Gene Expression Tests

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Oncology Indications

Thyroid Cancer

The multi-panel gene expression tests Afirma® and ThyraMIR™ are proven and medically necessary for assessing thyroid nodules that are not clearly benign or malignant based on fine-needle aspiration biopsy results alone.
Gene expression tests are unproven and not medically necessary for the following indications:

- Cancer of Unknown Primary
  - Identifying tissue of origin in difficult to diagnose cancers (e.g., ResponseDX Tissue of Origin® or CancerTYPE ID®)
- Colon Cancer
  - Predicting the likelihood of colon cancer recurrence (e.g., Oncotype DX® Colon Cancer Assay)
- Multiple Myeloma
  - Guiding therapy in patients with multiple myeloma (e.g., MyPRS®)
- Prostate Cancer
  - Predicting tumor aggressiveness and guiding disease management in patients with newly diagnosed prostate cancer (e.g., Oncotype DX® Prostate Cancer Assay and Prolaris®)
  - Predicting risk of recurrence and metastasis and guiding disease management following radical prostatectomy (e.g., Decipher® Prostate Cancer Classifier)
- Uveal Melanoma
  - Predicting metastatic risk of uveal melanoma (e.g., DecisionDx-UM)

**Note:** Named gene expression tests are listed as examples only. All gene expression tests are considered unproven and not medically necessary for the above indications.

There is insufficient evidence in the clinical literature demonstrating that gene expression tests have a role in clinical decision-making or have a beneficial effect on health outcomes for these indications. Further studies are needed to determine the clinical utility of these tests.

**Non-Oncology Indications**

**Coronary Artery Disease**

Gene expression tests are unproven and not medically necessary for predicting the likelihood of obstructive coronary artery disease (e.g., Corus® CAD).

There is insufficient evidence in the clinical literature demonstrating that this test has a role in clinical decision-making or has a beneficial effect on health outcomes. Further studies are needed to determine the clinical utility of this test.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0005U</td>
<td>Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81493</td>
<td>Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score</td>
</tr>
<tr>
<td>81504</td>
<td>Oncology (tissue of origin), microarray gene expression profiling of &gt; 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores</td>
</tr>
<tr>
<td>81525</td>
<td>Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score</td>
</tr>
<tr>
<td>81540</td>
<td>Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype</td>
</tr>
<tr>
<td>81545</td>
<td>Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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<td>88299</td>
<td>Unlisted cytogentic study</td>
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Gene expression is the process by which the coded information of a gene is translated into the structures present and operating in the cell (either proteins or ribonucleic acids (RNA)). Gene expression profiling (GEP) studies the patterns of many genes in a tissue sample at the same time to assess which ones are turned on (producing RNA and proteins) or off (not producing RNA or proteins). By simultaneously measuring the levels of RNA of thousands of genes, GEP creates a snapshot of the rate at which those genes are expressed in a tissue sample.

Gene expression tests are not the same as genetic tests. Genetic tests measure an individual DNA signature to identify genetic changes or mutations. Genetic tests can help estimate an individual’s risk of developing disease in the future. In contrast, gene expression tests measure the activity of RNA in a given tissue or bodily fluid at a given point in time to provide information about an individual’s current disease state or the likelihood of future disease. RNA levels are dynamic and change as a result of disease processes or environmental signals. Because gene expression changes under pathological conditions, dynamic changes in these processes can be studied over time. Certain patterns of gene activity may be used to diagnose a disease or to predict how an individual responds to treatment (Arnett et al., 2007; CardioDX website; Centers for Disease Control and Prevention; National Cancer Institute; National Human Genome Research Institute).

From 2000–2004, the Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics (OPHG) established and supported the ACCE Model Project, which developed the first publicly-available analytical process for evaluating scientific data on emerging genetic tests. The 4 main components of the ACCE process included analytic validity, clinical validity, clinical utility and ELSI. Analytic validity refers to how accurately and reliably the test measures the genotype of interest. Clinical validity refers to how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest. Is what's measured associated with the outcome of interest? Clinical utility refers to how likely the test is to significantly improve patient outcomes. What is the clinical value? ELSI refers to the ethical, legal and social implications that may arise in the context of using the test (CDC, 2010).

The CDC-supported EGAPP™ initiative builds on the ACCE model structure and experience. In 2004, the CDC launched the EGAPP initiative to establish and test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology that are in transition from research to clinical and public health practice. A key EGAPP goal is to provide objective, timely, and credible information that is clearly linked to available scientific evidence. This information serves to provide health care providers, policymakers, and others to distinguish genetic tests that are safe and useful (CDC, 2016).

**Thyroid Cancer**

Thyroid cancer is most commonly found on routine physical examination as a palpable thyroid nodule. A fine-needle aspiration (FNA) biopsy is usually performed to rule out malignancy. In some cases, the nodules are not clearly benign or malignant based on FNA results alone. Those patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though most of these nodules turn out to be benign.

miRNAs are small, highly conserved RNA molecules that are involved in the pathology of thyroid cancer by regulating key cellular processes such as cell-cycle progression or cell differentiation, proliferation, and survival. There is a differential expression of miRNAs in distinct histopathological tumor types and at various stages of tumor differentiation or progression (Labourier et al., 2015).

The Afirma Thyroid FNA Analysis gene expression classifier (GEC) examines the expression of 167 genes to classify nodules as benign or suspicious for malignancy (Veracyte® website).

The ThyraMIR GEC evaluates the expression levels of 10 microRNA (mRNA) genes within a fine needle aspiration biopsy (Interpace® Diagnostics website).

**Cancer of Unknown Primary**

Cancers are treated according to their primary site. Accurately classifying the site of a tumor’s origin helps physicians choose the best course of treatment for the patient. Cancers of unknown primary, also referred to as occult primaries, are tumors that have metastasized from an unknown primary site. Gene expression profiling has been proposed as a tool for guiding diagnosis, based on the premise that when a large number of genes from known cancers are examined with the use of tools such as DNA microarray or quantitative real-time polymerase-chain-reaction (rt-PCR) assays, metastatic tumors have molecular signatures that match their primary origin. The ResponseDX Tissue of Origin (TOO) test compares the molecular profile in a patient’s tumor tissue sample with the profiles of 15 known characterized tumor types (Response Genetics). CancerTYPE ID uses real-time reverse transcription polymerase chain reaction (RT-PCR) to measure the expression pattern of 87 genes associated with tumors and 5 reference genes. The
expression of these genes is then compared with a reference database that contains the gene expression of > 2000 tumors to calculate the most likely tumor type (BioTheranostics website).

**Colon Cancer**
The use of adjuvant chemotherapy in patients with stage II colon cancer remains controversial because recurrence does not develop in the vast majority of these patients (Boland and Goel, 2016). Gene expression profiling has been proposed as a method for predicting which of these patients are likely to have a recurrence. Although gene-expression signatures hold promise, they are difficult to use in clinical practice and are often not predictive of benefit from adjuvant chemotherapy (Dalerba, et al., 2016). The Oncotype DX Colon Cancer Assay is a reverse transcription PCR (RT-PCR)-based profiling test that measures the RNA gene expression pattern of 12-genes (7 colon cancer-related genes and 5 reference genes). Through a proprietary algorithm, the test provides an individualized score reflective of the risk of colon cancer recurrence for patients with stage II or stage III colon cancer (Genomic® Health website). ColoPrint® was a microarray-based gene expression profile for predicting the risk of distant recurrence of stage II and III colon cancer patients. According to the manufacturer, ColoPrint is no longer being provided for this indication. (Agenda® website).

**Multiple Myeloma**
Using microarray technology, My Prognostic Risk Signature (MyPRS) is a proposed tool for guiding treatment in patients with newly diagnosed, or relapsed multiple myeloma for the purpose of risk stratification that may affect the choice of therapies. MyPRS is performed on CD138-positive (CD138+) plasma cells derived from bone marrow aspirate, and analyzes all of the nearly 25,000 genes in a patient’s genome to determine the gene expression profile (GEP) that is associated with his/her condition. In the case of myeloma, the GEP is made up of the 70 most relevant genes (GEP70) which aide in the prediction of the patient’s outcome (Signal Genetics™; Hayes, 2016).

**Prostate Cancer**
Several molecular diagnostic tests aim to predict tumor aggressiveness or potential for metastasis in patients with prostate cancer. These tests are generally used in combination with conventional clinical criteria (i.e., Gleason score, prostate-specific antigen (PSA) levels and clinical disease stage). Test results are intended to assist clinicians in determining whether a patient should undergo therapy or active surveillance. The Prolaris genomic test is a 46-gene (31 cell cycle progression (CCP) genes and 15 housekeeper genes) polymerase chain reaction assay that measures gene expression in needle biopsy samples or tumor samples from patients with clinically localized prostate cancer to assess tumor aggressiveness and predict 10-year cancer-specific mortality risk. The Oncotype DX Genomic Prostate Cancer Assay is a 17-gene (12 cancer-related genes and 5 reference genes) polymerase chain reaction assay that measures gene expression in needle biopsy samples. The gene expression results are translated into a Genomic Prostate Score (GPS) algorithm that reflects prostate cancer aggressiveness. The Decipher Prostate Cancer Classifier examines 22 RNA biomarkers associated with aggressive prostate cancer to predict a tumor’s potential for metastasis after radical prostatectomy in high-risk men.

**Uveal Melanoma**
Uveal (ocular) melanoma (UM) is an aggressive cancer that often forms undetectable micrometastases before diagnosis of the primary tumor. The main goals of treatment are to reduce the risk of metastasis, prevent local growth and destruction of ocular tissues and preserve as much vision as possible. The DecisionDX-UM test is a multi-gene expression test which uses reverse transcription PCR (RT-PCR) of a set of 15 genes (including 3 controls) within an ocular melanoma tumor to identify the likelihood of metastasis in patients who have a near term (5-year) low risk (Class 1 molecular signature) versus high risk (Class 2 molecular signature). The DecisionDX-UM stratifies tumors into 3 risk classes to aid with prognosis. (Castle Biosciences website; Hayes, 2016)

**Coronary Artery Disease**
Gene expression profiling, using Corus CAD, has been proposed as a noninvasive diagnostic tool for evaluating patients who present with stable symptoms suggestive of obstructive coronary disease (CAD), such as chest discomfort or shortness of breath. Corus CAD is a blood test that integrates expression levels of 23 genes and other patient characteristics to predict the likelihood of obstructive CAD. According to the manufacturer, the test yields an objective result of cardiac risk in the form of a numeric score (0-40) that quantifies the likelihood that a patient with stable chest pain has obstructive CAD. The test is intended for nondiabetic patients without a history of obstructive CAD, who have not had a prior myocardial infarction or revascularization procedure and who are not currently taking steroids, immunosuppressive agents, or chemotherapeutic agents (CardioDX® website).

**CLINICAL EVIDENCE**

**Thyroid Cancer**
National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that molecular diagnostic testing to detect individual mutations or pattern recognition approaches using molecular classifiers may be useful in the
evaluation of FNA samples that are indeterminate to assist in management decisions. The choice of the precise molecular test depends on the cytology and the clinical question being asked. The NCCN Panel recommends (category 2B) molecular diagnostic testing for evaluating FNA results that are suspicious for 1) follicular Hürthle cell neoplasms; or AUS/FLUS (NCCN, 2016).

**Afirma**

Alexander et al. (2014) analyzed all patients who had received Afirma GEC testing at five academic medical centers between 2010 and 2013. Three hundred thirty-nine patients underwent Afirma testing of cytologically indeterminate nodules (165 atypical (or follicular lesion) of undetermined significance; 161 follicular neoplasm; 13 suspicious for malignancy). Of these 339 nodules, 174 (51%) were GEC benign, and 148 were GEC suspicious (44%). GEC results significantly altered care recommendations, as 4 of 175 GEC benign were recommended for surgery in comparison to 141 of 149 GEC suspicious. Of 121 cytologically indeterminate, GEC suspicious nodules surgically removed, 53 (44%) were malignant. Seventy-one of 174 GEC benign nodules had documented clinical follow-up for an average of 8.5 months, in which 1 of 71 nodules proved cancerous. The authors concluded that this clinical experience data confirms originally published Afirma test performance and demonstrates its impact on clinical care recommendations.

In a prospective, multicenter clinical validation study involving 49 sites, 3789 patients and 4812 fine-needle aspirates from thyroid nodules, Alexander et al. (2012) assessed the performance of a GEC (Afirma) on 265 cytologically indeterminate nodules. Of the 265 indeterminate nodules, 85 were malignant. The gene-expression classifier correctly identified 78 of the 85 nodules as suspicious (92% sensitivity), with a specificity of 52%. The negative predictive values for "atypia (or follicular lesion) of undetermined clinical significance," "follicular neoplasm or lesion suspicious for follicular neoplasm" or "suspicous cylogic findings" were 95%, 94% and 85%, respectively. Analysis of 7 aspirates with false negative results revealed that 6 had a paucity of thyroid follicular cells, suggesting insufficient sampling of the nodule. The authors concluded that these results suggest consideration of a more conservative approach for most patients with thyroid nodules that are cytologically indeterminate on fine-needle aspiration and benign according to gene-expression classifier results.

In a cross-sectional cohort study, Duick et al. (2012) demonstrated that obtaining a GEC test (Afirma) in patients with cytologically indeterminate nodules was associated with a reduction in the rate of diagnostic thyroidectomies. The authors reported that approximately one surgery was avoided for every two GEC tests run on thyroid fine-needle aspirations (FNA) with indeterminate cytology. Data was contributed retrospectively by 51 endocrinologists at 21 practice sites. Compared to a 74% previous historical rate of surgery for cytologically indeterminate nodules, the operative rate fell to 7.6% during the period that GEC tests were obtained. The rate of surgery on cytologically indeterminate nodules that were benign by the GEC reading did not differ from the historically reported rate of operation on cytologically benign nodules. The four primary reasons reported by the physicians for operating on nodules with a benign GEC reading were, in descending order, large nodule size (46.4%), symptomatic nodules (25.0%), rapidly growing nodules (10.7%) or a second suspicious or malignant nodule in the same patient (10.7%). According to the authors, these reasons are concordant with those typically given for operation on cytologically benign nodules.

Walsh et al. (2012) verified the analytical performance of the Afirma GEC in the classification of cytologically indeterminate thyroid nodule fine-needle aspirates (FNAs). Studies were designed to characterize the stability of RNA during collection and shipment, analytical sensitivity, analytical specificity and assay performance. The authors reported that analytical sensitivity, analytical specificity, robustness and quality control of the GEC were successfully verified, indicating its suitability for clinical use.

Chudova et al. (2010) based the Afirma GEC test on an empirical assessment of more than 247,000 mRNA transcripts associated with pathologically proven benign or malignant thyroid lesions.

In a retrospective analysis of 189 thyroid FNAs with indeterminate cytology, Yang et al. (2016) examined the refining role of the Afirma GEC test in a 20-month period after implementation. Correlation with surgical follow-up, when available, was performed. The excisional rate of atypia of undetermined significance-follicular lesion of undetermined significance in the pre-GEC category was 63%, which decreased to 35% in the post-GEC category, whereas the malignancy rate in the excised thyroids increased from 35% in the pre-GEC category to 47% in the post-GEC category. Similar findings also were obtained for suspicious for follicular neoplasm-follicular neoplasm lesions. The authors concluded that the strength of the GEC test appears to lie in its ability to reclassify 42% of indeterminate cytology cases as benign, thereby decreasing the number of unnecessary surgical procedures.

Pagan et al. (2016) investigated the prevalence of genetic alterations in diverse subtypes of thyroid nodules beyond papillary thyroid carcinomas (PTC) in 851 variants and 133 fusions in 524 genes. After adding a cohort of tissue samples, the authors found 38/76 (50%) of histopathology malignant samples and 15/75 (20%) of benign samples to harbor a genetic alterations. In a direct comparison of the same FNA also tested by an RNA-based gene expression classifier (GEC), the sensitivity of genetic alterations alone was 42%, compared to the 91% sensitivity achieved by the
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GEC. The specificity based only on genetic alterations was 84%, compared to 77% specificity with the GEC. Due to the finding that variants are also found in benign nodules, the authors conclude that testing only GEC suspicious nodules may be helpful in avoiding false positives and altering the extent of treatment when selected mutations are found.

Sipos et al. (2016) retrospectively evaluated the long-term follow-up of patients with a ‘benign’ Afirma GEC to determine impact on management compared to published data. During 36 months of follow-up, 17 of 98 patients (17.3%) had thyroid surgery; the majority (88%) being performed within 2 years. According to the authors, this represents a reduction in thyroid surgeries compared to patients that did not have a GEC performed on suspicious lesions. Limitations of this study are small patient population and non-randomization of patients.

In a meta-analysis of the gene expression classifier (GEC) for the diagnosis of indeterminate thyroid nodules, Santhanam et al. (2016) evaluated 7 out of 58 potential studies. The reference standard for determination of benign or malignant nodules was the histopathology of the thyroidectomy specimen. A QUADAS-2 report for all studies included in the final analysis was tabulated for risk of bias and applicability. The pooled sensitivity of the GEC was 95.7% (95% CI 92.2-97.9, I² value 45.4%, p = 0.09), and the pooled specificity was 30.5% (95% CI 26.0-35.3, I² value 92.1%, p < 0.01). Overall, the diagnostic odds ratio was 7.9 (95% CI 4.1-15.1). Although the meta-analysis revealed a high pooled sensitivity and low specificity for the Afirma GEC, patients with a benign GEC were not followed long enough to ascertain the actual false-negative rates of the index test.

**ThyraMIR**

In a multicenter cross-sectional cohort study, Labourier et al. (2015) evaluated surgically resected thyroid lesions and thyroid nodule FNAs (n=638) for the presence of genetic alterations in the BRAF, RAS, RET, or PAX8 genes. To sample a representative cohort of thyroid nodules with indeterminate cytology, consecutive FNAs with known mutation status collected from 12 distinct clinical sites in the United States were tested for miRNA expression. The set consisted of 109 nodules with AUS/FLUS or FN/SFN cytology and a traceable surgical outcome of primary benign or malignant thyroid lesion.

Multiplatform testing for DNA, mRNA, and miRNA can accurately classify benign and malignant thyroid nodules, increase the diagnostic yield of molecular cytology, and further improve the preoperative risk-based management of benign nodules with AUS/FLUS or FN/SFN cytology.

**Professional Societies**

**American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE)/ Associazione Medici Endocrinologi (AME)**

In a joint clinical practice guideline for the diagnosis and management of thyroid nodules (Gharib et al., 2016), the AACE, ACE and AME convey that although molecular analysis of FNA genetic material from thyroid nodules shows great promise in refining the diagnosis, prognosis, and treatment of thyroid cancer, there is currently insufficient data to support a universal recommendation for molecular testing in the further categorization of “indeterminate” thyroid nodules.

Because of the insufficient evidence and the limited follow-up, the AACE/ACE/AME do not recommend either in favor of or against the use of GECs for cytologically indeterminate nodules [BEL 2, GRADE B]. Molecular diagnostic testing should be considered to complement, not replace, evaluation [BEL 2, GRADE A], and as a general rule, molecular testing is not recommended in nodules with established benign or malignant cytologic characteristics [BEL 2, GRADE A].

The AACE also published a disease state commentary on molecular diagnostic testing of thyroid nodules with indeterminate cytopathology. The document states that, at present, molecular testing is meant to complement and not replace clinical judgment, sonographic assessment and visual cytopathology interpretation. As advances in the field are regularly occurring, clinicians need to stay informed, as recommendations for use within practice are expected to evolve (Bernet et al., 2014).

**American Thyroid Association (ATA)**

An ATA guideline on the management of adult patients with thyroid nodules (Haugen et al., 2016) makes the following recommendations on the use of molecular markers:
- If molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing and about the possible uncertainties in the therapeutic and long-term clinical implications of results. (Strong recommendation; low-quality evidence)
- If intended for clinical use, molecular testing should be performed in Clinical Laboratory Improvement Amendments/College of American Pathologists (CLIA/CAP)-certified molecular laboratories, or the international equivalent, because reported quality assurance practices may be superior compared to other settings. (Strong recommendation; low-quality evidence)
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Cancer of Unknown Primary (CUP) Site
An Agency for Healthcare Research and Quality (AHRQ) technology assessment (2013) on testing cancers of unknown primary concluded the following:
- The clinical accuracy of commercially available molecular pathology tests is similar.
- The evidence that these tests contribute to identifying cancers of unknown primary is moderate.
- There is insufficient evidence to assess the effect of these tests on treatment decisions and outcomes.
- Most studies evaluated were funded wholly or partially by the manufacturers of the tests.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that while there is diagnostic benefit of gene expression profiling (GEP) assays, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend tumor sequencing and gene signature profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors. In addition, pathologists and oncologists must collaborate on the judicious use of these modalities on a case-by-case basis, with the best individualized patient outcome in mind (NCCN, 2017).

Varadhachary and Raber (2014) reviewed the research, diagnosis and treatment of CUP, noting that the performance of tissue-of-origin molecular-profiling assays in known cancers has been validated with the use of independent, blinded evaluation of sets of tumor samples, with an accuracy of approximately 90%. Based on these findings, the authors comment that the feasibility of using formalin-fixed samples obtained from small, core-needle biopsy or using samples obtained by means of fine-needle aspiration makes this method practical for use in the clinic setting. However, without randomized, controlled trials it is difficult to gauge the therapeutic effect of tissue-of-origin molecular-profiling assays. Further, they suggest that creative trial designs are urgently needed in order to study subsets of unknown primary cancers and the effect of these assays on survival and quality of life of patients.

Pathwork/ResponseDX Tissue of Origin
As of April 2, 2013, Pathwork Diagnostics is no longer in business. Response Genetics has acquired all assets and intellectual property related to the Pathwork Tissue of Origin (TOO) Test and is marketing the test as ResponseDX Tissue of Origin™ (TOO) Test.

In a prospective, multicenter study, Handorf et al. (2013) compared the diagnostic accuracy of gene expression profiling (GEP) and immunohistochemistry (IHC) in identifying the primary site of metastatic tumors. Four pathologists rendered diagnoses by selecting from 84 stains in 2 rounds. Overall, GEP accurately identified 89% of specimens, compared with 83% accuracy using IHC. In a subset of 33 poorly differentiated and undifferentiated carcinomas, GEP accuracy exceeded that of IHC (91% to 71%). Further studies are needed to demonstrate that identifying the tissue of origin of unknown primary tumors leads to improvements in health outcomes.

Pillai et al. (2011) performed a validation study on the Pathwork TOO Test, a gene expression-based diagnostic test that aids in determining the tissue of origin using formalin-fixed, paraffin-embedded (FFPE) specimens. Microarray data files were generated for 462 metastatic, poorly differentiated, or undifferentiated FFPE tumor specimens obtained from small, core-needle biopsy or using microarrays obtained by means of fine-needle aspiration. The algorithm used for the test quantifies the similarity between RNA expression patterns of the study specimens and the 15 tissues on the test panel. Among the 462 specimens analyzed, overall agreement with the reference diagnosis was 89%. Further studies are needed to determine how test results change patient management and impact clinical outcomes.

Monzon et al. (2010b) evaluated the ability of a microarray-based gene expression test to identify the TOO in tumor specimens from 21 patients with a diagnosis of carcinoma of unknown primary (CUP). The Pathwork TOO Test was used to measure gene expression patterns for 1550 genes. These were compared for similarity to patterns from 15 known tissue types. The TOO Test yielded a clear single positive call for the primary site in 16 of 21 (76%) specimens and was indeterminate in 5 (24%). The positive results were consistent with clinicopathologic suggestions in 10 of the 16 cases (62%). In the remaining six cases the positive results were considered plausible based on clinical information. Positive calls included colorectal (5), breast (4), ovarian (3), lung (2) and pancreas (2). The Pathwork TOO Test reduced diagnostic uncertainty in all CUP cases and could be a valuable addition or alternative to current diagnostic methods for classifying uncertain primary cancers. Further studies are needed to determine how test results change patient management and impact clinical outcomes.

Monzon et al. (2009) conducted a large, blinded, multicenter validation study for the Pathwork TOO test, which consists of a test panel and a proprietary algorithm. Four separate laboratories processed 547 frozen specimens representing 15 tissues of origin using microarrays. Half of the specimens were metastatic tumors, with the remainder being poorly differentiated and undifferentiated primary cancers. The study found an overall sensitivity of 87.8% and an overall specificity of 99.4%. The test performed best using the undifferentiated and indeterminate tissue samples (n=289), yielding 90.7% agreement with the original diagnosis. Whereas the metastatic tissue samples (n=258) resulted in 84% agreement. The four facilities reported slightly different overall agreement percentages, but none of...
the differences were statistically significant. Results suggest that the test is sufficiently sensitive and informative for routine diagnostic use in patients presenting with uncertain primary cancers. Further studies are needed to determine how test results change patient management and impact clinical outcomes.

National Institute for Health and Clinical Excellence (NICE) guidelines state that gene expression-based profiling should not be used to identify primary tumors or guide treatment decisions in patients with provisional carcinoma of unknown primary (CUP). There is limited evidence that gene expression-based profiling improves the management or changes the outcomes for patients with CUP. Prospective randomized trials should be undertaken in patients with confirmed CUP to evaluate whether chemotherapy guided by gene-expression-based profiling is superior to treatment guided by conventional clinical and pathological factors. The guideline noted that this is a rapidly changing field (NICE, 2014).

**CancerTYPE ID**

In a prospective study, Hainsworth et al. (2013) used tumor profiling results to direct site-specific therapy for patients with carcinoma of unknown primary (CUP). Tumor biopsy specimens from previously untreated patients with CUP were tested with a 92-gene reverse transcriptase polymerase chain reaction cancer classification assay (CancerTYPE ID). When a tissue of origin was predicted, patients who were treatment candidates received standard site-specific first-line therapy. Of 289 patients enrolled, 252 had successful assays performed, and 247 (98%) had a tissue of origin predicted. Sites most commonly predicted were biliary tract (18%), urothelium (11%), colorectal (10%) and non-small-cell lung (7%). Two hundred twenty-three patients were treatment candidates, and 194 patients received assay-directed site-specific treatment. In these 194 patients, the median survival time was 12.5 months. When the assay predicted tumor types that were clinically more responsive, the median survival was significantly improved when compared with predictions of more resistant tumors (13.4 v 7.6 months, respectively). The authors concluded that molecular tumor profiling predicted a tissue of origin in most patients with CUP but noted that larger numbers of patients are required to make definitive statements regarding therapeutic implications of individual primary site predictions.

Kerr et al. (2012) conducted a multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier (CancerTYPE ID). Case selection incorporated specimens from more than 50 subtypes, including a range of tumor grades, metastatic and primary tumors and limited tissue samples. The assay showed overall sensitivities of 87% for tumor type and 82% for subtype. Analyses of metastatic tumors, high-grade tumors or cases with limited tissue showed no decrease in comparative performance. High specificity (96%-100%) was showed for ruling in a primary tumor in organs commonly harboring metastases. The assay incorrectly excluded the adjudicated diagnosis in 5% of cases. The authors concluded that results of this validation study support the clinical utility of the 92-gene assay in tumors of uncertain origin as a molecular adjunct to clinicopathologic evaluation for primary site diagnosis, discrimination between primary and metastatic tumor in common metastatic sites and for tumor subclassification. Prospective studies will help further define how molecular data can be successfully integrated into the clinical decision making process and allow for increased diagnostic certainty.

Erlander et al. (2011) reported the expansion of a second-generation gene expression profiling test (CancerTYPE ID) and demonstrated the ability of the 92-gene assay to classify 30 cancer types and 54 histological subtypes. For main cancer type, the sensitivity was 87% with a specificity of 100%, resulting in a positive predictive value (PPV) of 87% and a negative predictive value (NPV) of 100%. The accuracy for cancer subtype was a sensitivity of 85% and a specificity of 100%, resulting in a PPV of 85% and NPV of 100%. The authors also evaluated an additional 300 consecutive cases submitted for clinical testing to characterize clinical utility in a real-world setting: the 92-gene assay confirmed 78% of samples having a single suspected primary tumor and provided a single molecular prediction in 74% of cases with two or more differential diagnoses. To firmly establish the clinical validity of the 92-gene assay, a multi-institutional study is ongoing to determine the analytical performance within many diverse cancer types. In addition, prospective studies are being conducted to assess whether the use of the predictions from the 92-gene assay to select treatment positively affects patient outcome.

Hainsworth and Greco (2016) retrospectively reviewed CUP patients who had the 92-gene molecular cancer classifier assay (CancerTYPE ID; bioTheranostics, Inc.) performed on tumor biopsies to identify patients predicted to have NSCLC. The results showed that NSCLC was predicted by the molecular cancer classifier assay in 37 of 310 CUP patients. Twenty-one of these patients were tested for ALK rearrangements, and four had an EML4-ALK fusion gene detected. The diagnosis of lung cancer was strongly suggested in only one patient prior to molecular testing. One patient received ALK inhibitor treatment and according to the authors has had prolonged benefit. The authors concluded that although ALK inhibitors treatment experience is limited, this newly identifiable group of lung cancer patients should be considered for therapy according to guidelines for stage IV ALK-positive NSCLC.
In a clinical practice guideline on cancer of unknown primary site, ESMO states that gene expression profiling may aid in the diagnosis of primary tumor site in some patients with CUP, but the impact on patient outcome (by administration of primary site–specific therapy) remains questionable and unproven in randomized trials (Fizazi, et al., 2015).

**Colon Cancer**

Zhang et al. (2016) retrospectively reviewed the prognostic role of CDX2 expression in patients with stage I and stage III metastatic colorectal cancer (CRC) after complete surgical resection. The patient cohort (n=145) included 66 patients with CDX2-negative metastatic CRC and a comparison cohort of 79 patients with CDX2-positive metastatic CRC. The prevalence of absent CDX2 expression in this cohort was 5.6%. After adjusting for covariates in a multivariate model, the association of a lack of CDX2 expression and OS remained statistically significant (HR, 4.52; 95% CI, 2.50-8.17; PÃ< .0001). In addition, the median PFS (3 vs. 10 months; HR, 2.23; 95% CI, 1.52-3.27; PÃ< .0001) for first-line chemotherapy was significantly decreased in patients with CDX2-negative metastatic CRC. The authors concluded that the results showed that a lack of CDX2 expression in metastatic CRC is an adverse prognostic feature and a potential negative predictor of the response to chemotherapy. Further research with randomized controlled trials is needed to validate these findings.

To evaluate whether patients with CDX2-negative tumors might benefit from adjuvant chemotherapy, Dalerba et al. (2016) investigated the association between CDX2 status, and assessed at either the mRNA or protein level, the disease-free survival among patients who either did or did not receive adjuvant chemotherapy. Reviewing a database of 669 patients with stage II colon cancer and 1228 patients with stage III colon cancer, the authors reported that their results confirmed that treatment with CDX2 as a biomarker in colon cancer adjuvant chemotherapy was associated with a higher rate of disease-free survival in both the stage II subgroup (91% with chemotherapy vs. 56% without no chemotherapy, P = 0.006) and the stage III subgroup (74% with chemotherapy vs. 37% with no chemotherapy, P<0.001) of the CDX2-negative patient population (Fig. 5). A test for the interaction between the biomarker and the treatment revealed that the benefit observed in CDX2-negative cohorts was superior to that observed in CDX2-positive cohorts in both the stage II subgroup (P = 0.02 for the interaction) and the stage III subgroup (P = 0.005 for the interaction). In the authors’ opinion, their results indicate that patients with stage II or stage III CDX2-negative colon cancer might benefit from adjuvant chemotherapy and that adjuvant chemotherapy might be a treatment option for patients with stage II CDX2-negative disease, who are commonly treated with surgery alone. Given the exploratory and retrospective design of this study, these results will need to be further validated through randomized, clinical trials, in conjunction with genomic DNA sequencing studies. Boland and Goel (2016) remarked on prognostic subgroups among patients with stage II colon cancer, noting that prior studies to identify the subgroup of patients with high risk stage II colon cancer have not been robust. Further, the lack of prognostic and predictive criteria underscores the need to discover biomarkers that can facilitate the selection of patients for additional treatment.

AAHRO technical brief by Black et al. (2012) states that, although information is emerging about the use of gene expression profiling (GEP) assays to inform the decision about use of adjuvant chemotherapy in patients with stage II colon cancer, studies to date have not provided the type of information needed to address major uncertainties. Published studies have not provided information related to clinical utility. Limited information was found for analytic validity. The report concluded that the current evidence does not provide the type of information needed to answer major questions about use of GEP assays in these patients.

Lu et al. (2009) performed a systematic review and meta-analysis of gene expression profiles (GEps) to assess their utility for risk stratification and prediction of poor outcomes in stage II colorectal cancer (CRC). Eight cohorts involving 271 patients contributed to the analysis. The average accuracy, sensitivity and specificity were 81.9%, 76.2% and 84.5%, respectively, with a prognostic likelihood ratio (LR) of 4.7 and a prognostic odds ratio (OR) of 15.1. No evidence for significant interstudy heterogeneity was noted in either analysis. Subgroup analysis found no difference in results for the prediction of cancer recurrence or death. The authors concluded that GEP assays as predictors of poor outcomes in stage II CRC have promising potential, but to maximize their utility and availability, further studies are needed to identify and validate specific gene signatures.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that there is insufficient data to recommend the use of multigene assay panels to determine adjuvant therapy in colon cancer patients (NCCN,2017).

**Oncotype DX**

Yamanaka et al. (2016) evaluated the 12-gene Recurrence Score assay for stage II and III colon cancer without chemotherapy to reveal the natural course of recurrence risk in stage III disease (the Sunrise Study). A cohort-sampling design was used. From 1,487 consecutive patients with stage II to III disease who had surgery alone, 630
patients were sampled for inclusion with a 1:2 ratio of recurrence and nonrecurrence. Sampling was stratified by stage (II v III). The assay was performed on formalin-fixed, paraffin-embedded primary cancer tissue. Association of the Recurrence Score result with recurrence-free interval (RFI) was assessed by using weighted Cox proportional hazards regression. With respect to prespecified subgroups, as defined by low (< 30), intermediate (30 to 40), and high (≥ 41) Recurrence Score risk groups, patients with stage II disease in the high-risk group had a 5-year risk of recurrence similar to patients with stage IIIA to IIIB disease in the low-risk group (19% v 20%), whereas patients with stage IIIA to IIIB disease in the high-risk group had a recurrence risk similar to that of patients with stage IIC disease in the low-risk group (approximately 38%). The authors conclude that this validation study of the 12-gene Recurrence Score assay in stage III colon cancer without chemotherapy showed the heterogeneity of recurrence risks in stage III as well as in stage II colon cancer.

Gray et al. (2011) developed a quantitative gene expression assay to assess recurrence risk and benefits from chemotherapy in patients with stage II colon cancer. These assays were validated using RNA extracted from fixed paraffin-embedded primary colon tumor blocks from 1,436 patients with stage II colon cancer in the QUASAR (Quick and Simple and Reliable) study. A recurrence score (RS) and a treatment score (TS) were calculated from gene expression levels of 13 cancer-related genes (n = 7 recurrence genes and n = 6 treatment benefit genes) and from five reference genes with prespecified algorithms. Recurrence risks at 3 years were 12%, 18% and 22% for predefined low, intermediate and high recurrence risk groups, respectively. T stage and mismatch repair (MMR) status were the strongest histopathologic prognostic factors. The TS was not predictive of chemotherapy benefit.

A validation study by Clark-Langone et al. (2010) describes the analytical performance of the Oncotype DX Colon Cancer Assay. The study illustrates the algorithm used to calculate the recurrence score and reports the assay's performance regarding analytical sensitivity, analytical precision and reproducibility when used to test colon cancer specimens.

**Multiple Myeloma**

A Mayo Clinic consensus statement on the management of newly diagnosed patients with multiple myeloma states that due to current lack of influence on therapy, gene expression profiling (GEP) is neither routinely performed nor recommended in a nonresearch setting. However, as commercial tests are being developed, GEP will likely play a greater role in the management of multiple myeloma in the future (Mikhael et al., 2013).

The International Myeloma Workshop Consensus Panel 2 published recommendations for risk stratification in multiple myeloma. The document states that a more robust and comprehensive analysis is needed to analyze the significance of risk stratification using comparative genomic hybridization/single nucleotide polymorphism array. In the future, a specific polymorphism may help identify patients with differential response profile and/or higher risk of toxicity. However, there is lack of data to propose any specific single nucleotide polymorphisms that can be used for such decisions (Munshi et al., 2011).

Shaughnessy et al. (2007) performed gene expression profiling on tumor cells from 532 newly diagnosed myeloma patients treated on 2 separate protocols. The goal was to identify a signature associated with shorter survival. Seventy genes linked to shorter durations of complete remission, event-free survival and overall survival were identified. A subset of patients with a high-risk score had a 3-year continuous complete remission rate of only 20%, as opposed to a 5-year continuous complete remission rate of 60% in the absence of a high-risk score. Further analysis identified a 17-gene subset that performed as well as the 70-gene model.

To better define the molecular basis of multiple myeloma, Zhan et al. (2006) performed gene expression profiling on plasma cells from 414 newly diagnosed patients who went on to receive high-dose therapy and tandem stem cell transplants. The group identified and validated seven disease subtypes based on common gene expression signatures. Select subgroups were associated with superior event-free and overall survival. It was noted that the development of therapies that target the molecular pathways unique to high-risk disease should be encouraged.

Weinhold et al. (2016) reported clinical outcomes of GEP testing in relation to treatment type for subgroups of patients (n=1217) with multiple myeloma (MM) who participated in the University of Arkansas for Medical Sciences Total Therapy (TT) trials. Using log-rank tests for GEP data, the researchers identified 70 genes linked to early disease-related death. The UAMS GEP70 risk score is based on the ratio of the mean expression level of up-regulated to down-regulated genes among the 70 genes. Most up-regulated genes are located on chromosome 1q, and many down-regulated genes map to chromosome 1p. The predictor enabled the reliable identification of patients with shorter durations of complete remission, event-free survival, and overall survival that constitute 10–15% of newly diagnosed MM patients. The authors’ reported that impact of treatment differs between molecular subtypes of MM and that GEP gives important information that can help in clinical decision-making and treatment selection. Future studies should address whether strategies maximizing exposure to proteasome-inhibitors can further improve outcome in the MS subgroup. The authors’ note that comparison of GEP data of multiple paired samples showed differences in risk signatures, indicating the co-existence of HiR and LoR subclones (manuscript in preparation). Possibly, cells of a LoR
subclone were collected at relapse in these patients. the addition of thalidomide significantly improved outcome of LoR cases from maintenance and that outcome of LoR was improved further by the addition of bortezomib. The authors comment that they could not detect a significant improvement for HiR cases but this may be due to a lack of statistical power.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that gene expression profiling (GEP) has the potential to provide additional prognostic value to further refine risk-stratification, help therapeutic decisions and inform novel drug design and development. The NCCN panel unanimously agreed that although GEP is not routinely used in clinical practice during diagnostic workup, it may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment. No patient selection criteria were provided (NCCN, 2017).

**Prostate Cancer**

Results from initial analytical and clinical validity studies suggest that gene expression tests may have value to accurately predict the risk of recurrence or death from prostate cancer. However, the clinical utility of these tests in helping guide treatment decisions has yet to be established in prospective, randomized clinical trials.

In a review of tissue-based genomic biomarkers for prostate cancer, Moschini et al. (2016), report that available genomic assays have improved the prognostic ability over clinicopathologic parameters of localized PCs. Ideally, these assays should be prospectively applied, or even retrospectively applied to prospective studies, to further validate their clinical utility in prognostication and even prediction in terms of what treatment should be applied either at a new diagnosis or post-RP. In addition to their clinical value, more work is needed in regards to their financial impact on the cost of localized PCa care.

Rong et al. (2016) reviewed the literature on clinically available RNA profiling tests (Oncotype Dx, Prolaris, and Deciphe) of prostate tumors. They concluded that these RNA profiling panels have shown promising results in regard to clinical utility, several limitations are worth noting: (1) the current studies are retrospective with relatively small sample sizes, so larger-scale prospective randomized trials are necessary for validation; (2) RNA quality varies among panels (e.g., microdissection is needed for Deciphe [some medical center may not have the equipment], while for Prolaris, tissue extraction relies on the instruction from pathologist, which will lead to heterogeneity of the testing results); and (3) the relatively high prices limit potential use of the panels, will necessitate further evaluation of their cost-effective values.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical recurrence or progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. No randomized controlled trials have studied the utility of these tests. NCCN acknowledges that these tests have been developed with extensive industry support, guidance and involvement and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. In addition, although full assessment of their clinical utility requires prospective, randomized clinical trials (which according to the NCCN panel are unlikely to be done), the NCCN panel believes that future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer (NCCN, 2017).

Klein et al. (2016) retrospectively analyzed prostatectomy tissue of 337 Gleason 3+3 patients. To compare clinicopathologic variables across pathologic Gleason score categories, Fisher's exact test or analysis of variance F test were used. Distributions of Deciphe scores among different clinicopathologic groups were compared using Wilcoxon rank sum test. The association of Deciphe score and adverse pathology was examined using logistic regression models. Among men who had Gleason 3+3=6 disease only, 269 (80%) had low Deciphe scores with 43 (13%) and 25 (7%) harboring intermediate and high scores respectively. Thus a small proportion of histologic Gleason 6 tumors harbor molecular characteristics of aggressive cancer. The authors note that molecular profiling of such tumors at diagnosis may better select patients for active surveillance at the time of diagnosis and trigger appropriate intervention during follow-up.

**Prolaris**

Odera et al. (2016) assessed whether cell-cycle progression (CCP)-score (Prolaris) can improve the current risk assessment in newly diagnosed prostate cancer (PCa) patients. The CCP-score at biopsy was evaluated in 52 patients newly diagnosed with PCa who underwent radical prostatectomy. CCP-score was calculated as average RNA expression of 31 CCP genes, normalized to 15 housekeeping genes. The predictive ability of CCP-score was assessed in univariate and multivariate analyses, and compared to that of Ki-67 levels and traditional clinical variables including prostate-specific antigen, Gleason score, stage, and percentage of positive cores at biopsy. The authors reported that in spite of an overall good accuracy in attributing the correct risk class, 7 high-risk and 13 intermediate-risk patients
were misclassified by the Prolaris test, which is a limitation to this study. On analysis of variance, mean CCP-score significantly differed across different risk classes based on pathologic results (-1.2 in low risk, -0.444 in intermediate risk, 0.208 in high risk). CCP-score was a significant predictor of high-risk PCa both on univariate and multivariate analyses, after adjusting for clinical variables. Combining CCP-score and the European Association of Urology clinical risk assessment improved the accuracy of risk attribution by around 10%, up to 87.8%. CCP-score was a significant predictor of biochemical recurrence, but only on univariate analysis. The authors conclude that the CCP-score might provide important new information to risk assessment of newly diagnosed PCa in addition to traditional clinical variables. A correct risk attribution is essential to tailor the best treatment for each patient. Additional studies with larger patient sample sizes are needed to determine whether the use of this test in making treatment decisions improves patient outcomes.

Shore et al. (2014) evaluated the clinical utility of the CCP score in a U.S.-based clinical setting. Urologists who participated in a prospective clinical study were sent a retrospective questionnaire to assess the value of the CCP test results. Fifteen urologists participated in the study, representing 15 distinct urology group practices. Questionnaires were received for 294 evaluable patients. All patients had localized prostate cancer. Physicians found the CCP score valuable and indicated that 55% of tests generated a mortality risk that was either higher or lower than expected. Physicians also indicated that 32% of test results would lead to a definite or possible change in treatment. The data suggest that the test would have the net effect of shifting patients from more aggressive treatment to more conservative treatment. This was evidenced by the significant association between change in treatment and lower CCP scores. Results of this survey study provide only indirect evidence of clinical utility as the study measured the likelihood of change in treatment as estimated by the physician, not the actual change in treatment. The authors concluded that real-world use of the test is likely to lead to a change in treatment in a significant portion of tested patients, particularly by shifting patients towards more conservative management.

Crawford et al. (2014) conducted a prospective survey study evaluating the impact of the CCP score on physician treatment recommendations for prostate cancer. Physicians ordering the test completed surveys regarding treatment recommendations before and after they received and discussed test results with patients. Clinicians also rated the influence of the test result on treatment decisions. For patients originally targeted for interventional therapy, results of the CCP test led to a 37.2% reduction of interventional therapy. For patients originally targeted for noninterventional therapy, 23.4% of patients had treatment changes to interventional therapy based on test results. Overall, surgical interventions were reduced by 49.5%, and radiation treatment was reduced by 29.6% Author-reported limitations included physician selection of patients for testing, no evaluation of patient input in therapeutic choice and other potential treatment decision factors not queried by the survey. Results of this survey study provide only indirect evidence of clinical utility.

Cooperberg et al. (2013) conducted a validation study of 413 patients with prostate cancer. Using conventional prognostic factors, 67% of patients were classified as low risk. Overall, 82 patients (19.9%) experienced recurrence. The CCP score provided independent prognostic information on recurrence after radical prostatectomy particularly for those tumors deemed to be low risk by conventional clinical criteria.

Freedland et al. (2013) retrospectively evaluated the prognostic utility of the CCP score for predicting recurrence in men with prostate cancer. The primary therapy in this cohort was external beam radiation therapy (EBRT). The CCP score was derived from diagnostic biopsy specimens. Of 141 patients, 19 (13%) had recurrence. A multivariable analysis that included Gleason score, PSA, percent positive cores and androgen deprivation therapy, indicated that the CCP score was a significant predictor of biochemical recurrence, but only on univariate analysis. The authors concluded that, although the CCP score significantly predicted outcome and provided greater prognostic information than was available with clinical parameters. The authors noted that these results require validation in a larger cohort.

Cuzick et al. (2011) retrospectively assessed the prognostic value of the CCP score in two cohorts of patients with prostate cancer: those who had undergone radical prostatectomy (U.S.) and those who were being managed conservatively following diagnosis by transurethral resection of the prostate (TURP) (UK). The primary endpoint was time to recurrence for the prostatectomy cohort and time to death from prostate cancer for the conservatively managed cohort. In the full multivariate analysis of the prostatectomy cohort, CCP and PSA concentration were the most significant predictors of recurrence, and provided more prognostic information than any other variable. In the conservatively managed cohort, the CCP score was the most important variable for prediction of time to death from prostate cancer, although PSA concentration also added useful information. The authors concluded that, although the CCP score was predictive of outcome in both cohorts and provided more prognostic information than clinical variables alone, further validation studies using contemporaneous cohorts are needed. In a later study, Cuzick et al. (2012) reported similar results in a cohort of conservatively managed patients diagnosed by needle biopsy.

**OncotypeDx**

A racially diverse cohort of men was used to evaluate the association of a clinically validated 17-gene GPS with recurrence after radical prostatectomy and adverse pathology (AP) at surgery. Biopsies from 431 men treated for very low-, low- or intermediate-risk prostate cancer were tested to validate the association between GPS and BCR. GPS
results were obtained in 402 cases (93%): 62 men (15%) experienced BCR, 5 developed metastases and 163 had AP. Median follow-up was 5.2 years. GPS predicted time to BCR in univariable analysis and after adjusting for risk group. GPS was strongly associated with AP, after adjusting for risk group. Tumor aggressiveness and outcomes were similar in African American and Caucasian men (Cullen et al., 2015).

In a validation study, Klein et al. (2014) identified genes with expression associated with aggressive prostate cancer to develop the GPS, a biopsy-based, multigene signature test. GPS was validated for its ability to predict men who have high-grade or high-stage prostate cancer at diagnosis and may help men diagnosed with prostate cancer decide between active surveillance and immediate definitive treatment.

Knezevic et al. (2013) conducted a study to evaluate the analytical validity of the Oncotype DX Assay. Study authors assessed reproducibility and precision, and concluded that analytical validity was sufficient.

Brand et al. (2016) performed a meta-analysis of two independent clinical validation studies of a 17-gene biopsy-based genomic assay (Oncotype Dx Prostate Cancer Assay) as a predictor of favorable pathology at radical prostatectomy. Patient-specific meta-analysis was performed on data from 2 studies (732 patients) using the Genomic Prostate Score (GPS; scale 0-100) together with Cancer of the Prostate Risk Assessment (CAPRA) score or National Comprehensive Cancer Network (NCCN) risk group as predictors of the likelihood of favorable pathology (LFP). Risk profile curves associating GPS with LFP by CAPRA score and NCCN risk group were generated. Patient-specific meta-analysis generated risk profiles ensure more precise estimates of LFP with narrower confidence intervals either study alone. GPS added significant predictive value to each clinical classifier. The authors concluded that a model utilizing GPS and CAPRA provided the most risk discrimination, and in a decision curve analysis, greater net benefit was shown when combining GPS with each clinical classifier compared with the classifier alone. Although the clinical characteristics of the 2 patient cohorts were similar, there were nonetheless some key differences in the representation of different racial groups and higher risk patients. The risk estimates were numerically different in the 2 studies, although the confidence levels overlapped.

**Decipher**

Several validation studies have assessed the ability of Decipher, a genomic classifier (GC), to estimate a tumor’s potential for metastasis after radical prostatectomy. Results of these studies suggest that using Decipher, in addition to standard clinical information, may lead to changes in adjuvant therapy decision-making following surgery. Patients with a lower GC risk may benefit from delayed radiation therapy (Klein et al., 2015; Den et al., 2015; Cooperberg et al., 2015; Prensner et al., 2014; Den et al., 2014; Ross et al., 2014; Karnes et al., 2013; Erho et al., 2013).

Glass et al. (2016) published long-term outcomes to a previously reported validation study on Decipher. Study subjects (n=224) had aggressive prostate cancer with at least 1 of several criteria such as preoperative prostate specific antigen 20 ng/ml or greater, pathological Gleason score 8 or greater, stage pT3 disease or positive surgical margins at prostatectomy. Of the 224 patients treated 12 experienced clinical recurrence, 68 had biochemical recurrence and 34 experienced salvage treatment failure. At 10 years after prostatectomy the recurrence rate was 2.6% among patients with low Decipher scores but 13.6% among those with high Decipher scores (p=0.02). When CAPRA-S and Decipher scores were considered together, the discrimination accuracy of the ROC curve was increased by 0.11 compared to the CAPRA-S score alone (combined c-index 0.84 at 10 years after radical prostatectomy) for clinical recurrence. The authors conclude that Decipher improves the ability to predict clinical recurrence in prostate cancer and adds precision to conventional pathological prognostic measures. Long-term studies are needed to validate these results.

Badani et al. published two clinical utility studies evaluating the Decipher test with online surveys using hypothetical cases. Urologists were asked to indicate their treatment recommendations before and after receiving the results of the GC test. In Badani et al. (2015), recommendations for observation increased by 20% for patients assessed by the GC test to be at low risk of metastasis. Recommendations for treatment increased by 16% for patients at high risk of metastasis. A total of 110 patient case histories were available for review. In Badani et al. (2013), treatment recommendations changed from pre-GC to post-GC in 43% of adjuvant, and in 53% of salvage setting case evaluations. In the adjuvant setting, urologists changed their treatment recommendations from treatment (i.e., radiation and/or hormones) to close observation post-GC in 27% of cases. For cases with low GC risk (more than 3% risk of metastasis), observation was recommended for 79% of the case evaluations post-GC. Consistent trends were observed in the salvage setting.

Michalopoulos et al. (2014) assessed the effect of a GC test on urologists' adjuvant treatment decisions for high-risk patients. Data was submitted by U.S. board-certified urologists in community practices (n=15), who ordered the test for 146 prostate cancer patients with adverse pathologic findings following radical prostatectomy (pT3 or positive surgical margins). Over 60% of high-risk patients were reclassified as low risk after review of the GC test results. Overall, adjuvant treatment recommendations were modified for 30.8% of patients. With GC test results, 42.5% of patients who were initially recommended adjuvant therapy were subsequently recommended observation. The authors
Den et al. (2016) conducted a retrospective review of 2,341 consecutive radical prostatectomy patients to understand the relationship between the Decipher classifier test and patient tumor characteristics. Decipher score had a positive correlation with pathologic Gleason score (PGS; $r = 0.37$, 95% confidence interval (CI) $0.34 - 0.41$), pathologic T-stage ($r = 0.31$, 95% CI $0.28 - 0.35$), CAPRA-S ($r = 0.32$, 95% CI $0.28 - 0.37$) and patient age ($r = 0.09$, 95% CI $0.05-0.13$). Decipher reclassified 52%, 76% and 40% of patients in CAPRA-S low-, intermediate- and high-risk groups, respectively. The authors detected a 28% incidence of high-risk disease through the Decipher score in pT2 patients and 7% low risk in pT3b/pT4, PGS $8 - 10$ patients. There was no significant difference in the Decipher score between patients from community centers and those from academic centers ($P = 0.82$). The authors concluded that although Decipher correlated with baseline tumor characteristics for over 2 000 patients, there was significant reclassification of tumor aggressiveness as compared to clinical parameters alone. In their opinion, utilization of the Decipher genomic classifier can have major implications in assessment of postoperative risk that may impact physician-patient decision making and ultimately patient management.

In a review of the literature on precision medicine in the treatment of prostate cancer, Zhuang and Johnson (2016) reported that biopsy-based Decipher scores may represent another genomic tool to stratify biopsy-proven PCa patients to inform the choice of active surveillance versus curative treatment. It may also improve operative planning by indicating patients who require pelvic lymph node dissection or neoadjuvant therapy. Although this classifier has been validated based on retrospective analyses of patients who underwent radical prostatectomy, additional prospective randomized clinical trials are required to determine the test’s clinical utility.

**Professional Societies**

**American Society of Clinical Oncology (ASCO)**

In an endorsement of Cancer Care Ontario’s guideline on active surveillance of localized prostate cancer, ASCO comments that ancillary radiologic and genomic tests are investigational but may have a role in patients with discordant clinical and/or pathologic findings. Prospective validation of these tests is needed to assess their impact on patient outcomes such as survival (Chen et al., 2016).

**Uveal Melanoma**

Plasseraud et al. (2016) evaluated the continued clinical validity and utility of DecisionDx-UM in a prospective, multicenter, study (supported by Castle Biosciences, Inc.). 70 patients were enrolled to document patient management differences and clinical outcomes associated with low-risk Class 1 and high-risk Class 2 results indicated by DecisionDx-UM testing. Thirty-seven patients in the prospective study were Class 1 and 33 were Class 2. Class 1 patients had 100% 3-year metastasis-free survival compared to 63% for Class 2 (log rank test $p = 0.003$) with 27.3 median follow-up months in this interim analysis. Class 2 patients received significantly higher-intensity monitoring and more oncology/clinical trial referrals compared to Class 1 patients (Fisher’s exact test $p = 2.1 \times 10^{-13}$ and $p = 0.04$, resp.). In the authors’ opinion, the results of this study provide additional, prospective evidence in an independent cohort of patients for which Class 1 and Class 2 patients are managed according to the differential metastatic risk indicated by DecisionDx-UM. A study limitation is financial sponsorship/support by the manufacturer which increases the risk of bias.

In a prospective multi-center validation study, Onken et al. (2012) evaluated the prognostic performance of a 15 gene expression profiling (GEP) assay that assigned primary posterior uveal melanomas to prognostic subgroups: class 1 (low metastatic risk) and class 2 (high metastatic risk). A total of 459 patients were enrolled. Analysis was performed to compare the prognostic accuracy of GEP with Tumor-Node-Metastasis (TNM) classification and chromosome 3 status. Patients were managed for their primary tumor and monitored for metastasis. The GEP assay successfully classified 446 of 459 cases (97.2%). The authors concluded that the GEP assay had a high technical success rate and was the most accurate prognostic marker among all of the factors analyzed. The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. Further studies are needed to determine the clinical utility of these tests and the role they have in clinical decision-making.

To make the test more clinically practical, it was migrated from a microarray platform to a polymerase chain reaction (PCR)-based 15-gene assay. Onken et al., (2010) analyzed the technical performance of the assay in a prospective study of 609 tumor samples, including 421 samples sent from distant locations. Preliminary outcome data from the prospective study affirmed the prognostic accuracy of the assay.

Worley et al. (2007) compared the gene expression profile (molecular signature) to the chromosome 3 marker (monosomy 3) for predicting metastasis in 67 primary uveal melanomas. The gene expression-based molecular classifier assigned 27 tumors to class 1 (low risk) and 25 tumors to class 2 (high risk). Advanced patient age and scleral invasion were the only clinicopathologic variables significantly associated with metastasis. A less significant association with metastasis was observed for monosomy 3 detected by array comparative genomic hybridization.
In 2004, Onken et al., reported that primary uveal melanomas cluster into two distinct molecular classes based on gene expression profile: class 1 (low-grade) and class 2 (high-grade). The authors found that this molecular classification strongly predicted metastatic death and outperformed other clinical and pathological prognostic indicators.

The National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma do not include recommendations for the diagnostic workup of uveal melanoma (NCCN, 2017).

**Coronary Artery Disease**

In the IMPACT-CARD study, McPherson et al. (2013) assessed the impact of gene expression testing (Corus CAD) on clinical decision-making in patients with symptoms of suspected coronary artery disease (CAD) presenting to the cardiology setting. The study included a prospective cohort of 83 patients eligible for analysis, including 57 (69%) women. These patients were referred to six cardiologists for evaluation of suspected CAD and were matched to 83 patients in a historical cohort. The cardiologist’s diagnostic strategy was evaluated before and after gene expression score (GES) testing. The primary objective of the study was to measure whether the use of the GES changed the cardiologist’s evaluation and management of the patient. After GES, changes in diagnostic testing occurred in 58% of patients (n = 48). Of note, 91% (29/32) of patients with decreased testing had low GES (≤ 15), whereas 100% (16/16) of patients with increased testing had elevated GES. The historical cohort had higher diagnostic test use compared with the post-GES prospective cohort. The authors concluded that the GES showed clinical utility in the evaluation of patients with suspected obstructive CAD presenting to the cardiologist’s office. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up, small sample size and inclusion of individuals at low risk for CAD. Clinical trial #NCT01251302.

In a companion study (IMPACT-PCP), Herman et al. (2014) assessed the impact of gene expression testing (Corus CAD) on clinical decision-making in patients with symptoms of suspected coronary artery disease (CAD) presenting to a primary care setting. Providers initially determined patients’ pretest probability for CAD based on risk factors, assessment of clinical symptoms and results of any prior testing. All patients underwent gene expression score (GES) testing, with clinicians documenting their planned diagnostic strategy both before and after GES. The primary objective was to assess whether the use of GES altered patient management. The study enrolled 261 consecutive stable, nonacute, nondiabetic patients presenting with typical and atypical symptoms of CAD. Of the 251 eligible study patients, 140 were women (56%). After 30 days, a change in the diagnostic plan before and after GES testing was noted in 145 patients (58%). More patients had decreased (n=93, 37%) versus increased (n=52, 21%) intensity of testing. In particular, among the 127 low score Corus CAD patients (51% of study patients), 60% (76/127) had decreased testing, and only 2% (3/127) had increased testing. The authors concluded that the incorporation of GES into the diagnostic workup showed clinical utility above and beyond conventional clinical factors by optimizing the patient’s diagnostic evaluation. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up, modest sample size and inclusion of individuals at low risk for CAD. Clinical trial # NCT01594411.

The prospective, multicenter COMPASS validation study (Thomas et al., 2013) evaluated the performance of the Corus CAD test in symptomatic patients referred for myocardial perfusion imaging (MPI). Blood samples for gene expression scoring (GES) were obtained prior to MPI. Based on MPI results, 431 patients were referred for either invasive coronary angiography or computed tomographic angiography. Patients were followed for 6 months with clinical end points defined as major adverse cardiac events. Sensitivity, specificity and negative predictive value were reported at 89%, 52% and 96%, respectively. The GES outperformed clinical factors and showed significant correlation with maximum percent stenosis (≥50%). Six-month follow-up on 97% of patients showed that 27 of 28 patients with adverse cardiovascular events or revascularization had GES >15. The authors concluded that GES has high sensitivity and negative predictive value for obstructive coronary artery disease. In this population clinically referred for MPI, the GES outperformed clinical factors and MPI. A potential for bias exists due to manufacturer sponsorship of the study. Additional limitations include short term follow-up and inclusion of individuals at low risk for CAD. Clinical trial #NCT01117506.

The PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) trial was a prospective, multicenter validation study of a peripheral blood-based gene expression test for determining the likelihood of obstructive coronary artery disease (CAD). Patients with chronic inflammatory disorders, elevated levels of leukocytes or cardiac
protein markers or diabetes were excluded. Blood samples were obtained from 526 patients with chest pain or another indication for coronary angiography. Obstructive CAD was defined as ≥50% or greater stenosis in 1 or more major coronary arteries by quantitative coronary angiography. The sensitivity and specificity for the gene expression test were 85% and 43% respectively. The investigators reported a statistically significant but modest improvement in classification of patient CAD status compared with clinical factors or noninvasive imaging (myocardial perfusion imaging). Further studies are needed to define the performance characteristics and clinical utility of these tests in the general population (Rosenberg et al., 2010). A potential for bias exists due to manufacturer sponsorship of the study. Clinical trial #NCT00500617.

Assimes and Roberts (2016) summarized the evolution and discovery of genetic risk variants for CAD and their current and future clinical applications. In order to maximize the clinical utility of the current knowledge gained, the authors propose future tasks which include the identification of the remaining susceptibility loci for CAD, proving the clinical utility of genetic data in the prevention of CAD, and acquiring a solid appreciation of the cellular and/or extracellular mechanisms responsible for genetic associations observed at the population level. They conclude that extremely large sample sizes are needed for additional discoveries, given the distribution of effect sizes observed to date for both common and rare variants, as well as the estimated proportion of the heritability of CAD explained by these variants to date. In the coming years, the authors suggest that this need could be fulfilled by mega-biobanks to assist in the determination of the clinical utility of genetic risk scores, and to conduct additional, well-powered MR studies to complement studies published to date.

In a follow-up to the PREDICT study, Rosenberg et al. (2012) evaluated the relationship between gene expression testing and both major adverse cardiovascular events (MACE) and revascularization. A cohort of the original trial (n=1,116) underwent angiography and gene expression scoring (GES), and was followed for 1 year. A total of 267 (23.9%) patients had clinical endpoints within 30 days of testing. An additional 25 (2.2%) patients had clinical endpoints within a year. Overall, the rate of MACE was 1.5% for 12 months. Using a GES cutoff of ≤ 15 (i.e., low likelihood of CAD), the sensitivity, specificity, PPV and NPV for MACE or revascularization within 12 months of testing were 86%, 41%, 33% and 90%, respectively. The authors concluded that a low GES appeared to identify individuals at low risk for both obstructive coronary artery disease and subsequent procedures or events. The authors noted several limitations to the study including limited follow-up and exclusion of patients with high-risk unstable angina and low-risk asymptomatic patients. Further studies with larger patient populations and long-term outcomes are needed.

In an additional analysis of the PREDICT study, Lansky et al. (2012) reported that Corus CAD performed similarly in women and men.

Vargas et al. (2013) conducted a literature review and assessment regarding the analytical and clinical validity as well as the clinical utility of the Corus® CAD test in symptomatic non-diabetic patients. Given the scope of the deleterious effects of CAD and the considerable costs involved in diagnosing obstructive CAD, the authors comment that a blood test that can help in this determination is certainly valuable and that the Corus CAD test promises to have an important role in this regard particularly if it continues to perform this well in larger, more diverse cohorts. The authors caution that the results of this review should be interpreted carefully as patients with diabetes mellitus and chronic inflammatory or autoimmune disorders were excluded from test development and validation. Furthermore, this test was derived and tested in predominantly Caucasian patient populations. Given the known variations in the prevalence of CAD in different ethnic/racial backgrounds, results of this test in non-Caucasian populations should be interpreted with caution.

Using a series of microarray and real-time polymerase chain reaction (RT-PCR) data sets, comprising more than 1000 patients, Elashoff et al. (2011) developed a blood-based gene expression algorithm for assessing obstructive coronary artery disease (CAD) in non-diabetic patients. The algorithm consists of the expression levels of 23 genes, sex and age.

Wingrove et al. (2008) performed a microarray analysis on 41 patients with angiographically significant coronary artery disease (CAD) and 14 controls without coronary stenosis to identify genes expressed in peripheral blood that may be sensitive to the presence of CAD. A multistep approach was used, starting with gene discovery from microarrays, followed by real-time polymerase chain reaction (RT-PCR) replication. The authors observed that gene expression scores based on 14 genes, independently associated with the presence or absence of CAD, were proportional to the extent of disease burden. This study is limited by its size and retrospective nature. Larger, prospective studies are needed to confirm these initial results.

The U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors in coronary heart disease risk assessment do not address genetic/genomic markers (USPSTF, 2009).
Professional Societies
American College of Cardiology (ACC)
ACC guidelines do not address gene expression profiling for predicting the likelihood of obstructive coronary artery disease.

American Heart Association (AHA)
In an AHA scientific statement, Mital et al. (2016) affirm that advances in genomics are enhancing the understanding of the genetic basis of cardiovascular diseases, both congenital and acquired, and stroke. These advances include finding genes that cause or increase the risk for childhood and adult-onset diseases, finding genes that influence how patients respond to medications, and the development of genetics-guided therapies for diseases. The AHA recommends that cardiovascular and stroke clinicians develop a set of core competencies in genetics so that they can systematically and effectively integrate genetics into clinical practice.

In an AHA policy statement on genetics and cardiovascular disease, Ashley et al. (2012) strongly advocate the involvement of physicians and centers with expertise in cardiovascular genetics to guide the appropriate initiation, interpretation, and implementation of genetic testing and to gain clinical consensus as to what constitutes clinical utility. The potential of whole-genome sequencing to impact medicine is highly significant and as such, they recommend that genetics and genomics be included as a fundamental part of the training curriculum for all health professionals.

In a published scientific statement on the relevance of genetics and genomics for the prevention and treatment of cardiovascular disease (CVD), the AHA states that RNA gene expression profiling shows great promise. However, further results from large, patient cohorts are needed to determine the clinical utility of this methodology. The statement also proposes several recommendations to guide future research (Arnett et al. 2007).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Microarrays and next-generation sequencing represent core technologies in pharmacogenomics and toxicogenomics; however, before these technologies can successfully and reliably be used in clinical practice and regulatory decision-making, standards and quality measures need to be developed. The MicroArray Quality Control (MAQC) project is helping improve the microarray and next-generation sequencing technologies and foster their proper applications in discovery, development and review of FDA regulated products. Additional information is available at: http://www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/default.htm. (Accessed February 17, 2017)

The original version of the Tissue of Origin Test (Pathwork® Diagnostics) (now referred to as the ResponseDX Tissue of Origin Test) received FDA approval (K080896) on July 30, 2008. A second version of the test (K092967) was approved on June 8, 2010. The test is an in-vitro diagnostic intended to measure the degree of similarity between the RNA expression patterns in a patient’s formalin fixed, paraffin embedded (FFPE) tumor and the RNA expression patterns in a database of fifteen tumor types (poorly differentiated, undifferentiated and metastatic cases) that were diagnosed according to then current clinical and pathological practice.

The test is not intended to do any of the following:
- Establish the origin of tumors that cannot be diagnosed according to current clinical and pathological practice
- Subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathological practice
- Predict disease course, survival or treatment efficacy
- Distinguish primary from metastatic tumor.

See the following websites for more information:
(Accessed February 17, 2017)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)
Medicare does not have a National Coverage Determination (NCD) for gene expression tests. Local Coverage Determinations (LCDs) exist; see the LCDs for Assays for Vitamins and Metabolic Function, Biomarkers for Oncology,
REFERENCES

Agency for Healthcare Research and Quality (AHRQ). Technology assessment on genetic testing or molecular pathology testing of cancers with unknown primary site to determine origin. February 2013.


Gene Expression Tests


Response Genetics.
Signal Genetics™.

**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>07/01/2017</td>
<td>- Revised coverage rationale for oncology indications:</td>
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<td></td>
<td>o Added language to indicate ThyraMIR™ (multi-panel gene expression test) is</td>
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<td>proven and medically necessary for assessing thyroid nodules that are not</td>
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<td>o Updated language pertaining to unproven/not medically necessary indications:</td>
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<td>▪ Added notation to clarify the named gene expression tests are listed as examples only; all gene expression tests are considered unproven and not medically necessary for the listed indications</td>
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<td>▪ Modified language addressing clinical evidence/study findings to clarify there is insufficient evidence in the clinical literature demonstrating that gene expression tests have a role in clinical decision-making or have a beneficial effect on health outcomes for [the listed] indications; further studies are needed to determine the clinical utility of these tests</td>
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<td>• Updated supporting information to reflect the most current description of services, clinical evidence, FDA and CMS information, and references</td>
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