MOLECULAR ONCOLOGY TESTING FOR CANCER DIAGNOSIS, PROGNOSIS, AND TREATMENT DECISIONS

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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

Gene Expression Tests for Breast Cancer Treatment

The use of one of the following gene expression tests is considered proven and/or medically necessary to make a treatment decision regarding adjuvant chemotherapy in females or males with non-metastatic breast cancer when all of the following criteria are met.
However, the use of more than one gene expression test for the same tumor in an individual with breast cancer is unproven and/or not medically necessary.

**Gene Expression Tests for High Risk Breast Cancer**

Gene expression tests for high risk breast cancer, including MammaPrint (also referred to as the "Amsterdam signature" or "70-gene signature"), are considered proven and/or medically necessary to assess distant recurrence of disease in individuals with recently diagnosed non-metastatic breast cancer when all the following criteria are met:

- High clinical risk of recurrence based on at least one of the following criteria:
  - Lymph node positive (pN1-2); or
  - Tumor size greater than 2 cm; or
  - Poorly differentiated or undifferentiated histology (grade 3) AND tumor size greater than 1 cm; and
- Hormone receptor-positive (estrogen receptor positive, progesterone receptor positive or both); and
- HER2 receptor negative; and
- Adjuvant chemotherapy is not precluded due to any other factor (e.g., advanced age and/or significant co-morbidities); and
- Individual and treating physician have had a discussion prior to testing regarding the potential results of the test and determined to use the results to guide therapy.

MammaPrint is considered unproven and/or not medically necessary for all other indications.

**Gene Expression Tests for Intermediate and Low Risk Breast Cancer**

Oncotype Dx Breast, Prosigna PAM-50 Breast Cancer Prognostic Gene Signature Assay, EndoPredict and the Breast Cancer Index gene expression tests for intermediate and low risk breast cancer are considered proven and/or medically necessary to assess use of adjuvant chemotherapy in individuals with recently diagnosed non-metastatic breast cancer when all of the following criteria are met:

- Lymph node negative (pN0) or axillary lymph node micrometastasis less than 2mm (pN1mi); and
- Hormone receptor positive (estrogen receptor positive, progesterone receptor positive or both); and
- HER2 receptor negative; and
- Adjuvant chemotherapy is not precluded due to any other factor (e.g., advanced age and/or significant co-morbidities); and
- Individual and treating physician have had a discussion prior to testing regarding the potential results of the test and determined to use the results to guide therapy.

Oncotype Dx Breast, Prosigna PAM-50 Breast Cancer Prognostic Gene Signature Assay, EndoPredict, and the Breast Cancer Index are considered unproven and/or not medically necessary for all other indications.

Gene expression profiling assays for breast cancer treatment other than those previously described as covered are considered unproven and/or not medically necessary, including but not limited to:

- BluePrint (also referred to as "80-gene profile")
- Breast Cancer Gene Expression Ratio (also known as Theros H/I)
- BreastNext
- BreastOncPX
- BreastPRS
- Insight DX Breast Cancer Profile
- Mammostrat
- NexCourse Breast IHC4
- NuvoSelect eRx 200-Gene Assay
- Oncotype DX DCIS
- SYMPHONY Genomic Breast Cancer Profile
- TargetPrint
- TheraPrint
- The 41-gene signature assay
- The 76-gene "Rotterdam signature" assay

To date, the majority of the available studies fail to provide sufficient evidence that gene expression profiling is useful for managing the treatment of breast cancer and leads to improved health outcomes (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling as a technique of managing the treatment of breast cancer compared with traditional clinical factors to guide medical management and improve clinical outcomes.
Gene Expression Profiling to Identify the Tissue of Origin for Cancers of Unknown Primary Site

To identify the tissue of origin for cancers of unknown primary site, gene expression profiling assays are considered unproven and/or not medically necessary for all indications, including but not limited to:

- ResponseDX: Tissue of Origin Test
- CancerTYPE ID Test
- Rosetta Cancer Origin Test (miRview mets and miRview mets² tests)
- ProOnc TumorSourceDX Test

To date, the majority of the available studies fail to provide sufficient evidence that gene expression profiling to identify the tissue of origin for cancers lead to improved health outcomes (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling to identify the tissue of origin for cancers of unknown primary site compared with traditional clinicopathologic factors to guide medical management and improve clinical outcomes.

Gene Expression Profiling of Melanoma

In cutaneous and uveal melanoma, gene expression profiling assays are considered unproven and/or not medically necessary for all indications, including but not limited to:

- DecisionDx-Melanoma test
- DecisionDx-UM

To date, the majority of the available studies fail to provide sufficient evidence that gene expression profiling of melanoma leads to improved health outcomes (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling of melanoma compared with traditional clinical factors to guide medical management and improve clinical outcomes.

Gene Expression Profiling as a Technique for Colorectal Cancer (CRC) Risk Assessment or Management

In colorectal cancer (CRC) risk assessment or management, gene expression profiling assays are considered unproven and/or not medically necessary, including but not limited to:

- Oncotype DX Colon Cancer Assay
- Colorectal Cancer DSA
- GeneFx Colon
- OncoDefender-CRC

To date, the majority of the available studies fail to provide sufficient evidence that gene expression profiling as a technique for colorectal cancer (CRC) risk assessment or management lead to improved health outcomes (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profiling as a technique for colorectal cancer (CRC) risk assessment or management compared with traditional clinical factors to guide medical management and improve clinical outcomes.

Gene Expression Profile Tests for Evaluation or Management of Multiple Myeloma

Gene expression profile tests for evaluation or management of multiple myeloma are considered unproven and/or not medically necessary, including but not limited to:

- MyPRS/MyPRS Plus

To date, the majority of the available studies fail to provide sufficient evidence that gene expression profile tests for evaluation or management of multiple myeloma lead to improved health outcomes or to manage treatment decisions (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of gene expression profile tests for evaluation or management of multiple myeloma compared with traditional clinical factors to guide medical management and improve clinical outcomes.

Gene Expression Profile Tests for the Screening, Detection and Management of Prostate Cancer

Gene-based tests for the screening, detection and management of prostate cancer are considered unproven and/or not medically necessary, including but not limited to:

- Oncotype DX Prostate Cancer Assay
- TMPRSS2 fusion gene
- Prolaris Prostate Cancer Test
- Decipher Prostate Cancer Classifier

To date, the majority of the available studies fail to provide sufficient evidence that gene-based tests for the screening, detection and management of prostate cancer lead to improved health outcomes or to manage treatment decisions (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of
gene-based tests for the screening, detection and management of prostate cancer compared with traditional clinical factors to guide medical management and improve clinical outcomes.

**Topographic Genotyping**

Topographic genotyping is unproven and/or not medically necessary. Examples of such tests include, but are not limited to, the following:
- PathFinder TG

To date, the majority of the available studies fail to provide sufficient evidence that topographic genotyping lead to improved health outcomes (i.e., clinical utility). Well-designed randomized controlled trials (RCTs) are needed to determine the clinical utility of topographic genotyping compared with traditional clinical factors to guide medical management and improve clinical outcomes.

**Multi-Gene Cancer Panels for Diagnosis, Prognosis and Treatment Decisions (Molecular Profiling)**

Molecular profiling of tumors using a multi-gene cancer panel of up to 50 genes is considered proven and/or medically necessary for individuals with metastatic non-small cell lung cancer (NSCLC).

Use of more than one gene multi-gene cancer panel for the same individual with non-small cell lung cancer is unproven and/or not medically necessary.

Multi-gene cancer panels are considered unproven and/or not medically necessary for all other indications.

Multi-gene cancer panels of greater than 50 genes are considered unproven and/or not medically necessary for all indications.

**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.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<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>0011M</td>
<td>Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk</td>
</tr>
<tr>
<td>0012M</td>
<td>Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma</td>
</tr>
<tr>
<td>0013M</td>
<td>Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma</td>
</tr>
<tr>
<td>0019U</td>
<td>Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents</td>
</tr>
<tr>
<td>0021U</td>
<td>Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5’-UTR-BMI1, CEP 164, 3’-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score</td>
</tr>
<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
</tr>
</tbody>
</table>
Gene expression profiling tests analyze patterns of gene expression within cancer cells to aid in classifying disease in a manner that impacts clinical decision-making. In some cases, results of gene expression profiles help determine if individuals with particular cancers will benefit from specific treatments including chemotherapy. Expression patterns of defined genes (such as mRNA, microRNA, long non-coding RNA) are combined in a defined manner to provide an expression signature, a score, or a classifier for potential diagnosis and or prognosis of disease or to predict impact of intervention. The use of these assays can serve as a tool to identify those individuals who will benefit from chemotherapy or to guide the selection of therapeutic agents.

Molecular profiling is a method of genetic analysis that can identify mutation and certain other types of gene variants (e.g., insertion, deletion, rearrangement) in cancer cells. This testing assesses genetic characteristics of cancer cells. Results of molecular profiling may assist individuals and healthcare providers with selection of more effective and targeted cancer therapies. There are several molecular profiling assays that are being used to guide cancer treatment for individuals with certain types of cancers.

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</tr>
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<tbody>
<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRα, PDGFRβ, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
</tr>
<tr>
<td>81450</td>
<td>Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLI1, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed</td>
</tr>
<tr>
<td>81455</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLI1, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRα, PDGFRβ, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</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>81519</td>
<td>Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score</td>
</tr>
<tr>
<td>81520</td>
<td>Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score</td>
</tr>
<tr>
<td>81521</td>
<td>Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis</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>81541</td>
<td>Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score</td>
</tr>
<tr>
<td>81551</td>
<td>Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

**DESCRIPTION OF SERVICES**

Gene expression profiling tests analyze patterns of gene expression within cancer cells to aid in classifying disease in a manner that impacts clinical decision-making. In some cases, results of gene expression profiles help determine if individuals with particular cancers will benefit from specific treatments including chemotherapy. Expression patterns of defined genes (such as mRNA, microRNA, long non-coding RNA) are combined in a defined manner to provide an expression signature, a score, or a classifier for potential diagnosis and or prognosis of disease or to predict impact of intervention. The use of these assays can serve as a tool to identify those individuals who will benefit from chemotherapy or to guide the selection of therapeutic agents.

Molecular profiling is a method of genetic analysis that can identify mutation and certain other types of gene variants (e.g., insertion, deletion, rearrangement) in cancer cells. This testing assesses genetic characteristics of cancer cells. Results of molecular profiling may assist individuals and healthcare providers with selection of more effective and targeted cancer therapies. There are several molecular profiling assays that are being used to guide cancer treatment for individuals with certain types of cancers.
Gene Expression Tests for Breast Cancer Treatment

There are many laboratory tests developed to detect gene expression in breast tumor tissue. These results may be used to predict distant recurrence risk for women with early stage breast cancer. In turn, this may help with the decision of whether to include adjuvant chemotherapy.

The National Comprehensive Cancer Network (NCCN) clinical guidelines for breast cancer (2017) state that the use of DNA microarray technologies to characterize breast cancer has allowed for development of classifications of breast cancer by gene expression profile. Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling. In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and overall survival (OS).

Oncotype Dx® Breast

Oncotype Dx Breast (Oncotype DX; Genomic Health, Redwood City, CA) is a test that analyzes the expression of a panel of 21 genes within a tumor to determine a “Recurrence Score” which may correspond to a likelihood of breast cancer recurrence within 10 years. The test was initially developed for women with early-stage invasive breast cancer with ER+ cancers that are lymph node-negative, and subsequently evidence was gathered on individuals with up to 3 ipsilateral nodes positive. These individuals are typically treated with anti-hormonal therapy, such as tamoxifen or aromatase inhibitors, and Oncotype Dx® can help determine if chemotherapy should be added to the treatment regimen (Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, 2015).

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group (2016) found insufficient evidence to recommend for or against the use of Oncotype DX testing to guide chemotherapy treatment decisions in women with hormone receptor-positive, lymph node-negative, or lymph node-positive early breast cancer who are receiving endocrine therapy. This recommendation statement updates a 2009 EGAPP statement on the use of gene expression profiling tests in breast cancer. Evidence of clinical validity for Oncotype DX was confirmed by EGAPP as adequate. With regard to clinical utility, although there was evidence from prospective retrospective studies that the Oncotype DX test predicts benefit from chemotherapy, and there was adequate evidence that the use of Oncotype DX gene expression profiling in clinical practice changes treatment decisions regarding chemotherapy, EGAPP found no direct evidence that the use of Oncotype DX testing leads to improved clinical outcomes.

Prosigna® Breast Cancer Prognostic Gene Signature Assay

The Prosigna® (NanoString Technologies (Seattle, WA)) breast cancer prognostic assay provides a risk category and numerical score to assess an individual’s risk of distant recurrence of disease at 10 years in postmenopausal women with node-negative (Stage I or II) or node-positive (Stage II), hormone receptor-positive breast cancer. The Prosigna assay measures expression levels of 50 genes using formalin-fixed paraffin-embedded (FFPE) breast tumor tissue diagnosed as invasive breast carcinoma. The assay is not intended for individuals with 4 or more positive nodes (Gnant et al., 2013; Parker et al., 2009).

MammaPrint® (also referred to as the "Amsterdam Signature" or "70-Gene Signature")

MammaPrint® (Agenda, Amsterdam, The Netherlands) is a 70-gene expression test to assess breast cancer distant recurrence risk. The assay analyzes tumor tissue (fresh, frozen or formalin-fixed paraffin-embedded) for expression of 70 genes assumed to be important in cancer metastasis. Based on the test results, Mammprint may assist individuals considering adjuvant treatments. Individuals are assigned either a low risk or a high risk for a distant recurrence. The risk category may be taken into consideration for treatment options.

A recent randomized clinical trial evaluated Mammprint and found that “women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy. Given these findings, approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy. (Cardoso, et al., 2016).

The randomized, phase 3 clinical MINDACT trial included 6693 women with early-stage breast cancer with the primary goal to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be 92% (i.e., the non-inferiority boundary) or higher. Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did receive such therapy. In patients with discordant risk results, either the genomic risk or the clinical risk was used to determine the use of chemotherapy. The researchers found that among women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with...
chemotherapy. Given these findings, approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy (Cardoso et al., 2016).

**EndoPredict**

EndoPredict (Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016) is a 12-gene real-time RT-PCR that includes eight disease-relevant genes BIRC5, UBE2C, DHCRR7, RBBP8, IL6ST, AZGP1, MGP and STC2 are compared to three RNA normalization genes (CALM2, OAZ1 and RPL37A) and to one DNA reference gene (HBB).

In a comparison of comparison of EndoPredict (EP) and EPclin with Oncotype DX security score for prediction of risk of distant recurrence after endocrine therapy, Buus et al. (2016) concluded that EP and EPclin were highly prognostic for distance recurrence in endocrine-treated patients with ER+, HER2-negative disease. The researchers found that EPclin provided more prognostic information than recurrence score, which they determined was partly but not entirely because of EPclin integrating molecular data with nodal status and tumor size.

**Breast Cancer Index (BCI)**

Breast Cancer Index (BioTheranostics, San Diego, CA) is a prognostic biomarker assay that analyzes the combination of two indices: HOXB13:IL17BR and five cell cycle-associate gene index (BUB1B, CENPA, NEK2, RACGAP1, RRM2). The test is performed on a formalin-fixed, paraffin-embedded (FFPE) tissue block.

Sestak et al. (2016) conducted a retrospective analysis to examine cross-stratification between Breast Cancer Index (BCI) and the OncotypeDX Recurrence Score (RS) to directly compare their prognostic accuracy at the individual patient level. 665 patients with hormone receptor-positive (HR+) and lymph node-negative disease were included in this retrospective analysis. The authors concluded that demonstrated increased prognostic accuracy versus RS. Notably, BCI identified subsets of RS low and RS intermediate risk patients with significant and clinically relevant rates of DR. These results indicate that additional subsets of women with HR+, lymph node-negative breast cancer identified by BCI may be suitable candidates for adjuvant chemotherapy or extended endocrine therapy.

**Professional Societies**

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

In their 2016 evidence-based guideline on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer, ASCO (Harris et al., 2016a; Harris et al., 2016b) found sufficient evidence of clinical utility for the biomarker assays Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in specific subgroups of breast cancer. No biomarker except for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to guide choices of specific treatment regimens. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

For this guideline, the ASCO panel considered only prognosis and prediction in patients with newly diagnosed, nonmetastatic, primary breast cancer. Prognosis was defined as an indication of future risk of an event (recurrence, distant metastases, or death) independent of the effect of prior or anticipated therapy. Prediction was defined as the ability of a specific biomarker to indicate the likelihood of benefit from a particular therapy or a class of agent (e.g., endocrine, biologic, or chemotherapy).

ASCO considers the conclusions on prognostic and predictive biomarkers in early-stage invasive breast cancer to be limited by the lack of prospective confirmatory studies; findings of insufficient clinical utility; and, in many cases, a lack of data on clinical validity and reproducibility of assays. The expert panel awaits the completion and publication of several randomized trials to establish the clinical utility of some of these assays. Extensive research is needed to validate some of the biomarker candidates described and to identify promising new biomarkers. ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

The guideline provides specific recommendations on the use of individual biomarker assays.

**American Society of Clinical Oncology/College of American Pathologists (CAP)**

In an clinical practice guideline for human epidermal growth factor receptor 2 testing in breast cancer (Wolff et al., 2013), ASCO and CAP Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). In addition:

- Testing criteria to define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area).
• If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH).
• Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens.
• The Committee urges testing be performed in a laboratory accredited by CAP or another accrediting entity, and that providers and health systems cooperate to ensure the highest quality testing.

**Gene Expression Profiling to Identify the Tissue of Origin for Cancers of Unknown Primary Site**

National Comprehensive Cancer Network (NCCN) clinical practice guidelines for occult primary (cancer of unknown primary site) 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, the NCCN suggests that pathologists and oncologists collaborate on the judicious use of these modalities on a case-by-case basis, with the best individualized patient outcome in mind (NCCN, 2016).

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.

Meleth et al. (2013) conducted a technology assessment on genetic testing or molecular pathology testing for cancer of unknown primary cancers with CancerTypeID, miRview, or PathworkDx to determine analytical validity, clinical validity, and clinical utility. The results showed that the clinical accuracy of all the three tests is similar, ranging from 85 percent to 88 percent. The evidence that the tests contribute to identifying a TOO is moderate; however the researchers noted that they did not have sufficient evidence to assess the effect of the tests on treatment decision and outcomes.

In a guideline on the diagnosis and management of metastatic malignant disease of unknown primary origin in adults, the National Institute of Health and Care Excellence (NICE) (2010) does not recommend the use of gene-expression-based profiling to identify primary tumors in patients with provisional CUP. They also do not recommend the use of gene expression-based profiling when deciding which treatment to offer patients with confirmed CUP.

**Professional Societies**

**European Society for Medical Oncology (ESMO)**

In a clinical practice guideline for the diagnosis, treatment and follow-up on cancers of unknown primary (CUP) site, ESMO (Fizazi et al., 2015) did not identify any significant differences in the tumor microRNA expression profile when CUP metastases biologically assigned to a primary tissue of origin were compared with metastases from typical solid tumors of known origin. Although they noted that these tests may aid in the diagnosis of the putative primary tumor site in some patients, their impact on patient outcome via administration of primary site-specific therapy remains questionable and unproven in randomized trials.

**Gene Expression Profiling of Melanoma**

**Cutaneous Melanoma (CM)**

Berger et al. (2016) conducted a retrospective analysis to ascertain clinical management changes to 156 patients with cutaneous melanoma, based on the outcome of DecisionDx-Melanoma. Molecular risk classification by gene expression profiling has clinical impact and influences physicians to direct clinical management of CM patients. The vast majority of the changes implemented after the receipt of test results were reflective of the low or high recurrence risk associated with the patient's molecular classification. Because follow-up data was not collected for this patient cohort, the study is limited for the assessment of the impact of gene expression profile based management changes on healthcare resource utilization and patient outcome.

NCCN (2016) clinical practice guidelines for melanoma note that while there is interest in the newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanoma at low versus high risk for metastasis, routine (baseline) testing of primary cutaneous melanoma (before or following SLNB) is not recommended outside of clinical study (trial).
**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 x 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.

NCCN clinical practice guidelines for melanoma do not include recommendations for the diagnostic workup of uveal melanoma (NCCN, 2016).

**Gene Expression Profiling as a Technique for Colorectal Cancer (CRC) Risk Assessment or Management**

Zhang et al. (2016) retrospectively reviewed the prognostic role of CDX2 expression in patients with stage 1 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; PÂ < .0001). In addition, the median PFS (3 vs. 10 months; HR, 2.23; 95% CI, 1.52-3.27; PÂ < .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% with 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.

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 IIIC 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.

In a prospective multicenter study of the impact of oncotype DX colon cancer assay results on treatment recommendations in stage II colon cancer patients, Srivastava et al. (2014) assessed patient tumor specimens by the RS test (quantitative reverse transcription-polymerase chain reaction) and mismatch repair (immunohistochemistry). For each patient, the physician’s recommended postoperative treatment plan of observation, fluoropyrimidine monotherapy, or combination therapy with oxaliplatin was recorded before and after the RS and mismatch repair results were provided. Of 221 enrolled patients, 141 patients had T3 MMR-P tumors and were eligible for the primary analysis. Treatment recommendations changed for 63 (45%; 95% confidence interval: 36%-53%) of these 141 T3 MMR-P patients, with intensity decreasing for 47 (33%) and increasing for 16 (11%). Recommendations for chemotherapy decreased from 73 patients (52%) to 42 (30%), following review of RS results by physician and patient. Increased treatment intensity was more often observed at higher RS values, and decreased intensity was observed at lower values (p = .011). The researchers concluded that compared with traditional clinicopathological assessment, incorporation of the RS result into clinical decision making was associated with treatment recommendation changes for 45% of T3 MMR-P stage II colon cancer patients in this prospective multicenter study. Use of the RS assay may lead to overall reduction in adjuvant chemotherapy use in this subgroup of stage II colon cancer patients. Additional studies are needed to validate these findings.

Venook et al., (2013) conducted a validation study of of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581 of 1,713 randomly assigned patients with stage II colon cancer to treatment with edrecolomab or observation and found no survival difference. The analysis reported included all patients with available tissue and recurrence (n = 162) and a random (approximately 1:3) selection of nonrecurring patients. RS was assessed in 690 formalin-fixed paraffin-embedded tumor samples with quantitative reverse transcriptase polymerase chain reaction by using prespecified genes and a previously validated algorithm. Association of RS and recurrence was analyzed by weighted Cox proportional hazards regression. The researchers concluded that 12-gene RS predicts recurrence in stage II colon cancer in CALGB 9581, which is consistent with the importance of stromal response and cell cycle gene expression in colon tumor recurrence. RS appears to be most discerning for patients with T3 MMR-I tumors, although markers such as grade and lymphovascular invasion did not add value in this subset of patients.

In a validation study of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin, Yothers et al. (2013). Recurrence Score was assessed in 892 fixed, paraffin-embedded tumor specimens (randomly selected 50% of patients with tissue). Data were analyzed by Cox regression adjusting for stage and treatment. Based on the results, the authors concluded that 12-gene Recurrence Score predicts recurrence risk in stage II and stage III colon cancer and provides additional information beyond conventional clinical and pathologic factors. Incorporating Recurrence Score into the clinical context may better inform adjuvant therapy decisions in stage III as well as stage II colon cancer.

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

**Gene Expression Profile Tests for Evaluation or Management of Multiple Myeloma**

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 bortezomb. 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 for multiple myeloma 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 utilized 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, 2016).

**Gene Expression Profile Tests for the Screening, Detection and Management of Prostate Cancer**

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 PCa. 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.

Na et al. (2016) reviewed the literature on clinically available RNA profiling tests (Oncotype Dx, Prolaris, and Decipher) 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 Decipher [some medical centers 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.

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 Decipher scores among different clinicopathologic groups were compared using Wilcoxon rank sum test. The association of Decipher score and adverse pathology was examined using logistic regression models. Among men who had Gleason 3+3=6 disease only, 269 (80%) had low Decipher 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.

Oderda 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.

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.

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.

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.

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.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines for prostate cancer 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).

**Professional Societies**

**American Urological Association (AUA)**

In a clinical practice guideline on early detection of prostate cancer (Carter et al., 2013; reviewed and confirmed 2015) based on a systematic review and meta-analysis, the AUA notes that an improved understanding of the interaction between inherited risk alleles and the environment (lifestyle choices) could provide a potential means of prevention. Future studies of the genetic and epigenetic basis of disease development and progression may provide biomarkers and/or panels of biomarkers with improved specificity when compared to PSA. When available, risk assessment tools combining multiple predictors will need to be evaluated in carefully designed trials to be generalizable to the population in which they would be used.

**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).

**Topographic Genotyping**

In a systematic review of loss-of-heterozygosity based topographic genotyping with PathfinderTG®, Trikalinos et al. (2010) found no studies that demonstrated longer survival, longer time to tumor recurrence, or fewer adverse outcomes as a result of this testing. The authors reported several limitations with eligible studies including limited sample size and lack of patient selection criteria.

**Multi-Gene Cancer Panels for Diagnosis, Prognosis and Treatment Decisions**

**Non-Small Cell Lung Cancer (NSCLC)**

Frampton and colleagues (2013) conducted an analytical and clinical validation study to evaluate massively parallel DNA sequencing using the FoundationOne assay to characterize base substitutions, indels, copy number alterations, and selected fusions across 287 cancer-related genes from routine formalin-fixed and paraffin-embedded (FFPE) clinical specimens. The authors implemented a validation strategy with reference samples of pooled cell lines that modeled key drivers of test accuracy, including mutant allele frequency, indel length and amplitude of copy change. Test sensitivity achieved was 95% to 99% across alteration types, with high specificity (positive predictive value [PPV] >99%). The authors confirmed accuracy using 249 FFPE cancer specimens characterized by established assays. Application of the test to 2,221 clinical cases revealed clinically actionable alterations in 76% of tumors, three times the number of actionable alterations detected by current diagnostic tests. This study did not evaluate the clinical utility of such findings in improving care and outcome of patients by tailoring treatments or predicting response to treatment. Hence, it is important to note that the clinical utility of genomic profiling using massively parallel DNA sequencing remains unknown. In addition, study authors colleagues did not categorize the data regarding sensitivity, specificity, and positive predictive value (PPV) by cancer type, so it is not clear how well the test performed among patients with NSCLC.

Drilon et al. (2015) identified 31 patients with lung adenocarcinoma with a ≤ 15 pack-year smoking history whose tumors previously tested "negative" for alterations in 11 genes (mutations in EGFR, ERBB2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA, and AKT1 and fusions involving ALK, ROS1, and RET) via multiple non-NGS methods. A broad, hybrid capture–based NGS assay (FoundationOne) was performed (4,557 exons of 287 cancer-related genes and 47 introns of 19 genes frequently rearranged in solid tumors). A genomic alteration with a corresponding therapeutic consequence was identified in 100% of patients (26% (n = 8 of 31) of patients. The drivers identified in tumors from these 8 patients were EGFR G719A, BRAF V600E, SOCS5-ALK, HIP1-ALK, CD74-ROS1, KIF5B-RET (n = 2), and CCDC6-RET. Six of these patients went on to receive targeted therapy. The authors noted that the reasons for non-detection of these genomic alterations via non-NGS testing can be varied as lower sensitivity, complex rearrangements undetectable by standard FISH, and, possibly, heterogeneity between different tumor biopsies or sites. They concluded that broad, hybrid capture–based NGS assays have the potential to uncover clinically actionable genomic alterations in never smokers or ≤15 pack-year smokers whose lung adenocarcinomas do not harbor a potential driver via non-NGS testing.

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (NCCN, 2017) strongly endorse the use of broad molecular profiling (also known as precision medicine) to detect certain rare mutations using multiplex or NGS. Presence of EGFR-activating mutations represents a critical biological determinant for proper therapy selection in patients with lung cancer, stating “determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to an increasing number of drugable targets, primarily tyrosine kinase inhibitors (TKIs)”. Data has shown that targeted therapy is potentially very effective in patients with specific gene mutations or...
molecular profiling. The guidelines specifically report that “EGFR and ALK testing be conducted as part of broad molecular profiling.” The NCCN Panel states that such testing would ensure that patients receive the most effective available targeted treatment for NSCLC.

A National Institute for Health and Care Excellence (NICE) guidance document for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer states that there is insufficient evidence to make a recommendation on next generation sequencing for EGFR-TK mutations. NICE noted that research is currently being conducted on this method to evaluate panels of lung cancer genes. Study authors concluded that NGS is likely to be an important method for identifying EGFR-TK mutations in the future (NICE, 2013).

**Professional Societies**

**American College of Chest Physicians (ACCP)**

In an evidence-based clinical practice guideline for the diagnosis and management of lung cancer, the ACCP states that the epidemiology of lung cancer is an active field. According to the ACCP, researchers in the area of molecular epidemiology are making advances in the identification of biomarkers of risk and for early detection, although these are not yet mature enough for clinical application (Detterbeck et al., 2013).

**Other Cancers**

Molecular profiling has many theoretical clinical applications in the field of oncology. Published clinical studies have addressed the use of molecular profiling for the following:

- Acute myeloid leukemia (Port et al., 2014; Link et al., 2012)
- Adrenocortical cancer (Zheng et al., 2016; Ross et al., 2014a)
- Breast cancer (Ganesan et al., 2014; Wheler et al., 2014)
- Gastric and gastrointestinal cancer (West et al., 2017; Ali et al., 2015, Vignot et al., 2015; Miura et al., 2014)
- Head and neck cancer (Wang et al., 2017; Chung et al., 2015)
- Melanoma (Wheler et al., 2015; Hutchinson et al., 2013)
- Gynecological cancer (Rodriguez-Rodriguez et al., 2016; Ross et al., 2013)
- Pancreatic cancer (Zhou et al., 2017; Chmielecki et al., 2014; Chantrill et al., 2015)
- Prostate cancer (Chua et al., 2017; Beltran et al., 2013)
- Unknown primary cancer site (Ross et al., 2015; Gatalica et al., 2014)
- Urothelial carcinoma/urinary bladder adenocarcinoma (Roy et al., 2017; Ross et al., 2014b; Millis et al., 2015)

There is insufficient published evidence to support the use of molecular profiling for these cancers. The main evidence deficiencies for molecular profiling for these cancers are insufficient data on analytical validity, clinical validity, and clinical utility. Published studies evaluating molecular profiling for these conditions are mainly case reports or case series with a limited number of patients.

Hirshfield et al., (2016) conducted a prospective clinical study on 100 patients with diverse-histology, rare, or poor-prognosis cancers to evaluate the clinical implications of a comprehensive genomic profiling assay (FoundationOne), using formalin-fixed, paraffin-embedded tumors. The primary objectives were to assess utility, feasibility, and limitations of genomic sequencing for genomically guided therapy or other clinical purpose in the setting of a multidisciplinary molecular tumor board. Of the tumors from the 92 patients with sufficient tissue, 88 (96%) had at least one genomic alteration (average 3.6, range 0–10). Use of comprehensive profiling led to implementable clinical action in 35% of tumors with genomic alterations, including genomically guided therapy, diagnostic modification, and trigger for germline genetic testing. Although use of targeted next-generation sequencing in the setting of an institutional molecular tumor board led to implementable clinical action in more than one third of patients with rare and poor-prognosis cancers, major barriers to implementation of genomically guided therapy were clinical status of the patient and drug access. Early and serial sequencing in the clinical course and expanded access to genomically guided early-phase clinical trials and targeted agents may increase clinical application.

Johnson et al. (2014) retrospectively assessed demographics, next-generation sequencing (NGS) results, and therapies received for patients undergoing targeted NGS using the FoundationOne test. Co-primary endpoints were the percentage of patients with targeted therapy options uncovered by mutational profiling and the percentage who received genotype-directed therapy. Samples from 103 patients were tested; most frequently breast carcinoma (26%), head and neck cancers (23%), and melanoma (10%). Most patients (83%) were found to harbor potentially actionable genetic alterations, involving cell-cycle regulation (44%), phosphatidylinositol 3-kinase-AKT (31%), and mitogen-activated protein kinase (19%) pathways. With median follow-up of 4.1 months, 21% received genotype-directed treatments, most in clinical trials (61%), leading to significant benefit in several cases. The most common reasons for not receiving genotype-directed therapy were selection of standard therapy (35%) and clinical deterioration (13%). The authors concluded that mutational profiling using a targeted NGS panel identified potentially actionable alterations in a majority of advanced cancer patients. The assay identified additional therapeutic options and facilitated clinical trial enrollment. According to the authors, there are many unanswered questions regarding
implementation of this technology. First, based on this study, some patients with potentially actionable alterations did not respond to genotype-directed therapy, highlighting the still underdeveloped understanding of the pathophysiologic implications of many genetic alterations. Second, the most appropriate indications for obtaining targeted NGS are not yet clear. Third, randomized studies in the future will need to assess whether targeted NGS improves overall outcomes.

Kato et al. (2015) investigated the clinical correlates of CDK4/6 and CDKN2A/B abnormalities in diverse malignancies. Patients with various cancers who underwent molecular profiling by targeted next generation sequencing (Foundation Medicine; 182 or 236 cancer-related genes) were reviewed. Of 347 patients analyzed, 79 (22.8%) had aberrant CDK 4/6 or CDKN2A/B. Only TPS3 mutations occurred more frequently than those in CDK elements. Aberrations were most frequent in glioblastomas (21/26 patients; 81%) and least frequent in colorectal cancers (0/26 patients). Aberrant CDK elements were independently associated with EGFR and ARID1A gene abnormalities. CDK aberrations were associated with poor overall survival. In multivariate analysis, PTEN and TPS3 aberrations were independently associated with poorer survival; CDK aberrations showed a trend toward worse survival. There was also a trend toward worse progression-free survival (PFS) with platinum-containing regimens in patients with abnormal CDK elements (3.5 versus 5.0 months). In conclusion, aberrations in the CDK pathway were some of the most common in cancer and independently associated with EGFR and ARID1A alterations. Patients with abnormal CDK pathway genes showed a trend toward poorer survival, as well as worse PFS on platinum-containing regimens. According to the authors, further investigation of the prognostic and predictive impact of CDK alterations across cancers is warranted. This study was limited due to it being performed retrospectively in a single institution with a relatively limited number of patients.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at:

https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm
(Accessed January 31, 2018)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) specifically addressing molecular oncology testing for cancer diagnosis, prognosis and treatment decisions. Local Coverage Determinations (LCDs) exist; refer to the following LCDs at https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?kq=true:

- Biomarkers for Oncology
- Biomarkers Overview
- BRCA1 and BRCA2 Genetic Testing
- Gene Expression Profiling Panel for use in the Management of Breast Cancer Treatment
- Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML)
- Genomic Sequence MolDX- CDD: NSCLC, Comprehensive Genomic Profile Testing
- Analysis Panels in the Treatment of Non-Small Cell Lung Cancer
- MolDX- CDD: NSCLC, Comprehensive Genomic Profile Testing
- MolDX: BRCA1 and BRCA2 Genetic Testing
- MolDX: Breast Cancer Assay: Prosigna
- MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease
- MolDX: Genetic Testing for Lynch Syndrome
- MolDX: Molecular Diagnostic Tests (MDT)
- MolDX-CDD: NSCLC, Comprehensive Genomic Profile Testing
- Molecular Diagnostic Tests (MDT)
- Molecular Pathology Procedures
- Noncovered Services
- Pathology and Laboratory: BRCA1 and BRCA2 Genetic Testing
- Pathology and Laboratory: K-ras Testing prior to Treatment of Colorectal Cancer (CRC)
- Pathology and Laboratory: Partial Genome Profiling in Non-Small Cell Lung Cancer (NSCLC)
(Accessed November 14, 2017)

REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/2018</td>
<td>- Revised coverage rationale:</td>
</tr>
<tr>
<td></td>
<td>- Updated list of unproven/not medically necessary gene expression profiling</td>
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<tr>
<td></td>
<td>assays for colorectal cancer (CRC) risk assessment or management; removed</td>
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<tr>
<td></td>
<td>“fecal DNA testing, i.e., ColonSentry”</td>
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<tr>
<td></td>
<td>- Replaced language indicating:</td>
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<td></td>
<td>- “[The listed services] are proven and medically necessary” with ”[the</td>
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<td>listed services] are proven and/or medically necessary”</td>
</tr>
<tr>
<td></td>
<td>- “[The listed services] are unproven and not medically necessary” with</td>
</tr>
<tr>
<td></td>
<td>“[the listed services] are unproven and/or not medically necessary”</td>
</tr>
<tr>
<td></td>
<td>- Replaced reference to “patient” with ”individual”</td>
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<tr>
<td></td>
<td>- Updated list of applicable CPT codes; added 0012M*, 0013M*, 81520, and 81521</td>
</tr>
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<td></td>
<td>(*quarterly code edit)</td>
</tr>
<tr>
<td></td>
<td>- Updated supporting information to reflect the most current references</td>
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<td>- Archived previous policy version 2018T0588C</td>
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