers to say something about issues of concern regarding rapidly emerging genomic tests (e.g., adequate clinical validation, sufficient data on impact on clinical outcomes), even in some cases those that have been FDA approved. This may emphasize the importance of awareness of these tests and that they warrant consideration for scrutiny and systematic reviews. I don't feel strongly about this, but it might further support the need for these TAs to continue.	We have added this information to our discussion section.
1	Methods	Exclusion criteria: Were direct-to-consumer genetic tests for cancer susceptibility excluded? This is implied but not specifically stated.	Yes, direct-to-consumer genetic tests are excluded. We have stated this in the eligibility criteria.

1	Methods	Clinical applications of genetic tests: The definition of a predictive genetic test does not seem to be consistent with the accepted understanding of a predictive genetic test. According to GeneTests, a predictive genetic test is testing offered to asymptomatic individuals with a family history of a genetic disorder and a potential risk of eventually developing the disorder. The items listed here would seem to fit better under Prognostic.	Thank you for pointing this error. We have edited this information throughout the document.
1	Methods	The stated search strategy is unclear. Were each of the terms searched separately or were all terms combined in a single search? Was "FDA + cleared genetic test" a separate search or were these terms combined with the other search terms in a single search? If it was combined, were searches for non-FDA cleared tests also conducted?	Yes, we also searched for genetic tests that were not cleared by FDA. We have clarified this in the methods section.
1	Methods	How was the list of commercial diagnostic laboratories compiled? There appear to be some notable exclusions (e.g. Mayo Medical Laboratories, Baylor College of Medicine Medical Genetics Laboratories, GeneDx, Emory Molecular Genetics Laboratory, PreventionGenetics, Ambry Genetics, among others).	We searched many diagnostic laboratories other than those listed in the table. We have clarified this information in the table and text. We have reviewed some of the labs that you have suggested and added tests that are already not in our database (such as PreventionGenetics and Ambry genetics).
2	Methods	Inclusion/exclusion criteria and categories of testing applications are clear. They clearly describe the ways in which they seek out information and the limitations that are inherent to this type of horizon scanning. They also seem to be adding and documenting new approaches as this process moves forward, and continually updating the database established. The one-page summaries are succinct and contain useful information. The exploratory search criteria and number of hits are particularly helpful to those who are considering a systematic review and to those who just want to learn more about the test or biomarker.	Thank you
3	Methods	The Methods are adequately explained.	Thank you.
1	Results	There are a number of tests on the market that were not identified in the report. These include, but are not limited to:	Thank you, we have added eligible tests from this list of genetic tests to our one-page summary. The first 2 tests did not have sufficient information to create a one-page summary.

		o OncoVue (InterGenetics, Inc.) o CancerTYPE ID (bioTheranostics, Inc.) o ResponseDX: Colon (Response Genetics, Inc.) o MelanoSITE (NoeGenomics Laboratories) o Myeloma Prognostic Risk Signature (MyPRS Plus) (Signal Genetics LLC) o BreastNext (Ambry Genetics Corp.) o CancerNext (Ambry Genetics Corp.) o ColoNext (Ambry Genetics Corp.) o OvaNext (Ambry Genetics Corp.) o Panexia (Myriad Genetics, Inc.) o PreOvar KRAS-Variant Test (Mira Dx Inc.) o VeriStrat (Biodesix Inc.) o Oncotype DX DCIS (Genomic Health, Inc) o Afirma Thyroid FNA Analysis Test (Veracyte, Inc.) o miRInform Thyroid (Asuragen, Inc.)	We excluded Veristrat, Afirma Thyroid, and miRInform Thyroid as they did not meet our eligibility criteria for genetic tests in cancer condition.
2	Results	It is useful to provide tables not only for the newly identified tests, but also the growing database (and those pulled off the market). Unfortunate that Progensa PCA3 just missed your deadline. A thought for moving forward that may be beyond the scope. As you review the web sites containing information on the tests, it might be useful to add a line to the one-pager if the web site provides any information or specifies reference(s) on test performance. I find that rarely occurs, but, optimistically, pointing it out may be a motivator. Also, an optional thought.	Progensa PCA3 was already included in the 2011 report. As we expected, some Web sites do provide references, although not necessarily on test performance.
3	Results	The follow-up on tests that were “emerging” in 2006 (only about 1/5 made it to the clinic) is very informative.	Thank you.
1	Discussion/Conclusion	The limitations of the search strategies used are duly noted. However, it would be useful to include suggestions or ideas for improving strategies to optimize test identification.	Yes, we have added.

3	Discussion/Conclusion	This section repeats material in previous section and does not suggest any ways to improve surveillance for genetic tests. The suggestion to consult the NIH GTR in the future implies that the AHRQ report will no longer be published. Is this true? The NIH GTR presently includes very limited information on cancer genetic tests other than those used in diagnosis of familial cancer syndromes. It would be good for AHRQ / EPC to share its know-how with the NIH GTR.	The funding for this report has ended, and we are not aware of any further continuation of these reports.
1	Tables	No comments	None
2	Tables	Concise and useful.	Thank you
3	Tables	Tables 1 and 2 are very useful. It would be good to hyperlink from each test name in Table 2 to its relevant page in the report.	We have added hyperlink to each test name in table 2 linking to the one page description in the appendix, when available.
1	Figures	No comments	None
1	Appendices	The one-page information sheets are improved over previous iterations. Inclusion of key abstracts for each test would be beneficial as would cost information (if this is available) and CPT codes.	Thank you, these are deemed beyond the scope of this project.
2	Appendices	One page summaries are logically formatted and informative.	Thank you
3	Appendices	These are the data that users will consult. The contents are good but the layout does not enhance usability. There should be space between sections, hyperlinks to websites, and consistent use of fonts. The intermediate pages (“Breast,” “Colon,” etc) are not useful for navigating the appendices. Table 2 could serve as a better table of contents if hyperlinks to each page were provided. I did not try out the proposed Medline searches and am not sure how to evaluate them. Some are much more involved than others, although this is not explained in the Methods.	We have added a hyperlink to each test name in table 2 linking to the one page description in the appendix, when available. We have described search terms in the Methods. The PubMed generates additional search details that are often variable.
1	References	The literature cites appears to be very limited given the interest in this area of genetic testing. Where websites are cited, the date accessed should be included in the citation.	We confirm that we were able to access all Web sites at the time of the draft revision and the date is provided in the methods section.

2	References	No additional thoughts.	None
3	References	The References are very limited and do not provide a guide to further reading for those interested in keeping abreast of cancer genetic tests. At minimum, a reference should be included (when available) for each of the genetic test databases used in searching, such as PharmGKB.	We have added a reference for PharmGKB. Other Web site searches have their links listed in Table 1

[1] Peer reviewers are not listed in alphabetical order.

[2] If listed, page number, line number, or section refers to the draft report.

[3] If listed, page number, line number, or section refers to the final report.

Project Name: Update on Genetic Tests Currently Available for Clinical Use in Common Cancers
Project ID: GEND0511

Table 2: Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Mary Steele Williams	Association for Molecular Pathology	General	The Association for Molecular Pathology (AMP) appreciates the opportunity to comment on the recent AHRQ Draft Report, "Update on Genetic Tests Currently Available for Clinical Use in Common Cancers." In reviewing this update in light of your 2006 and 2011 reports, AMP has identified methodologic flaws in the data gathering process that have led to gaps in the report's findings. These concerns would likely have been obviated by including pathologists with subspecialty expertise in molecular pathology, i.e., the medical practitioners who are largely responsible for performing and interpreting molecular tests in solid and hematopoietic tumors, as well as geneticists with subspecialty interests in hereditary cancer syndromes, in drafting and reviewing the report. Molecular pathologists and cancer geneticists primarily work at academic medical centers and cancer centers; AMP recommends that they and their laboratory test menus should be included as informational resources in this TA. AMP will be happy to provide a list of such experts to AHRQ. In addition, a few examples of cancer center and academic medical center molecular pathology laboratories include those of MD Anderson, the test menu of which is readily available on the internet, Memorial Sloan Kettering, and the University of Pittsburgh Division of Molecular Genomic Pathology. However, it should be understood that molecular pathology procedures for cancer are likely performed by well over a hundred academic medical centers.	Thank you. We have reviewed suggested Web sites. We have included tests that have not been previously included in reports. We find peer and public review particularly helpful in identifying new/emerging tests. The purpose of this report is to identify emerging genetic tests that are currently being rapidly adopted into clinical use. The report is solely based on grey literature sources. To the best of our knowledge there are no available methodologies to follow during grey literature searching of genetic testing. This is an area for important future research. Once tests are identified, we index information as reported

				on the Web sites without additional interpretation of findings. However, when decisions are made to identify topics for a full systematic review, we do include clinical experts including pathologist during topic development. We did not find a listing of emerging genetic tests of cancers at the major Academic laboratory Web sites. Therefore, we relied heavily on the commercial laboratories Web sites and Web sites of suppliers of genetic tests.
Mary Steele Williams	Association for Molecular Pathology	General	While providing a summary of the commercial laboratories, the report fails to capture and describe the numerous tests validated and performed in academic and hospital based labs throughout the US. It is unclear why the report's authors chose to only focus on larger commercial labs and not the molecular pathology labs providing a significant portion of these clinical tests. Further, AHRQ's contracted Evidence-based Practice Center (EPC) has produced a scattered, unorganized list of tests comprised of antigen, protein, biochemical, flow cytometry, in situ hybridization, and immunohistochemistry tests, along with some amplification-based molecular tests that use PCR, sequencing, or chip based variant detection. Their list also includes somatic disease, inherited predisposition to cancer - encompassing both Mendelian diseases and dubious tests for low odds ratio cancer predisposing single nucleotide polymorphisms obtained from GWAS studies, drug metabolizing enzymes or other general pharmacokinetic	The purpose of this report is to identify emerging genetic tests that are currently being rapidly adopted into clinical use. Since the 2006 report, we have organized tests based on cancer types. We agree that our list of genetic tests is collected based on a broad definition. While we strive to identify rapidly emerging tests that are in clinical use for common

			or pharmacodynamics characteristics, and tests for genetic variants that predict of response or lack of response to specifically targeted therapies. Hence, the list is disorganized, incomplete and at times, incorrect in its characterization and inclusion of specific tests for cancer.	cancers, we acknowledge that our methodology relying solely on internet searches can limit the yield. Furthermore, it is not the purpose of this report to determine if a genetic test performance is poor or to exclude tests based on poor test performance. We have made efforts to incorporate tests that are suggested by peer and public reviewers.
Mary Steele Williams	Association for Molecular Pathology	Method	In the stated inclusion criteria, the EPC incorporates tests that have "applications in the common solid tumors (breast, lung, colorectal, pancreas, etc.) as well as tests that are used in hematologic cancers (leukemia, lymphoma) and are already available in clinical practice." As discussed in the previous paragraph, the EPC has chosen to include an extremely broad range of test types, many of which would not typically be considered as molecular pathology or even "genetic" tests. As a result, in some cases there are but a few examples from test categories that themselves potentially represent significant numbers of tests.	The genetic test definition that we used for this report relied on previous reports. The definitions of genetic tests that are available are very heterogeneous (PMCID: PMC3312940)
Mary Steele Williams	Association for Molecular Pathology	Method	In order to achieve manageability, completeness, and coherence we recommend only including tests that interrogate or measure levels of DNA or RNA, unless the test represents a direct alternative to a DNA or RNA-based test. Further, if the horizon scan is to include tests used in both somatic and inherited diseases, as well as drug metabolizing alleles, the assays should be separated in tabular form in this manner. If organ specificity is also used, tests should still be broken down into these categories under the specific organ. There are many inherited conditions that predispose to cancer, most of which do not appear to have been included in the horizon scans to date. Inherited cancer syndromes often result in a multiplicity of cancer types.	Our previous reports, specifically the 2006 publication, identified all or most of the tests that were on inherited cancers. The recent tests are mostly on somatic cancers.

			Therefore, while organ specificity can be useful for the categorization of some inherited cancers, it is also very limiting approach to classifying tests for these entities.	
Mary Steele Williams	Association for Molecular Pathology	Method	Because somatic tests usually have very different implications and uses than tests for inherited cancer syndromes, these should also be separately identified. In addition, it should be noted that increasingly somatic tests are being applied in more than one cancer or organ type. AHRQ should also be aware that methodologic breakdown into amplification-based molecular diagnostics, in situ hybridization, and other categories, e.g. flow cytometry, if these are to be included. There are significant numbers of these types of assays, and the failure to understand the methodologic and clinical differences in and implications of these types of tests probably contributes to the scattered and very incomplete nature of the report. Finally, expression array testing, which represents a novel class of assays that are largely proprietary commercially provided tests, should be distinguished from more conventional tests that are performed by multiple laboratories because of the differences in their delivery models, their novelty, and their more limited use and/or the more limited evidence regarding their clinical performance.	The details of somatic versus inherited cancers as well as the commercial versus propriety are not extensively discussed in our reports. The purpose of this report is to list or update on the genetic tests that are rapidly getting to clinical use.
Mary Steele Williams	Association for Molecular Pathology	Method	The EPC's search methods should be expanded to include an advisor who is an expert in the relevant testing to greatly enhance the search design, interpretation, and the application of results. The search terms the EPC used appeared to be far too limiting. For example, somatic genetic tests are frequently referred to as molecular pathology or molecular oncology tests by practitioners in the field, and there many other search terms that could be used to capture tumor testing. The websites selected for review were extremely focused commercial laboratories, many of which have limited and/or unusual test menus. The failure to include cancer centers and academic medical centers not only contributed to the absence of many tests within the same categories as those that have been included, but conveyed to the investigators and therefore to AHRQ and your readers a false understanding of the actual delivery of these services.	We conduct detailed searches when a topic matures into a full systematic review and do involve a range of experts in evidence synthesis. After the current review period, we searched academic Web sites and have added more tests. We have also flagged tests that examine somatic mutations.
Mary Steele Williams	Association for Molecular Pathology		To improve the utility and accuracy of this report, AMP encourages the authors to include tests offered by laboratories in cancer centers and academic centers and further organize the tests based on type,	Most inherited cancers have associated conditions so genetic

			technology, tumor site, and whether or not the test is for a somatic or inherited mutation.	tests are usually applied at younger age groups. Therefore our eligibility criteria and applicability for older populations often limit the number tests for inherited mutations.
Mary Steele Williams	Association for Molecular Pathology		Lastly, the American Medical Association (AMA) CPT Editorial Panel has published new Molecular Pathology CPT codes that went into effect on January 1, 2013. These codes include placement of over 650 molecular pathology tests, including many for somatic tumor testing and syndromes that predispose to cancer as a primary feature. These CPT codes are an invaluable listing of amplification-based molecular tests, and can serve as an important resource within the EPC's gray literature.	The purpose of this report was to generate topics for conducting systematic reviews. Future research should aim at synchronizing horizon scan reports with CPT codes.
Anonymous 1		General	Will this agency require hospitals, thier vendors, and pharmaceutical companies to be transparent in thier pricing etc.?	AHRQ does not create or enforce policy.
Anonymous 2		General	Although they mention the difference between germline and somatic tests, they do a terrible job of differentiating between them. I would strongly recommend that they have separate tables for genetic tests being performed on the germline and genetic tests being performed on the tumor.	The details of somatic versus inherited cancers as well as the commercial versus propriety are not extensively discussed in these reports. Our previous reports, specifically the 2006 publication identified all or most of the tests that were on inherited cancers. The recent tests are mostly on somatic cancers.
Anonymous 2		General	They are completely missing emerging germline gene panels like "BreastNext," "ColoNext," "OvaNext" and "CancerNext" by Ambry (http://www.ambrygen.com/hereditary-cancer-panels) and others like them (the	Thank you, we have added these suggested tests

			University of Washington is beginning to role out the "BROCA" test and "ColoSeq" panels). This is just two "off-the-cuff" examples but points to shortcomings in their methodology.	
Helena Duncan	College of American Pathologists	General	The College of American Pathologists (CAP), the nation's largest association of board-certified pathologists, appreciates this opportunity to provide comments to the Agency for Healthcare Research and Quality (AHRQ) on the Update on Genetic Tests Currently Available for Clinical Use in Common Cancers technology assessment. The CAP, celebrating 50 years as the gold standard in laboratory accreditation, is a medical society serving more than 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The College advocates accountable, high-quality, and cost-effective patient care. CAP Laboratory Accreditation Program is responsible for accrediting more than 7,000 clinical laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and also serve as inspectors in the CMS-deemed CAP accreditation program. The CAP also provides laboratories with a wide variety of proficiency testing programs and has the responsibility to evaluate the accuracy of test performance and interpretation in more than 23,000 laboratories worldwide.	No response needed.
Helena Duncan	College of American Pathologists	General	Pathologists, as physicians specializing in the diagnosis of disease through laboratory methods, have a long track record of delivering high-quality diagnostic services to patients and other physicians. One of a pathologist?s responsibilities to patients is molecular evaluation of tumors. Each tumor has unique biological characteristics, behavior, and genome. Overlying this variability in tumor biology is the critical issue of tissue sampling, an area demanding the professional expertise of a pathologist. A diagnosis may be achieved by cytologic evaluation of cellular material, fine needle aspiration, fine needle biopsy, endoscopically obtained biopsy, excisional biopsy, or therapeutic resection, all methods which produce different, and often limiting, amounts of tumor tissue for characterization. It is the pathologist?s responsibility to evaluate any of these specimens appropriately using the best ancillary methods and tests available to	No response needed.

			secure a reliable diagnosis for each individual patient.	
Helena Duncan	College of American Pathologists	Method	The CAP believes that the report?s inclusion of acquired mutations in the definition of genetic testing is scientifically inaccurate. A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or metabolites to detect inheritable genotypes, mutations, or chromosomal changes. All genetic tests are fundamentally the same in that they all detect an inherited genotype, mutations, or chromosomal changes. However, tests differ in the results? impact on patients. (See Table 1). Table 1: Types of Genetic Tests Type of Genetic Testing Clinical Conditions Examples Carrier screening or Testing for asymptomatic individuals Healthy individual Cystic fibrosis (CF) BRCA 1 and BRCA 2, Long QT syndrome Detect inherited genotypes, mutations Individuals with current disease manifestations Factor V Leiden HLA typing/blood antigen genotyping for transplant/transfusion Pharmacogenomic testing Predictive of individual?s Immunological identity, metabolic capacity KRAS	Further research is needed to achieve consensus among various entities regarding definitions of genetic tests. The definitions of genetic tests that are available are very heterogeneous (PMCID: PMC3312940). Some of the tests mentioned are already included in our prior reports. We agree with you that all genetic tests can detect inherited mutations. Since the population of interest for our report is the Medicare-eligible population, these tests are often applied to detect somatic mutations. Individuals with inherited mutations often have other diseases or syndromes that such tests may be applied at an early age.
Helena Duncan	College of American Pathologists		The CAP believes that molecular tests for acquired mutations are not genetic tests. These tests evaluate acquired, rather than inherited, mutations. While these tests will typically target nucleic acid substrates (eg, DNA, RNA, chromosomes) and employ the basic terminology of genetic testing (eg, genotype, mutation, karyotype), these tests and analytes have absolutely no heritable consequences. Unlike a true	Further research is needed to achieve consensus among various entities regarding definitions of genetic tests. The definitions of

			genetic abnormality, they may not be constant through an individual?s lifetime nor be evident in every cell of in an individual. For example, specific laboratory testing of malignant tumor cells for the identification and classification of malignancies. The targets of these tests may be tumor-specific mutations (ie, somatic mutations), or alterations in gene expression patterns related to malignant processes, or both (eg, testing, BCR-ABL in chronic myelogenous (or myeloid) leukemia (CML), HER2/NEU FISH (fluorescence in situ hybridization), EGFR mutations in non-small cell lung cancer (NSCLC), mRNA testing for tumors of unknown origin (TUO), c-kit mutations in GISTs [gastrointestinal stromal tumors], CIMP in CRC).	genetic tests that are available are very heterogeneous (PMCID: PMC3312940). Some of the tests mentioned are already included in our prior reports.
Helena Duncan	College of American Pathologists		It is important to note that a number of genes occur in acquired and inheritable mutations depending on the clinical context. Consequently, tests to identify and characterize alterations in those genes in malignant tumor cells might also be used in the evaluations of those genetic syndromes. Some common examples are P53 gene, KRAS gene, BRAF gene, and MLH1 gene. (See Table 2). These genes may be inactivated by various mechanisms in tumor cells, both by mutation and by epigenetic silencing, but such alterations are tumor-specific and are not transmittable to the patient?s progeny (ie, they are characteristics of that specific tumor.) Table 2: Common Gene Examples Gene Malignancy Genetic Syndrome P53 Lung, colon, liver, et al Li-Fraumeni KRAS Colon, lung, pancreas Noonan Syndrome, Cardiofaciocutaneous Syndrome BRAF Colon, thyroid, melanoma Cardiofaciocutaneous Syndrome, Leopard Syndrome MLHI gene Colon, endometrium Lynch Syndrome	Thank you, some of the examples for potential inherited gene tests have been included in our prior reports. Most of the tests identified in our prior reports have listed genetic tests that are identified here.
Helena Duncan	College of American Pathologists		Test Nomenclature The CAP believes that standardized nomenclature should be used for testing rather than brand names. In 2012, the American Medical Association published current procedural terminology (CPT?), which	Thank you, we have added a table separating gene test results by inherited and acquired

			included molecular pathology procedural codes. These codes included terminology for laboratory testing involving analyses of nucleic acids to detect variants in genes that may be indicative of germline or somatic conditions. The nomenclature was developed based on specific genes that were described using Human Genome Organization (HUGO) approved gene name(s) as well as from the Human Genome Variation Society (HCVS). We believe that this terminology should be used. (See Appendix)	mutations.
Helena Duncan	College of American Pathologists		Since this report was developed in response to the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) for their internal discussions in the area of genetic tests for cancer conditions as well as for decisions on future topics for systemic reviews, the CAP offers two recommendations for use in future reports, which are to: ? Broaden the title of the report to reflect more accurately the listed tests; and ? Use test nomenclature included in the 2012 AMA current procedural terminology (CPT) manual.	Thank you, we have not made any changes to the nomenclature, since nomenclatures vary across different agencies. The main purpose of this report is to generate topics for future systematic reviews and is not meant for coverage decisions.
Helena Duncan	College of American Pathologists	General	The CAP recognizes the importance of obtaining clinical information for new clinical tests in this area for clinicians, patients, and payers; however, we believe that the quality of information provided in the AHRQ reports and systemic reviews should assist clinicians, patients, and payers to make informed decisions regarding these services. The CAP endeavors to provide AHRQ and patients the best and most efficient information on cancer treatment for patients. Please feel free to contact Helena Duncan, CAP Assistant Director, Economic and Regulatory Affairs at hduncan@cap.org if you have any questions on these comments.	The main purpose of this report is to generate topics for future systematic reviews and is not meant for coverage decisions. Once the topic is identified for conducting systematic review, there will be additional information on the available evidence regarding effectiveness of a test.
Stephanie Kaplan	American Society of Hematology	General	The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the Agency for Healthcare Research and Quality regarding the Agency's draft report entitled "Update on Genetic Tests Currently Available for Clinical Use in Common Cancers."	Thank you.

			ASH represents more than 14,000 clinicians and scientists worldwide committed to the study and treatment of blood and blood-related diseases. These diseases encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma and non-malignant conditions such as sickle cell anemia, thalassemia, aplastic anemia, venous thromboembolism, and hemophilia. In addition, hematologists have been pioneers in the fields of stem cell biology, regenerative medicine, bone marrow transplantation, transfusion medicine, gene therapy, and the development of many drugs for the prevention and treatment of heart attacks and strokes. ASH membership is comprised of basic scientists, physician scientists, physicians, and hematopathologists working in diverse settings, including universities, hospitals and private practices. ASH's comments focus on recommended edits to the two hematologic genetic tests listed in Appendix A (on pages A 30 & 31). If you have any questions and/or need additional information, pleae contact ASH Government Relations and Practice Manage Stephanie Kaplan at skaplan@hematology.org or 202-776-0544.	
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 30	Gene Test Information: 5q del, 7q del/-7 FISH test, Acute myeloid leukemia and myelodysplastic syndrome ASH suggests the following rewrite to the description section: Description: Chromosomal abnormalities are detected in 40-60% of patients with de novo myelodysplastic syndromes (MDS). Myelodysplastic syndrome (MDS) with interstitial deletion of a segment of the long arm of chromosome 5q [del(5q)] as an isolated cytogenetic abnormality is characterized by bone marrow erythroid hyperplasia, atypical megakaryocytes, thrombocythemia, refractory anemia, and low risk of progression to acute myeloid leukemia(AML) compared with other types of MDS. In published studies Presence of -7/7q- was associated with shorter overall survival than absence of such aberrations.	Thank you, we have incorporated suggested changes.

			FISH 7q could be beneficial in patients with intermediate WHO morphologic risk stratification and no evidence of -7/7q- by cytogenetics. Under "Availability," Arup laboratories is listed as the only provider that performs this test, however there are many other laboratories that perform the test (including: community laboratories, academic centers and commercial labs).	
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 30	ASH suggests the following rewrite to the diseases section: Diseases: Acute myelogenous leukemia AND myelodysplastic syndrome	Thank you, we have re-written those sections.
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 30	ASH suggests the following rewrite to the clinical uses section: Clinical Uses: The 5q del, 7q del/-7 FISH test may aid in prognosis of acute myeloid leukemia AND myelodysplastic syndrome. It helps a subset of patients get treatment tailored to their unique genetic profile	Edited.
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 30	ASH suggests the following rewrite to the organ (Medline Search) section: Organ (Medline Search): Acute myeloid leukemia AND myelodysplastic syndrome	Edited.
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 31	Gene Test Information: Multiple myeloma panel by FISH ASH suggests the following rewrite to the description section: Description: Chromosomal abnormalities are important prognostic indicators in multiple myeloma. In this test, fluorescence in situ hybridization (FISH) panel is performed on bone marrow or tissue containing neoplastic plasma cells for multiple myeloma prognosis-specific genomic abnormalities: (e.g. CKS1B (1q gain), ASS1 (+9), CCND1/IGH (IGH/CCND1 fusion or +11), IGH rearrangement, PML (+15) and p53 (17p deletion)). Under "Availability" Arup laboratories is listed as the only provider that performs this test, however there are many other laboratories that perform the test (including: community laboratories, academic centers and commercial labs).	Edited.
Stephanie Kaplan	American Society of Hematology	Appendix A, Page 31	ASH suggests the following rewrite to the clinical uses section: Clinical Uses: The FISH evaluation of neoplastic plasma cells may aid in prognosis of multiple myeloma. It helps a subset of patients get	Edited

			treatment tailored to their unique genetic profile	
Shannon T Knuth	Cellay, Inc.	Executive Summary	One of the research gaps identified in this technology assessment is that a panel of probes rather than single probes could be used to capture a greater variety of chromosomal changes (page ES-22). We support this statement and suggest that a panel of chromosome enumeration probes for aneuploidy detection may be a beneficial add-on test for patients with LSIL or ASCUS cytology results. Aneuploidy is widely described in the mechanisms of HPV related cancers and may be detectable 6 months before any cytological or histological changes occur. FISH testing for aneuploidy can take place in about 2 hours when using OligoFISH Probes or about 24 hours when using genomic-derived probes. FISH signals lend themselves to use of an automatic imaging and analysis to assist with processing/scoring of slides which leads to greater consistency and higher throughput in results.	Thank you. This is a horizon scan and further evidence regarding FISH testing for aneuploidy are currently being examined in full systematic review.
William Lawrence	AHRQ	General	It appears that the EPC missed Myriad Genetics in their scan, which includes a prognostic test for prostate cancer, evaluation of the PTEN gene which is apparently prognostic for several cancers, and a genetic test for 5-FU metabolism, which might be considered as part of the therapeutic monitoring (loose, but they should explicitly exclude it if they do not include it).	Thank you. These tests have been added.
William Lawrence	AHRQ	General	Also, it looks like they are limiting it to somatic mutations rather than germ line mutations, eg. BRCA, HNPCC, etc. These tests are prognostic? in terms of developing cancer rather than developing recurrences per se, but since they affect management due to the possibilities of second primaries (e.g. someone who is BRCA positive might elect bilateral mastectomy rather than breast conserving surgery or a unilateral mastectomy due to the high risk of second breast primaries). They could include or not, but they should be explicit about what they are doing here, and what the implications are.	Thank you. These tests have been listed in our 2006 report.
Sabine Luik	Boehringer Ingelheim Pharmaceuticals, Inc.	General	On behalf of Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI), we appreciate this opportunity to submit comments on the Agency for Healthcare Research and Quality?s (AHRQ) draft technology assessment, ?Update on Genetic Tests Currently Available for Clinical Use in Common Cancers.?	Thank you.

			BIPI is a leading global research organization with extensive expertise developing therapies to treat a variety of chronic and life threatening diseases, including cancer. BIPI?s investigational oncology compound, afatinib, is currently undergoing Priority Review at the Food and Drug Administration (FDA). [1] Afatinib is in Phase III clinical development in advanced non-small cell lung carcinoma (NSCLC), head and neck and breast cancer.	
Sabine Luik	Boehringer Ingelheim Pharmaceuticals, Inc.	General	In reviewing this draft report, it has come to our attention that Qiagen?s therascreen? EGFR RGQ PCR Kit, a companion diagnostic that was developed in collaboration with BIPI to determine which NSCLC patients would be potentially eligible for treatment with afatinib, is not noted in the report. Qiagen submitted a Premarket Approval (PMA) application for use of the therascreen? EGFR test to the Food and Drug Administration (FDA) in January 2013.[2] The test, which identifies patients with EGFR mutation-positive tumors, is pending FDA-approval. Since the AHRQ report has endeavored to include tests that are both FDA-approved and undergoing FDA approval, as stated in the report?s methodology, BIPI recommends that Qiagen?s therascreen? EGFR RGQ PCR Kit also be added to the report. While the test is pending pre-market approval in the US, the therascreen? EGFR test has been gaining a steadily growing presence in the clinical community, both internationally and domestically within the US. In late 2011, the test received regulatory approval in Japan, the world's second largest market for personalized healthcare. While BIPI submitted a Marketing Authorization Application to the European Medicines Agency seeking approval of afatinib as a treatment for patients with EGFR mutation-positive NSCLC in September 2012, the therascreen? EGFR test is already being evaluated and expects to be recommended for use as a companion diagnostic. Most recently, on March 9, 2013, the United Kingdom?s National Institute for Health and Care Excellence (NICE) issued a draft guidance recommending a number of tests and test strategies as options for detecting epidermal growth factor receptor-tyrosine kinase (EGFR-TK) mutations in the tumors of adults with previously untreated, locally advanced or metastatic NSCLC. The report concludes, ?the therascreen? EGFR RGC PCR Kit appears to have the best overall performance for	EGFR genetic tests appear in our prior reports and; therefore, we have not added this test in this report.

			discriminating between patients who are likely to benefit from EGFR-TK inhibitor treatment and patients who are not.?[3] These international developments are also reflective of and in alignment with recent clinical guidelines released by various groups within the US. In addition to reviewing evidence and data on EGFR testing, these clinical guidelines all recommend EGFR mutational testing for selection of EGFR-TK inhibitor therapy over EGFR copy number analyses such as fluorescence in-situ hybridization (FISH), the latter of which was one of the 44 new tests identified in AHRQ?s report.[4,5] In consideration of the fact that therascreen? EGFR is gaining acceptance in the broader clinical community, and is being actively reviewed in the USFDA as a co-developed companion diagnostic, AHRQ should consider adding it to the list of genetic tests as an important addition in this growing field of personalized medicine.	
Sabine Luik	Boehringer Ingelheim Pharmaceuticals, Inc.	General	BIPI appreciates the opportunity to comment on the draft technology assessment on genetic tests currently available for clinical use in common cancers. As it has since its first iteration in 2006, we expect that this report will continue to serve as a valuable reference on available genetic tests for many other stakeholders in the near future.	Thank you.
Sabine Luik	Boehringer Ingelheim Pharmaceuticals, Inc.	General	BIPI invites any opportunity to discuss our comments and recommendations in further detail. Please feel free to contact me at sabine.luik@boehringer-ingelheim.com if you have any questions or if you need additional information. ? [1] Boehringer Ingelheim. (2013). U.S. FDA Grants Priority Review to Boehringer Ingelheim?s Afatinib NDA for EGFR Mutation-Positive Advanced NSCLC. [Press release]. Retrieved from http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2013/16_january_2013_oncology. html [2] Qiagen. (2013). Qiagen submits companion diagnostic to FDA to guide treatment decisions for new investigational lung cancer compound. [Press release]. Retrieved from http://www.qiagen.com/About-Us/Press-Releases/PressReleaseView/?PressReleaseID=401 [3] Epidermal growth factor receptor tyrosine kinase (EGFR-TK)	Thank you.

			mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer: diagnostics consultation. NICE technology appraisal guidance (2013). [4] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology? for Non-Small Cell Lung Cancer. Version 2 (2013). [5] Lindeman, Neal, et al. ?Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors.? Archives of Pathology & Laboratory Medicine. (2013).	
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	General	Dear AHRQ Draft TA Developers, Thank you for the opportunity to provide comments with regard to the draft report entitled, "Update on Genetic Tests Currently Available for Clinical Use in Common Cancers." The report represents a good overview, but there were some errors that were identified, as well as the opportunity to provide clearer descriptions, or more in-depth discussions, in some areas.	We have edited as per your suggestion.
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	Results	We would recommend the addition of the Genomic Health, Inc. website, www.genomichealth.com, in the general search of websites found in Table 1 on page 6 of the document. While the title of the table does indicate that it is a "selected" list, we would suggest including the site in future versions of the document, since the website is kept up to date with the newest publications and presentations arising from Genomic Health, Inc. research.	Added.
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	Table	Noticeably absent from Table 2 was reference to the Oncotype DX? Colon Cancer Assay. While it is mentioned in Table 1 in Appendix B, it should be noted that the assay has had additional validation recently published, with two large-enrollment trials having been published. The first, from the QUASAR study (Gray R, Quirke P, Handley K, et al. Validation Study of a Quantitative Multigene Reverse Transcriptase?Polymerase Chain Reaction Assay for Assessment of Recurrence Risk in Patients with Stage II Colon Cancer. J Clin Oncol Dec 10, 2011, vol. 29, 35:4611-4619), showed the Recurrence Score?, generated from the RT-PCR expression of 12 genes from FFP colon tissue, to be highly predictive of recurrence risk and prognosis in stage II colon cancer. The most recently published paper, Vanook A, Niedzwiecki D, Lopatin M, et al.	The Oncotype DX Colon Cancer Assay test has been reviewed in prior report. This report focuses on emerging tests that we identified since the publication of last report. We have added Oncotype Dx Prostate cancer Assay.

			Biologic Determinants of Tumor Recurrence in Stage II Colon Cancer: Validation Study of the 12-Gene Recurrence Score in Cancer and Leukemia Group B (CALGB) 9581. J Clin Oncol Mar 12, 2013, 45:1096, confirmed the findings of the QUASAR study, with the Recurrence Score proving to be the only statistically significant predictive of disease recurrence, when compared with all other existing clinical and pathological features currently used to identify prognostic probability. While the assay was commercially introduced in 2010 and appropriately identified as such in terms of being placed in Appendix B, it may be more appropriate to include the assay in Table 2 of the main report, given the new data available. If the decision is made not to move the assay to the main report, then the Table 1 in Appendix B should reflect that colon assay is prognostic and an X should be placed in that box.	
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	Table	We believe Table 3 in Appendix B should probably include both the Oncotype DX Breast and Colon assays as having ?matured to clinical use? since 2006, as data has been produced and acceptance by payers has occurred since that date.	We would like to clarify that Oncotype Dx Breast cancer and colon cancer has already been indexed in our 2006 report (please see appendix B6) and 2011 report.
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	Appendix A-11	Page A-11 of the report incorrectly lists Genomic Health, Inc. as the available party and the Genomic Health, Inc. website as the information source for the MammaPrint test. This assay is not provided by Genomic Health, Inc.	Thank you. We have edited this section.
Steven L Richardson, MD, MS	Medical Affairs, Genomic Health, Inc.	Appendix	The one page summary for the Oncotype DX Breast Cancer Assay?, page A-14, would more accurately explain the assay if it were to include this information: ?The Oncotype DX Breast Cancer Assay measures the expression of 21 genes in breast cancer tissue to provide individualized prognosis and recurrence risk over 10 years, as well as chemotherapy benefit prediction, in early stage estrogen receptor positive, HER2- negative patients treated for 5 years with tamoxifen. It has been validated in 13 published studies of over 4000 women and is the only breast cancer genomic assay to be incorporated into NCCN?, ASCO?, ESMO? and St. Gallen guidelines.? Further, there have been a number of published clinical utility studies which show that the assay is used to guide treatment and changes clinical decisions up to 37% of	We would like to clarify that Oncotype Dx has already been indexed in our 2006 report (please see appendix page B-6) as a genetic test that has already been in use. The subsequent list of tests appearing on page B-7 was originally identified as tests in research by the 2006 report and has

			the time.	then matured into full clinical use.
Art Small	Genentech	General	The objective of the draft report is to provide the Coverage and Analysis Group at CMS an updated list of genetic tests for cancer since 2011. We applaud the effort and would like to add a few tests that were not included in the draft report for consideration. 1) EGFR mutation tests for lung cancer, in addition to EGFR FISH. EGFR mutation testing is pending FDA-approval for the treatment of first-line nonsmall cell lung cancer with Tarceva (erlotinib). The package insert for Tarceva is available here: http://www.gene.com/download/pdf/tarceva_prescribing.pdf 2) 17p del FISH test for hematologic cancer, particularly for chronic lymphocytic leukemia is a prognostic test routinely performed for newly diagnosed CLL. Novel molecules are in development, which target a high-risk 17p deletion patient subset. 3) cobas? 4800 BRAF V600 Mutation test from Roche Molecular Systems is the first FDA-approved in vitro diagnostic test for detection of the BRAF V600E mutation in DNA extracted from melanoma tissue. The test is intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with ZELBORAF? (vemurafenib) tablets.(www.cobasbraftest.com). The package insert for ZELBORAF? is available here: http://www.gene.com/download/pdf/zelboraf_prescribing.pdf The package insert for the cobas? 4800 BRAF V600 Mutation test is available here: http://1roche.mylabonline.com/rs/roche/images/05952590001-01_R03558.pdf	Thank you. EGFR mutation tests have been extensively presented in our prior reports. We have added 17p del FISH for CLL We also have added COBAS® 4800 BRAF V600 Mutation test.
Art Small	Genentech	General	With the rapidly evolving science of personalized cancer care, Genentech appreciates the opportunity to provide comments to ensure a comprehensive list of genetic tests available for cancer will be incorporated in the final	Thank you.

			technology assessment report. Furthermore, a robust technology assessment report will facilitate access to new and emerging genetic tests that can advance personalized medicine for cancer. If you have any questions about our comments, please contact Art Small, Head of BioOncology Outcomes Research, at 1-650-467-4516, or small.art@gene.com.	
Wendy Wifler	Agendia Inc.	General	We thank the authors for the thorough review of the topic of genetic tests currently available for clinical use in common cancers. We submit several comments to the document. We have revised and added language on Agendia?s four tests included in the report. We have also added a new page for one additional test which was not included in the draft report which we believe should be included. ColoPrint? Colon Cancer Gene Expression Test was launched worldwide on June 1st 2012. We add general comments on four mutation analyses tests included in Appendix A.	Thank you, we have added Coloprint®.
Wendy Wifler	Agendia Inc.	Introduction/Background	In section "Description of grey literature sources": We believe these additional sources would prove valuable grey literature information sources:? AMP Test Directory http://www.amptestdirectory.org/index.cfm ? BIOBASE HGMD? Professional database http://www.biobase-international.com/product/hgmd ? GeneTests: Laboratory Directory http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab ? McKesson Diagnostic Exchange https://app.mckessondex.com	We have indexed sources that are freely available to the public and those that we have used to identify tests. Due to limited time available, we will not have the time to search new Web sites. In addition BIOBASE HGMD requires a subscription fee.
Wendy Wifler	Agendia Inc.	Discussion/Conclusion	Page 12 ? consider removal of the word ?with? from last line on page ?least one other group.(4) We did not contact [with] the companies and, this process limits our?	Edited
Wendy Wifler	Agendia Inc.	Table 2	In ?Table 2. Genetic tests for cancer found between March 2011 and January 2013? on page 10 The following Tests should be designated with the following Purposes [brackets indicate changes to Draft Report] ? BluePrint = [Diagnostic], Therapeutic Management ? MammaPrint = Prognostic/Predictive, Recurrence, Therapeutic Management ?	Edited.

			SYMPHONY = Prognostic/Predictive, Diagnostic, [Recurrence], Therapeutic Management ? TargetPrint = [Diagnostic], Therapeutic Management ? [ColoPrint = Prognostic/Predictive, Recurrence, Therapeutic Management]	
Wendy Wifler	Agendia Inc.	Appendix A-4	Please replace content on Page A-4 with this revised content: Gene Test Information: BluePrint, breast cancer Test Name: BluePrint? Molecular Subtyping Signature Description: BluePrint is an 80-gene profile that classifies breast cancer into molecular subtypes. The profile separates tumors into Basal-type, Luminal-type and ERBB2-type subgroups by measuring the functionality of downstream genes for each of these molecular pathways to inform the physician of the potential effect of adjuvant therapy. Purpose: Therapeutic management of breast cancer Availability: Agendia Specimen: Formalin fixed paraffin-embedded, fresh or frozen breast tumor tissue Methodology: Genomic signature by microarray-based RNA gene expression Diseases: Breast cancer Clinical Uses: BluePrint? provides information on the sub-classification of the tumor which guides the choice of therapies and combinations of therapies. Sources: www.agendia.com Marker (Medline Search): BluePrint Organ (Medline Search): breast Medline Searches: BluePrint[All Fields] AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) medline hits=22 FDA approved: No	Edited.

Wendy Wifler	Agendia Inc.	Appendix A-11	Please replace content on Page A-11 with this revised content: Gene Test Information: MammaPrint, breast cancer Test Name: MammaPrint? Breast Cancer Recurrence Signature Description: MammaPrint is a 70-gene profile that classifies breast cancer into ?Low Risk? or ?High Risk? of recurrence, by measuring genes representative of all the pathways of cancer metastases which were selected for their predictive relationship to 10-year recurrence probability. MammaPrint is indicated for women who have stage I or II breast cancer, are lymph node positive or negative, are ER-positive or negative and tumor size of less than five centimeters. Purpose: Prognosis, recurrence, predictive and therapeutic management of breast cancer Availability: Agendia Specimen: Formalin fixed paraffin-embedded, fresh or frozen breast tumor tissue Methodology: Genomic signature by microarray-based RNA gene expression Diseases: Breast cancer Clinical Uses: MammaPrint determines if the patient is a candidate for chemotherapy. Sources: www.Agendia.com Marker (Medline Search): MammaPrint Organ (Medline Search): Breast Medline Searches: MammaPrint[AII Fields] AND ("breast neoplasms"[MeSH Terms] OR ("breast"[AII Fields] AND "neoplasms"[AII Fields]) OR "breast neoplasms"[AII Fields] OR ("breast"[AII Fields] AND "cancer"[AII Fields]) OR "breast cancer"[AII Fields]) Medline hits=7 4 FDA approved: First and only FDA-cleared IVDMIA breast cancer recurrence assay	Edited.

Wendy Wifler	Agendia Inc.	Appendix A-18	Please replace content on Page A-18 with this revised content: Gene Test Information: SYMPHONY?, Breast Cancer Test Name: SYMPHONY? Personalized Breast Cancer Genomic Profile Description: SYMPHONY? provides complete tumor profiling and is used to support therapeutic choices for breast cancer. SYMPHONY includes four assays to support breast cancer treatment decisions: MammaPrint? determines the risk of recurrence. BluePrint? determines molecular subtypes and TargetPrint? determines estrogen receptor (ER), progesterone receptor (PR), and HER2 status. TheraPrint? identifies alternative types of therapy for metastatic disease. Purpose: Diagnostic, prognostic, recurrence, and therapeutic management Availability: Agendia Specimen: Formalin-fixed, paraffin-embedded, fresh or frozen breast tumor tissue Methodology: Panel of several genomic tests; microarray-based RNA gene expression methodology Diseases: Breast cancer Clinical Uses: SYMPHONY provides comprehensive genomic information assisting with therapeutic decisions even for cases that have been otherwise classified as indeterminate, such as grade 2, small tumors, HER2 and/or lymph node positive. MammaPrint? determines if the patient is a candidate for chemotherapy. TargetPrint? determines if the patient is a candidate for hormonal therapy. BluePrint? provides information on the sub-classification of the tumor which guides the choice of therapies and combinations of therapies.	Edited.

			TheraPrint? identifies alternative types of therapy for metastatic disease. Sources: Agendia Marker (Medline Search): Mamma print AND BluePrint AND TargetPrint AND TheraPrint Organ (Medline Search): breast cancer Medline Searches: Mammaprint [Title] AND BluePrint[Title] AND TargetPrint[Title]AND breast[Title] AND cancer[Title] medline hits= 1 FDA approved: No	
Wendy Wifler	Agendia Inc.	Appendix A-19	Please replace content on Page A-19 with this revised content: Gene Test Information: TargetPrint, Breast Cancer Test Name: TargetPrint? ER/PR/HER2 Expression Assay Description: TargetPrint is a microarray-based gene expression test which offers a quantitative assessment of the patient's level of estrogen receptor (ER), progesterone receptor (PR) and HER2/neu overexpression within her breast cancer. Purpose: Therapeutic management Availability: Agendia Specimen: Formalin fixed paraffin-embedded, fresh or frozen breast tumor tissue Methodology: Panel of three separate single gene readouts by microarray- based RNA gene expression Diseases: Breast cancer Clinical Uses: TargetPrint delivers an added benefit to the diagnostic process. Immunohistochemistry provides a semi-quantitative positive or negative result, whereas the gene expression result provided by TargetPrint allows physicians to integrate the absolute level of ER, PR and HER2 gene expression	Edited

			into treatment planning. TargetPrint? determines if the patient is a candidate for hormonal therapy. Sources: www.Agendia.com Marker (Medline Search): TargetPrint and breast cancer Organ (Medline Search): breast Medline Searches: TargetPrint[AII Fields] AND ("breast neoplasms"[MeSH Terms] OR ("breast"[AII Fields] AND "neoplasms"[AII Fields]) OR "breast neoplasms"[AII Fields] OR ("breast"[AII Fields] AND "cancer"[AII Fields]) OR "breast cancer"[AII Fields]) Medline hits=4 FDA approved: No	
Wendy Wifler	Agendia Inc.	Appendix A-20	Please add a new page in the Colorectal Cancer section, following page A-20 with this new content: Gene Test Information: ColoPrint?, Colon Cancer Test Name: ColoPrint? Colon Cancer Gene Expression Test Description: ColoPrint is an 18-gene profile that classifies colon cancer into ?Low Risk? or ?High Risk? of relapse, by measuring genes representative of the metastatic pathways of colon cancer metastases which were selected for their predictive relationship to 5-year distant metastases probability. ColoPrint is indicated for stage II colon cancer, and provides relapse risk stratification independent of clinical and pathologic factors such as T4-stage and MSI status. Purpose: Prognosis, recurrence, predictive and therapeutic management of colon cancer Availability: Agendia Specimen: Fresh tumor tissue	We have added this test in a new page.

			Methodology: Genomic signature by microarray-based RNA gene expression Diseases: Colon cancer Clinical Uses: ColoPrint determines if the patient is a candidate for chemotherapy. Sources: www.Agendia.com Marker (Medline Search): - Organ (Medline Search): - Medline Searches: - FDA approved: No - New page - - Addition to Colorectal section, starting on page A-20 -	
Wendy Wifler	Agendia Inc.	Appendix	We also recommend a more thorough vetting of the following mutation analyses: KRAS, page A-22 - many labs offer this test for a variety of clinical uses BRAF, page A-40 - many labs offer different versions of this test for multiple clinical uses PIK3CA, page A-42 - many labs offer different versions of this test for multiple clinical uses [new to add] EGFR mutation analysis by RGQ PCR - many labs offer different versions of this test for multiple clinical uses	Thank you, we have clarified in our methods that some tests can be offered by many labs and have modified availability accordingly.
Alan T. Wright	Roche Diagnostics Corporation	General	The purpose of the draft report is to provide the Coverage and Analysis Group of the Centers for Medicare and Medicaid Services with an updated report of genetic tests for cancer conditions to serve as a reference for both their internal discussions in this area as well as a source of information for decisions on future topics for systematic reviews. We applaud the authors? efforts on this draft report; however, we would like to address a few key areas that may require further attention and updates. In general, numerous places throughout the report refer to Roche Diagnostics as a commercial diagnostic laboratory. Roche Diagnostics is the world leader in in-vitro diagnostics, and supplies a wide range of rapid, reliable instruments and tests for disease screening and diagnosis in laboratories. Roche Diagnostics is not a commercial diagnostic laboratory, however.	Thank you, we have revised according to your suggestion.
Alan T.	Roche	General	We have also identified tests that meet the inclusion criteria identified in	We have incorporated

Wright	Diagnostics Corporation		the ?Methods? section of the draft report but are not currently described in the draft report. We address these points in more detail in the appropriate sections below.	your suggestions.
Alan T. Wright	Roche Diagnostics Corporation	Executive Summary	Page ES-3: Roche Diagnostics is referred to as a "commercial diagnostic laboratory". We recommend re-wording this sentence such that it is clear that Roche Diagnostic is an in vitro diagnostic company commercializing supplies, instruments and tests. It is not a commercial laboratory.	Thank you. We deleted this.
Alan T. Wright	Roche Diagnostics Corporation	Table 2	Table 2: Under the "Lung" section, we recommend including the cobas? EGFR Mutation Test. This test, which is pending FDA clearance, is a real-time PCR test for the qualitative detection and identification of mutations in exons 19 and 21 of the epidermal growth factor receptor (EGFR) gene in DNA derived from formalin-fixed paraffin-embedded (FFPE) human non-small cell lung cancer (NSCLC) tumor tissue. The test is intended to be used to identify patients with advanced NSCLC whose tumors harbor deletion mutations in exon 19 and the L858R point mutation in exon 21 of the EGFR gene, and to select patients for treatment with the tyrosine kinase inhibitor (TKI) Tarceva? (erlotinib) (for more information, see: http://molecular.roche.com/assays/Pages/cobasEGFRMutationTest.aspx and http://www.roche.com/media/media_releases/med-cor-2011-12-01.htm).	EGFR tests have been extensively reviewed in our prior reports and therefore, we have not reviewed in this report.
Alan T. Wright	Roche Diagnostics Corporation	Table	In January 2013, Astellas Pharma US, Inc. announced that the U.S. Food and Drug Administration (FDA) accepted for filing a supplemental New Drug Application (sNDA) for Tarceva? (erlotinib) for first-line use in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) activating mutations. The application has been granted Priority Review status and a decision from the FDA on approval of the supplement is expected in the second quarter of 2013. (http://www.prnewswire.com/news-releases/fda-accepts-supplemental-new-drug-application-for-tarceva-erlotinib-tablets-for-genetically-distinct-form-of-	EGFR tests have been extensively reviewed in our prior reports and therefore, we have not reviewed in this report.

			advanced-lung-cancer-187096801.html).	
Alan T. Wright	Roche Diagnostics Corporation	General	We recommend including information for the cobas EGFR Mutation Test.	EGFR tests have been extensively reviewed in our prior reports and; therefore, we have not reviewed these tests in this report.
Alan T. Wright	Roche Diagnostics Corporation	Appendix	It also appears that the BRAF gene mutation test that is identified in the draft report is not specific to a test that detects BRAF mutations in human melanoma tissue. The cobas? 4800 BRAF V600 Mutation Test is the only diagnostic test approved by the FDA to help identify patients with the BRAF V600E mutation. The test has been validated for use as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib. Therefore, we request that either (1) the following changes be incorporated into the existing summary on page A-40, or (2) the following changes be incorporated into a new page in this section: Test Name: cobas? BRAF V600 Mutation Test. (The cobas? 4800 BRAF V600 Mutation Test is the first and only diagnostic test approved by the FDA to help identify patients with the BRAF V600E mutation.) Description: The cobas? 4800 BRAF V600 Mutation Test detects the BRAF V600E mutation in formalin-fixed, paraffin-embedded (FFPET) human melanoma tissue. It is designed to help select patients for treatment with ZELBORAF? (vemurafenib), an oral medicine designed to treat patients whose melanoma tumors harbor a mutated form of the BRAF gene. (http://molecular.roche.com/assays/Pages/cobas4800BRAFV600MutationTest.aspx) Availability: Roche Diagnostics Diseases: Melanoma Clinical Uses: The test has been validated for use as an aid in selecting	Thank you. We have incorporated the suggested changes into a new page in this section.

			melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib. Sources: http://molecular.roche.com/assays/Pages/cobas4800BRAFV600MutationTest.aspx FDA approved: Yes	

[1] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.
[2] Affiliation is labeled "NA" for those who did not disclose affiliation.
[3] If listed, page number, line number, or section refers to the draft report.
[4] If listed, page number, line number, or section refers to the final report.