Evidence-based Practice Center Protocol for Technical Brief

Project Title: Gene Expression Profiling for Predicting Outcomes in Patients With Stage II Colon Cancer

I. Background

Stage II Colon Cancer

Colon cancer is a common malignancy affecting both women and men. In 2012, it is expected to be the fourth most commonly diagnosed cancer (after prostate, breast, and lung cancer) with an estimated 103,170 new cases and the second most common cause of cancer deaths (after lung cancer) with 51,690 deaths.[1]

The most important prognostic factor for colon cancer is stage at diagnosis. About 40 percent of patients with colon cancer are initially diagnosed with stage I disease (these localized tumors do not invade through the muscularis propria). Stage I disease has a 5-year survival rate of over 95 percent.[2] Five-year survival rates for patients diagnosed with stage II disease are between 58 and 83 percent. Stage II colon cancer is characterized by full-thickness tumor invasion of the bowel wall and the absence of lymph node and distant metastases. According to National Comprehensive Cancer Network guidelines, stage II disease is now subdivided into IIA (T3 tumors that invade through the muscularis propria into the pericolorectal tissues), IIB (T4a tumors that directly penetrate to the surface of the visceral peritoneum), and IIC (T4b tumors where tumor directly invades or is adherent to other organs or structures).[3] The relative 5-year survival rate for stage II T4a tumors is higher than for T4b lesions.[4] Stages III and IV have a worse prognosis.

Most patients with stage II colon cancer are cured with surgery alone; however, 25 to 30 percent of those with resected stage II disease will develop recurrence or die from their disease. In this group, adjuvant chemotherapy may produce a small improvement in overall survival when compared with surgery alone, and it may afford a small reduction in the risk of disease recurrence. In a recent review Midgley et al. commented, "For example, we have to treat 100 stage II patients to cure 3 or 4, while accepting that up to 40 [percent] of those treated will suffer significant toxicity…."[5]Thus, routine use of adjuvant therapy is usually recommended only in subgroups with stage II disease that may be at higher-than-average risk for recurrence, such as those whose initial diagnosis is complicated by bowel perforation. For patients where a decision is made to administer adjuvant chemotherapy, an additional decision has to be made about the specific adjuvant regimen that will be used.

A number of negative prognostic factors (factors associated with increased risk of recurrence) have been identified in stage II disease including T4 tumors (which tend to be large); obstruction or bowel perforation at initial diagnosis; an inadequately low number of sampled lymph nodes at surgery (12 or fewer); poorly differentiated histology, vascular, lymphatic, and perineural invasion; a high preoperative level of

Source: www.effectivehealthcare.ahrq.gov
Published Online: March 13, 2012

carcinoembryonic antigen; and the presence of indeterminate or positive resection margins.

Identifying the individuals in whom the potential benefits of chemotherapy outweigh the risks is challenging. The current system used to assess recurrence risk using the prognostic factors noted above (e.g., a T4 tumor) may be inadequate for determining individual risk. To that end, advances in molecular and genomic medicine, such as gene expression profiling, may improve the clinician's ability to assess individualized risk and predict response to adjutant therapy, as long as the test results provide new information that is clinically valid and useful.

Gene expression profiles (GEPs), also known as gene expression patterns or signatures, measure the activity of "expression" of multiple genes using a single sample. Gene expression is determined by analyzing RNA in the sample, generally using either reverse transcriptase polymerase chain reaction or DNA microarrays. GEP tests use defined protocols to evaluate the specimens to be analyzed: preparing the RNA samples, normalizing the raw expression measurements, and computing summary results (summary indices). Data from a GEP test can provide information about a cell's type, its current state of activity, and its local environment. This report will focus on the use the summary results of GEP tests for two types of clinical outcomes: prognostic and predictive. In this report, prognostic outcomes relate to disease prognosis, generally measured by rate of disease recurrence. Predictive outcomes reflect the rate of response to adjuvant chemotherapy.

According to Midgley et al., "[T]here are good examples of gene expression profiles being used to improve disease classification in lymphoma and breast cancer and aid in determination of prognosis in breast cancer."[5] Using GEP tests could improve the current staging system for colon cancer. However, in a 2009 publication, based on eight cohorts from six studies, Lu noted that existing GEP tests produced sufficiently high false-positive and false-negative rates to preclude routine use and commented that additional validation studies were needed.[6] GEP tests were noted to be in various stages of development for use in colon cancer. Given the additional studies on tests reported in that publication and the emergence of new tests, follow-up of the Lu study with a Technical Brief is warranted. This Technical Brief will summarize the state of the science and indicate the extent to which there are, or are not, important evidence gaps in the existing published literature.

A number of publications and reviews, for example a recent review by Vilar and Gruber,[7] provide information on the implications of microsatellite instability and mismatch repair (MMR) deficiency in colon cancer. The data indicate that MMR deficiency or high microsatellite instability (MSI-H) may identify a small (15–20%) population of patients with stage II disease who may derive no benefit or may even experience deleterious effects from adjuvant fluorouracil/leucovorin (FU/LV)-based chemotherapy.[7] Colon malignancies with these characteristics (i.e., MSI-H) may also have a better prognosis. MSI testing is widely available and used along with clinical risk factors to help make decisions about adjuvant chemotherapy in patients with stage II colon cancer. Thus, it is important that published reports on using GEP tests in colon cancer treatment decision-making specifically comment on whether (and how) they measured MSI status and how they took this into account in their analysis. For example,

the GEP test may be studied only after patients with MSI-H are excluded; alternatively, investigators may attempt to include the MSI findings as part of their GEP test. While either way may be acceptable, the potential impact of MSI status needs to be considered.

Over the last decade the schedule and duration of adjuvant chemotherapy in treating colon cancer has changed from a 12-month course of bolus FU and levamisole combination to a 6-month course of either infusion FU combined with leucovorin (LV) and oxaliplatin or an oral fluoropyrimidine such as capecitabine. Thus, in completing this review, it will be important to note, as suggested by Tabernero and Baselga,[8] the chemotherapy regimen(s) for which response was predicted. Some GEP test results may indicate a patient-specific, preferred regimen (greatest likelihood of response) for adjuvant chemotherapy.

Because this report is on GEP testing in stage II colon cancer and GEP is based on results from multiple genes, this report will not include review of single-gene mutations. These single-gene markers may be used to predict response to chemotherapy, prognosis, potential for chemotherapy-related adverse events, or chemotherapy-related dose adjustments but are not included in the scope of this report. New assays that measure RNA to detect tumor cells are also beyond the scope of this report. Since this report is on patients with stage II colon cancer, publications on the use of GEP for other stages of colon cancer will not be included, unless the publication presents information on patients with stage II separately. (This report will tabulate a listing of publications that used GEP testing and included patients with stage II disease but did not provide stage II-specific results.)

Thus, GEP testing of patients following surgical resection of stage II colon cancer has potential implications, but the magnitude is unknown. Selecting appropriate patients for adjuvant chemotherapy could improve net outcomes, by giving adjuvant therapy to those likely to benefit while avoiding it in those for whom the risk of recurrence is sufficiently low that they would not benefit from therapy. On the other hand, introducing routine testing without a clear understanding of benefits and risks could result in those who would benefit from adjuvant therapy not receiving it.

The objective of this Technical Brief is to provide an overview of the "state of the science" for the use of GEP testing in predicting clinical outcomes, such as risk of recurrence and response to adjuvant chemotherapy, in patients with stage II colon cancer. This Technical Brief will also provide a potential framework for assessing the applications and implications or use of GEP testing for stage II colon cancer and a summary of both ongoing research and future research needs. This report will focus on the Guiding Questions (GQs) in the following section. This Technical Brief will not synthesize study results. A Technical Brief format was selected for this topic because of the importance of the question but the limited availability of data related to outcomes. However, the conceptual framework and issues identified in this report can inform future comparative effectiveness research.

II. Guiding Questions

Question 1

What are important aspects of GEPs?

a. What GEP products are available for clinical use in patients with colon cancer?
b. What types of tissue specimens (e.g., frozen tissue) are analyzed for the GEP?
c. What is the test turn-around time?
d. What are the potential benefits and harms of this testing compared to current practice?
e. Is GEP testing a replacement or add-on technology?
f. Are there additional specific features of this testing (technology) that need to be considered?

In completing background work for this study protocol, several GEPs that have been studied in stage II colon cancer have been identified. As this project proceeds, additional tests will likely be identified. Those identified thus far are as follows:

- Oncotype DX® Colon Cancer test (Genomic Health, Inc., Redwood City, CA). This is a 12-gene assay that produces an individualized score reflective of the risk of colon cancer recurrence for individual patients with stage II colon cancer.
- Affymetrix® microarray solutions using the Affymetrix® Human Genome U133 Plus 2.0 GeneChip Expression Array (Affymetrix, Inc., Santa Clara, CA).
- Coloprint® (Agendia, Inc., Irvine, CA). This is a microarray-based GEP used for predicting the risk of distant recurrence of stage II and III colon cancer patients.

Question 2

What is the clinical approach for using GEP assays?

a. Are all patients with stage II colon cancer included in studies of GEPs?
b. What is the U.S. Food and Drug Administration (FDA) status of these tests?
c. Currently, how widely used are these tests?

In summarizing the published studies, this report will indicate whether GEP was analyzed using all patients with stage II colon cancer or whether GEP was used only after certain groups of patients were excluded, such as those with microsatellite instability or those with T4 tumors. Whether GEP is being used primarily as a prognostic marker (recurrence rates) or predictive marker (response to adjuvant chemotherapy) will also be noted.

The primary regulatory bodies overseeing genetic tests such as GEPs in the United States are the FDA and the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The FDA addresses the safety and effectiveness of diagnostic tests and the quality of the design and manufacture of these tests, whereas CLIA regulates laboratory personnel qualifications, quality-control procedures, and proficiency testing programs. The FDA has jurisdiction over both laboratory developed tests (LDTs) for use in an in-house laboratory and tests classified as "in-vitro devices" that are distributed to other

laboratories as test kits. Historically, the FDA has subjected test kits to premarket review of safety and effectiveness but not most LDTs. Depending on the manufacturing process, GEPs may be marketed as either in-vitro devices or LDTs. As a result, GEPs marketed as LDTs may enter the U.S. market with analytical validation under laboratory regulations imposed by CLIA but without evidence of clinical validity or utility.

Question 3

What is the current evidence for the technology/intervention?

a. What published and unpublished studies, including both derivation and validation studies, have reported on the clinical validity and clinical utility for each of the GEPs for potential use in patients with stage II colon cancer?
b. How extensively have the clinical validity and clinical utility of these tests been validated?
c. Was a reclassification analysis performed with risk stratification using GEP when compared with that obtained with standard risk factors?
d. What information is available regarding analytic validity?
e. Determine the state of the current research for the following information on available studies (see Section III.2.A. Information Management in the Methods section below for data abstraction variables):

- Name of the GEP and type of assay
- Patient inclusion/exclusion criteria (only patients with stage II colon cancer)
- Study design (prospective vs. retrospective; cohort vs. convenience sample; derivation, validation, or both), sample size, and study goal (analytic validity, clinical validity, and/or clinical utility)
- Comparator used in comparative studies, if relevant
- Outcomes evaluated (accuracy, reliability, recurrence, survival, response to adjuvant chemotherapy, avoidance of unnecessary adjuvant chemotherapy [and avoiding potentially toxic medications], not receiving needed adjuvant chemotherapy, and quality of life)
- Length of followup (the study will require at least 2 years of followup for the outcomes of cancer recurrence or death)

For this report, data for *clinical validity* is defined as the relationship (e.g., sensitivity, specificity, accuracy, etc.) of the GEP results to the risk of disease recurrence and/or death after surgery for stage II colon cancer. Whether or not data are available about the incremental information provided by GEP testing when compared with standard clinical and pathological risk factors will be reported. Clinical validity is also defined as the relationship (e.g., sensitivity, specificity, accuracy, etc.) of the GEP results to the response to adjuvant chemotherapy currently used after surgery for stage II colon cancer. Again, the

availability of data on the incremental information provided by GEP testing when compared with standard clinical and pathological risk factors will be noted.

Clinical utility is defined as the balance of benefits and harms when GEP testing is used to impact clinical decisionmaking, that is, the decision about using adjuvant chemotherapy. Clinical utility should reflect patient outcomes such as improved survival.

As noted by Simon et al.,[9] clinical utility requires that a test be actionable, that is, the medical indication for using the test is clear and the magnitude of outcomes or treatment effects associated with different test results are sufficiently great as to influence treatment decisions.

The *analytic validity* of the GEP test is also important, and information about the extent of information on analytic validity will be assessed. Analytic validity relates to the reliability and validity of the test itself, that is, does it measure the genes that are part of the assay, and are the test results reproducible? (Lack of reproducibility could result from both preanalytic factors [e.g., sample preparation] as well as analytic factors [such as reagents used].)

Question 4

What important issues are raised by using GEP testing for stage II colon cancer?

a. What are the key unresolved or controversial issues with using GEP testing in patients with stage II colon cancer?
b. What are the implications of the current level of diffusion and/or further diffusion of this technology/intervention given the current state of the evidence?
c. What key studies are currently underway? What are the important questions for future research?

III. Methods

Several sources will be used to inform this Technical Brief. Information will be collected in a review of published medical literature, narrative review articles, a search of the grey literature, and discussions with Key Informants. In addition, the Scientific Resource Center will request Scientific Information Packets.

Guiding Questions (GQs) 1 and 2 above will rely on information from published narrative reviews and clinical guidelines and information in the grey literature. The latter will include information culled from companies, patient advocacy groups, and other sources as identified in an Internet search.

GQ 3 will be addressed through a review of the literature. The Key Informants have provided guidance on the potential clinical outcomes of interest and the potential benefits and harms of GEP testing; that input has been incorporated into this protocol.

GQ 4 will rely on integrating information from Key Informants, grey literature, narrative reviews, and review of the literature.

Given the current role of GEP testing in patients with breast cancer, questions formulated in a report for the Agency for Healthcare Research and Quality (AHRQ) on

GEP testing in patients with breast cancer[10] are being used to inform the literature review and the summary of this state-of-the-science" report of GEP testing in patients with colon cancer. Some questions from that previous review that will be considered in this review include the following:

- Do the tests that are offered commercially use the same methods that have been used in derivation and validation reports?
- Do publications discuss test discrimination, that is, the test's ability to separate patients into distinct risk classes with different outcomes?
- Have factors such as race/ethnicity been evaluated for their impact on clinical validity, since this could impact the ability to generalize results to other populations?

This Technical Brief will also consider comments on using archived specimens and assessing tumor marker utility.[9,11] For these topics, the following items will be taken into consideration in reviewing studies:

- For prospective-retrospective studies, was archived tissue, adequate for a successful assay, available on a sufficiently large number of patients from the pivotal prospective trials? (It is suggested that samples from at least two-thirds of the patients must be available for analysis.)
- For test validation, was the analysis plan for the biomarker evaluation completely developed before the performance of the biomarker assays? This includes the mathematical formula for combining the individual components for multigene classifiers.

1. Data Collection:

A. Discussions With Key Informants

The Key Informants include clinical experts, payers, and patients. The clinical experts will come from the disciplines of medical oncology, surgical oncology, laboratory medicine, and clinical genetics and have expertise in colon cancer and/or genetics.

At least one group conference call will be scheduled for the Key Informants. During the first call, the Key Informants will provide general guidance on the literature review, for example, key outcomes, potential tests, and proposed inclusion/exclusion criteria for the literature search. As a follow-up to the group conference call, the Key Informants will be interviewed individually by telephone, using a semi-structured interview outline that will provide the content experts the opportunity to share their experiences with GEP testing in patients with colon cancer and their opinions on unresolved or controversial issues related to GEP testing.

B. Grey Literature Search

Internet searches will be conducted in the FDA Web site concerning the various GEP tests available. Information will be used in answering GQs1, 2, and 4.

Web sites of companies who are developing and currently offering GEP tests for colon cancer will be searched to inform GQs 1 and 2. Examples include Genomic Health (http://www.genomichealth.com), Agendia, Inc. (http://www.agendia.com/pages/coloprint/), and Affymetrix, Inc. (http://www.affymetrix.com).

Clinical guidelines for colon cancer will be reviewed for recommendations on using GEP testing for stage II colon cancer. Examples include the American Society of Clinical Oncology guidelines (http://www.asco.org) and the National Comprehensive Cancer Network guidelines (http://www.nccn.org).

Patient advocacy Web sites for colon cancer will be searched. Examples include the Colon Cancer Alliance (http://www.ccalliance.org), Fight Colon Cancer (http://fightcolorectalcancer.org), and the American Cancer Society (http://www.cancer.org).

Current trials involving GEP testing for stage II colon cancer will be identified by searching clinicaltrials.gov (http://www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry platform (http://www.who.int/ictrp/en).

C. Published Literature Search

A scan of the published medical literature will be conducted to address GQ 3. Searches will be performed in MEDLINE®, EMBASE®, and the Cochrane Library (specifically CENTRAL, DARE, and the HTA Database).

The proposed search strategy for MEDLINE (start date of 1946) is shown below; this strategy will be adapted for the other databases.

Draft Search Strategy for Ovid MEDLINE

1. exp Colorectal Neoplasms/
2. ((colorectal or colon$ or rectal or Sigmoid) adj3 (neoplasm$ or cancer$ or carcino$ or tumo?r$)).tw.
3. 1 or 2
4. Gene Expression Profiling/
5. (gene expression adj (profil$ or monitor$ or pattern$ or signature$ or predictor$ or test$ or chip$ or regulation)).tw.
6. transcript$ expression analys$.tw.
7. transcriptom$.tw.
8. ((DNA or cDNA or tissue) adj (fingerprint$ or microarray$)).tw.
9. ((mrna or mirna or Microarray or MicroRNA) adj2 (profil$ or expression or signature$)).tw.
10. array sequence analysis.tw.
11. oncotype dx.tw.
12. Affymetrix.tw.
13. Coloprint.tw.
14. (Mismatch repair deficiency status or dmmr).tw.

15. microsatellite instability/
16. Microsatellite Repeats/
17. replication error phenotype$.tw.
18. or/4-17
19. recurrence/
20. (recur$ or relaps$).tw.
21. exp treatment outcome/
22. (respons$ or outcome$ or react$ or eligibl$).tw.
23. Chemotherapy, Adjuvant/
24. (adjuvant or chemotherap$).tw.
25. or/19-24
26. incidence/
27. exp mortality/
28. follow up studies/
29. prognos$.tw.
30. predict$.tw.
31. course$.tw.
32. or/26-31
33. and/3,18,25,32
34. (animals not humans).sh.
35. 33 not 34

Studies will be included in this Technical Brief if they were original studies that used GEP assays (e.g., cDNA or oligonucleotide microarrays), included a stage II or Duke B colon cancer (colorectal cancer) study population, and reported cancer recurrence or death with at least 2 years of followup. (Two years is the minimum followup time needed to adequately assess whether or not a patient is free of recurrence; the Key Informants indicated that 3 years of followup is used more often.) In addition, this report will collect information on response to adjuvant chemotherapy as another outcome marker. Whether or not the information for categorizing individual patients according to predicted and actual prognosis can be obtained from the original publication will be noted. Reports in abstract form that meet these inclusion criteria will also be summarized.

The DistillerSR Systematic Review Tool (Evidence Partners Inc., Manotick, ON, Canada) will be used to facilitate the screening and study selection process, as follows. Titles and abstracts will be screened independently by two reviewers to detect potential articles relevant to the topic. Full-text articles of those marked as potentially relevant will be retrieved and screened independently by two reviewers for inclusion or exclusion in the report. Articles will be included if they describe analytic validity, clinical validity, or clinical utility for GEP testing in patients with stage II colon cancer.

2. Data Organization and Presentation

A. Information Management

There are three main sources of information for this Technical Brief: published literature, grey literature, and Key Informants. The data to be abstracted from included articles is as follows.

For all articles:

- Article (details regarding author(s), institutions, funding)
- Which test(s) were used?
  - Type(s) of tissue used (e.g., fresh tissue)
  - Time for analysis (turnaround time)
- Inclusion and exclusion criteria
  - Was only a subset of patients with stage II disease used? If so, which one?
  - For adjuvant chemotherapy, which regimens were used?
    - Sample size (number of patients/specimens)
  - If samples are from previous studies, which studies?
    - Is there information to assess the completeness of sampling from previous studies?

For articles that describe analytic validity:

- Was information provided about preanalytic factors (e.g., handling of specimens)?
- What aspects of analytic validity were measured (e.g., accuracy, reproducibility)?
- Does it provide narrative summary of results related to analytic validity?

For articles that describe clinical validity and clinical utility:

- What outcomes were measured, for example, recurrence rates, response to adjuvant chemotherapy (regimen-specific), avoidance of chemotherapy (with reduction in medication side effects), et cetera?
- What was the study design?
  - Prospective, retrospective, or prospective-retrospective
  - Randomized trial, controlled trial, cohort study, or case (convenience) series
  - Derivation and/or validation (For validation, when was the method of analysis and interpretation determined?)
- Was a reclassification analysis performed (to determine if the GEP test results provide new (additional) information when compared with that obtained with usual predictors)?
- Was MSI (MMR) status determined?
  - If so, by which method?
- Was MSI (MMR) status considered in the overall analysis?
  - If so, how?
- Was the GEP performed (analysis, calculation, interpretation) as described in initial studies for derivation and/or studies of analytic validity?

Source: www.effectivehealthcare.ahrq.gov
Published Online: March 13, 2012

- Does the final classification provide discrimination among groups of patients; that is, are the patients grouped into a specific category that is distinct and different from other categories? (In addition, when the GEP predicts risk groups, how were the cut-points for various groups determined?)
- Do the authors comment on factors such as race and ethnic background that could impact the generalizability of the findings?
- For blinding, were determinations of the outcomes and the GEP result made independently, that is, did those assessing outcomes know the results of GEP testing?
- Does the publication provide individual patient level data for observed vs. predicted outcomes in patients with stage II colon cancer?

  The following additional information will be obtained from these articles (related to the validity of the outcomes):

  - For recurrence of disease, how was it measured (duration of follow-up, biopsy result, imaging finding, level of carcinoembryonic antigen, etc.)?
  - For response to adjuvant chemotherapy, how was it measured?
  - For disease-free survival, how was it determined?

  Note: Study results will NOT be abstracted.

Information about potential clinical indications will be abstracted from guidelines and reviews in the medical literature and from company Web sites and will be organized in a Microsoft® Excel spreadsheet. Information from Key Informants and patient advocacy Web sites will be of a qualitative nature and will be managed in a Microsoft® Word document.

B. Data Presentation

There will be a graphical presentation of the level of evidence of GEP use for each of the assays, indicating the number of studies published and the number of unique patients, with specific attention given to validation phases, included in the studies. There will be summary tables of the published studies for each gene expression profile, which will include the following information: numbers of studies, number of patients, funder of the study, location (country), type(s) of outcomes measured, approach to validation including numbers of patients, and reclassification results. A narrative summary for each GEP test will incorporate the information gathered from the medical literature, the grey literature, and the Key Informants and will describe the current state of GEP testing for stage II colon cancer, and a discussion of the key unresolved or controversial issues regarding the testing.

As part of this section, an evidence map will be presented. This "map" will summarize the characteristics of the research reported to date and will compare the evidence to the information needed to answer the questions relevant to use of this

technology. The evidence map summarizes the extent and distribution of current evidence, it provides information about the amount and type of research available and the characteristics of that research.

IV. References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29. PMID: 22237781.
2. Libutti SK, Saltz LB, Willett CG. Cancer of the colon. In: DeVita VT, Lawrence TS and Rosenberg SA, eds. Cancer: principles & practice of oncology. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011: 1084-1126.
3. National Comprehensive Cancer Network. NCCN Guidelines®. Colon Cancer. Version 3.2012. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed March 11, 2012.
4. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 2010;28:264-71. PMID: 19949014.
5. Midgley R, Rasul K, Al Salama H, et al. Gene profiling in early stage disease. Cancer J 2010;16(3):210-3. PMID: 20526098.
6. Lu AT, Salpeter SR< Reeve AE, et al. Gene expression profiles as predictors of poor outcomes in stage II colorectal cancer: a systematic review and meta-analysis. Clin Colorectal Cancer 2009;8(4):207-14. PMID: 19822511.
7. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer—the stable evidence. Nat Rev Clin Oncol 2010;7(3):153-62. PMID: 20142816.
8. Tabernero J, Baselga J. Multigene assays to improve assessment of recurrence risk and benefit from chemotherapy in early-stage colon cancer: has the time finally arrived, or are we still stage locked? J Clin Oncol 2010;28(25):3904-7. PMID: 20679612.
9. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 2009;101(21):1446-52. PMID: 19815849.
10. Marchionni L, Wilson RF, Marinopoulos SS, et al. Impact of Gene Expresion Profiling Tests on Breast Cancer Outcomes. Evidence Report/Technology Assesment No. 160 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-01-0018). Rockville, MD: Agency for Healthcare Research and Quality; January 2008. AHRQ Publication No. 08-E002. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/brcancergene/brcangene.pdf.
11. Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 1996;88(20):1456-66. PMID: 8841020.
12. Lesko LJ, Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Annu Rev Pharmacol Toxicol 2001;41:347-66. PMID: 11264461.

Source: www.effectivehealthcare.ahrq.gov
Published Online: March 13, 2012

13. Subramanian J, Simon R. What should physicians look for in evaluating prognostic gene-expression signatures? Nat Rev Clin Oncol 2010;7(6):327-34. PMID: 20421890.
14. Centers for Disease Control and Prevention Web site. Public Health Genomics. Genomic Testing: ACCE Model Process for Evaluating Genetic Tests. Available at: http://www.cdc.gov/genomics/gtesting/ACCE/. Accessed February 15, 2012.

V. Definitions of Terms

Biomarker:

The Biomarkers Definitions Working Group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[12]

Gene expression profile (or signature):

A gene expression profile (GEP) is one type of biomarker. According to Subramanian and Simon,[13] a GEP is a biomarker in which the expression levels of multiple genes are combined in a defined manner to provide a score or a classifier. GEPs measure the activity or "expression" of multiple genes in a single RNA sample, which may reflect both normal and malignant cellular function. Various methods exist to measure gene expression, including the reverse transcriptase polymerase chain reaction and DNA microarrays. If found to be reliable, valid, and clinically useful, GEPs may have an important role to play in determining prognosis and guiding treatment decisions.

Analytic validity:

How accurately and reliably the test measures the genotype of interest.[14]

Clinical validity:

How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.[14]

Clinical utility:

How likely the test is to significantly improve patient outcomes.[14]

VI. Summary of Protocol Amendments

Currently there are no protocol amendments.

VII. Key Informants

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is currently used or might be used, and which features may be important from a patient or policy standpoint. They may include clinical experts, patients, manufacturers, researchers, payers, or other perspectives, depending on the technology/intervention in question. Differing viewpoints are expected, and all statements are crosschecked against available literature and statements from other Key Informants. Information gained from Key Informant interviews is identified as such in the report. Key Informants do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published within 2 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Source: www.effectivehealthcare.ahrq.gov
Published Online: March 13, 2012