Project Name: Update of Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancers
Project ID: GEND0508

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	This update can be a valued addition to contributing to current knowledge about the availability of genetic tests for cancer. In reviewing, there were several issues raised that should be addressed.	Thank you
1	Introduction/ Background	Page 8: it is stated that a main objective is to provide a preliminary estimate on the amount of published literature available on each genetic test. It should be noted that literature covers a broad range of topics associated with a particular test ranging from research studies not having clinical applications to those that do.	This is stated on the page 11 under exploratory PubMed search.
1	Methods	Page 10. Are predictive tests excluded? If not you may wish to include this as a category at the top of this page. Understandably, it is less applicable to the Medicare population although detecting disease recurrence is a form of predictive testing. Page 10. Under inclusion criteria for tests offered by Internet sites requiring a physician order, I would add the caveat to include those performed in a laboratory certified under the CLIA regulations. This gets into the DTC realm which as you know is tricky. Page 10. With regard to your exclusion criteria, do you want to say tests for conditions that exclusively result in death before reaching adulthood? This is difficult because some conditions occur, as a consequence of the genetics, before and after adulthood. Perhaps it is better to address this in the inclusion criteria as tests for conditions that manifest within the Medicare population. Page 11. It is not clear how the categories are reflected in the tables presented later in this report. There does not appear to be "category" entry. Possibly the "Purpose" entry? Page 12. I would not completely discount the published literature but would say that it has significant limitations for some of the reasons mentioned. I would delete the first reason- search strategies can be devised, I would probably delete the second - this is a limitation of your effort and not the concept, your 5th reason seems irrelevant since you will not be addressing the publication of associations; only tests. Another reason is the peer-reviewed literature is simply not the primary forum for	Page 10: We will add the term predictive tests as these are not excluded from the database. Page 10. Any genetic tests that require a physician order are of interest to the report. Page 10. We have reworded the exclusion criteria. Page 11. We have edited the categories so that they are fairly matched with those listed in the table Page 12: Only the tests are obtained through grey literature searching, sometimes may include review of selected narrative reviews. The description of the test and its clinical application does include a variety of sources including peer reviewed literature. Page 13: This statement directly reflects what was posted on the website. The last

		providing information about new tests. This should be mentioned. Page 12. It is questionable whether GeneReviews is grey literature since entries are peer reviewed; albeit by a somewhat different that a journal but with similarities. Page 13 - The international laboratory is not as broad-based as implied. It fundamentally focuses upon molecular testing with fewer entries for cytogenetic and biochemical genetic testing. Comment - Did you look at the Association for Molecular Pathology test directory (www.amp.org) that specifically deals with cancer testing (at least a part of the directory)? Page 15 - Under clinical use - It seems that the only clinical use this report is addressing is "clinical" use. This would be consistent with the title of this report. Otherwise, the title may need to be change as well as the stated focus for this effort. Page 16 - Instead of 9) Marker - why not be more direct and call this entry "Medline search parameters"? Page 16 - With regard to the "Organ" entry - Do you wish to differentiate between primary site and metastases? For example, renal cell carcinoma begins in the organ but metastasizes to multiple other organs. If you wish to list all possible organ sites, you should differentiate primary from others.	line in our introduction clarifies this. Thank you for directing us to the website, we will include any tests that are not currently listed in our database, but are available at the amp.org website. Our inclusion criteria are similar to that listed in the 2006 report to focus on the most common cancers. Page 15. Thank you. Page 16. We have clarified this. Page 16. The suggested search strategy is more applicable for focused systematic reviews.
1	Results	Page 19 - last sentence - It is unclear how the graphics plot may be used for identifying tests for future focused reviews.	At the suggestion of many reviewers the graphic plots have been omitted out.
1	Discussion/ Conclusion	Page 23 - I would be hesitant to state that "in this report along with genetic tests identified in our 2006 report are fairly comprehensive" without the caveat that other tests are available that would not be expected to be described within the sources interrogated. For example, it is common for academic medical center laboratories to develop/offer some tests at the request of their physicians. These tests would not typically be offered or marketed beyond the academic center in which they are offered and if not for a heritable condition, would less likely be considered for entry into the GeneTests database. Page 24 - In stating, "we have selected those that are available for clinical applications in screening, diagnosis, prognosis, disease management, or patient monitoring....." Should "prediction" and/or "disease recurrence" be included or is	Page 23. Thank you for pointing this; we have added a statement to clarify the same. Page 24. We have added the suggested terms in the discussion.

		this covered. It is not clear where this is included within these categories although it is mentioned earlier in the manuscript. I am ok with inclusion in one of these categories but should be expressively stated earlier in the manuscript.	
1	Tables	Consistent fields for "availability" are not used. This needs to be considered. For instance, in some cases, a generic heading such as "commercial laboratory" is provided and in other cases, a specific company is cited. Also, you include both manufacturers (e.g., Roche), and reference to performing laboratories. With regards to "tests in development" (e.g., Roche Amplichip for breast cancer) - do you wish to include these selectively because there are probably hundreds of which only a few will make it to clinical use. It may be useful to have somewhat of an expanded discussion about the graphs provided under each entry. I would speculate that references cited address both basic and clinical research findings. If this is not true and references are specific to the application of the test in clinical use, this should be stated. If this level of specificity is not possible, this limitation should be described. You include a number of immunohistochemical and immunostaining tests in your table. It should be stated in the text that for purposes of this report, you are considering these genetic tests because specific analytes are targeted. This is important because some professionals would not consider such tests as "genetic". For example, the Hybridtech free PSA test for prostate cancer would not be considered a genetic test by some professionals. Similarly, the NMP22(R) test kit which is a quantitative assay would be on the fringes for what might be considered a genetic test. Most would probably consider this more a quantitative immunochemical than a genetic test. When designating the purpose as "pharmacogenetic", it would be helpful to further classify according to one of your criteria - screening, diagnosis, prognosis, disease management, or patient monitoring. In some instances, you mention county/region specific availability - this should be consistently presented throughout all entries. Wtih regards to LBA(R)AFP-L3 testing, the purpose is a different category not previously described - arguing again for the need to use consistent descriptors. It is important to strongly emphasize that the description is pulled from an external source. For instance, in stating that "MammaPrint" uses the latest in molecular technology should not be interpreted as an AHRQ conclusion.	Thank you we have removed this test as it is still in development. All included tests have fully been developed and are available for clinical use. Yes, we have clarified the nature of preliminary searches conducted during horizon scanning. We have clarified in our text that the graphs accompanying each one page are from preliminary searches and can address both basic and clinical research findings. However, the searches are limited to studies conducted in human. Our report used a broad definition of genetic tests put forth by the 2008 SACGHS report and it is possible that the tests included under this definition may not be defined as “genetic test” by other professional groups. We have changed pharmacogenetic to therapeutic management consistent with our categories. Thank you, we have made an effort to make our descriptors consistent.

		With regards to MGMT methylation testing, this raises the need to state that you are also including epigenetic testing in your review. This can be stated in the main text. The term will need to be defined. With regards to Oncotype DX, you note that this test has limited availability. "limited" can have several meanings and in the context of other tests described, this might not be the only one. I would not say "limited".	Thank you we have made edits.
2	General	Moreover, the report was excellent. The draft could benefit from a final, careful proofreading for a few minor grammatical issues but overall it looks very good. I would have liked to see more information on the database that is mentioned in the report. Specifically, are there plans to make the GeneTestTracker publically available, and if so, will it be freely accessible? Can anything be said about differences between the database and the planned Genetic Testing Registry from NIH?	We have shared our database with those at NIH who are involved in Genetic Testing Registry, since some of the fields are similar. Currently, we are not aware of any plans to make the GeneTestTracker publically available.
2	Introduction/ Background	This section was brief but generally adequate. I appreciated the contrasting between cancer vs. non-cancer tests by the relatively larger number of tests for somatic mutations in the former, however, it made me wonder if this is the major reason why scanning and reports are divided along cancer/non-cancer lines? If so, this should be clearly stated. If additional contrasts can be made, this might be helpful as well. I also wondered whether anything can be said about the absolute number of different genetic tests currently available for cancer vs. non-cancer disorders	Based on our original reports and further work assignments, the reports are published alternate years. The tests are selected based on their applicability to the elderly population and hence do not reflect the absolute number of different genetic tests currently available for cancer vs. non-cancer disorders for all age groups.
2	Methods	Table 1 is very helpful, but it made me wonder about the details on how the selection of labs was made. It might be good to explain why none of the academic laboratories (e.g., Emory University School of Medicine and Baylor College of Medicine) that offer molecular genetic testing for a large number diseases are included in the search. Also it appears that the laboratories that offer molecular genetic tests for the highest numbers of diseases (according to GeneTests data: ftp://ftp.ncbi.nih.gov/pub/GeneTests/reports/IX/IXB1_report.txt) were not included and it may be a good idea to address this in the report. This may be as simple as the fact that some only offer tests for rare, Mendelian disorders, or that an international lab may not offer services in the U.S. I was not sure, but felt additional information here would be helpful to readers.	We do search major academic searches and specifically, Baylor College of Medicine has been listed in one of our previous reports. Listed laboratories in this report are the ones that we have had some recent success in identifying genetic tests. We are unable to list all the laboratories that conduct each of the tests available in the database, since the purpose of the report is to identify new tests and the availability of published studies for each of the identified test.
2	Results	See comments on table 2 in the Tables section below.	
2	Discussion / Conclusion	Last page refers to “this comprehensive list of genetic tests,” which seems at odds with the caveats and limitations detailed in the same section. Specifically, I don’t know how the list can be characterized as comprehensive with any degree of certainty. This is not a criticism of methodologies used, simply a suggestion to	Thank you, we have reworded the sentence.

		describe the results in more accurate detail.	
2	Tables	See comments on table 1 in Methods section above. Table 2 is very informative, however, the authors may want to consider splitting the purpose column into multiple columns with each individual purpose written out completely (using vertical text alignment), and tick marks or bullets used to indicate which tests (rows) correspond to each purpose. This would obviate the need for readers to refer to the legend to differentiate between P, Pp, and PGx, for example. Also in table 2, some test names have a ™ symbol while others have an ® symbol. Since I assume that the intended audience for the report consists primarily of those with clinical or scientific, rather than legal, expertise, it could be helpful to discuss what significance, if any, can be attributed to the difference.	We have edited the table to obviate the need for readers to refer to the legends. The tests are indicated with ™ and ® as reported in individual Websites.
2	Appendices	Ordinate scales on the Medline search charts may be confusing to some readers, since they are not consistent between different tests (some don't begin at 0, others range from 0.0 to 1.0). Trend lines never go down, so I assume the measure of hits is cumulative for each year, rather than being categorical by publication date, but this should be specified. In some cases I felt the charts could be omitted and results described in text (for example when publication numbers are very low or when no publications that are returned with the selected search string.	At the suggestion of many reviewers we have omitted the graphic plots.
2	References	Need a space in reference 4, after the first period. Also need a period at the end of reference 4.	We have corrected this.
3	General	Horizon scanning for health-related genetic tests is challenging because the development of these tests is rapidly evolving and decentralized, involving government, academic, and commercial entities. The draft report aims to summarize key information on genetic tests currently available for clinical use in cancer. The information in the report is valuable but is likely to become quickly outdated: comparison with the last AHRQ Technology Assessment of genetic tests in cancer (2006) shows how quickly the field is changing. A more continuous horizon scanning process, together with an online database (such as the GeneTestTracker) that could be continuously updated and made available to a wider range of users, would be more useful than a periodic report published at infrequent intervals.	The database is continuously updated and we have clarified that in the text and results section.
3	Executive summary	This draft report does not include an Executive Summary.	Thank you, it is now included.
3	Introduction/ Background	The first paragraph clearly enumerates the different ways that genetic tests can be used in cancer, i.e., in screening, diagnosis, risk stratification, therapeutic management, and as a clinical decision-making tool to aid disease monitoring and prognosis. Definition of these categories is very important in evaluating the validity and utility of cancer genetic tests, especially those that have been proposed for multiple uses (e.g., both therapeutic management and prognosis) because the relevant evidence depends on the proposed use. Although full definitions are	Thank you. The report does not assess clinical validity or utility of the tests in this report.

		provided in the Methods section, I'm glad that the authors have drawn attention to this point in the Introduction.	
		In addition to summarizing "all newly identified tests since 2006," it would be helpful to provide a list of tests reviewed in 2006 with an update on their status—e.g., to note whether in the interim, they have been approved by FDA, modified by the test developer, or taken off the market. That would provide users of the report with a comprehensive list of tests meeting the inclusion criteria listed on pg. 10. The SACGHS definition of genetic tests provided on pg. 9 is not really adequate for this report. Although the definition includes "acquired" genotypes, the purposes it describes for genetic testing are almost entirely from the clinical genetics perspective, which focuses on heritable diseases. As explained in the Introduction, "Genetic tests for cancer differ from genetic tests for noncancer conditions in the relatively larger number of tests for somatic mutations." As noted on pg. 10, the report "excluded tests that are performed for conditions that result in early death before reaching adulthood, such as metabolic or heritable disorders." The authors should at least make note of the discrepancy, if not point out the need for a more comprehensive definition. A word seems to be missing from this sentence on pg. 10: "We summarized all genetic tests that we found **[that?]** can be used to provide diagnostic and prognostic information, monitor patient status, or detect disease recurrence." Google News searches (described on pg. 13) do not use the same query structure as PubMed. The query "gene OR genetic OR genomic test OR epigenetic" in PubMed would be represented in Google News advanced search as *Find results with at least one of the words* "gene genetic genomic epigenetic." It's not clear why the word "test" would follow "genomic" in either query—it seems that it should be added with AND to the PubMed query and excluded from the Google query as too non-specific. The Google query equivalent to "FDA cleared test" would be *Find results with all of the words* "FDA cleared test." The search strategy should be described more precisely, including the frequency with which e-mail alerts were reviewed, especially because many news links are ephemeral and inaccessible after a short time. Were the laboratory web sites (listed on pg. 14) searched regularly or only once?	We have added how many tests that were in development have matured to a clinical application since 2006 and which of those are approved by the FDA. However, it is difficult to identify how many were modified by the test developer or were taken off the market (except for one) without personal communication with the companies. Such communications can be very useful for the grey literature process, but are out of the scope of the current work assignment. The SACGHS definition does include somatic mutations. We have edited this section for the most recent definition. We have edited this sentence. The Google News does allow searches to be conducted using "OR" and additional search terms can be added to the Google email alert. We have removed "OR" within the test because it resembles that of PubMed searches. We view email alerts once a week. Those are great questions, we can only identify those changes to genetic tests only through contact with the companies or a company voluntarily deposits such information. Currently we do not have mechanisms to identify multiple commercial
3	Methods	How does the horizon scanning process treat multiple commercial names for the same test (e.g., when a test has been licensed from one company to	

		another)? How does it deal with changes to a test that keeps the same name (e.g., when additional SNPs are added to a genotype test)? Details of the development of GeneTestTracker (pp. 16-18) seem somewhat superfluous to the report, especially because it appears that this is an in-house system, available only to AHRQ and CMS users. The system was already described in the last AHRQ report on noncancer genetic tests. If this online database will be made accessible to a wider group of users, the software development project could be published in a citable informatics journal.	names to the same test as well as any changes made to the genetic test. We have added this as a limitation to the web-based horizon scanning process.
3	Results	The report states (pg. 19) that the GeneTestTracker contains information on 100 genetic tests (in 149 test-disease combinations); of these, 38 are cancer-related tests identified since 2006. How do these results correspond with those reported in earlier AHRQ horizon scans for genetic tests? For example, the 2006 report identified 104 cancer-related genetic tests "in development"; the 2010 report on noncancer tests identified 22 new tests since 2007. It's not clear how these results fit together or how the GeneTestTracker is updated. Can it be used to describe the evolution of specific tests (or the field as a whole) or does it provide only cross-sectional data (i.e., more details on tests described in the published reports)? We conducted a pilot project (also based on Google News Alerts) to assess the former question and encountered several challenges (see Horizon scanning for new genomic tests, PMID: 21233720, DOI: 10.1097/GIM.0b013e3182011661). During a 6-month period, we identified 188 new, health-related genetic tests, of which 122 (or approximately 2/3) were related to cancer; after the pilot phase, we continued to identify 2-3 new tests per week. Although we applied less stringent eligibility criteria (to capture tests that were still in development or just being introduced for clinical use), these findings reflect a very rapidly developing field.	The 2006 report identified "tests in development" contacting various companies to identify 104 cancer-related tests in development. Only if these tests have matured to clinical use are added to the electronic database, but those that are still in development are currently being tracked to identify their status.
3	Discussion/ Conclusion	Some of the issues mentioned above could be addressed briefly in the Discussion.	Thank you we have added many of your valuable points to our discussion
3	Tables	No additional comments.	
3	Figures	Figure 2 is not needed because it duplicates (with less detail) information already presented in Table 2.	Deleted.
3	Appendices	The one-page summaries provide key information about each test; however, they are not easy to search or analyze. Is there any significance to their order? Could it be changed to correspond with the order in Table 2 (i.e., breast cancer first, then prostate cancer, etc)? Ideally, readers would be allowed to use the GeneTestTracker database for searching and access to more detailed information retrieved for the technology assessment. The charts of "Medline hits" are dramatic but they take up a lot of space. It might be	We have rearranged the one-pagers according to the table 2. At the suggestion of many reviewers, we have omitted the graphic plots.

		more helpful to show these data in a table. It would be easier to make comparisons among tests (e.g., to see which ones might have sufficient data available for a systematic review) using numbers. Vastly differing scales on the charts highlight trends while down-playing the actual numbers of citations.	
3	References	Suggest referencing other attempts to summarize information on genetic tests, such as: Kuehn BM. NIH launching genetic test registry. *JAMA* 2010;303:1685.	Thank you. We have added in the discussion.
4	General	A glossary of the genetic/genomic terms used would be a welcome addition.	Many of the terms are explained within text.
4	Methods	A major omission in the search strategy is the test directory maintained by the Association for Molecular Pathology (AMP) http://www.amptestdirectory.org/index.cfm Unlike the GeneTests website which mostly includes tests for inherited forms of cancer, the AMP directory includes genetic tests for both inherited and acquired cancer. Although a wide range of reference laboratory and manufacturer websites were included, it is likely that the many hospital and university-based laboratories that provide genetic tests for cancer were missed with this search strategy.	We have searched academic laboratories with limited yield for new tests. We have added AMP.org as one of our resource for current and future horizon scanning.
4	Results	There are a number of notable omissions in the list of available tests including KRAS for NSCLC and CRC, BRAF in CRC, ERCC1 in NSCLC, deCODE ProstateCancer, DecisionDx-GBM, DecisionDx-UM, CYP2D6 in breast cancer, JAK2 in myeloproliferative disorders, PathfinderTG (multiple applications), Previstage GCC in CRC, TargetNow Molecular Profiling test, THEROS CancerTYPE ID.	Thank you, we have included tests that provided complete one-pager information.
4	Discussion / Conclusion	Limitations of the study are appropriately noted but perhaps greater emphasis on the dynamic nature of genetic/genomic testing for cancer applications is needed and a more definite schedule for updating both the existing information sheets and the addition of new tests is needed. At a minimum such a scan should be performed annually	Yes, the updates are ongoing and we have clarified in the method section.
4	Figures	Figure 2 does not seem to add any useful information to the report. I would recommend omitting it	We have deleted the figure.
4	Appendices	Suggestions for the test information sheets: o Expand description of test; define terms used o Provide a date for the literature search o Delete figure that shows increase in publications – this will not be meaningful to most users o Include a few key abstracts or at least links o Write sources in proper citation style; include links to websites, if used	The database searches the last date of finalizing the draft report (March 2011). The current output is directly from the database. The current database is structured similar to the Excel and Word databases included in the 2006 report.
4	References	This reference list seems very short – I assume more resources were used? If so, they should be cited. Dates of access of websites should be included.	The web sources are listed within the text.

[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 of Horizon Scans of Genetic Tests
Project ID: GEND0508

Table 2: Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
1	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 on the Agency for Healthcare Research Quality (AHRQ) Update on Horizons Scan of Genetic tests currently available for Clinical Use in Cancer (November 2010). The College is a national medical specialty society representing 17,000 pathologists who practice pathology and laboratory medicine. The College?s Commission on Laboratory Accreditation through its Laboratory Accreditation Program (LAP) is responsible for accrediting more than 6,000 laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and serve as inspectors in the laboratory accreditation program. General Comments: The report would be more appropriately titled Update on Horizons Scan of Molecular Diagnostic Tests currently available for Clinical Use in Cancer. The use of the terminology ?genetic test? is inappropriate - a terminology consistently used in this document to refer to ACQUIRED somatic mutations in cancer or pre-cancer cells. Though the Introduction appropriately differentiates genetic and somatic mutations, the authors create confusion by using the SACGHS definition which is broad enough to include any molecular test used for cancer patients. In addition, the individual summaries in the Appendix fail to note which tests are for genetic variation and which are for somatic mutations which we believe is an important distinction. The College is concerned that AHRQ would publish a report	We have been using the SACGHS definition for the past 5 years. The definition is comprehensive and fits very well within the range of products that have been commercially available under “genetic tests.” Our tests include both molecular as well as somatic mutations genetic / genomic tests, when available. The purpose of our report is to succinctly summarize the results of horizon scanning of new genetic/genomic tests. Further classification will be adequately addressed during a focused systematic review. The focus of this report is to catalogue the tests available and marketed commercially. We do involve

			composed by a group that inappropriately fails to include relevant stakeholders. The authorship of any report involving lab tests should include pathologists who are providers of the spectrum of lab tests covered in the report. As we have noted before, the College is concerned about the performance of horizon scans and other literature reviews divorced from an understanding of the clinical use of the tests which can result in incorrect categorization of tests.	stakeholders, when a test is reviewed in detail for analytical validity, clinical validity and clinical utility through a systematic review of published studies.
1	College of American Pathologists	Introduction/ Background	The introduction provides a good description of the differences between genetic and somatic mutation, however, this important distinction was not addressed beyond the introduction and should be noted for each test summary in the Appendix.	Thank you.
1	College of American Pathologists	Methods	Literature Search: The authors should broaden their search to include additional resources. The web searches used for data discovery specifically excluded the ?gold standard? source for finding cancer molecular diagnostic tests in real-world service labs, namely the AMP test directory (amp.org). GeneTests, heavily emphasized as a prime data source, specifically EXCLUDES tests for acquired cancer-associated mutations. In addition, the CAP Proficiency testing products catalog would be an excellent resources. The catalog lists oncology tests for which proficiency testing (PT) is available thru CAP for tests that are used in clinical settings (focus on DNA or RNA based tests, but not the many other tests that CAP members provide like morphology and lipid/protein-based tests relevant to oncology). The emphasis seems to be misplaced onto the NUMBER of new cancer tests that can be found ? rather than the much more appropriate (and harder to get) data on the VOLUME of such testing (ie, sample numbers) in routine clinical practice ? which will be a much better surrogate for clinical utility. Similarly, the emphasis on ?number of Medline hits? seems quite misplaced, Medline hits being, by definition, a surrogate for quantitating perhaps research emphasis, but certainly not clinical usage/utility. Clinical Application of Tests: Definitions for terms used in the report are important. "Therapeutic management" includes all kinds of therapy from drugs to behavioral therapy to nutrition counseling. The terms screening, diagnostic, monitoring, prognostic and predictive are typically used to categorize oncology tests. There needs to be explicit clarity between predictive and prognostic tests. The report currently has a category of ?prevention? that includes predictive testing. A specific definition of pharmacogenetic tests is	We relied on several sources including GeneTests.org. Thank you for suggesting the website (amp.org). We will review the list of genetic tests against those currently captured in our database and add any new tests that we may have missed out. The purpose of conducting Medline hits is to assess available evidence for a topic review through a systematic review and analysis. The purpose of this horizon scanning is not to assess the volume of testing or to assess the clinical utility. We have clarified the terminologies and we have changed pharmacogenetic to

			also needed as this term is used inappropriately in some summaries in the Appendix.	therapeutic management.
1	College of American Pathologists	Results	Table2 The list of tests does not include prognostic brain tumor markers such as deletions on chromosome 1p and 19q or testing for NF1 which is associated with numerous cancers (malignant peripheral nerve sheath tumors, gliomas, sarcomas, neuroendocrine tumors, and leukemia). Patients with these malignancies commonly do not develop malignancies until after reaching adulthood and therefore do not meet the exclusion criteria for conditions that result in early death before reaching adulthood. The College believes these tests and others were missed due to the methodology and focus on commercial laboratories. There are a number of analytes that are not listed in Table 2 for which the college offers PT. While excluding the tests noted above, the list includes such test as cytokeratin 20 (CK20) and alpha fetoprotein (AFP) that are not genetic tests, or even somatic mutations at all, but rather indicators of cell type and differentiation. While an important test, the digene High-Risk HPV HC2 DNA Test is neither a genetic test nor a somatic test but rather tests for an infectious agent etiologically related to cervical cancer and which is used in the context of cytologic evaluation of cervical specimens in some women. Electronic Database We noted that the electronic database created for this reports duplicates some of the efforts of the National Institute of Health to create a genetic testing registry. We commend the Tufts Medical Center Evidence-base Practice Center for developing this resource.	Preference of entry is usually given to common cancers that are more applicable to the older adults. Thank you we will add tests suggested, since the update is ongoing. There are many more tests listed in our previous report, and this is an update to the report published in 2006. The one pagers are available in the pdf/word format at the following weblink: http://archive.ahrq.gov/clinic/ta/gentests/ We have used a broad definition put forward by SAGCHS. Their definition of a genetic test also includes biochemical tests for gene products such as enzymes and other proteins. We have deleted the digene High-Risk HPV HC2 DNA Test since this falls under the category of non-medical genetic testing mainly for the identification of the presence of animal/viral materials. The efforts by AHRQ/CMS to create and maintain this database precede some of the recent efforts of the National Institute of Health to create a genetic testing registry. These reports have been ongoing for the past five years with a focus to identify topics for a thorough future evidence evaluation. To this extent we have shared our database with the NIH.
1	College of American Pathologists	Discussion/ Conclusion	The CAP appreciates this opportunity to comment on this Updated Horizon Scan. Due to the short review period, we could not provide a more detailed review of the one page summaries in the Appendix but hope that overall our comments are helpful. If you have any	Thank you for the contact information.

			questions on the issues raised herein, please do not hesitate to contact, Fay Shamanski, Ph.D., Assistant Director, Public Health and Scientific Affairs (202-354-7113/fshaman@cap.org)	
1	College of American Pathologists	Appendices	While we did not have sufficient time to provide detailed edits in general we found the purpose of the tests to be inappropriately described in some cases. In particular, some tests were listed as pharmacogenetic that are not involved in drug metabolism but rather used for therapeutic management. Pharmacogenetic implies both that genetic variation is inherited and that it is involved in drug metabolism(1). For example, DPD 5-FU GenotypR (TM) fits the definition of a pharmacogenetic test, while tests such as Her2 neu overexpression are probably more accurately described as used for therapeutic management. (1)For example, one definition is the heritable component of variation among individuals with respect to drug response or adverse reaction. www.nature.com/nrg/journal/v5/n5/glossary/nrg1325_glossary.html	We have add the therapeutic management since this is similar to our categories.
2	Bristol-Myers Squibb Company		Bristol-Myers Squibb is a global biopharmaceutical company firmly focused on its Mission to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. We are proud to acknowledge and support the initial Draft Report entitled ?Update on Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancers?. We appreciate the opportunity to provide comment(s) on this research effort. We believe the attempt to capture the field of genetic testing via a web search is limited in that many of the tests reported were not based on the manufacturer's information, but on secondary websites that reported about the tests without attribution to the manufacturer's name or website. Additionally, the term ?genetic? testing is utilized throughout the document , yet, a number of the tests are protein based and not genetic while the inclusion criteria is unclear. As a web search was used, it cannot be assessed how well they identified all tests available. In table 1, the listing of websites used does not include a number of major manufacturers, with a corresponding lack of tests reported in the appendix. There are several hundred Diagnostics manufacturers, and the number of tests offered through CLIA labs is virtually impossible to determine. Lastly, it would be useful to have the ability for the public to search the Tuft?s GeneTest Tracker database system and obtain high level information on these	The attempt to identifying genetic testing through web searching has been replicated by a recent publication from the members at the CDC (Gwinn et al PMID:21233720). The purpose is to identify as many tests as possible with the caveat that there are many tests available that would not be captured within the sources interrogated. This limitation has been added to our discussion section. We are using a broad definition as put forward by the SACGHS. This definition does include the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes. There are many more tests listed in our previous report, and this is an update to the report published in 2006. The one pagers are available in the

			types of tests.	pdf/word format at the following weblink: http://archive.ahrq.gov/clinic/ta/gentests/
3	Amgen Inc.		Amgen Inc. (Amgen) wishes to provide comments to the recently-released Agency for Healthcare Research and Quality (AHRQ) draft Technology Assessment (TA) entitled, ?Update on Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancer?, issued for public review and comment on December 22, 2010. This letter is intended to emphasize the importance of including Kristen-RAS (KRAS, a member of the rat sarcoma virus (ras) gene family of oncogenes) testing in any comprehensive review of genetic tests currently available for clinical use in cancer. As a science-based, patient-driven company that is committed to using evidence-based science and innovation to dramatically improve patient?s lives, Amgen respectfully submits this short comment letter to help support and supplement the careful analysis completed by the team at the Tufts-New England Medical Center Evidence-based Practice Center (EPC). KRAS mutation analysis was one of the topics discussed in the June 7, 2010 Technology Assessment report (Project ID: GEN0609) entitled ?Systematic Reviews on Selected Pharmacogenetic Tests for Cancer Treatment: CYP2D6 for Tamoxifen in Breast Cancer, KRAS for anti-EGFR antibodies in Colorectal Cancer, and BCR-ABL1 for Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia?. As reviewed, KRAS analysis is an important pharmacogenetic test for colorectal cancer patients being considered for anti-EGFR therapy. This finding was arrived at through analysis of several randomized controlled trial-based analyses of progression-free survival, where treatment benefit was found to be unlikely for colorectal cancer patients whose tumors carried KRAS mutations, in comparison to colorectal cancer patients whose tumors were KRAS wild-type. And, as Amgen previously publicly commented on this TA (Amgen comment letter dated February 12, 2010), two additional phase 3 chemotherapy/anti-EGFR combination studies have been completed and subsequently published (footnotes 1 & 2). In both studies, panitumumab in combination with either FOLFOX or FOLFIRI significantly improved progression free survival (PFS) in patients with KRAS wild-type tumors, including in 1st line use. In contrast, patients with KRAS mutant tumors did not show an	We thank you for the comments as well as for the contact information. We would like to clarify this is a horizon scan report listing tests that are currently available for clinical practice. This is not a full systematic review.

			improvement in median PFS. In the 1st line study, in patients with tumors harboring activating KRAS mutations, PFS was significantly inferior in the panitumumab arm. Further underscoring the importance of KRAS pharmacogenetic testing, the labels for this class of drugs were modified to state that retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit in patients whose tumors had KRAS mutations in codon 12 or 13 (footnote 3). We appreciate AHRQ?s and the Tufts-New England Medical Center EPC?s careful consideration around either formally adding KRAS testing to this report, or, at least clearly referencing this important cancer test in the final, published technology assessment. Furthermore, we look forward to continuing to work with AHRQ, CMS, as well as with our industry colleagues and others, to further explore this rapidly evolving and promising field of pharmacogenomic testing in cancer. As your interest allows, we would welcome the opportunity to provide additional information in support of your on-going efforts. Please contact Sarah Wells Kocsis by phone at (202) 585-9713 or by email at wellss@amgen.com if you have any questions regarding our comment, or, wish to arrange a meeting. Footnotes: 1. Douillard, J.-Y. et al. Randomized phase III study of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. J. Clin. Oncol. 28, 4697?4705 (2010) 2. Peeters, M. et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J. Clin. Oncol. 28, 4706?4713 (2010) 3. FDA Press Release July 17, 2009 describing Class Labeling Changes to anti-EGFR monoclonal antibodies, cetuximab (Erbitux?) and panitumumab (Vectibix?) http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm	We thank you for the comments as well as for the contact information. We would like to clarify this is a horizon scan report listing tests that are currently available for clinical practice. This is not a full systematic review. We have included references that are needed for grey literature search purposes.
4	University of Ottawa	General	This draft only has come to my attention within the past week, so I have not had the opportunity to do a thorough review.	Thank you for pointing us this error. We have deleted the digene High-Risk HPV HC2 DNA Test since this falls

			I was particularly struck by some of the one-page summaries in Appendix A, notably for PSA (page 28 and page 47), and high-risk HPV (HC2; page 46). I can see that PSA and related testing fits in with the definition of genetic testing presented on page 9. The test for high-risk HPV is a test for specific types of viral infection, so it does not fit the "human" definition on page 9. That said, it is a test that looks at variant types of viral DNA (and arguably this becomes problematic when this DNA is integrated with that of the human host, although the test does not test for integration per se). I'm aware that there are more tests for HPV available, but I assume that these were not included because they have not been cleared by FDA, or are in status of pending clearance.	under the category of non-medical genetic testing mainly for the identification of the presence of animal/viral materials. Other tests do qualify based on the definition chosen for the horizon scanning.
4	University of Ottawa	Appendix A	I note that the purpose of test 2 (complexed PSA, page 28) is listed as "diagnosis and monitoring" in adjunctive testing with DRE, but the description given suggests the test would be applicable to screening. The purpose of test 19 (free PSA, page 47) is listed as "screening, diagnostic". Are these the same tests that are used in PSA testing in annual physicals? It would be very helpful to clarify this, and refer to the evaluations of PSA screening http://www.ahrq.gov/clinic/uspstf/uspsprca.htm. and Lin K, Lipsitz R, Miller T, Janakiraman S. Benefits and Harms of Prostate-Specific Cancer Screening: An Evidence Update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 63. AHRQ Publication No. 08-05121-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality. August 2008. With regard to test #18 (HC2 for high-risk HPV), note that this is a test for viral infection. It is highly sensitive for detection of cervical intraepithelial neoplasia (stage 2 or more severe). CIN is a precancerous lesion. This does not quite fit in with the definition of prevention on page 11, as it is not detecting inherited susceptibility in persons who do not have cancer, and although it does pick up early stage cancer, I think a key property is detection of CIN2/3 along the lines of the Pap test. There are many evaluations of HPV testing both as a primary screening test, and in triage of women with low-grade cervical cytological abnormalities (e.g. by Marc Arbyn and	We have included tests that fit the inclusion criteria per our definition. Further clinical validity or utility issues are best addressed during a systematic review. We have deleted the digene High-Risk HPV HC2 DNA Test.

			colleagues; I note also that there is a Cochrane review group http://www.hpv2009.org/CochraneWebsite.pdf) [I must declare an interest because of my involvement in the UK TOMBOLA trial]	
5	Technology Evaluation Center, Blue Cross Blue Shield Association	General	The Blue Cross Blue Shield Association Technology Evaluation Center has reviewed the draft technology assessment, Update on Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancers, and submits the following comments for consideration: 1) As noted, ?The current report updates the database of genetic tests for cancer conditions . . . for all newly identified tests since 2006? and provides a listing and individual test summaries for only those new tests. The reader is referred to the 2006 test listing in citations and via a web link in Appendix A. However, a synthesized list would constitute a more useful and comprehensive update with indications of which tests are new since 2006, which 2006 tests are still available, and which are no longer available (e.g. PreGen). 2) The 2006 report also provided a ?tests in development? list which this draft does not update. It would be helpful to know which of the 2006 listed tests in development moved to 2010 tests available list, which are still in development, and which are no longer in development. Will an updated ?tests in development list? be added to this report? 3) This draft assessment describes a ?GeneTestTracker? database to which ?users can add a new genetic test by simply clicking the ?add new? button.? It is not clear how accessible this ?password protected? database will be, who will have password access to add new tests, and who will curate the information. The report does note that ?CMS would like the report and the accompanying database to be a ready reference for their internal discussions in this area and for decisions on future topics for systematic reviews.? Does that mean that the database is limited to CMS use only? That would preclude the potentially broader utility of such a database. In addition, this database begins to duplicate, in concept (and limited to cancer) the proposed NIH Genetic Test Registry. Is there discussion of integrating the two databases? 4) The new test listing seems to be missing tests; see below for several quickly and randomly picked examples that we could not find in either the 2006 or 2010 reports (note: although some diagnostic	We have added additional information on the evolution of genetic tests in the results section. The Office of Public Health Genomics at the Centers for Disease Control and Prevention published paper utilizes similar approach to our literature search and they do count tests both that have matured to clinical use and that are currently listed as in development. The members of this office are included as reviewers in this report and their input at this stage of review is insightful.

			laboratory websites may not detail the components of multi-gene profiles, where such tests are commercially available, test indications are stated, and it is clear that the test is nucleic acid-based, it would seem to meet inclusion criteria). 5) Regarding grey literature sources, GeneTests.org (focused largely on diseases of Mendelian inheritance) and commercial laboratories are certainly viable sources, but there are other groups with well-tested, ongoing grey literature search mechanisms for current information on genetics and genetic tests who could have been consulted or perhaps made partners in this update (e.g. the Office of Public Health Genomics at the Centers for Disease Control and Prevention). 6) The EGAPP Working Group maintains a running list (although not necessarily comprehensive) of available genetic tests on its public website. This list does not appear to have been consulted. As examples, the PI3K and JAK2 tests listed below appear in the EGAPP website listing. Random examples of tests not on either 2006 or 2010 genetic test lists: Response Genetics has developed PCR-based genetics tests?ResponseDX: Lung?, ResponseDX: Colon?, ResponseDX: Gastric?? ?to help physicians with therapeutic treatment decisions for patients with non-small cell lung cancer (NSCLC), colorectal cancer (CRC) and gastric cancer.? (http://www.responsegenetics.com/). ALK Gene Rearrangement (Clarient) PI3K mutations (Clarient) Breast Profile (CombiMatrix Diagnostics; http://www.cmdiagnostics.com/oncology/index.html) ?Our Breast Profile offers all of the benefits of HER2 PRO, plus the added clinical utility derived from a complete genomic analysis of each patient?s unique tumor DNA.? Heme Profile (CombiMatrix Diagnostics) ?The DNAarray assay for Hematologic Malignancies such as Chronic Lymphocytic Leukemia (CLL) and MyelodysplaStic Syndrome (MDS) combines the high resolution of FISH with the genome-wide copy number assessment found in traditional cytogenetics testing.?	The members of the Office of Public Health Genomics at the Centers for Disease Control and Prevention have been peer reviewers of our report. Thank you, we have added additional tests with complete one-pager information.

			Tumor Profile (CombiMatrix Diagnostics) ?The DNAarray Tumor Profile allows for the rapid identification of key amplifications and deletions across the genome, which can yield important prognostic and predictive information for both physician and patient.? JAK2 (widely available) Confirm diagnosis in individuals with clinical suspicion of myeloproliferative disorders ColoSure? Colorectal Cancer Detection (Vimentin Gene Methylation Assay; LabCorp)	
6	Novartis Oncology		Dear AHRQ Committee members, Novartis Oncology, a business unit within Novartis Pharmaceuticals Corporation, is pleased to submit comments for consideration by the Committee as it discusses the impact of pharmacogenetic testing on the health outcomes of specified groups of patients with cancer. Specifically, we are submitting comments against the recommendation to use KIT Asp816Val Mutation Analysis as a pharmacogenetic test in patients with chronic myeloid leukemia (CML) who are resistant to imatinib therapy. In support of this position, we will summarize the current evidence regarding the role of imatinib on the oncoprotein BCR-ABL in CML, as well as its action on off-target kinases such as c-KIT and platelet-derived growth factor receptor alfa (PDGFRA). In addition, we appreciate the opportunity to review the effect of mutant c-KIT on specific cancers. CML and BCR-ABL CML is a clonal disease characterized by the presence of the Philadelphia (Ph+) chromosome and its oncogenic product, BCR-ABL, a constitutively active tyrosine kinase, that is present in >90% of patients.(1) The Ph stems from a reciprocal chromosomal translocation of the BCR gene from chromosome 9 and the ABL gene from chromosome 22. The BCR-ABL fusion gene drives the pathogenesis of CML.(2) The development of selective BCR-ABL tyrosine kinase inhibitors (TKIs), including Gleevec? (imatinib mesylate) and more recently Tasigna? (nilotinib) and Sprycel? (dasatinib), have positively impacted clinical outcomes in CML, and have become the current standard of care for treating newly diagnosed patients with Ph+ CML.(3) Most patients who receive TKI therapy for CML in chronic	Our introduction clearly states that the purpose of horizon scan “The main objective of this report is to provide a broad overview with sufficient information on each identified genetic test, and to provide a preliminary estimate on the amount of published literature available on each genetic test. This report is not meant to be an in-depth review of each test. Systematic review of selected tests will be the subject of future focused reviews.

			phase now achieve a complete cytogenetic response (CCyR) during the course of treatment. Clinical studies have demonstrated an overall survival rate of 85%, and a freedom from progression to AP or BC of 92% at 8 years on imatinib therapy.(4, 5, 6) The clinical use of specific BCR-ABL inhibitors has significantly improved prognosis, response rate, overall survival, and patient outcome in CML patients compared with previous therapeutic regimens.(1) Although point mutations in the ABL-tyrosine kinase domain contribute to imatinib resistance,(7) a review of published literature and internet search revealed a paucity of published scientific evidence documenting the presence or incidence of KIT Asp816 Val mutation in patients with CML. Furthermore, no published scientific evidence suggests that the KIT Asp816 Val mutation confers clinical or prognostic significance in patients with CML. There is no published evidence documenting the sensitivity and validity of this genetic test in patients with CML or that the results of this test can provide therapeutic guidance for practitioners. Imatinib inhibits BCR-ABL, PDGFRA, and c-KIT Imatinib not only inhibits BCR-ABL but has been found to be almost equally potent in vitro against PDGFRA, and c-KIT receptor tyrosine kinases.(8) KIT is a receptor tyrosine kinase that is functionally relevant for hematopoiesis, mast cell development and function, gametogenesis and melanogenesis.(9) Imatinib targets KIT at the ATP-binding site, thereby maintaining the receptor in a nonactivated state.(10) While in humans, loss-of-function KIT mutations have been associated with piebaldism?an autosomal dominant condition characterized by depigmented patches of skin and hair?gain-of-function KIT mutations are usually acquired, and have been associated with myeloid malignancies including core binding factor acute myeloid leukemia and systemic mastocytosis (SM), germ cell tumors, gastrointestinal stromal tumors (GIST) and sinonasal T cell lymphomas.(9) Imatinib as treatment for GIST GIST are the most frequent mesenchymal tumors of the gastrointestinal (GI) tract and represent <1% of all malignant GI neoplasms.(11) KIT mutations are detected in about 75% to 85% of GIST patients, while PDGFRA mutations are found in 5% to 10%.(12) Since KIT and PDGFRA mutations are central events in GIST pathogenesis, and imatinib was known to act on these receptors, imatinib was evaluated in the treatment of patients with	The contents in the database and in the report reflect the data obtained from manufacturers' Web sites or other commercial Web sites, and should not be construed as definitive clinical evidence." We have added few more words "or as a recommendation for clinical use"

			GIST whose tumors expressed activated c-KIT, with promising efficacy and safety.(13) Following clinical trials, imatinib was approved for the treatment of GIST in February 2002.(11) Resistance to imatinib in patients being treated for GIST can generally be ascribed to the presence of secondary mutations, usually affecting the catalytic domain of KIT. The Val654Ala substitution, affecting the ATP-binding pocket of the kinase, is one of the most commonly detected mutations.(11) Sunitinib has recently been approved as second-line therapy for patients with GIST who became resistant to imatinib treatment.(14) Systemic mastocytosis and the KIT Asp816Val mutation Stem cell factor (SCF)-dependent activation of KIT is critical for mast cell homeostasis and function. However, when KIT is inappropriately activated, accumulation of mast cells in tissues results in mastocytosis.(10) KIT Asp816Val is the most prevalent KIT mutation in mast cell disease and occurs in more than 90% of patients with systemic mastocytosis (SM).(9) Detection of a mutation at the 816 codon is included as 1 of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib.(15, 16) Notably, SM with PDGFR mutations are highly sensitive to treatment with imatinib, whereas the more common SM containing KIT Asp816Val mutations are usually resistant to imatinib, because of an induced conformational change at the ATP-binding domains of KIT, which confers constitutive activity(17) and interferes with the association of imatinib and the receptor.(18, 19) Determination of the presence or absence of a KIT Asp816Val point mutation by cytogenetic analysis in patients with SM is therefore important for establishing a diagnosis, as well as for guiding pharmacologic therapy.(20, 21) A similar pharmacological profile has been reported for the imatinib mimetics; therefore, development of KIT kinase inhibitors that overcome the drug-resistance associated with the KIT Asp816Val mutation remains a focus of ongoing research.(22) Although SM can occur concurrently with myeloid diseases such as CML or chronic myelomonocytic leukemia,(23) there is no literature documenting the incidence, implications or prognosis in patients with concurrent CML and SM with a KIT Asp816Val point mutation. Conclusion	The tests are listed as those available in clinical use. The report does not attest the clinical validity or utility of the tests.

			In conclusion, while determination of the presence or absence of the KIT Asp816Val mutation in patients with SM offers a useful adjunct in establishing a diagnosis and therapeutic treatment plan for this complex and heterogeneous disease, there is no evidence or rationale to support testing for this mutation in patients with CML, as recommended in the draft Update on Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancers. Although imatinib simultaneously targets BCR-ABL and c-KIT, and is considered standard therapy in the treatment of CML, there exists no published scientific evidence that the KIT Asp816Val mutation has any relevance to patients with CML, and therefore genetic analysis of the KIT Asp816Val mutation should not be recommended for guiding imatinib therapy in CML patients. In an era of cost consciousness, it is neither rational nor prudent to recommend the KIT Asp816Val genetic test for patients with CML. Furthermore, patients with CML should not be subjected to painful, costly and unnecessary bone marrow sampling without established clinical merit. Finally, there is no pharmacoeconomic analysis to suggest that the information derived from this genetic test offers valuable information that would direct clinical decisions and decrease health care costs in patients with CML. Novartis Oncology respectfully submits that the recommendation to use KIT Asp816Val mutation analysis for CML patients be removed from the draft, as no evidence for using KIT Asp816Val mutation analysis for CML or for guiding treatment with imatinib could be identified in the scientific and medical literature. We appreciate the opportunity to respond to your request for information and would be happy to provide additional information and/or answer any questions you may have on this topic. Please do not hesitate to contact me if I can be of further assistance. We appreciate the opportunity to submit a response. Our comments are of a general nature; therefore, we have included our response in the "General" category. ---------References---------- 1. An X, Tiwari AK, Sun Y, Ding PR, Ashby CR, Jr., Chen ZS. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review. Leuk Res.	The tests are listed as those available in clinical use. The report does not attest the clinical validity or utility of the tests. Thus evidence around these tests are not assessed in this report to suggest removal of these tests.

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			basis and management of gastrointestinal stromal tumors. World J Gastroenterol. Jun 14;16(22):2726-2734. 14. SUTENT(R) (sunitinib malate) capsules. [Sutent Prescribing Information]. July 2010 July 2010;New York, NY:Pfizer Labs. 15. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res. Jul 2001;25(7):603-625. 16. Jaffe ES HN, Stein H. World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the Haematopoietic and Lymphoid Tissues. 2001:291-302. 17. Foster R, Griffith R, Ferrao P, Ashman L. Molecular basis of the constitutive activity and STI517 resistance of Asp816Val mutant KIT receptor tyrosine kinase. J Mol Graph Model. 2004;23:139-152. 18. Scheinfeld N. A comprehensive review of imatinib mesylate (Gleevec) for dermatological diseases. J Drugs Dermatol. Feb 2006;5(2):117-122. 19. Akin C, Brockow K, D'Ambrosio C, et al. Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit. Exp Hematol. Aug 2003;31(8):686-692. 20. Pardanani A, Ketterling RP, Brockman SR, et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood. Nov 1 2003;102(9):3093-3096. 21. Valent P, Akin C, Sperr WR, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol. Sep 2003;122(5):695-717. 22. Gleixner KV, Mayerhofer M, Aichberger KJ, et al. PKC412 inhibits in vitro growth of neoplastic human mast cells expressing the D816V-mutated variant of KIT: comparison with AMN107, imatinib, and cladribine (2CdA) and evaluation of cooperative drug effects. Blood. Jan 15 2006;107(2):752-759. 23. Agis H, Sotlar K, Valent P, Horny HP. Ph-Chromosome-positive chronic myeloid leukemia with associated with bone marrow mastocytosis. Leuk Res. 2005;29:1227-1232.	Thank you, this report is not an extensive evidence review.
Mary Steele Williams	Association for Molecular Pathology		Thank you for the opportunity to submit comments on the Technology Assessment (TA), ?Update on Horizon Scans of Genetic Tests Currently Available for Clinical Use in Cancers.? The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 1,800 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from	We are aware that some professional societies vary in their interpretation of a “genetic test” and our description as defined by the SACGHS uses a broad definition of a “genetic test”. This definition has been used by our previous reports. The current report utilizes the updated definition and we

			molecular biology, genetics and genomics. Membership includes professionals who work within academic medicine, government, and the in vitro diagnostics industry. First, the term ?genetic test? and its definition are used both too liberally as well as sometimes incorrectly in the document. The document includes and summarizes numerous tests that are not typically considered genetic or even molecularly based, i.e., not dependent upon the analysis of DNA or RNA. If AHRQ wishes these tests to remain in the document and for the document to remain factually correct, AMP strongly encourages the authors to rename the TA a scan of laboratory tests, or at least genomic tests, and not strictly genetic tests. As for genetic testing, this list is incomplete. An example is testing for mutations in the PMS2 gene associated with non-polyposis colorectal cancer (Lynch syndrome), which was first offered in 2008. Additionally, the definition of genetic test included on page 9 of the TA is erroneously cited as being from the Secretary?s Advisory Committee on Genetics, Health and Society 2008 report on US System of Oversight of Genetic Testing. However, the definition in the TA is actually the definition from the Secretary?s Advisory Committee on Genetic Testing report on Enhancing the Oversight of Genetic Tests issued in 2000. AMP requests that the authors modify the TA to use the more recent definition of genetic tests. It is important for the value of the document that a distinction be made between genomic tests that assess inherited genetic mutations, acquired somatic mutations, and pharmacogenomics (tests for common genetic variation involved with therapeutic drug response)). Additionally, AMP recommends that predictive genetic testing be distinguished from diagnostic testing. All of these distinctions will help to ensure that the report is viewed as a credible and useful tool by private and public payers and other policy makers. AMP has previously submitted comments and sent letters to federal agencies on the nomenclature used to describe molecular tests. Whenever possible, AMP encourages the authors to describe tests based on their molecular entities rather than their brand names since numerous labs might offer the same or similar test under a different name. By listing tests using their brand names, some may read this as a de facto endorsement of one test over another by the agency, something AMP suspects AHRQ does not intend.	have edited for the most recent citation. The main objective of this report is not identify which are LDT based or manufacturer based, but to have a horizon scanning of new genomic tests that fit into the pre-defined eligibility criteria. Thank you for your interest in participating in future TAs.

			The authors may be aware that stakeholders and federal regulators are currently engaged in discussions on the appropriate oversight of laboratory-developed tests (LDTs). In contrast to in vitro diagnostic test kits, most LDTs are developed and validated for use in a single laboratory and currently not subject to FDA approval or clearance. Developers of LDTs do not consider themselves to be manufacturers as they do not manufacture or produce products, i.e., test kits, for sale. AMP requests that the TA be modified to distinguish between test manufacturers and clinical laboratories offering LDTs to ordering physicians. While AMP respects the specific expertise represented by the authors from the Tufts Medical Center Evidence-based Practice Center, the absence of genetics and molecular-based medical expertise in this report is of great concern. Inclusion of subject matter experts as authors (or at least as editors) would not only help ensure that the document is a comprehensive survey of currently available tests, but also would fulfill the most rudimentary requirements of such a survey, e.g., differentiating genetic from non-genetic tests. AMP respectfully requests that the authors include subject matter experts prior to the finalization of this report to improve its accuracy and completeness. AMP stands ready to offer assistance to AHRQ on this report and future reports on molecular diagnostics. Thank you very much for the opportunity to comment on this draft TA and we hope these comments improve the document, enhance its utility and assist AHRQ in putting out the highest quality educational instrument. AMP offers its assistance as AHRQ moves forward on this and other technology assessments.	We will definitely use your expertise during the process of conducting a full systematic review.

[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.