Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Jersey Only)

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➲ Instructions for Use

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Related Policies

- FDA Cleared or Approved Companion Diagnostic Testing (for New Jersey Only)
- Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Jersey Only)

Application

This Medical Policy only applies to the state of New Jersey.

Coverage Rationale

This policy applies to tests that have not been granted approval as an FDA cleared or approved Companion Diagnostic.

Breast Cancer Gene Expression Profiling (GEP)

The use of one of the following GEP tests – MammaPrint®, Oncotype Dx® Breast, Prosigna® Breast Cancer Prognostic Gene Signature Assay (formerly PAM-50), Breast Cancer Index™ (BCI), and EndoPredict® – is proven and medically necessary when used to inform treatment decisions in individuals with invasive breast cancer in the following situations:

- Newly diagnosed (within the last 6 months) when all the following criteria are met:
  - Lymph node negative (including lymph nodes with micrometastases no greater than 2 mm) or 1-3 positive ipsilateral axillary lymph nodes; and
  - No distant metastases; 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)

  or
- Currently receiving adjuvant hormonal therapy (e.g., Tamoxifen or an aromatase inhibitor) for a breast cancer when all of the following criteria are met:
  - Hormone receptor-positive (estrogen receptor positive, progesterone receptor positive, or both); and
  - HER2 receptor negative; 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 a decision regarding extended adjuvant hormonal therapy

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The use of more than one predictive GEP for the same tumor in an individual with breast cancer is unproven and not medically necessary due to insufficient evidence of efficacy.

Note: This limitation does not apply to BCI testing, which can be used once in the evaluation of the role of extended endocrine therapy in a breast cancer that may have already had GEP to determine the role of adjuvant chemotherapy.

Due to insufficient evidence of efficacy, GEP for breast cancer for other indications [including ductal carcinoma in situ (DCIS)] or treatment decisions are unproven and not medically necessary. Such tests may include but are not limited to:

- BluePrint
- DCISionRT®
- Oncotype DX Breast DCIS Score® test

Lung Cancer

Multigene molecular profiling (including no more than 50 genes, or for more than 50 genes only when used in a manner consistent with the FDA Cleared or Approved Companion Diagnostic Testing Medical Policy (for New Jersey Only) performed using tumor tissue or via Liquid Biopsy [cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA)] is proven and medically necessary for non-small cell lung cancer.

Prostate Cancer Gene Expression Profiling (GEP)

The use of the Genomic Prostate Score® (GPS) test (previously Oncotype DX® GPS) is proven and medically necessary for individuals with biopsy-proven, untreated, localized adenocarcinoma of the prostate (no clinical evidence of metastasis or lymph node involvement) when:

- Test is ordered by a physician specializing in the treatment of organ confined prostate cancer including surgical oncology/urology, radiation oncology, or medical oncology; and
- Results will be used to assist with treatment decision-making when the individual has not yet received treatment for prostate cancer and is a candidate for either active surveillance or definitive therapy and all of the following:
  - Life expectancy is greater than 10 years; and
  - Risk group is one of the following:
    - Very Low-Risk Prostate Cancer; or
    - Low-Risk Prostate Cancer; or
    - Favorable Intermediate-Risk Prostate Cancer

The use of the Prolaris® Biopsy prostate cancer prognostic test or Decipher® Prostate Biopsy genomic classifier is proven and medically necessary for individuals with biopsy-proven, untreated, localized adenocarcinoma of the prostate (no clinical evidence of metastasis or lymph node involvement) when:

- Test is ordered by a physician specializing in the treatment of organ confined prostate cancer including surgical oncology/urology, radiation oncology, or medical oncology; and
- Results will be used to assist with treatment decision-making when the individual has not yet received treatment for prostate cancer and is a candidate for either active surveillance or definitive therapy and all of the following:
  - Life expectancy greater than 10 years; and
  - Risk group is one of the following:
    - Very Low-Risk Prostate Cancer; or
    - Low-Risk Prostate Cancer; or
    - Favorable Intermediate-Risk Prostate Cancer; or
    - Unfavorable Intermediate-Risk Prostate Cancer; or
    - High-Risk Prostate Cancer

The use of Decipher Prostate RP genomic classifier is proven and medically necessary to inform adjuvant treatment after radical prostatectomy for either of the following:

- Adverse features are found (e.g., high-grade disease, Gleason score 8 or higher, extracapsular extension, positive surgical margins, seminal vesicle invasion); or
- PSA is greater than zero at any point following prostatectomy

Molecular screening panel tests for prostate cancer are unproven and not medically necessary due to insufficient evidence of efficacy (e.g., ExoDx™ Prostate Test, My Prostate Score™, Confirm mdx™, Select mdx™).

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Thyroid Cancer or Indeterminate Thyroid Nodule Testing

The use of molecular testing for thyroid nodules with indeterminate cytology [e.g., Afirma® Genomic Sequencing Classifier (GSC), ThyroSeq® V3, ThyGeNEXT®/ThyraMIR®] is proven and medically necessary when all of the following criteria are met:

- Follicular pathology on fine needle aspiration is indeterminate (Bethesda III/IV); and
- The results of the test will be used for making decisions about further surgery

CGP of confirmed anaplastic thyroid cancer is proven and medically necessary.

Molecular tests for indeterminate thyroid nodules or thyroid cancer are unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.

Due to insufficient evidence of efficacy, other molecular tests for indeterminate thyroid nodules or thyroid cancer are unproven and not medically necessary including but not limited to:

- Afirma® Xpression Atlas (XA)
- Comprehensive Genomic Profiling (CGP) (e.g., NeoTYPE® Thyroid Profile)

The use of more than one molecular profile test in an individual with an indeterminate thyroid nodule is unproven and not medically necessary due to insufficient evidence of efficacy.

Uveal Melanoma Gene Expression Profiling (GEP)

GEP (e.g., DecisionDx®-UM) is considered proven and medically necessary when used to assist with predicting disease severity and making treatment decisions in the following situations:

- Individual has primary, localized uveal melanoma; and
- There is no evidence of metastatic disease; and
- Individual has not previously had DecisionDx-UM testing for current diagnosis

Unproven Molecular Tests

Due to insufficient evidence of efficacy, all other molecular testing (tissue or Liquid Biopsy specimens) for solid tumor cancer using any method of testing is unproven and not medically necessary, including but not limited to:

- NGS panels of > 50 genes or CGP unless otherwise specified
- Afirma® Xpression Atlas (XA)
- CancerTYPE ID®
- Blood based colorectal cancer screening tests (e.g., ColoHealth™, Signal-C®, Guardant Shield™)
- Decipher® Bladder
- DecisionDx®-Melanoma, DiffDx™-Melanoma, DecisionDx®-SCC, DermTech PLA™, Merlin (SkylineDx), myPath® Melanoma
- ExoDX™ Prostate Test, MyProstateScore™(MPS), MyProstateScore 2.0, Confirm mdx™, Select mdx™, TMPRSS2 fusion gene
- Measurable Residual Disease (MRD) assays in solid tumor cancers, whether tumor-informed or tumor-naïve, using any method of testing (e.g., Invitae Personalized Cancer Monitoring™, Signatera™, RaDaR®, Guardant Reveal™, Haystack MRD™)
- Multi-cancer early detection/screening tests (e.g., Galleri®)
- NavDx®
- Oncotype DX Colon Recurrence Score®, Genefx® Colon (also known as ColDx), ColonSentry®
- PancraGEN®, PancreaSeq® Genomic Classifier
- Percepta® GSC
- Solid tumor profiling that includes Whole Exome, Whole Genome, or whole transcriptome Sequencing [e.g., CancerVision (Inocras), Tempus xE, Tempus xR, OncoExTra™]
- Tempus Immune Profile Score (IPS)
- Whole genome methylation profiling

Definitions

Comparative Genome Hybridization (CGH): CGH is a technology that can be used to detect genomic copy number variations (CNVs). Tests can use a variety of probes or single nucleotide polymorphisms (SNPS) to provide copy number

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and gene differentiating information. All platforms share that tumor (patient), and reference DNA are labeled with dyes or fluorescing probes and hybridized on the array, and a scanner measures differences in intensity between the probes, and the data is expressed as having greater or less intensity than the reference DNA (Cooley et al., 2013).

Comprehensive Genomic Profiling (CGP): A type of next-generation sequencing test that is able to detect all classes of genomic alterations, including cancer biomarkers, with a single sample (Singh et al., 2020).

Favorable Intermediate-Risk Prostate Cancer: Clinical/pathological features must include all of the following: No high- or very high-risk group features, Grade Group 1 or 2, less than 50% of biopsy cores are positive (e.g., < 6 of 12 cores) and has one intermediate risk factor (T2b-T2c, PSA 10-20 ng/mL, Grade Group 2 or 3) (NCCN Prostate Cancer, v1.2025).

Gene Expression Profiling (GEP): A laboratory test that analyzes messenger RNA (mRNA) patterns to determine gene activity (Kim et al., 2010). Also referred to as gene expression testing, gene expression classifier testing, or gene expression assay.

High-Risk Prostate Cancer: Clinical/pathological features must include all of the following: Does not meet criteria for very high risk but has one or more of the following high-risk features: T3-cT4, Grade Group 4 or 5, PSA greater than 20 ng/mL (NCCN Prostate Cancer, v1.2025).

Liquid Biopsy: Testing performed on a sample of bodily fluid to identify cancer cells from a tumor or pieces of DNA, RNA or other molecules that have been released from tumor cells and are circulating in an individual's body fluids. Liquid Biopsy may be used for early detection of cancer, to help identify effective treatments or to monitor for return of cancer [National Cancer Institute (NCI), Liquid Biopsy, 2023].

Low-Risk Prostate Cancer: Clinical/pathological features must include all of the following, but cancer does not qualify for very low-risk: PSA is less than 10 ng/mL, Grade Group 1, and T1-T2a disease (NCCN Prostate Cancer, v1.2025).

Measurable Residual Disease (MRD): Also known as minimal residual disease, MRD is a term used to describe a very small number of cancer cells or cell contents detectable in the body during and after cancer treatment, even though the affected individual may have no signs or symptoms of disease. These cells or genetic material are not detectable through routine screening techniques or cellular morphology assessment. Residual evidence of cancer in the body of an individual that has undergone cancer treatment can be associated with earlier relapse or recurrence of disease. MRD measurement is most often used for blood cancers and can help providers form treatment plans and determine if the treatment is effective. Current assessments of MRD use real-time quantitative polymerase chain reaction (PCR), multiparametric flow cytometry and/or NGS (National Cancer Institute [NCI] Dictionary of Cancer Terms, 2024; Yu et al., 2023).

Next Generation Sequencing (NGS): New sequencing techniques that can quickly analyze multiple sections of DNA at the same time. Older forms of sequencing could only analyze one section of DNA at once (Kamps et al., 2017).

Unfavorable Intermediate-Risk Prostate Cancer: Clinical/pathological features must include: No high- or very high-risk group features and one or more of the following: Grade Group 3, at least 50% biopsy cores are positive (e.g., ≥ 6 of 12 cores), and 2 or 3 intermediate risk factors (T2b-T2c disease, Grade Group 2 or 3, PSA 10-20 ng/mL) (NCCN Prostate Cancer, v1.2025).

Very High-Risk Prostate Cancer: Clinical/pathological features must include at least two of the following: T3-T4 disease, Grade Group 4 or 5, and PSA greater than 40 ng/mL (NCCN Prostate Cancer, v1.2025).

Very Low-Risk Prostate Cancer: Clinical/pathological features must include all of the following: PSA is less than 10 ng/mL, Grade Group 1, less than 3 biopsy fragments/cores positive with no more than 50% cancer in each core,T1c disease and PSA density < 0.15 ng/mL/g (NCCN Prostate Cancer, v1.2025).

Whole Exome Sequencing (WES): About 1% of a person's DNA makes protein. These protein-making sections are called exons. All the exons together are called the exome. WES is a DNA analysis technique that looks at all the exons in a person, or a tissue type such as a tumor, at one time, rather than gene by gene (MedlinePlus, 2021).

Whole Genome Sequencing (WGS): WGS determines the sequence of the entire DNA in a person, or a tissue type, such as a tumor, which includes the protein-making (coding) as well as non-coding DNA elements (MedlinePlus, 2021).

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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 federal, state, or contractual requirements 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 Guidelines may apply.

CPT Code	Description
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
*0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk
0012M	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 urothelial carcinoma
0013M	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
*0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)
*0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
*0019U	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
0020M	Oncology (central nervous system), analysis of 30000 DNA methylation loci by methylation array, utilizing DNA extracted from tumor tissue, diagnostic algorithm reported as probability of matching a reference tumor subclass
*0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence or absence of variants and associated therapy(ies) to consider
*0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result (“Positive, high probability of malignancy” or “Negative, low probability of malignancy”)
0036U	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0045U	Oncology (breast ductal carcinoma in situ), 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 recurrence score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
*0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
*0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score

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CPT Code	Description
*0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
*0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)
*0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result
*0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
*0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
*0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
*0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
*0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue
*0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
*0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations [SNVs (single nucleotide variant), small insertions and deletions, one amplification, and four translocations], microsatellite instability and tumor-mutation burden
*0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score
*0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
*0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
*0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (e.g., human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
*0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification

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CPT Code	Description
*0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
*0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
*0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
*0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD
*0307U	Oncology [minimal residual disease (MRD)], next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
*0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (i.e., negative, low probability of neoplasia or positive, high probability of neoplasia)
*0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)
*0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (i.e., Class 1, Class 2A, Class 2B)
*0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
*0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
*0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint-inhibitor therapy
*0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
*0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
*0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
*0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
*0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer

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CPT Code	Description
*0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
*0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture-enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
*0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
*0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer
*0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden
*0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
*0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
*0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability
*0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma
*0421U	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk
*0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
*0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer
*0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
*0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s)
*0452U	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer
*0453U	Oncology (colorectal cancer), cell-free DNA (cfDNA), methylation-based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)

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CPT Code	Description
*0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
*0473U	Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden
*0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
*0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
*0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction
*0487U	Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidy-corrected gene copy number amplifications and losses, gene rearrangements, and microsatellite instability
*0496U	Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk
*0497U	Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
*0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation
*0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffin-embedded (FFPE) tissue, next-generation sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection
*0501U	Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA)
*0507U	Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
*0510U	Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA whole-transcriptome data, reported as probability of predicted molecular subtype
*0523U	Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single-nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change
*0530U	Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy-number alterations, with therapy association
0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, > 2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative
0538U	Oncology (solid tumor), next-generation targeted sequencing analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant

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CPT Code	Description
0539U	Oncology (solid tumor), cell-free circulating tumor DNA (ctDNA), 152 genes, next-generation sequencing, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
0549U	Oncology (urothelial), DNA, quantitative methylated real-time PCR of TRNA-Cys, SIM2, and NKX1-1, using urine, diagnostic algorithm reported as a probability index for bladder cancer and/or upper tract urothelial carcinoma (UTUC)
0562U	Oncology (solid tumor), targeted genomic sequence analysis, 33 genes, detection of single-nucleotide variants (SNVs), insertions and deletions, copy-number amplifications, and translocations in human genomic circulating cell-free DNA, plasma, reported as presence of actionable variants
0565U	Oncology (hepatocellular carcinoma), next-generation sequencing methylation pattern assay to detect 6626 epigenetic alterations, cell-free DNA, plasma, algorithm reported as cancer signal detected or not detected
0566U	Oncology (lung), qPCR-based analysis of 13 differentially methylated regions (CCDC181, HOXA7, LRRC8A, MARCHF11, MIR129-2, NCOR2, PANTR1, PRKCB, SLC9A3, TBR1_2, TRAP1, VWC2, ZNF781), pleural fluid, algorithm reported as a qualitative result
0569U	Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate
0571U	Oncology (solid tumor), DNA (80 genes) and RNA (10 genes), by next-generation sequencing, plasma, including single-nucleotide variants, insertions/deletions, copy-number alterations, microsatellite instability, and fusions, reported as clinically actionable variants
0572U	Oncology (prostate), high-throughput telomere length quantification by FISH, whole blood, diagnostic algorithm reported as risk of prostate cancer
0578U	Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence
0585U	Targeted genomic sequence analysis panel, solid organ neoplasm, circulating cell-free DNA (cfDNA) analysis from plasma of 521 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, and microsatellite instability, report shows identified mutations, including variants with clinical actionability
0586U	Oncology, mRNA, gene expression profiling of 216 genes (204 targeted and 12 housekeeping genes), RNA expression analysis, formalin-fixed paraffin-embedded (FFPE) tissue, quantitative, reported as log2 ratio per gene
0592U	Oncology (hematolymphoid neoplasms), DNA, targeted genomic sequence of 417 genes, interrogation for gene fusions, translocations, rearrangements, utilizing formalin-fixed paraffin-embedded (FFPE) tumor tissue, results report clinically significant variant(s)
0597U	Oncology (breast), RNA expression profiling of 329 genes by targeted next-generation sequencing and 20 proteins by multiplex immunofluorescence, formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic analyses to determine tumor-recurrence risk score
0611U	Oncology (liver), analysis of over 1,000 methylated regions, cell-free DNA from plasma, algorithm reported as a quantitative result
0612U	Oncology (liver), analysis of over 1,000 methylated regions, cell-free DNA from plasma, algorithm reported as a quantitative result
0613U	Oncology (urothelial carcinoma), DNA methylation and mutation analysis of 6 biomarkers (TWIST1, OTX1, ONECUT2, FGFR3, HRAS, TERT promoter region), methylation-specific PCR and targeted next-generation sequencing, urine, algorithm reported as a probability index for bladder cancer and upper tract urothelial carcinoma
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis

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CPT Code	Description
81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
*81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
*81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
*81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
*81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
*81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
*81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81479	Unlisted molecular pathology procedure
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	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
81520	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
81521	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
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
81524	Oncology (central nervous system tumor), DNA methylation analysis of at least 10,000 methylation sites, utilizing DNA extracted from formalin-fixed tumor tissue, algorithm(s) reported as probability of matching a reference tumor family and class, and MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation status, if performed
81525	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

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CPT Code	Description
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
81540	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
81541	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
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)
81551	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
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
81599	Unlisted multianalyte assay with algorithmic analysis

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HCPCS Code	Description
*G0327	Colorectal cancer screening; blood-based biomarker

Codes labeled with an asterisk (*) are not on the State of New Jersey Medicaid Fee Schedule and therefore may not be covered by the State of New Jersey Medicaid Program.

Description of Services

Technologies used for molecular profiling of solid tumor cancers vary, and can include, but are not limited to, tests that evaluate variations in the genes, such as Chromosome Microarray Analysis and Next Generation Sequencing, as well as others that assess the gene products, such as gene expression arrays and microRNA analysis. The amount of genetic material evaluated can range from a single gene to the whole exome or genome of a tumor. For the purposes of this policy, multi-gene analysis generally refers to a gene panel containing five or more genes, though some exceptions may apply as noted specifically in the policy. In some tests, expression patterns of certain genes 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. Results of molecular profiling may assist individuals and healthcare providers with determining prognosis and selection of more effective and targeted cancer therapies (Chantrill et al., 2015).

Clinical Evidence

Breast Cancer

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

Hyams et al. 2024 conducted an assessment and systematic review of the leading commercially available gene expression assays (GEAs) for early-stage BC. The systematic review was intended to build upon prior reviews focusing on the following GEAs: Breast Cancer Index (BCI), EndoPredict, MammaPrint, Oncotype DX, and Prosigna, assessing each GEA's utility for prognostication and/or prediction of adjuvant therapy benefit. In all, 1053 articles were identified for inclusion in the review and analysis and the Tumor Marker Utility Grading System (TMUGS) was used to analyze the level of evidence (LOE) of studies identified. After review of the dataset, the authors concluded that the five widely

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commercialized assays all have some high-level evidence supporting prognostic capability in varying patient subsets. Most of the tests were validated initially via “prospective-retrospective” studies which confirmed their competency for prognostication with high LOE. Several of the GEAs identify low-risk individuals for whom adjuvant chemotherapy is difficult to justify. Two assays (MammaPrint and Oncotype DX) identify those who might avoid even endocrine therapy (ET), although current data remain preliminary. Some of the assays provide late prognostic information that could impact the selection of extended endocrine therapy (EET). The most commonly used test in this setting, BCI, appears to be predictive of response to anti-estrogens. Despite this, several of the GEAs remain unvalidated in certain sub-populations based on menopausal and lymph node status. Of the GEAs assessed in this review, just two (MammaPrint and Oncotype DX) have been the focus of large, prospective clinical trials and only Oncotype DX has a high LOE supporting its ability to predict the benefit of adjuvant chemotherapy. Two of three prospective trials of the Oncotype DX assay identified a relationship between chemotherapy benefit and age and/or menopause, underscoring the importance of large, high-quality trials in enhancing clinical care for individuals with BC. Overall, the reviewers assert that the abundance of recent data focused on the five most well-known commercial GEAs has provided a basis for comprehensive evaluation of each of the assays and their ability to deliver clinically applicable prognostic and/or predictive information.

In 2022, Griguolo et al. explored the evidence on the most widely used, commercially available gene-expression signatures (Oncotype DX, MammaPrint, PAM50, EndoPredict, and BCI) for individuals receiving neoadjuvant therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative BC (HR+/HER2- BC). The authors evaluated the data for the association of gene expression signatures and responses to neoadjuvant chemotherapy (NCT) or neoadjuvant endocrine treatment (NET) and the clinical suggestions from the data to guide clinical decision-making in early HR+/HER2- BC. A consistent association was observed between higher risk (as per gene expression signatures) and higher pathological complete response (pCR) rate after NCT across the GEAs studied. Association between lower risk based on gene expression signatures and higher pCR after NET was observed. The evidence, however, is limited and based on small retrospective studies. Larger prospective trials are needed to confirm results for the use of GEAs in this context. The researchers assert that the potential use of gene expression signatures to assist with selection of neoadjuvant therapy (chemotherapy versus endocrine therapy) in early BC merits further exploration.

Harnan and colleagues (2019) conducted a systematic review and economic analysis to determine the efficacy and cost-effectiveness of the tumor profiling tests Oncotype DX, MammaPrint, Prosigna, EndoPredict, and immunohistochemistry 4 (IHC4). Studies included individuals with estrogen receptor-positive (ER+), HER2-, stage I or II cancer with zero to three positive lymph nodes (LN+). The review included 153 articles on the five tests. In all five tests, the proportions of individuals who were lymph node-negative (LN0) getting endocrine monotherapy, 9% to 33%, were categorized as high-risk, according to the literature. For individuals who were LN+, three tests: Prosigna, EPClin, and IHC4 plus clinical factors (IHC4+C), categorized more (38% to 76%) individuals who were LN+ than those who were LN0 as high-risk according to the studies of endocrine monotherapy. Oncotype DX categorized high-risk in the LN0 and LN+ subsets as equal. Oncotype DX classified more individuals as low-risk in LN+ when compared to other tests (57% in Oncotype DX vs 4% to 28% in other tests), but worse ten-year DR/relapse-free survival/DR/relapse-free interval outcomes (82% in Oncotype DX vs 95% to 100% in other tests). An increase of 1% to a decrease of 23% was seen in United Kingdom (UK) studies and a reduction of 0% to 64% across European studies on the net change of individuals who were recommended chemotherapy or decision pre/posttest. Limitations included gaps in the literature, the risk of bias, and limited data relating to the ability of Oncotype DX and MammaPrint to predict benefits from chemotherapy. Additional long-term studies can show the impacts and changes in chemotherapy decisions for Oncotype DX and MammaPrint. The authors concluded that the evidence indicates that all the tests deliver prognostic data regarding the risk of relapse, although greater variation was seen in individuals with LN+ status than those with LN 0 status.

Oncotype Dx Breast

Oncotype Dx Breast (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 (RS) which may correspond to a likelihood of BC recurrence within ten years. The test was initially developed for women with early-stage invasive BC with early-stage cancers that are LN0, and subsequently evidence was gathered on individuals with up to three 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, 2016).

Sparano et al. 2024 explored Oncotype DX’s role in providing prognostic information for late DR when added to clinicopathologic prognostic factors through a patient-specific meta-analysis. Included in the meta-analysis were 10,004 women who were enrolled in three trials, which was updated by using the extended follow-up data from the TAILORx trial (including integration of the RS with histologic grade, tumor size, and age at surgery for the RSClin tool). Likelihood ratio (LR) tests were used to compare Cox models integrating clinicopathologic factors and the RS. In addition, external

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validation of prognosis for DR in years 0 to 10 and 5 to 10 was performed in an independent cohort of 1098 women from a real-world registry. The results showed that RSClin delivered substantially more prognostic data than either the clinicopathologic factors (ΔLR chi-square, 86.2; p < 0.001) or RS alone (ΔLR chi-square, 131.0; p < 0.001). The model was predictive in an independent cohort for DR 10 years after diagnosis (standardized hazard ratio, 1.56; 95% confidence interval, 1.25 to 1.94), was associated with late DR risk between five and ten years after diagnosis (standardized hazard ratio, 1.78; 95% confidence interval, 1.25 to 2.55), and was near the observed ten-year DR risk (Lin concordance, 0.87) and five- to ten-year DR risk (Lin concordance, 0.92). The limitations of the analysis included the risk of limited external generalizability as it was developed in those who met the inclusion criteria for the associated trials. The authors concluded that the 21-gene RS is prognostic for both DR and overall survival (OS) in individuals with early breast cancer (EBC). In addition, they suggest that a model integrating the 21-gene RS and an individual's clinicopathologic factors improved estimates of DR risk when compared with either the 21-gene RS or clinicopathological factors used alone, and additionally, assists with stratification of late DR risk.

Nash and colleagues (2023) investigated the benefit of chemotherapy based on RS in younger women (aged 40-50) who were eligible for oncotype testing. Participants were selected from the National Cancer Database (NCBD) and grouped by age, RS, nodal status, and receipt of chemotherapy. A total of 15,422 individuals met inclusion criteria for the study. Of these 43.5% received chemotherapy. Log-rank tests were used to assess for differences between groups and Kaplan-Meier curves compared the unadjusted OS between groups. The analysis revealed that individuals who received chemotherapy were more likely to have higher-stage and higher-grade tumors, tumors that were PR-negative, and higher RS (p < 0.001 for all). RS was prognostic for OS regardless of nodal status. After adjustment, chemotherapy was associated with a significant improvement in OS only in the pN1 RS 31-50 subgroup (p = 0.02). The authors concluded that RS remains prognostic in younger individuals with early-stage HR-positive, HER2- BC. The survival benefit with chemotherapy was only found in those aged 40-50 with pN1 disease and RS of 31-50. As such, chemotherapy decision-making should be especially preference-sensitive in women aged 40-50 with intermediate RS, where survival benefit may not be enhanced for many women.

The 21-gene expression assay (Oncotype DX Breast Recurrence Score) is commonly and increasingly used to assist with decision-making regarding adjuvant chemotherapy in ER+/HER2- BC with one to three positive lymph nodes (N1) disease. To evaluate patterns in practice related to the use of the RS for decision-making regarding chemotherapy and survival outcomes in these individuals, Li et al. (2023) retrospectively evaluated 35,137 individuals with T1-2N1M0 and ER+/HER2- BC from the Surveillance, Epidemiology, and End Results (SEER) Oncotype DX Database. Both breast cancer specific survival (BCSS) and OS were included in the assessment. In this study, older age, lower tumor grade, T1 stage, fewer positive lymph nodes, and progesterone receptor-positive disease (all p < 0.05) were all associated with use of the 21-gene test. RS had a significant association with chemotherapy treatment in the group that had the 21-gene test, whereas age was the primary factor significantly associated with chemotherapy treatment in the group that did not receive 21-gene testing. For individuals who underwent 21-gene testing, the probably of chemotherapy was 30.8%; in the group who did not undergo the 21-gene test, probably of chemotherapy was higher at 64.1%. Based on multivariate prognostic analysis, use of the 21-gene test was associated with both improved BCSS (p < 0.001) and OS (p < 0.001) when compared to individuals who did not receive the test. From this data, the authors concluded that the 21-gene assay is related to lower rates of adjuvant chemotherapy use and improved survival outcomes. They indicate their support for the use of the 21-gene assay in individuals with ER+/HER2- BC with N1 disease.

In a 2022 systematic review and network meta-analysis, Davey et al. evaluated the Oncotype DX 21-gene RS for its ability to estimate locoregional recurrence (LRR) in ER+/HER2- BC. The review uncovered 16 articles together with 21,037 individuals. The average RS was 17.1, and the average follow-up was 66.4 months. Employing standard RS cut-offs, 49.7% of individuals had RS < 18 (3944/7935), 33.8% had RS 18–30 (2680/7935), and 16.5% had RS > 30 (1311/7935). Those with RS 18–30 and RS > 30 were significantly more likely to experience LRR than those with RS < 18. Using the TAILORx cut-off, 16.2% of individuals had RS < 11 (1974/12,208), 65.8% had RS 11–25 (8036/12,208), and 18.0% with RS > 30 (2198/12,208). LRR rates were comparable for individuals with RS 11–25; however, those with RS > 25 had a considerable risk of LRR versus those with RS < 11. The authors concluded that RS testing correctly estimates the risk of LRR for individuals being treated with the intent to cure early-stage ER+/HER2− BC. RS testing is a valid method to measure the risk of distant disease recurrence; however, awareness of its ability to predict LRR is significant to create effective locoregional control of the breast and axilla. Future prospective, randomized studies can confirm the predictive value of RS for estimating LRR and the application of RS to create suitable locoregional control in high-risk cases.

In 2021, Kalinsky et al. published the results of a prospective randomized clinical trial (RCT) to find the effect of chemotherapy on invasive disease-free survival in individuals with positive lymph-node disease and determine whether the RS based on the 21 gene assay (Oncotype Dx) influenced the outcome. A total of 5018 women with hormone-

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receptor-positive, HER2- BC, 1 to 3 positive axillary lymph nodes, and an RS of 25 or lower were randomly grouped into an ET alone subset or a chemotherapy with endocrine (chemoendocrine) therapy subset. The intention-to-treat analysis included the participants who declined the assigned treatment, with 402 (16.2%) participants allocated to chemoendocrine therapy and 144 (5.8%) given to ET. The trial did not show a clinically applicable or statistically significant rise in invasive disease-free survival with the addition of adjuvant chemotherapy to ET in the global population with the same characteristics. In the 67% of participants who were post-menopausal, no chemotherapy advantage was found, while adjuvant chemotherapy led to a relative increase of 40% in invasive disease-free survival and a relative increase of 42% in distant relapse-free survival (RFS) in premenopausal women. Invasive disease-free survival at five years was 91.9% among post-menopausal women in the endocrine-only group and 91.3% in the chemoendocrine group, with no chemotherapy advantage. In the group of premenopausal women, invasive disease-free survival at five years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine treatment, with a comparable rise in distant RFS. Per the authors, the trial showed that in premenopausal women with one to three positive lymph nodes (N1) and an RS of 25 or less, individuals who received chemoendocrine therapy had a lengthier invasive disease-free survival and distant RFS than those who received endocrine-only treatment. In contrast, post-menopausal women with the same characteristics did not show benefit from adjuvant chemotherapy.

Hayes published a Molecular Test Assessment addressing the use of the Oncotype DX Breast Recurrence Score for individuals with ER+, HER2-, lymph node positive BC to determine the capability of the test to estimate the risk of DR and the predict the likelihood of chemotherapy benefit in 2020. For individuals with N1 disease, limited but consistent evidence supports the use of the Oncotype DX test for predicting the risk of nine-year DR, but there is insufficient evidence supporting the test's ability to predict the benefit of chemotherapy. Oncotype DX may improve outcomes for individuals with N1 cancer by lessening the total population of individuals treated with chemotherapy, thereby avoiding detrimental side effects. Insufficient evidence was found to support the use of Oncotype DX testing for estimating the risk of DR and the potential benefit of chemotherapy for individuals with N2 disease (four to nine positive lymph nodes) (Hayes, Oncotype DX Breast Recurrence Score [Genomic Health Inc.] for Lymph Node–Positive Patients, 2020, updated 2023).

In a 2020 Hayes Molecular Test Assessment, the Oncotype DX Breast Recurrence Score was assessed as a prognostic indicator for nine-year distant BC recurrence and predictive indicator for chemotherapy benefit in individuals diagnosed with ER+, HER2-, and node-negative (N0) invasive BC. The evidence presented in the assessment suggests that the Oncotype DX test can estimate the risk of DR and the likely benefit of chemotherapy for guiding proper treatment decisions for individuals, thus impacting provider management and decisions related to therapy. Additional study addressing the range of scores necessary for predicting the likelihood of chemotherapy benefits in specific subgroups is recommended. Clinical utility studies reporting health outcomes after recurrence score-based treatments are needed as well (Hayes, Oncotype DX Breast Recurrence Score for Lymph Node–Negative Patients [Genomic Health Inc.] 2020, updated 2023).

Poorvu et al. (2020) evaluated women less than 40 years of age with early-stage ER+ and HER2- BC to decide if the 21-gene RS could inform chemotherapy recommendations. The prospective TAILORx phase three trial enrolled 509 individuals and the RS assay was performed either clinically (189 participants) or on banked specimens (320 individuals). The median follow-up time was 6 years. Of the 509 individuals, 300 (59%) had N0 BC and 195 of them had a RS of 11-25, of which 86 received chemotherapy. The six-year DR free survival (DRFS) varied by the RS with < 11 associated with 94.4% N0 and 92.3% N1. For those with RS 11-25, DRFS was 96.9% N0 and 85.2% N1 and for those with RS > 26, the DRFS was 85.1% N0 and 71.3% N1. The researchers concluded that the assay is prognostic for young women with N0 and limited N1.

Wang et al. (2019) examined the value of Oncotype Dx when determining the prognosis in female individuals with BC and tumor stage 1-2 (tumor is 20-55mm), LN+ and no evidence of metastasis (T1-2 N1M0). The study reviewed 4059 cases to categorize them to prognostic stages IA and IIB and used data derived from the National Cancer Institute's limited use SEER 18 registry databases, released in November 2017. Cases in the SEER database was linked to RS results from assays performed by Genomic Health. All cases with RS had negative HER2, and the authors selected female ER+ invasive ductal carcinoma (IDC) cases in T1-2N1M0 stage with Oncotype RS results diagnosed between 2004 and 2012. Individuals were categorized into low-risk (RS < 11), intermediate-risk (RS 11–25), and high-risk (RS > 25) groups. The median age of the individuals was 59 years. Of these participants, 2898 (71.4%) had stage T1 cancer, 1854 (45.7%) had stage N_{1mic} cancer, 743 (18.3%) had grade 3 cancer, and 3746 (92.3%) had positive progesterone receptor (PR) status. They were stratified into the RS low-risk group (794, 19.6%), the RS intermediate-risk group (2667, 65.7%), and 598 (14.7%) were in the RS high-risk group. The high-risk group tended to have younger individuals, larger tumors, a higher percentage of grade 3 disease, negative PR, and more advanced cancer staging. They also had more frequent use of chemotherapy. Otherwise, the RS groups did not differ much in race, N stage, surgery, or radiation. In terms of pathological prognostic stages, there were 2781 individuals (68.5%) in stage IA, 829 (20.4%) in stage IB, 360 (8.9%) in

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IIA, and 89 (2.2%) in IIB. The distributions of clinical and pathological characteristics, including BCSS and OS, were compared between RS and pathological staging groups using a variety of statistical analysis. The median follow-up period was 57 months. The results showed a statistically significant correlation ($p < .001$) between the RS groups and pathological stage results. In the low and high-risk RS groups, the BCSS and OS were similar between RS and pathological staging groups. In the intermediate RS group, however, survival rates differed significantly between RS staging and pathological staging. The survival rates were inversely correlated with the escalation of prognostic stages. Similar trends were seen in the high-risk group but were not statistically significant. In this retrospective study, RS was an independent prognosticator for BCSS, and with pathological stage for OS. The authors concluded that Oncotype Dx could complement the prognostic staging system in N+ individuals.

Prosigna Breast Cancer Prognostic Gene Signature Assay (Formerly PAM-50)

The Prosigna Breast Cancer Prognostic Gene Signature Assay (NanoString Technologies, Seattle, WA) is a prognostic BC assay that provides a risk category and numerical score to assess an individual's risk of DR of disease at ten years in postmenopausal women with N0 (Stage I or II) or N+ (Stage II), HR+BC. 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 N2 (Gnant et al., 2013; Parker et al., 2009).

Fitzal et al. (2021) conducted a prospective multicenter RCT (The Austrian Breast and Colorectal Cancer Study Group [ABCSG] 8) to investigate if the PAM50 based 46-gene assay brings prognostic value for the risk of local recurrence of BC. The trial compared five years of adjuvant tamoxifen with sequential therapy involving tamoxifen for two years and then anastrozole for three years in postmenopausal women with endocrine receptor-positive early-stage BC. All participants were regularly followed up every three months for one year, at six-month intervals over the second and third years, and annually afterward. Ribonucleic acid (RNA) was extracted from FFPE blocks from BC excision specimens from the ABCSG-8 trial. Participants were distributed randomly to either the group who received five years of tamoxifen (525 participants) or tamoxifen, followed by anastrozole (509 participants) after surgery group. There were 765 individuals (74%) with a low risk of recurrence (ROR) score (< 57). The existing data showed that the PAM50 ROR score and intrinsic molecular subtypes could detect a low-risk genomic population in individuals with a clinically minimal risk of local recurrence. The PAM50 ROR score is consistently associated with the prospect of disease recurrence. Authors explored if the PAM50 test may predict the value of radiotherapy following breast conservation, using a subgroup of 170 women in the ABCSG-8 trial who did not have adjuvant radiotherapy. The trial suggested that a PAM50-based assay is helpful as a prognostic instrument for local recurrence risk in postmenopausal women with HR+BC treated with ET; however, it is not predictive of the benefit of radiotherapy. The trial is limited by its retrospective nature. The authors concluded that a PAM50-based assay brings value for the risk of local recurrence of BC for postmenopausal women with HR+BC treated with ET.

MammaPrint (Also Referred to as the "Amsterdam Signature" or "70-Gene Signature") and BluePrint

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

BluePrint (Agendia, Amsterdam, The Netherlands), a complementary test to MammaPrint, measures the expression of 80 genes to classify the tumor as one of three subtypes. The tumor subtype is used to predict future behavior of the cancer, long term prognosis and response to systemic therapy. Evidence addressing use of Blueprint in conjunction with MammaPrint is insufficient to support clinical utility at this time.

Rastogi et al. (2024) conducted a study to examine MammaPrint for predicting extended letrozole therapy (ELT) benefit in those with early-stage BC from the NSABP B-42 trial. To carry out the study, MammaPrint was employed in 1866 individuals randomly assigned to receive either ELT or a placebo. The primary outcome measure was DR; secondary endpoints included disease-free survival (DFS) and BC-free interval (BCFI). Classification of tumors were as follows: either MammaPrint high risk (MP-HR), or low risk (MP-LR). Tumors classified as MP-LR tumors were further categorized as ultralow risk (MP-UL) or low non-ultralow risk (MP-LNUL). The researchers found no statistically significant difference in the advantage of ELT for DR between MP-HR and MP-LR (interaction $p = .38$). MP-LR tumors ($n = 1160$) revealed a statistically significant ten-year benefit of 3.7% for DR (hazard ratio [HR], 0.43 [95% CI, 0.25 to 0.74]; $p = .002$), while MP-HR tumors ($n = 706$) displayed a nonsignificant 2.4% benefit (HR, 0.65 [95% CI, 0.34 to 1.24]; $p = .19$). The ten-year ELT benefit was significant for DFS (7.8%) and BCFI (7.0%) for MP-LR tumors, while MP-HR tumors did not show significantly benefit (interaction DFS: $p = .015$, BCFI: $p = .006$). The ten-year ELT benefit was significant and more distinct in MP-

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LNUL (n = 908) tumors: 4.0% for DR, 9.5% for DFS, and 7.9% for BCFI; the benefit in MP-UL (n = 252) tumors was not significant: 3% for DR, 1.8% for DFS, and 4.1% for BCFI in an exploratory analysis. The study's limitations included its prospective-retrospective design and lack of multiplicity adjustment for secondary and exploratory analyses. The authors concluded that the primary hypothesis of the predictive capability of MammaPrint on DR was not verified, but the secondary endpoint results indicated that MammaPrint is predictive of ELT response and it detected a subset of people with early-stage hormone receptor-positive BC (MP-LR) that showed better outcomes from ELT. These findings could expand the clinical utility of MammaPrint beyond just prognostic indication because they provide the initial data suggesting that MammaPrint may be predictive of EET benefit. The authors recommend further study incorporating clinicopathological characteristics to further optimize selection of appropriate individuals for treatment. They suggest that the confirmation of the utility of the MammaPrint genomic classifier will allow women in specific categories (postmenopausal with HR+BC) to avoid unneeded treatment while helping to identify individuals who require additional adjuvant ET.

Van't Veer et al. (2024) performed a secondary analysis of the IDEAL randomized clinical trial to establish the utility of MammaPrint, a 70-gene expression risk-of-recurrence assay, in the identification of those individuals with EBC in the IDEAL trial that could benefit from five years of treatment with letrozole versus two-and-a-half years of the same treatment. In this study, the researchers assessed postmenopausal women with HR+EBC who had been assigned to either two-and-a-half or five years of EET. Follow-up assessment occurred ten years after randomization. To carry out the analysis, a 70-gene assay was used to classify tumors as high, low, or ultralow risk. After five years of ET, participants were randomized to two-and-a-half or five years of EET with letrozole. The primary endpoint was DR; Cox proportional hazard regression models and likelihood ratios were used to analyze the interaction between treatment and GEA. Adverse event (AE) incidence and treatment compliance were also measured. Of the 515 women included (mean [SD] age at randomization, 59.9 [9.5] years), 265 were in the two-and-a-half-year treatment arm and 250 were in the five-year treatment arm. A total of, 223 (43.3%) of those with 70-gene assay-classified low-risk tumors had a significant absolute benefit of 10.1% for DR (HR, 0.32; 95% CI, 0.12-0.87; p = .03). Treatment interaction was not significant for DR. Of those with either 70-gene assay–classified high-risk tumors (259 [50.3%]) or ultralow-risk tumors (33 [6.4%]), five years vs two-and-a-half years of EET had no statistical association with improved benefit for DR. The rate of AEs and treatment discontinuation rates were similar among the different 70-gene assay risk groups in each treatment arm. The study was limited by its retrospective design and the inclusion of a subset of individuals due to limited tissue sample availability, which prevented analyses to be adjusted for covariates. In addition, the study participants were of limited racial diversity, only individuals who were postmenopausal were included, and the sample size for the ultralow risk group was small. Lastly, non-significant treatment by risk interactions were observed for DR and BCFI, potentially due to low event rates seen in the translational cohort. The authors concluded that MammaPrint was able to detect individuals with low-risk tumors who may benefit from five year vs two and a half year EET, suggesting that this 70-gene expression-risk-of-recurrence assay may have utility beyond guiding neoadjuvant and adjuvant chemotherapy decisions; it may have value for information treatment decisions regarding adjuvant endocrine therapy as well. They suggest additional study of MammaPrint for use as a biomarker to determine EET benefit, specifically focusing on populations including premenopausal women.

Marin-Liebana et al. published an initial analysis from the DETERMIND study in 2023. DETERMIND is a prospective, open-label, multicenter study evaluating the utility of the MammaPrint/BluePrint (MP/BP) signature related to determining optimal therapy for individuals with operable, clinically high-risk HR+/HER2- EBC, stage II-IIIA (up to N1) who have received a recommendation for NCT. One hundred sixty-five individuals from 11 centers have been included in this analysis, with data collected at baseline, at the time of MP/BP results and finally at one and three year follow-ups. The first analysis incorporated 99 participants with a median age of 57 years (range 31-85). Ninety-four percent of these were stage II, with 51% cN1. At the time of MP/BP, 37 individuals (37%) were classified as Luminal A, 58 (59%) were Luminal-B, and four presented as a non-Luminal phenotype (3 Basal, 1 HER2). Corresponding with MP/BP results, 44 pts did not receive NCT. In the MP/BP Luminal A group, 35 (95%) did not receive NCT; for 19 of these individuals, it was replaced by NET. Individuals with MP High-Risk results received NCT in 53 cases (85%). MP/BP results significantly increased confidence on the final treatment decision made collaboratively by the treating physicians and participants. The authors concluded that in individuals with clinical high-risk HR+/HER2- EBC, there is a high frequency (35%) of MP/BP Luminal A, who were able to de-escalate NCT. The use of MP/BP also bolstered the decision to administer NCT in the majority (85%) of those with MP High Risk. The authors assert that these findings support the utility of MP/BP in high clinical risk HR+/HER2- EBC to inform neoadjuvant therapy decisions and increase confidence in clinicians and their patients during shared-decision making. The study was sponsored by Agendia, the manufacturer of the MP/BP test, which presents potential bias. Larger, high-quality prospective trials are needed to further validate these findings.

Pellicane et al. (2022) addressed the need for reliable biomarkers to identify individuals with HR+HER2- BC tumors who are likely to receive benefit from neoadjuvant endocrine therapy (NET) in a recent observational registry trial of 1091

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individuals with early-stage BC. Participants, who were scheduled to receive neoadjuvant therapy, were prospectively enrolled into the Neoadjuvant Breast Registry Symphony Trial (NBRST), sponsored by Agendia. NBRST compared the prognostic value of the 70-gene risk classifier (MammaPrint) and the 80-gene molecular subtyping signatures (BluePrint) with standard pathological classification methods in response to neoadjuvant treatment. The association of these signatures with clinical response and five-year outcome of participants who underwent treatment with NET (n = 67) were evaluated in a sub-analysis. Standard of care genomic testing with MammaPrint and BluePrint was performed, and participants underwent therapy with NET per their physician's discretion. Primary outcome was pathologic partial response (pPR). Secondary outcomes included distant metastasis-free survival (DMFS) and OS. The researchers defined clinical benefit as a pPR or stable disease (SD) with use of NET. Of individuals with genomically Luminal A-Type tumors, 94.4% displayed clinical benefit (50.0%pPR and 44.4% SD). Ninety-five percent of individuals with Luminal B-Type tumors exhibited benefit (55.0% pPR and 40.0% SD). At 5 year assessment, individuals with genomically Luminal B tumors had substantially worse DMFS (75.6%, 95% CI 50.8 - 89.1) than those with genomically Luminal A tumors (91.1%; 95% CI 74.8–97.1; p = 0.047). The trend for OS was similar, but was not significant (81.0%, 95% CI 56.9–92.4 and 91.1%, 95% CI 74.8–97.1, respectively; p = 0.13). The authors concluded that individuals with 70-gene signature low risk results and genomically Luminal A tumors who were treated with ET alone have excellent outcomes at 5 years. In addition, most individuals with genomically-defined Luminal A- and B-type tumors respond well to NET, which suggests NET may be a safe option for treatment; however those with genomically Luminal B tumors will also need post-operative chemotherapy or CDK4/6 inhibitors to improve their long-term outcomes. The researchers indicate that genomic classification (defined by the combined use of 70- and 80- gene signatures) is prognostic of long-term outcomes and is related to tumor response, supporting the use of these tests in making neoadjuvant treatment decisions in individuals with early-state HR+HER2- BC. This study was observational and the number of individuals receiving NET was limited, so the sample size was small and prevented further subgroup analyses. In addition, NBRST participants receiving NET instead of NCT despite features associated with high clinical risk were more likely to be older and postmenopausal. Larger, prospective trials, such as the ongoing FLEX trial (NCT030631983), are needed to confirm the findings of this study.

In 2022, Vliek and colleagues published a ten-year follow-up of the observational RASTER study. The prospective RASTER study assessed the tumors of 427 individuals with cTanyN0M0 BC. The study aimed to decide the 70-gene signature (MammaPrint)'s ability to guide adjuvant chemotherapy decisions for individuals with ER+ and HER2- BC. The authors evaluated 310 of the 427 individuals at ten years of follow-up. Of the clinically high-risk individuals, 45 (49%) were classified as genomically low-risk. In this subcategory, at ten years, distant recurrence-free interval (DRFI) was comparable among individuals treated with (95.7% [95% CI 87.7–100]) and without (95.5% [95% CI 87.1–100]) chemotherapy. In the group of clinically low-risk individuals, 56 (26%) were classified as genomically high-risk. For the clinically low-risk group, a variance was seen among the genomically high- and low-risk subgroup after five years, resulting in a ten-year DRFI of 84.3% (95% CI 74.8–95.0) and 93.4% (95% CI 89.5–97.5), respectively. Genomic ultralow-risk individuals' outcomes were a ten-year DRFI of 96.7% (95% CI 90.5–100), primarily (79%) without systemic therapy. Limitations to the RASTER study include the observational nature and the risk of bias. The authors concluded that over ten years, individuals with clinically high-risk, genomic low-risk tumors have excellent results irrespective of the use of chemotherapy. The updated outcomes of the MINDACT trial and RASTER study collectively demonstrate that the data supports the use of the MammaPrint in ER+, HER2-, and N0, clinically high-risk individuals with BC.

In NBREaST II, a prospective, neoadjuvant study, Göker et al. (2022) measured the treatment response and five-year survival outcome in the molecular subgroups by combining the MammaPrint and BluePrint. MammaPrint and BluePrint were carried out on 256 individual core needle biopsies (CNB) to quantify chemosensitivity or endocrine sensitivity in the molecular subgroups. The outcomes measured were DMFS, RFS, and BCSS at long-term follow-up. In the group of individuals who received NCT (n = 234), MammaPrint and BluePrint categorized 50 tumors as Luminal A-Type (21%), 110 as Luminal B-Type (47%), 27 as HER2-Type (12%), 47 as Basal-Type (20%). Of individuals that attained a pCR in response to NCT (n = 47), 4% had a MammaPrint Low-Risk result, and 96% had a High-Risk outcome. All BluePrint-defined HER2-Type and Basal-Type tumors had a High-Risk MammaPrint outcome. At five years, DMFS was significantly lower (p = 0.039) in MammaPrint High-Risk tumors (83.8%; 95% CI 77.4–88.6) versus MammaPrint Low-Risk tumors (91.4%; 95% CI 78.6–96.7). Similar outcomes were seen for five-year RFS; however, not for BCSS. Limitations to the study include a small sample size, with no differences in five-year survival when stratifying the cohort into subgroups. The study confirms previous conclusions signifying that MammaPrint and BluePrint can predict chemosensitivity and five-year results more precisely versus traditional pathological sub-typing, supporting informed decision-making.

Crozier et al. (2022) prospectively collected 139 matched CNB and surgical resection (SR) specimens from women with established EBC registered in the ongoing FLEX study (NCT03053193). The goal was to decide the concordance of MammaPrint and BluePrint results among CNB and SR to safeguard reliable prognostic information that can be apprehended from a CNB. FLEX is an ongoing, multi-institutional prospective study of individuals with Stage I–III EBC. Overall, 121 individuals from the FLEX study database with diagnostic MammaPrint and BluePrint results with matched

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CNB and SR specimens were involved in the study. In total, 50 individuals had High-Risk CNB and SR specimens, and 60 had Low-Risk CNB and SR specimens, resulting in 90.9% total agreement (κ = 0.817), 95.2% negative predictive value (NPV), and 86.2% positive predictive value (PPV). The authors concluded the concordance of BluePrint between CNB and SR to be 98.3%. For more than 97% of individuals in this study, treatment decisions and probable outcomes are precise and consistent based on MammaPrint testing of the CNB. According to the authors, this analysis is the most extensive powered study using prospective real-world numbers to assess the concordance of a genomic assay on matched CNB and SR samples. The limitation of the study is the lack of data maturity, as individual follow-up data is not available to correlate outcomes with MammaPrint and BluePrint results from the CNB and SR samples. The authors concluded that the high concordance rates of MammaPrint and BluePrint result among paired samples strongly support the value of these assays to acquire reliable prognostic data on core biopsy tissue, which can guide prompt and proper treatment decisions.

In 2021, Piccart et al. produced updated results the MINDACT trial, including long-term follow-up with an exploratory analysis by age. MINDACT was a randomized, phase three, multicenter trial conducted in 112 academic and community hospitals in nine countries that enrolled individuals that had confirmed primary invasive BC with N1, no distant metastases, and a WHO performance status of 0-1, and their genomic risk was decided using the MammaPrint 70-gene signature. Enrolled in the trial were 6693 individuals with a mean follow-up of 8.7 years. The eight-year estimates for DMFS in the intention-to-treat population were 92.0% (95% CI 89.6–93.8) for chemotherapy set against 89.4% who received no chemotherapy. The eight-year DMFS in the exploratory analysis by nodal status in these individuals was 91.7% (95% CI 88.1–94.3) with chemotherapy and 89.2% (85.2–92.2) without chemotherapy in 699 N0 individuals (absolute difference 2.5 percentage points [SE 2.3, 95% CI −2.1 to 7.2] and 91.2% (87.2–94.0) as opposed to 89.9% (85.8–92.8) for 658 individuals with N1. The exploratory analysis conducted to determine the effects of chemotherapy administration on eight-year DMFS according to age resulted in 93.6% with chemotherapy set against 88.6% without chemotherapy in 464 women aged 50 years or younger and 90.2% vs 90.0% in 894 women older than 50 years. This long-term follow-up of phase three randomized MINDACT trial showed the 70-gene signature's capability of detecting women with high clinical risk, a subgroup, and specific individuals with low genomic risk, with an exceptional DMFS when treated with ET by itself. For this group of women, the size of the profit from adding chemotherapy to ET continues to be small and is not improved by nodal positivity. The benefit is age-dependent and is solely seen in women under 50; further study is needed in younger women, who may need reinforced ET to forego chemotherapy. The authors concluded that MammaPrint ought to be a portion of informed, shared decision-making.

Soliman et al. (2020) conducted a prospective case-only trial (IMPACt) enrolling 452 individuals with state I-II, HR+, HER2- BC to evaluate the variation in treatment decision and physician assurance based on the 70-gene ROR signature and the 80-gene molecular subtype signature (80-GS, BluePrint) in early-stage BC. According to clinical risk assessment via the MINDACT criteria, 63.4% (n = 227/358) of individuals were categorized as low-risk, and 36.6% (n = 131/358) of individuals were classed as high-risk of DR. For individuals with clinically minimal risk, 77.5% (176/227) were suggested not to have chemotherapy by their doctors, while 62.6% (82/131) of individuals with clinically high-risk were recommended treatment plans that involved chemotherapy. The 70-GS categorized 62.5% (n = 224/358) of individuals as low-risk and 37.5% (n = 134/358) as high-risk. Following the 70-GS results, doctors elected to change the chemotherapy treatment (CT) recommendation in 24.0% (n = 86/358) of all cases. After-70-GS treatment plans were, 88.5% (n = 317/358) agreeing with 70-GS results, 83.6% (n = 112/134) for CT in 70-GS high-risk individuals, 91.5% (n = 205/224) for no CT in 70-GS low-risk individuals. The IMPACt trial displayed that the majority (88.5%) of treatment plans were accordant with 70-GS results, showing that doctors make treatment decisions based on the 70-GS result in clinical practice. Physicians also described a rise in confidence in 72.2% of their suggested treatment plans after receiving the 70-GS results. A limitation of the study is that individuals were enrolled both before and after the MINDACT trial results were published, which may have impacted physicians' decisions for treatment. The authors concluded that these results propose that doctors feel the proper individuals (high-risk) are being presented chemotherapy, and they feel confident sparing 70-GS individuals with low-risk from the high clinical and financial burden of chemotherapy. The trial shows that doctors can avoid overtreatment and the adverse effects of chemotherapy treatments for individuals who are not likely to obtain meaningful clinical benefits.

In 2019, Wuerstlein and colleagues reported on the prospective, observational multicenter WSG-PRIMe study designed to gauge the effect of MammaPrint and BluePrint on adjuvant chemotherapy treatment decisions in individuals with early-stage BC specifically to show an overall switch percentage of at least 15% regarding chemotherapy. These individuals had MammaPrint considered as part of their standard clinical procedure. Included in the study were 452 individuals who were HR+ and HER2-. Physicians supplied preliminary treatment recommendations created on clinicopathological factors. Post-test therapy recommendations and actual therapy were documented after prospective risk classification by MammaPrint/BluePrint was revealed. MammaPrint allocated 63.5% of participants to the low-risk group and 36.5% to the high-risk group. In 125/430 (29.1%) individuals (95% CI 24.8–33.6%), the recommendation transformed from

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chemotherapy to no chemotherapy or vice versa. Chemotherapy had been recommended to 164 individuals (38.1%) pre-test. In 60/164 (36.1%) of the individuals who were recommended chemotherapy, the therapy recommendation converted to the omission of chemotherapy post-test; most (59/60, 98%) of these changes happened in low-risk individuals, according to MammaPrint. On the contrary, deletion of chemotherapy been suggested to 266 individuals (61.9%) pre-test; in 65/266 (24.4%) cases, recommendations converted to chemotherapy post-test; most (64/65, 98.4%) of these modifications happened in MammaPrint high-risk individuals. The physician observance of MammaPrint risk calculation was 92.3% for low-risk and 94.3% for high-risk scores. Three-fourths (n = 59/79, 74.7%) of physicians initially recommending chemotherapy converted to no chemotherapy subsequent low-risk MammaPrint results (72.7% in pN0, 77.1% in pN1); on the contrary, nearly nine tenths (n = 64/72, 88.9%) of physicians originally recommending chemotherapy omission from treatment converted to chemotherapy recommendations following high-risk MammaPrint outcomes (88.1% in pN0, 92.3% in pN1). The authors concluded that the WSG-PRIMe study proves that the use of the gene expression profiles, MammaPrint and BluePrint, has a powerful influence on adjuvant therapy recommendations. The results showed that physicians changed their ultimate recommendation for systemic therapy in 29.1% of cases subsequent MammaPrint testing. The study verified that there is improved, genomically determined individualization of treatment regimens that can lead to a reduced risk of over- or undertreatment of individuals. Overall, the high adherence to genomically determining risk assessment signifies a significant prerequisite for reaching further targeted disease management in early-stage BC.

van Steenhoven et al. (2018) evaluated the ability of 70-GS (MammaPrint) and 80-GS (BluePrint) molecular subtyping to surrogate pathological subtyping (PS) for determining treatment options and prognosis. Between 2013 and 2015, 595 intermediate risk individuals who are ER+ with early-stage BC were studied. HER2 receptor status was determine through routine immunohistochemistry and fluorescent in situ hybridization. The overall concordance between molecular sub-typing and PS for luminal cancers type A and B together was 98%. Individually it was poor, at 64%. The ability of the 80-GS assay to differentiate between luminal, HER2-type and basal-like cancers was limited, and furthermore the concordance between PS and the 70-GS approach was low. The authors concluded that two classification methods had significant disparity in outcomes, resulting in the risk of inadequate treatment. More studies are needed to demonstrate the efficacy of this test.

The randomized, phase three clinical MINDACT trial included 6693 women with early-stage BC with the primary goal to assess whether, among individuals 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 five-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, while those at high clinical and genomic risk did receive such therapy. For individuals 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 BC 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 five-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 BC who are at high clinical risk might not require chemotherapy (Cardoso et al., 2016).

EndoPredict

EndoPredict (Myriad, Salt Lake City, UT) is a 12-gene real-time genomic test that includes eight disease-relevant genes *BIRC5, UBE2C, DHCR7, RBBP8, IL6ST, AZGP1, MGP* and *STC2*, three RNA normalization genes (*CALM2, OAZ1* and *RPL37A*) and one DNA reference gene (*HBB*). EndoPredict also incorporates information on nodal status and tumor size. Results are given as an “EPclin Risk Score;” a number between 1.1 and 6.2 which relates to cancer recurrence risk.

In a Hayes Molecular Test Assessment, the clinical validity, clinical utility, and analytical validity of EndoPredict were evaluated. The assessment uncovered limited but positive evidence suggesting EndoPredict may estimate the ten-year risk of DR for individuals with ER+, HER2-, N0, and early-stage BC; however, it remains unclear if the test can prospectively distinguish low-risk individuals from others or if the test is equally applicable for premenopausal women. There is limited evidence suggesting EndoPredict may estimate the ten-year risk of DR for individuals with ER+, HER2-, N1, and early-stage BC, and conflicting results to determine if the EPclin low-risk group was genuinely associated with a low-risk of DR in this population. For the EndoPredict test to estimate the likelihood of DR five to fifteen years from diagnosis and the absolute benefit of chemotherapy at ten years for individuals with ER+, HER2-, N0/N1, early-stage cancer, there are limited studies and data to support the test results. No prospectively designed studies were found regarding the clinical validity of EndoPredict; additional studies are necessary to examine diverse demographics and possibly improve health outcomes resulting from the EndoPredict test (Hayes, EndoPredict [Myriad Genetics Laboratories Inc.], 2020, updated 2023).

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In the prospective, translational, randomized phase two ABCSG-34 trial directed by Dubsky et al. (2020), the ability of EndoPredict to predict response to NCT or NET was assessed. HR+, HER2- samples were gathered from participants, and EndoPredict testing was completed to produce a 12-gene MS. Participants were randomized to have either NCT or NET based on menopausal status, HR expression, grade, and Ki67. The outcome measured was calculated via the residual cancer burden (RCB). Overall, 134 individuals who were HR+ received NCT, and 83 received NET as their preoperative SoC treatment. Out of 134 participants who received NCT, nine had low-risk disease according to the 12-gene MS, and 125 had high-risk disease. The 12-gene MS exhibited strong sensitivity for NCT (100%, 95% CI 89.4%-100%), even though specificity was small (8.9%, 95% CI 4.2%-16.2%). Of the participants treated with NET, 44 out of 83 had low-risk disease, and 39 had high-risk disease. According to the authors, this is the first study that prospectively proves the predictive probability of the 12-gene MS for its response to NET. The RCB 0-I outcome for individuals with NET in the low-risk 12-gene MS subset was 27% in contrast to 7.7% in individuals with high-risk MS. The data presented in this trial shows that the 12-gene MS offers supplementary predictive data beyond the traditional clinicopathologic factors used to evaluate risk and is a valuable instrument preoperatively.

Sestak et al. (2020) retrospectively investigated a cohort of individuals with invasive lobular carcinoma (ILC) from previously conducted clinical trials (ABCSG-6, ABCSG-8, TransATAC). The main objective of the study was to determine the prognostic value of EPclin, either alone or in combination with clinical parameters, for DR in women with ILC. All participants had received five years of endocrine treatment as the only adjuvant therapy. Information compiled from the three clinical trials included data from 2630 postmenopausal women with ER+, HER2- BC. As part of that group, 470 (19.5%) had ILC, 1944 (80.5%) had IDC and 216 (8.2%) had another histological subtype. The researchers found that in this study, EPclin was highly prognostic in women with ILC [HR = 3.32 (2.54–4.34), $p < .0001$] and provided better prognostic value than the Clinical Treatment Score [CTS; HR = 2.17 (1.73–2.72)]. Further, they found that EPclin was prognostic in women with IDC (n = 1944) overall [HR = 2.36 (2.11–2.65), $p < 0.0001$], though not to the level of ILC. They concluded that EPclin provided substantial prognostic information and risk stratification for women with ILC. This study was included in Hayes, EndoPredict (Myriad Genetics Laboratories Inc., 2020), and the Hyams et al. (2024) systematic review discussed above.

Penault-Llorca et al. (2020) led a prospective single-arm multicenter trial calculating the clinical and psychological influence of EndoPredict use for individuals with ER+HR- localized BC. The trial assessed the quantity of change from the initial adjuvant decision and the last administration of chemotherapy. Secondary measures involved post-test (Day 17) and one-year patient-reported results. The trial encompassed 203 participants from 25 centers: 201 had an EPclin assessment. Overall, the decision to treat compared to the initial decision was changed for 72/200 (36%, 95% CI 29.3-42.7) individuals. Chemotherapy was first recommended to 48% of individuals, of which only 26% underwent chemotherapy. Chemotherapy was withdrawn in 57 cases (28.4%, 95% CI 22.2-34.8), and in 15 cases (7.5%, 95% CI 3.8-11.2), chemotherapy was added. The choices to change therapy were often associated with the EPclin outcomes. The trial exposed that in individuals with early BC at intermediate risk, using EPclin to back up the treatment choice resulted in a 35.8% change in whether adjuvant chemotherapy was given. The trial shows how the test permits a decrease in centers and physicians' therapy decision heterogeneity. The trial has limitations associated with the non-randomized method, open design, and risk of bias in participant selection. The authors concluded that the EPclin test has an established influence that can reduce adjuvant chemotherapy treatments under ordinary circumstances.

Breast Cancer Index (BCI)

BCI (BioTheranostics, San Diego, CA) is a gene expression-based signature that analyzes the combination of two biomarker panels: the *HOXB13*:*IL17BR* ratio (H/I) and the Molecular Grade Index (MGI), consisting of the average expression of five cell cycle-associate gene index (*BUB1B, CENPA, NEK2, RACGAP1, RRM2*). The test is performed on a FFPE tissue block and results in a single prognostic score quantifying both the risk of late (5-10 years) and overall (0-10 years) DR (Sgroi et al., 2022).

The evidence supporting predictive tests for the extension of ET in individuals with BC has been limited to date. Woolpert et al. (2023) explored the role of biomarker tests in the prediction of clinical response to extended ET in a systematic review and meta-analysis. A total of five studies met eligibility requirements and were included; four investigated the BCI assay in three unique study populations and one explored the predictive ability of Ki67 and progesterone receptor status. The studies focused on BCI reliably demonstrated that the BCI score predicted response to an extension of ET in 1946 combined participants (primarily non-Hispanic white and postmenopausal). The authors recommend further study of an assortment of biomarkers in diverse populations of individuals. Studies by Noordhoek et al. (2021), and Bartlett et al. (2019), previously discussed in this policy, were included in the Woolpert systematic review and meta-analysis.

Hayes evaluated the use of the BCI test for predicting likelihood of benefit from EET (greater than five years) and estimating risk of late (greater than five years from diagnosis) and cumulative DR risk over ten years in individuals

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diagnosed with HR+, N0 or N1 invasive BC treated with five years primary adjuvant ET or primary ET. The Hayes assessment found insufficient evidence to support the BCI test for the prediction of likelihood of benefit from EET or to estimate the risk of late and cumulative DR risk over ten years in these situations. For individuals with HR+, N1 invasive BC, Hayes again found the evidence supporting the use of BCI for predicting benefit of EET or estimating risk of DR in individuals treated with five years of primary adjuvant chemotherapy to be lacking. Further investigation including large, prospective, randomized trials examining diverse populations and health outcomes related to use of the BCI test are recommended. The 2023 update to these BCI Molecular Test Assessments indicate no change to the current Hayes ratings (Hayes, Breast Cancer Index [BioTheranostics Inc.] for Lymph Node–Negative Patients, 2020, updated 2023; Hayes, Breast Cancer Index [BioTheranostics Inc.] for Lymph Node–Positive (1-3) Patients, 2020, updated 2023).

Sestak et al. (2018) provided a secondary analysis of data obtained from the Anastrozole or Tamoxifen Alone or Combined RCT, comparing five-year treatment with anastrozole vs tamoxifen with ten-year follow-up data. The objective was to compare the prognostic value of Oncotype Dx recurrence score, PAM50 based Prosigna ROR, BCI, EndoPredict, Clinical Treatment Score, and four-marker immunohistochemical score to the Clinical Treatment Score (nodal status, tumor size, grade, age, and endocrine treatment) for DR for zero to ten years and five to ten years after diagnosis. The analysis included 774 post-menopausal women with estrogen positive, HER2- disease. Five hundred and ninety-one had N0 disease. All genomic signature tests provided significantly more information than the clinical treatment score, the RS and the four marker immunohistochemical score alone. The most valuable tests were the PAM50 and BCI. In the 183 individuals with N1, there was limited information provided by the molecular tests, and BCI and EndoPredict provided the most value. The authors concluded that the data provided by molecular testing could help oncologists and individuals consider chemotherapy or extended endocrine testing. This study is included in Hayes EndoPredict (Myriad Genetics Laboratories Inc.), 2020, Hayes Breast Cancer Index (BioTheranostics Inc.) for Lymph Node–Negative Patients, 2020, as well as the Hyams et al. 2021 systematic review discussed above.

Zhang et al. (2017b) examined the predictive ability of BCI results, when integrated with tumor size and grade Breast Cancer Index Model (BCIN), to accurately identify outcomes in a well annotated retrospective series of N+ individuals. A total of 402 participants with N1 who were treated with adjuvant ET with or without chemotherapy using a prespecified model. The primary endpoint was time to DR. BCIN classified 20% of participants as low-risk with a 15-year DR rate of 1.3% and 321 individuals as high-risk with a DR risk of 29%. When the results were unblinded and compared to participant outcome, BCI alone was significantly prognostic ($p < .0001$), and when tumor size was added the prognostic ability was even further improved ($p < .0003$) but only incrementally with adding tumor grade ($p = .01$). Overall, BCIN identified 20% of individuals who were N+ with a limited ROR over 15 years that could avoid extended endocrine treatment. Further studies on combined genomic and clinical algorithmic predictions are needed on N+ individuals. This study is included in Hayes, Breast Cancer Index (BioTheranostics Inc.) for Lymph Node–Positive (1-3) Patients, 2020.

Other Breast Cancer Profiling Assays

Gene expression profiling assays for BC treatment other than those previously described, including but not limited to, Breast Cancer Gene Expression Ratio (also known as Theros H/I), DCISionRT, Oncotype DX DCIS, the 41-gene signature assay, and the 76-gene "Rotterdam signature" lack sufficient evidence to support clinical utility at this time.

DCISionRT

DCISionRT (Prelude Corporation, Laguna Hills, CA) is a risk assessment test for individuals with ductal carcinoma in situ (DCIS) which is designed to quantify an individual's ten-year risk of DCIS recurrence and determine whether radiation therapy would be of benefit. DCISionRT assesses 7 genes along with other clinical risk factors to provide a DCISionRT score ranging from 0 to 10**.** Scores 0-3 are considered low risk and scores 3-10 are considered elevated risk.

In a 2023 a systematic review and meta-analysis, Ouattara et al. evaluated women with DCIS who had been treated with breast-conserving surgery (BCS) to determine the impact of adjuvant radiotherapy (RT) on local recurrence (LR) according to risk stratification per molecular signature testing. Five studies including 3478 women with DCIS who had been treated with BCS were included in this evaluation. A molecular assay was performed for each of the women included. The effect of BCS and RT versus with BCS alone on LR was analyzed. The analysis included both ipsilateral invasive breast events (InvBE) and total breast events (TotBE). Two molecular signature tests were used: the Oncotype Dx DCIS (prognostic of LR) and DCISionRT (prognostic of LR and predictive of RT benefit). In the high risk group, for DCISionRT, pooled HR of BCS+RT versus BCS was 0.39 (95%CI 0.20–0.77) for InvBE and 0.34 (95%CI 0.22–0.52) for TotBE. In the low-risk group, pooled HR of BCS+RT versus BCS was significant for TotBE at 0.62 (95%CI 0.39–0.99) but was not significant InvBE (HR = 0.58 [95%CI 0.25–1.32]). The researchers maintain that molecular signature tests can discriminate high- and low- risk individuals; individuals at high-risk showed a significant benefit of RT for reduction of invasive and in situ LR and individuals at low-risk did not show benefit for prevention of recurrence of invasive BC. While

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molecular signatures may be a promising tool for balancing over- and undertreatment of DCIS, further understanding of the basis of invasive cancer is needed. The study was limited by the lack of data on breast-cancer specific mortality and individual data on recurrence-free survival. Further high quality evaluation, including studies focused on impact on mortality are required.

Hayes (2022) published a Molecular Test Assessment evaluating the use of the DCISionRT test to assist individuals with DCIS and their providers with decision-making regarding the use of BCS alone or BCS plus RT. Hayes found a lack of published evidence to support the use of the DCISionRT test. The 2024 update of this assessment identified three newly published studies that may meet the inclusion criteria set out in the original report and an unlikely change in the current Hayes rating of D2 (Hayes, DCISionRT [Prelude Corp.], 2022, updated 2024).

Shah et al. (2021) documented the results of the PREDICT study; a prospective, multi-institutional observational registry designed to evaluate the clinical utility of testing with DCISionRT on clinical recommendations regarding RT for individuals who had undergone BCS for a diagnosis of DCIS. The study included 539 women over the age of 25 who had been treated with BCS for unilateral DCIS. All women were eligible to receive RT and received DCISionRT testing as part of the study. Prior to testing, 69% of all participants had received a recommendation of treatment with RT. After testing with DCISionRT, 46% of those that had previously received recommendation for RT had a change in recommendation to not receive RT. Conversely, for women who were not initially recommended to undergo RT, 35% had a change in recommendation for treatment to include RT. In summary, a change in RT treatment plan was made for 42% of women in the study, with a net reduction in overall RT recommendation of 20%. The elevated DS had the strongest association with an RT recommendation (OR 43.4) compared to other factors such as age, grade, size, and margin status. The authors concluded that DCISionRT testing made a significant difference, including an absolute net decrease in RT recommendations overall in women with DCIS who had undergone BCS, and was the factor most strongly associated with RT recommendations compared with traditional measures used to drive treatment decisions. The authors also noted limitations to the study. One such limitation was the lack of patient or physician-reported outcomes regarding satisfaction or quality (pending at time of publication). In addition, data on recommendations for RT were only based on two points in time; pre-testing and post-testing. Finally, there is a lack of long-term clinical outcomes and data on subsequent resource utilization related to treatment decisions. These items are planned for further evaluation and assessment when longer follow-up data become available. This study was included in the 2022 Hayes DCISionRT (Prelude Corp.) Molecular Test Assessment.

Choosing the optimal treatment approach for individuals diagnosed with DCIS has been a significant challenge and a topic of active research. A major goal is to understand the ROR for DCIS. In a 2020 publication, Weinmann et al. (included in the systematic review and meta-analysis by Ouattara et al. [2023], discussed above, and the Hayes 2022 DCISionRT Molecular Test Assessment) described the results of their external prospective–retrospective clinical validation of DCISionRT, a ten-year recurrence/progression risk assessment test using monoclonal protein markers and clinicopathologic factors (age at diagnosis, palpability, tumor size and surgical margin status) for individuals with DCIS who had undergone BCS. The outcome of the DCISionRT test is called the decision score (DS). Study participants included 455 Kaiser Permanent Northwest members over the age of 25 diagnosed with DCIS and treated with BCS with or without radiotherapy from 1990 to 2007. Kaplan Meier analysis and Cox regression were used to measure the ability of the DS to predict outcomes beyond that of clinicopathology factors. The researchers found a positive association of the DS produced by DCISionRT with total breast event and invasive breast event risk after adjustment for radiotherapy in the Cox regression analysis. Kaplan-Meier analyses showed that elevated-risk DS scores showed more than twice the ten-year risk of total breast events compared to low-risk DS scores. The authors concluded that DS score from DCISionRT test was prognostic for risk of later breast events in this study group. Despite these promising results, the study had some noteworthy limitations. Most study participants with DCIS received adjuvant radiotherapy, so there were fewer BCS without radiotherapy participants in the study to analyze. Statistical power was more limited for assessment of DS associated with invasive BC because approximately half of the total breast events were invasive. In addition, some participants had received ET, which may have impacted overall outcomes. While the study indicates elevated DS scores would suggest a preferential radiotherapy benefit, this study design did not assess radiotherapy benefit. In addition, some of the risk difference between radiation treated and nontreated cohorts might be related to the individuals' selection for treatment, since the study was not randomized or rule based. Further research is needed to provide more evidence to support routine DCISionRT testing.

Bremer et al. (2018, included in the systematic review and meta-analysis by Ouattara et al. [2023], discussed above) reported on the development and cross-validation of DCISionRT (PreludeDX). DCISionRT is a risk assessment test that uses a combination of molecular and clinicopathologic factors to generate a biological signature which calculates an individualized DS. The relationship between DS and ten-year risk of invasive breast cancer (IBC) or any ipsilateral breast event (IBE) was assessed in this study. Benefit of radiotherapy was evaluated as a function of DS, by risk group. Study

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population included 526 individuals diagnosed with a primary DCIS and treated with BCS, with or without radiotherapy, from two study sites. The study used archived tissue samples. Treatments for the study participants were neither randomized nor strictly rules based. The researchers found a significant association with IBC and IBE risk. In study participants who had been treated without RT, the DS identified a low group with ten-year IBC risk of 4% (7% IBE) and an elevated risk group with IBC risk of 15% (23% IBE). The elevated risk group received significant RT benefit in analysis of DS and RT by group. In a clinicopathologically low-risk-subset, 42% of participants were reclassified into the elevated risk group by using DS. When an interaction analysis of DS and RT was performed, participants whose DS was elevated had significant RT benefit over baseline. The authors concluded that DS appeared to be prognostic for risk and for predicting benefit of RT for individuals with DCIS status-post BCS and was able to identify a clinically meaningful low-risk group and an elevated ten-year risk group, whose members may receive significant benefit from RT over baseline. However, further clinical validations are required to provide more evidence on the capabilities, both prognostic and predictive, of the biological signature and DS.

Oncotype Dx DCIS

The Oncotype Dx DCIS assay (Genomic Health, Redwood City, CA) uses reverse transcription polymerase chain reaction (PCR) with DNA extracted from excised tumor tissue to assess expression levels of 12 genes. A Breast DS designed to represent the risk of BC recurrence within ten years of original diagnosis (0 to 100) is then calculated for the individual.

In 2024, Hayes published a Molecular Test Assessment addressing the Oncotype DX Breast DCIS Score (Exact Sciences). The assessment revealed an overall low-quality body of evidence addressing the use of the DCIS score test for individuals recently diagnosed with DCIS to evaluate ten-year recurrence risk and assist with treatment decision-making. Although there is limited evidence suggesting that the DCIS score test may be correlated with reduced RT in those individuals with low DCIS score results, clinical outcomes of DCIS score-based treatment decisions are unknown. No studies that assessed the performance or clinical utility of the current version of the test, and no studies directly comparing the DCIS score test with other clinical tools for predicting recurrence risk and informing treatment were identified.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In 2022, Andre et al. updated ASCO recommendations regarding the appropriate use of biomarker assay results to inform decisions regarding adjuvant endocrine and chemotherapy in early-stage BC. Evidence for these recommendations was based on information from 24 applicable studies (14 RCTs and ten prospective-retrospective). The recommendations include the following:

- Oncotype DX, MammaPrint, BCI, and EndoPredict may be used to guide adjuvant endocrine and chemotherapy in postmenopausal individuals or individuals over the age of 50 years with early-stage ER+, HER2- BC that is node-negative or with one to three positive nodes.
- BCI and ProSigna may be used in postmenopausal individuals with node-negative ER+, HER2- BC.
- For premenopausal individuals, Oncotype DX may be used with node-negative ER+, HER2- BC.
- BCI may be offered to individuals with zero to three positive nodes who have undergone five years of ET with no evidence of recurrence to aid with decision-making regarding EET.
- No assays are recommended for individuals with HER2+ or triple-negative BC.

Evidence from ASCO's review indicates that premenopausal women with one to three positive nodes will show benefit from chemotherapy regardless of genomic assay results. No data supporting the use of genomic tests for informing adjuvant chemotherapy in in individuals with four or more positive nodes was identified. When access to genomic tests is not available, Ki67 in combinations with other parameters or an IHC4 score may be used to assist with decision-making regarding adjuvant therapy. ASCO further recommends the incorporation of factors such as disease stage, comorbidities, and patient preference into decision-making.

In 2020, Hassett et al. published recommendations for managing male BC. These recommendations were the result of a review of 26 reports/observational studies by an ASCO Expert Panel which formed the base of evidence on which the recommendations were developed. The panel found that several of the management methods used for men with BC are predominantly the same as those used for women and include the following recommendations regarding molecular testing:

- Gene expression profiling should be used to guide adjuvant treatment decision-making.
- Targeted therapy guided by HER2, programmed death ligand 1 (PD-L1), PIK3CA and germline BRCA mutation status may be used for treatment of metastatic/advanced male BC with the same indications and combinations that are routinely offered to women.

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- Males with BC should be offered genetic counseling and testing for germline mutations.

European Society for Medical Oncology (ESMO)

In the 2024 ESMO Clinical Practice Guideline addressing diagnosis, treatment and follow up of early BC, Loibl et al. made the following recommendations regarding the use of GEP:

- When uncertainty about indications for adjuvant chemotherapy exist after consideration of all clinical and pathological factor, GEP and endocrine response assessment in the preoperative setting can be used (Level of Evidence II, Grade of Recommendation B).
- Treatment strategy for each individual should be based on their own risk-benefit analysis, considering many factors including tumor burden and biology (including biomarkers and gene expression), as well as age, menopausal status, general health, and individual preference (Level of Evidence I, Grade of Recommendation A).

(Level of evidence and grades of recommendation adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)

National Comprehensive Cancer Network (NCCN) Clinical Guidelines

NCCN BC guidelines indicate that "gene expression assays provide prognostic and therapy-predictive information that complements tumor (T), node (N), distant metastasis (M) and biomarker information. Use of these assays is not required for staging." The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel since it has been clinically validated for the prognosis and prediction of chemotherapy benefit. While other GEAs can provide prognostic information, they do not necessarily predict chemotherapy benefit. NCCN notes that the BCI test is predictive of benefit of extended adjuvant endocrine therapy (NCCN Breast Cancer, v6.2024).

NCCN categorizes the primary GEAs for consideration of adjuvant systemic therapy in individuals with invasive BC as follows:

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene Oncotype DX for pN0	Yes	Yes	Preferred	1
21-gene Oncotype DX for pN1 (1–3 positive nodes)	Yes	Yes	Postmenopausal: Preferred	1
21-gene Oncotype DX for pN1 (1–3 positive nodes)	Yes	Yes	Premenopausal: Other	2A
70-gene MammaPrint for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1
50-gene Prosigna for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
12-gene EndoPredict for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Predictive of benefit of ext. adjuvant endocrine therapy	Yes	Other	2A

National Institute for Health and Care Excellence (NICE)

The 2024 NICE guideline addressing tumor profiling tests for informing adjuvant chemotherapy decisions in early BC makes the following recommendations regarding gene expression tests:

- EndoPredict, Oncotype DX, or Prosigna may be used as options along with consideration of clinical risk factors to guide adjuvant chemotherapy decisions for the treatment of ER- or PR- positive, HER2-negative early BC with one to three positive lymph nodes for women who have been through the menopause, men and/or trans, non-binary or intersex people, depending on their hormonal profile. Clinical judgement should be used to determine is testing is appropriate for men, trans or non-binary or intersex individuals

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- EndoPredict, Oncotype DX, or Prosigna should not be used to guide adjuvant chemotherapy decisions for ER- or PR-positive, HER2-negative early BC with one to three positive lymph nodes in women who have not been through menopause
- MammaPrint should not be used to guide adjuvant chemotherapy decisions for individuals with ER- or PR-positive, HER2-negative early BC with one to three positive lymph nodes
- EndoPredict, Oncotype DX or Prosigna can be used in the National Health Services (NHS) to guide adjuvant chemotherapy decisions for individuals with ER- or PR-positive, HER2-negative, and LN-negative (including micro metastatic disease) EBC while more evidence is generated if:
  - Individual has an intermediate risk of DR per use of a validated tool such as Predict or the Nottingham Prognostic Index
  - Clinicians and companies make timely, complete, and linkable record-level test data available to the National Cancer Registration and Analysis Service
- MammaPrint and IHC4+C should not be used to guide adjuvant chemotherapy decisions for people with ER- or PR-positive, HER2-negative, and LN-negative EBC
- EndoPredict, Oncotype DX or Prosigna may be used to guide adjuvant chemotherapy decisions for ER- or PR-positive, HER2 negative early BC if:
  - The individual undergoing testing will use the results to help in the decision, along with their healthcare professional, whether or not to have adjuvant chemotherapy
  - The tests are used within their intended purpose:
    - EndoPredict (ER-positive, or both ER- and PR-positive)
    - Oncotype DX (ER- or PR-positive, or both)
    - Prosigna (ER- or PR-positive, or both; only for women who have been through the menopause)
  - The companies provide the tests to the NHS with the discounts agreed in the access proposal
  - Laboratories that process the tests take part in a UK national external quality assurance scheme
- The test and results should be used alongside NICE's guideline on shared decision making. An oncologist should explain to the individual what their tumor profiling test results mean, and the risks and benefits of treatment options based on all available risk factors

Lung Cancer

A 2023 (updated 2024) Hayes Molecular Test Assessment evaluated the Percepta Genomic Sequencing Classifier (GSC)(Veracyte). One poor-quality study assessing clinical validity reported high negative predictive values for downclassifying risk of malignancy (ROM) in individuals at low- and intermediate-risk, mixed positive predictive values for upclassifying ROM in individuals at intermediate- and high-risk, and unknown clinical performance for individuals with unchanged ROM after Percepta GSC testing. With regard to clinical utility, one poor quality study reported statistically insignificant reductions in invasive procedure plans for individuals whose ROMs were downclassified (74% reduction) and unchanged (50% reduction). This low quality body of evidence is insufficient to fully assess the clinical benefits of the Percepta GSC. The 2024 update to this Hayes assessment revealed no newly published studies that met inclusion criteria for evaluation of this test.

Liquid biopsy analysis using circulating tumor DNA (ctDNA) or cell-free DNA (cfDNA) is a developing technology that can be used as an alternative to tissue profiling in non-small cell lung cancer (NSCLC). In a systematic review and meta-analysis, Zaman et al. (2023) sought to assess the prognostic value of molecular profiling via ctDNA or cfDNA in NSCLC. Twenty-seven studies including 3419 individuals were included in the analysis. Eleven studies including 1359 participants reported on the association of baseline ctDNA with progression-free survival (PFS) and 16 studies including 1659 participants reported on dynamic changes in ctDNA associated with PFS. The analysis revealed that individuals with negative baseline ctDNA trended towards improved PFS (pooled hazard ratio [pHR] = 1.35; 95%CI: 0.83-1.87; $p < 0.001$; $I^2 = 96\%$) when compared to individuals who were ctDNA-positive. In addition, when early reduction/clearance of ctDNA levels occurred after treatment, individuals showed improved PFS (pHR = 0.71; 95%CI: 1.85-3.65; $I^2 = 89.4\%$) in comparison with individuals showing no reduction/persistence in ctDNA levels. Only good and fair quality studies (based on assessment via the Newcastle-Ottowa Scale [NOS]) exhibited improvement in PFS (pHR = 1.95; 95%CI: 1.52-2.38 and pHR = 1.99; 95%CI: 1.09-2.89, respectively); this did not occur in poor quality studies included in the analysis. The authors note that this review and analysis revealed a high level of heterogeneity and publication bias, but despite these limitations, baseline negative ctDNA levels and an early reduction in ctDNA after therapy may be robust prognostic indicators for PFS and OS in individuals who undergo targeted therapies for advanced NSCLC. The authors recommend additional studies including serial ctDNA testing to further support clinical utility in the management of advanced NSCLC.

Sakata et al. (2022) conducted a multi-center retrospective study to evaluate the success rate of genetic alteration testing in four driver genes (epidermal growth factor [*EGFR*], anaplastic lymphoma kinase [*ALK*], c-ros oncogene 1 [*ROS*1], and

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v-raf murine sarcoma viral oncogene homolog B1 [*BRAF*] using the Oncomine Dx Target Test Multi-CDx System in individuals with NSCLC. A total of 533 participants with NSCLC whose diagnoses were confirmed using histological or cytological methods, and who had undergone testing for 46 genes using the Oncomine Dx Target Test Multi-CDx System between June 2019 and January 2020 were enrolled in the study. The median age was 72 years (range 25-94 years) and 345 participants (64.7%) were male. The percentages of participants with adenocarcinoma detected histologically or those with stage IV disease were 73.2% and 46.0%, respectively. PD-L1 status was evaluated in 497 participants; among these, 133 (25.0%) showed more than 50% PD-L1 expression. Evaluation of participant smoking history showed that 138 (25.9%) had never smoked, whereas 394 participants (74.1%) had a history of smoking. The success rate of genetic alteration testing for all four genes was 80.1% (95% CI 76.5%-83.4%). Surgical resection was associated with the highest success rate (88.0%), which was significantly higher than that for bronchoscopic biopsy (76.8%, p = .005). Multivariate analysis revealed a difference for surgical resection alone (p = .006, 95% CI 1.36-6.18, odds ratio 2.90). The authors concluded that optimizing specimen quantity and quality may improve the use of driver gene testing in clinical settings. Limitations include the absence of data on the exact number of submitted slides and the amount of DNA or RNA input in the submitted samples for Oncomine Dx Target Test Multi-CDx System testing. In addition, the study is limited by its retrospective observations conducted immediately after approval of the Oncomine Dx Target Test Multi-CDx System. Subsequently, several modifications were made for conducting next-generation sequencing (NGS) tests, including those using the Oncomine Dx Target Test Multi-CDx System at each hospital.

A comparison study by Yao et al. (2021) was performed to develop a quick gene testing procedure using fresh core needle biopsy samples from individuals with NSCLC. Thirty participants with NSCLC confirmed by frozen section examination were enrolled to compare the results of multi-gene mutation testing using fresh frozen (FF) tissues and paired formalin-fixed paraffin-embedded (FFPE) tissues. A total of 77 fresh NSCLC tissue samples obtained from core needle biopsy were evaluated by frozen section examination. The 77 participants consisted of 39 males (50.6%) and 38 females (49.4%) with a median age of 65 years (range, 42–85 years) of which 32 were smokers (41.6%) vs 45 nonsmokers (58.4%). Frozen section examination revealed 70 (90.9%) AC, 6 (7.8%) SCC, and 1 (1.3%) adenosquamous carcinoma (ASC), which is consistent with the final pathological diagnosis using FFPE tissues. If the NSCLC diagnosis and adequate tumor cell counts were confirmed by histopathology, the fresh tissues were used to extract DNA and subsequent gene testing by ARMS-PCR. The paired FFPE core needle biopsy samples were from 30 individuals with NSCLC in stage IV, randomly selected for this study, who also underwent gene testing. The 77 fresh samples showed an EGFR mutation rate of 61.0%. The clinical treatment strategy for participants was optimized based on gene test results. Using this procedure of gene mutation testing, the time interval between physicians requesting and obtaining a test result has been shortened to fewer than 2 days. Following a comparison of gene testing results with fresh tissues and paired FFPE tissues from the 30 participants, no difference in the DNA concentration extracted from fresh tissues and FFPE tissues was found. DNA purity, however, was higher in fresh tissues than that in FFPE tissues. Gene testing detected the same gene mutations in 93.3% of cases in fresh tissues and paired FFPE tissues. The authors concluded that gene testing procedure using fresh biopsy samples greatly shortens waiting time. The multi-gene mutation testing using fresh core needle biopsy samples from individuals with NSCLC is a reasonable, achievable, and quick approach. The authors stated that fresh tissues may serve as a potential alternative to FFPE tissues for gene testing in individuals with NSCLC. Limitations to this study include a risk of misdiagnosis during frozen section examination and uncertain diagnosis of fresh tissues related to lack of pathologist experience. Additionally, the sensitivity and specificity of gene testing using FF tissues are 96 and 75% when compared with FFPE tissues. The high sensitivity and low specificity may be attributed to the selection of cases through frozen section examination. The sample size is too small to prove the usefulness of this test as a diagnostic tool. Further research with randomized controlled trials is needed to validate these findings.

Wang et al. (2020) conducted a cohort study using a multiplexed PCR-based panel developed to simultaneously test 118 hotspot mutations and fusions in nine driver genes capable of comprehensively determining individual genotypes as tumor predictive biomarkers. Surgically resected samples from 214 participants with NSCLC (168 with adenocarcinomas and 46 with squamous cell cancers) were included in this cohort study. A multiplexed PCR-based assay was developed to simultaneously test 118 hotspot mutations and fusions in nine driver genes. The sensitivity of the kit was 1% for gene mutation and 450 copies for gene fusion. Genetic alterations were detected in 143 (66.8%) participants by the assay. The three most common alterations identified were *EGFR* mutations (50.9%), *KRAS* mutations (8.4%) and *ALK* fusions (4.7%). Eight (3.7%) participants harbored concurrent mutations, and the most common partners were *EGFR* mutations which were observed in the eight participants. No associations between survival and *EGFR, KRAS*, and *ALK* status were observed. Participants with two or more alterations exhibited shorter DFS compared to those with single mutations (p = 0.032), whilst had no difference in overall survival (OS) (p = 0.245). However, only TNM stage was an independent predictor of OS (HR = 2.905, p < 0.001) as well as DFS (HR = 2.114, p < 0.001) in this cohort in multivariate analysis. Participants with the *L858R* mutation had longer DFS (p = 0.014) compared to other sensitizing mutations and tended to have better OS (p = 0.06). The authors concluded that the mutational profile of oncogenic driver genes plays an important role in NSCLC as several core oncogenic driver genes have been considered to be tumor predictive biomarkers.

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Furthermore, the authors stated that this study suggested a multiplex gene panel testing technique may be used to detect nine driver genes in a limited number of specimens. In addition, this methodology would have the potential to save both specimens and time compared to the combination of all assays by other methods. A small sample size which may have reduced statistical power makes it difficult to decide whether these conclusions can be generalized to a larger population. The findings of this study need to be validated by well-designed studies.

Drilon et al. (2015) identified 31 individuals with lung adenocarcinoma along 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 (Foundation One) 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 targeted therapeutic based on the National Comprehensive Cancer Network (NCCN) guidelines for non–small cell lung cancer (NSCLC) was found in 26% (n = 8 of 31) of participants . The drivers identified in tumors from these eight participants were *EGFR G719A, BRAF V600E, SOCS5-ALK, HIP1-ALK, CD74-ROS1, KIF5B-RET* (n = 2), and *CCDC6-RET*. Six of the participants 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 such as lower sensitivity, complex rearrangements undetectable by standard fluorescence in situ hybridization (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. (Oxnard et al., 2016, Riediger et al., 2016).

Clinical Practice Guidelines

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 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).

American Society of Clinical Oncology (ASCO)

ASCO endorsed the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update with minor modifications (Kalemkerian et al., 2018). The guidelines, supported by ASCO, include the following relevant points, considered to be expert consensus opinion.

- Physicians may use molecular biomarker testing in tumors with:
  - An adenocarcinoma component
  - Nonsquamous, non–small-cell histology
  - Any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver (e.g., young age [< 50 years]; light or absent tobacco exposure)
- *BRAF* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics. *RET*, or *KRAS*, or *MET* molecular testing are not recommended as single gene routine stand-alone assays outside the context of a clinical trial. It is appropriate to include these as part of larger testing panels performed either initially or when routine *EGFR, ALK, BRAF*, and *ROS1* testing is negative
- Multiplexed genetic sequencing panels are preferred where available over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK, BRAF*, and *ROS1*
- Circulating tumor cell free DNA testing, also called a liquid biopsy, should not be routinely considered due to lack of evidence of efficacy. However, the expert consensus opinion provided is that cfDNA may be used in some clinical settings in which tissue is limited and/or insufficient for molecular testing to identify *EGFR* mutations

College of American Pathologists/Association for Molecular Pathology/International Association for the Study of Lung Cancer/Pulmonary Pathology Society/LUNGevity Foundation

In 2024, the College of American Pathologists convened a panel of experts in non-small cell lung cancer and biomarker testing to develop evidence based guidelines on the testing of program death ligand-1 (PD-L1) and tumor mutation burden (TMB) in patients with advanced non-small cell lung cancer (Sholl et al.):

- In patients with advanced non–small cell lung cancer, pathologists should use a validated PD-L1 immunohistochemistry expression assay, in conjunction with other targetable genomic biomarker assays where appropriate, to optimize selection for treatment with immune checkpoint inhibitors. (Strength of Recommendation: Strong; Certainty of Evidence: Moderate)

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- Clinicians should not use TMB alone to select patients with advanced NSCLC for immune checkpoint inhibitors, based on insufficient evidence in this population. (Strength of Recommendation: Conditional; Certainty of Evidence: Very Low)

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for NSCLC (version 1.2025) indicate that numerous gene alterations impacting treatment selection have been identified. Thus, testing for these alterations is necessary to identify the most effective targeted therapies and avoid treatment unlikely to provide clinical benefit. NCCN recommends that when feasible, testing be performed via a broad, panel-based approach, most often using NGS, acknowledging that many of the marketed NGS-based assays used to fully genotype NSCLC are larger than 50 genes. Use of these larger panels may be practical to achieve full genotyping information. In addition, the guidelines include a discussion of the role of plasma cell-free/circulating tumor DNA testing, stating that cell-free/circulating tumor DNA testing should not be used in lieu of a tissue diagnosis and is generally not recommended in settings other than advanced/metastatic disease. However, NCCN also suggests that the use of cell-free/circulating tumor DNA testing (using clinically validated tests) can be used in certain clinical circumstances, including the following:

- The patient is medically unfit for invasive tissue sampling
- There is insufficient tumor tissue available for molecular analysis; however cell-free/circulating tumor DNA should be followed by tissue based analysis when an oncogenic driver is not identified

In addition, peripheral blood testing (most commonly using plasma-based testing of ctDNA) can be performed in conjunction with tissue-based testing in order to accomplish the necessary genotyping for recommended biomarkers. Concurrent testing can improve turnaround time for results and should be considered in appropriate clinical circumstances.

Prostate Cancer

Genomic Prostate Score Assay (GPS) (Formerly Oncotype DX Genomic Prostate Score), Decipher, Prolaris, and Promark

In a 2024 meta-analysis, Cui et al. (included in the 2024 Hayes Genomic Prostate Score (Mdxhealth Inc.) for Lower-Risk Localized Prostate Cancers Molecular Test Assessment) evaluated the prognostic value of the 17-gene Genomic Prostate Score (GPS) test in 1962 individuals with clinically localized prostate cancer (PCa). Eight articles based on seven cohort studies were included and all were deemed high quality by the reviewers. Follow-up periods ranged from 20 months to 15.5 years. Five studies reported on the association between GPS scores and distant metastases; the pooled hazard ratio (HR) of distant metastases was 5.22 for the high GPS group versus the low GPS group, with no evidence of significant heterogeneity among the studies. Further analysis of these five studies revealed that each 20 unit increase in GPS was significantly associated with distant metastases (HR 2.99; 95% CI 1.97–4.53). Six studies reported on the relationship between GPS and biochemical recurrence (BCR). The pooled HR of BCR was 4.41 (95% CI 2.29–8.49) for the high GPS group versus the low GPS group, with significant heterogeneity between studies (I^2 = 78.4%, p = 0.010). In this analysis, a 20 unit increase in GPS had a significant association with BCR (HR2.18; 95% CI 1.64–2.89). Subgroup analysis showed improved prognostic value per 10 point GPS increase for studies that reported greater than 5 years of follow up. Four studies reported results on the relationship between GPS and PCa-specific mortality (PCSM); these showed a pooled HR of 3.81 (95% CI 1.74–8.33) for the high GPS versus the low GPS group, with no evidence of significant heterogeneity between studies. For this analysis, there was, again, a significant association between a 20 unit increase in GPS and PCSM (HR 3.14; 95% CI 1.86–5.30). Based on these results, the researchers assert that higher GPS predicts distant metastases, BCR and PCSM in individuals with clinically localized PCa. They suggest that use of the GPS test may improve accuracy of risk stratification and assist with clinical decision-making in affected individuals and encourage further large-scale prospective studies. Studies by Janes et al. (2023), Helfland et al. (2022), Brooks et al. (2021), and Kornberg et al. (2019), previously discussed in this policy, were included in this meta-analysis.

Morgan et al. (2024) published results from a prospective, randomized, controlled cluster-crossover trial (G-MINOR) which evaluated the impact of Decipher genomic classifier (GC) results on adjuvant treatment after radical prostatectomy (RP) as compared to usual care. The study enrolled 175 participants who underwent testing with GC and 163 participants who received usual care (UC). Eligible enrollees had undergone RP within nine months of study enrollment, had pT3-4 disease and/or positive surgical margins, and had PSA levels of < 0.1 ng/mL. On average, participants in the GC arm received adjuvant treatment 9.7% of the time compared with 8.7% of the time for participants in the UC arm at 18 months after RP (0.99% mean difference, 95% CI -7.6%, 9.6%, p = 0.8). Higher GC scores were associated with an increased likelihood of adjuvant treatment, but it was not statistically significant (odds ratio [OR] = 1.35 per 0.1 increase in GC score, 95% CI 0.98–1.85, p = 0.066). Using GC risk groups, a high GC risk was associated with significantly greater odds of receiving adjuvant treatment when compared with a low GC score (OR = 6.9, 95% CI 1.8, 26, p = 0.005, adjusted for Cancer of the

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Prostate Risk Assessment [CAPRA] Postsurgical score). Other symptoms, such as patient-reported urinary and sexual function did not differ between the two groups. The authors concluded that GC testing impacted adjuvant therapy administration when considered with risk categories in the participants' reports, but the study results did not provide sufficient evidence to conclusively support GC testing in the adjuvant treatment setting. In addition, long-term results were not measured in this data set as oncologic outcomes were immature. The researchers indicate that long-term follow up from this and other studies will address remaining uncertainties regarding whether genomic testing provides meaningful benefit and improved outcomes in individuals with PCa.

In an effort to measure the associations between Decipher GC testing results and risk of metastasis and BCR after prostate biopsy and RP in a real-world setting, Leapman et al. (2024) performed a retrospective cohort study using a newly developed linkage of transcriptomic data from Decipher GC and clinical data obtained from insurance claims, pharmacy data, and electronic health records across various payors and sites of care. A total of 58,935 subjects who had undergone Decipher GC testing were included; 33,379 individual samples were from biopsies and 25,556 samples were from RP. Median GC score was 0.43 in the group whose tests were biopsy-based and 0.54 in the group whose tests were RP-based. The researchers found that the Decipher GC was independently associated with risk of metastasis in both the biopsy group and the RP group after adjusting for baseline clinical and pathologic risk factors. Decipher GC was also associated with risk of BCR in the RP group in models that were adjusted for age and CAPRA scores. Based on these findings, the authors concluded that their results support the prognostic validity of the Decipher GC across varying clinical populations and settings. Noted limitations include the retrospective study design and use of real-world data as well as the lack of control and comparator groups and limited follow-up time periods. There was also potential for bias, as several study authors had affiliations with the GC test manufacturer.

In a 2024 Molecular Test Assessment, Hayes evaluated the clinical validity and utility of the Genomic Prostate Score (GPS) test for guiding treatment choice between active surveillance or more aggressive treatments in individuals with untreated, lower risk localized PCa. Hayes concluded that the overall body of evidence is very low-quality and insufficient to draw conclusions regarding use of the GPS assay for assisting with treatment decisions in these individuals. Overall, the evidence suggests that the GPS assay may be a useful tool for informing management decisions, but evidence for its accuracy in lower-risk populations is limited, and it is not clear whether GPS-influenced management decisions resulted in more favorable outcomes for these individuals. Limited evidence suggests that GPS assay can predict adverse pathology at radical prostatectomy and can help direct decisions in terms of treatment intensity and active surveillance. Evidence comparing GPS to other risk stratification tools is also limited; the additive use of GPS may improve upon the CAPRA risk stratification tool, but not NCCN risk group stratification, for predicting adverse pathology. Finally, evidence focused on whether GPS testing generally leads to increased or decreased treatment intensity and whether any treatment decisions based on GPS testing are appropriate and beneficial for the patient is conflicting (Hayes, Genomic Prostate Score (Mdxhealth Inc.) for Lower-Risk Localized Prostate Cancers).

In another 2024 Molecular Test Assessment, Hayes evaluated the clinical validity and utility of the GPS for informing treatment intensity in individuals with untreated, localized PCa meeting NCCN unfavorable intermediate-risk or high-risk criteria. Hayes identified an overall low quality body of evidence which provided insufficient data upon which to draw conclusions for this population. While some evidence suggests that the GPS assay may predict risk of PCa recurrence, metastasis, and death in individuals with higher risk localized disease and potentially inform treatment decisions, the overall body of evidence is small with limited comparisons to other risk prediction models. No studies evaluated the impact of the testing on health outcomes of affected individuals (Hayes, Genomic Prostate Score (Mdxhealth Inc.) for Higher-Risk Prostate Cancers).

Boyer et al. (2024) conducted a systematic review to evaluate the prognostic capability of three GCs; Decipher, GPS, and Prolaris, for biochemical recurrence, development of metastases, and PCa-specific mortality in individuals with localized PCa. All subjects had been treated with definitive surgery and/or radiation. The prognostic ability of the three GCs for clinical outcomes was compared to standard clinical risk stratification models. Thirty-nine studies comprising over 10,000 individuals were included. The results of the review revealed that each of the three GCs showed a slightly improved prognostic ability for biochemical recurrence, development of metastatic disease, and PCa-specific mortality in comparison with commonly used risk-classification methods. However, the certainty of evidence was low to very low; this was predominantly due to bias related to the retrospective nature of 37 of the 39 studies, heterogeneity in treatments received, and the time period in which subjects were treated (before the 2000s; detection and management of PCa has advanced significantly since this time). In addition, the risk classification models used as comparators to the GS results were not consistent across the studies reviewed. Nevertheless, the authors concluded that based on the overall results, GCs do provide a small but consistent improvement on the predictive ability of standard risk stratification models, which could influence treatment decisions when there is uncertainty regarding the best option(s) for treatment. They recommend further analysis with more up-to-date data. Of note, multiple studies included in the systematic review were sponsored or

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co-authored by companies with rights to the GC tests. Publications by Brooks et al. (2021), Kornberg et al. (2019), Berlin et al. (2019), Klein et al. (2016), and Glass et al. (2016), previously discussed in this policy, were included in this systematic review.

Hayes addressed the Decipher Prostate Biopsy GC as well as the Decipher Prostate RP GC in separate 2024 Molecular Test Assessments. For the Prostate Biopsy GC, Hayes identified a very low quality body of evidence limiting the ability to draw conclusions regarding the use of this test. The Prostate Biopsy GC uses whole transcriptome analysis to evaluate the expression of 22 genes from biopsy tissue samples and was designed to determine risk of adverse outcomes and/or assist with treatment decision-making in individuals with localized PCa. Although evidence has shown that a higher Decipher score is associated with a greater risk of metastatic disease in individuals with primarily intermediate- to high-risk cancer as classified per NCCN guideline, questions remain about overall test performance and impact to clinical outcomes. Additional research in NCCN lower-risk groups is needed; it is not clear if this testing changes clinical management or clinical outcomes in these groups. There is little evidence for superior performance of the Decipher Biopsy GC when compared to standard non-genomic methods of risk stratification, such as NCCN risk groups. Regarding the Decipher Prostate RP GC, which is used to predict risk of metastasis or PCSM in individuals whose PCa has been treated with radical prostatectomy (RP), Hayes found some low quality evidence supporting the usefulness of this test to assist with decision-making for post-RP adjuvant treatments, but the evidence was insufficient to ascertain whether the testing improves long-term outcomes. Evidence comparing the performance of the Decipher RP to other risk-calculating tools as well as evidence addressing optimal selection of individuals for testing was found to be inadequate, especially for individuals who have undergone RP but had no preoperative high-risk features.

In a 2023 systematic review, Spohn et al. explored the evidence on the use GCs for individuals treated with radiation therapy (RT) and conducted a survey of experts using the Delphi method to address the role of GC use in personalized treatments for the purposes of identifying areas of future clinical research. Initially, a total of 26 studies met inclusion criteria and were sent to a multidisciplinary, international team of experts for review. An updated literature search was performed during the peer-review process time period and an additional 5 studies were identified and sent to the reviewers, for a total of 31. Ongoing clinical trials were also screened and nine studies on GCs use with RT were identified and shared with the expert reviewers as well. There were two rounds of questions; 31 experts completed the first round and 30 completed the second round. When survey results showed ≥ 75% agreement, the question/response was considered relative and included in the qualitative synthesis. The majority of the studies (65%) focused on the Decipher test. The researchers found that the evidence for GCs as predictive biomarkers is primarily focused on the postoperative RT setting, although validation of GCs as prognostic markers in the definitive RT setting is emerging. The experts surveyed used GCs in individuals with extensively metastatic PCa (30%), in the postoperative setting (27%), and in newly diagnosed PCa (23%). Of the experts surveyed, 47% do not use GCs in their clinical practice, although the consensus of the experts was that GCs are indeed promising tools for risk-stratification in individuals with primary and oligo-/metastatic PCa in addition to existing classifications. The experts also felt that GCs have potential for use in guiding treatment decisions for RT-field definition and intensification/deintensification over various stages of disease. The study authors postulate that the outcome of this study confirms 1) the value of GCs and 2) the promising evidence that is emerging regarding the utility of GC with respect to RT. The authors recommend ongoing study of GCs as prognostic biomarkers and the predictive ability of GCs for optimization of RT and/or systemic therapy and await the results of prospective clinical trials focused on the role of GCs in the setting of RT which may help to validate the role of GCs for guiding personalized cancer treatment. Publications by Janes et al. (2023), Marascio et al. (2020), and Berlin et al. (2019), previously discussed in this policy, were included in the Spohn et al. systematic review.

Participants enrolled in NRG Oncology/RTOG 01-26, a randomized phase three trial, comprised the population of an analysis by Spratt et al. (2023, included in the Hayes Decipher Prostate Biopsy Genomic Classifier Molecular Test Assessment above) investigating the performance of the 22-gene Decipher GC in individuals with intermediate-risk PCa. This study is the first validation of a biopsy-based gene expression classifier (GEC) that evaluates both prognostic and predictive value using data from a randomized, phase three clinical trial of individuals with intermediate risk PCa. The NRG Oncology/RTOG 01-26 trial randomized these individuals to 70.2 Gy versus 79.2 Gy of radiation therapy with no androgen deprivation therapy. With NCI approval, biopsy slides from NRG Oncology/RTOG 01-26 were obtained and RNA was extracted from the highest-grade tumor foci to generate a locked 22-gene GC model. A total of 215 individual samples met quality control standards and were analyzed. The median follow up time was 12.8 years. The primary outcome for this ancillary study was progression of disease, using a composite of biochemical failure, local failure, distant metastases, PCa-specific mortality, and use of salvage therapy. Using multivariable analysis, the 22-gene GC was independently prognostic for disease progression (subdistribution hazard ratio [sHR], 1.12; 95% confidence interval [CI], 1.00-1.26; p = .04), biochemical failure (sHR, 1.22; 95% CI, 1.10-1.37; p < .001), distant metastasis (sHR, 1.28; 95% CI, 1.06-1.55; p = .01), and PCa-specific mortality (sHR, 1.45; 95% CI, 1.20-1.76; p <. 001). In participants with GC low-risk results, ten-year distant metastasis was 4% compared with 16% in GC high-risk results. The authors contend that the 22-

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gene Decipher GC improves risk stratification and can help inform treatment decisions in individuals with intermediate-risk disease. A limitation of this study was the limited availability of sufficient quality tissue samples which impacted the power of the study and prohibited well-powered subset analyses.

To further evaluate the association between the Oncotype DX Genomic Prostate Score (GPS) and final pathology (including extraprostatic extension [EPE], positive surgical margin [PSM] and seminal vesicle invasion [SVI]), a retrospective analysis of 749 individuals who had undergone Oncotype DX testing was performed by Covas Moschovas et al. (2022, included in Hayes 2024 Molecular Test Assessment for GPS for Lower-Risk Localized Prostate Cancers). After testing, the participants had robotic RP performed by the same surgeon. In odds ratio assessment with multivariable analyses per 20 point GPS change, GPS was an independent predictor of EPE (OR 1.8, 95% CI 1.4-2.3) and SVI (OR 2.1, 95% CI 1.3-3.4). Furthermore, percentage of cases with EPE and SVI increased with GPS quartile when they were grouped by quartile. Based on these results, the authors assert that the Oncotype DX GPS is significantly associated with adverse pathology after RP, noting that the risk of EPE and SVI will increase with the GPS, and contend that the use of Oncotype DX GPS may help providers improve preoperative counseling and implement surgical plans for individuals with greater risk of EPE or other negative pathology.

In a 2021 systematic review, Jairath et al. evaluated the available evidence supporting clinical utility of the Decipher genomic classifier (GC.) A total of 144 studies were identified and of those, 42 studies including 30,407 individuals met inclusion criteria for this review with GC performance data available for localized, post-prostatectomy, nonmetastatic castration-resistant and metastatic hormone-sensitive PCa. Participants were part of retrospective studies (n = 12,141), prospective registries (17,053) and prospective and post hoc randomized trial analyses (n = 1213). On multivariate analysis, 32 studies showed that GC was independently prognostic for study endpoints including biochemical failure, metastasis, adverse pathology, and both cancer-specific and overall survival. In 24 studies, GC improve discrimination over standard of care and in five studies, GC changed clinical management in the settings of active surveillance and post-prostatectomy. The strength of the evidence was found to be levels 1 and 2 as per Simon criteria for all disease states except high-risk PCa and was found to be grade A and B by American Urological Association (AUA) criteria, depending on state of disease. Based on this review, the authors assert that consistent data has emerged from diverse levels of evidence and when evaluated overall, clinical utility of the Decipher GC has been demonstrated. Utility is strongest for intermediate-risk PCa and postprostatectomy use in clinical decision-making. Publications by Marascio et al. (2020), Berlin et al. (2019), Kim et al. (2019), Klein et al. (2016), Glass et al. (2016), and Marrone et al. (2015), previously discussed in this policy, were included in this systematic review.

Feng et al. (included in the Hayes 2024 Decipher Prostate RP Genomic Classifier Molecular Test Assessment, the 2023 Spohn et al. systematic review, and the 2024 Boyer et al. systematic review, all above) performed an ancillary study to validate the Decipher GC in men who received salvage radiation for elevated prostate-specific antigen (PSA) after surgery in the context of a phase three randomized trial (2021). They used specimens from the placebo-controlled, phase three NRG/RTOG 9601 clinical trial and extracted RNA from the highest-grade tumor tissue available in 2019 (NRG/RTOG 9601 was conducted 1998-2003). Median follow up time was 13 years. GC scores were assigned (0-1) to whole transcriptomes and the predictive ability of GC for distant metastasis was evaluated. Additional outcomes including PCa-specific mortality (PCSM) and overall survival (OS) were also measured. The authors analyzed GC scores from 352 randomized participants who met quality-controlled inclusion criteria. The GC was found to have an association with distant metastasis (hazard ratio [HR], 1.17; 95% CI, 1.05-1.32; p = .006), PCSM (HR, 1.39; 95% CI, 1.20-1.63; p < .001) and OS (HR, 1.17; 95% CI, 1.06-1.29; p = .002) after adjusting for Gleason score, T stage, margin status, age, race/ethnicity, entry PSA and treatment arm, suggesting that not all men with biochemically recurrent cancer after surgical intervention will benefit equally from addition of hormone therapy to salvage radiotherapy. The researchers propose that the Decipher GC may hold promise for risk stratification and treatment decisions involving hormone therapy for PCa recurrence after surgery. Noted study challenges include the limited availability of samples from NRG/RTOG 9601 and ability of available samples to meet quality control requirements (22.4% of total trial samples did not pass quality control), as the median age of tissue samples was older than 20 years.

Decipher Biopsy testing was used in a multi-institutional study of 855 men newly diagnosed with PCa between February 2015 and October 2019. Vince et al. (2021, included in the Hayes 2024 Molecular Test Assessment for the Decipher Prostate Biopsy Genomic Classifier [Veracyte Inc.], and the Boyer et al. 2024 systematic review) sought to assess the clinical utility of this test in individuals with localized PCa. Participants were tracked through the prospective Michigan Urological Surgery Improvement Collaborative and were linked to the Decipher Genomics Resource Information Database. An independent third party performed patient matching using two or more unique identifiers. Of the 855 men in the study, 264 participated in active surveillance and 454 went on to radical therapy. In the men that elected active surveillance, after adjustment for NCCN risk group, PSA, prostate volume, body mass index, percent positive cores and age, a high risk Decipher score was independently associated with shorter time to treatment. This was true for participants

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who underwent radical therapy as well; high risk Decipher score was independently associated with a shorter time to failure of treatment. The authors concluded that in this prospective statewide registry, there was a strong association with a high-risk Decipher Biopsy score and conversion from active surveillance to definitive treatment and treatment failure. The authors mention a phase three randomized trial NCT04396808 which is estimated to conclude in 2025, and which will, in their opinion, provide level one evidence of the clinical impact of Decipher biopsy testing.

In a retrospective, observational study, Morris et al. (2021) compared the predictive ability and clinical utility of the cell cycle progression (CCP) GEP test (Prolaris), multiparametric magnetic resonance imaging (mpMRI) with Prostate Imaging Reporting and Data Systems (PI-RADS) scoring and clinical/pathological data in individuals with localized PCa, a CCP score and an mpMRI PI-RADS v2 score. The study was made up of two cohorts; the first included 156 individuals with newly diagnosed PCa (with or without previous negative biopsy) and the second included 66 individuals who had initiated active surveillance without CCP testing, but then received the test during their active surveillance. Each individual was given a combined score using CCP results and UCSF CAPRA score; this was the clinical cell-cycle risk score (CCR). The researchers found small but significant correlations between PI-RADS score and CCP (r_s = 0.22, p = 8.1 x 10-4), CAPRA (r_s = 0.36, p = 4.8 x 10^{-8}), or CCR (r_s = 0.37, p = 2.0 £ 10^{-8}. This may indicate that a large part of the prognostic information identified in the testing performed is independent. PI-RADS score did not prove to be a significant factor for prediction of post-radical prostatectomy Gleason score. However, both CCP and CCR were shown to be significant and independent, in their predictions regarding active surveillance versus curative treatment in cohort 1 per multivariate analysis. CCR at or below the threshold for active surveillance reduced the likelihood of choosing curative treatment over active surveillance, which the authors assert validates the clinical utility of the active surveillance threshold. Overall, the authors state that their results support CCP as a better tool to predict both tumor grade and management of individuals with PCa than PI-RADS. They stress the importance of obtaining molecular information from men with newly diagnosed PCa to assess risk and determine the best clinical management for the individual. Notably, the majority of the authors associated with this study are either employed by or associated with the manufacturer of the test under study. Additional limitations include the retrospective nature of the study, cohort sizes, dependence on quality and accuracy of biopsy and the lack of long-term outcomes.

Eggener et al. (2019, included in the 2024 Hayes Genomic Prostate Score (Mdxhealth Inc.) for Lower-Risk Localized Prostate Cancers Molecular Test Assessment)) performed a multi-center study seeking to validate the 17 gene Oncotype DX Genomic Prostate Score (GPS) gene expression assay when used on biopsy tissue to predict adverse pathology in a group of 1200 prospectively enrolled individuals with very low-, low-, and favorable intermediate-risk PCa. A prespecified sub analysis of GPS from biopsy and its relationship with adverse pathology found on RP was performed on the group of participants who immediately proceeded to RP. A total of 114 individuals underwent RP and of those, 40 had adverse pathology. In this study, GPS results were shown to be a significant predictor of adverse pathology based on results of univariable analysis (odds ratio per 20 GPS units [OR/20 units]: 2.2; 95% CI 1.2-4.1; p = 0.008). Significance persisted after adjustments were made for biopsy Gleason score, clinical T-stage and logPSA (OR/20 units: 1.9; 95% CI 1.0-3.8; p = .04), or NCCN risk group (OR/20 units: 2.0; 95% CI 1.1-3.7; p = .02). The researchers also evaluated the impact of GPS scores on physician and patient attitudes about decision-making related to their management; Decisional Conflict Scores improved significantly (from 27 to 14) after GPS testing was performed. Based on the overall results, the authors concluded that the GPS assay was confirmed to be an independent predictor of adverse pathology at surgery and was also related to a reduction of conflict in terms of decision-making.

In a multicenter, retrospective, observational study, Kaul et al. (2019, included in Hayes, Prolaris Biopsy Test, 2019) aimed to evaluate the selection of active surveillance along with the safety and durability of the clinical cell cycle risk (CCR) score, which is a combination score of clinical data and molecular data (Prolaris). Individuals with low-risk PCa (according to both CCR score (DSM ≤ 3.2%) and NCCN guidelines) who had previously undergone CCP testing during the course of their care were tracked. Initial treatment selection (active surveillance vs treatment) and duration of active surveillance were evaluated. Adverse events measured were biochemical recurrence and metastasis of disease. Of 664 individuals with low-risk disease (per CCR score and NCCN guideline), 82.4% (547) chose active surveillance and 17.6% underwent definitive treatment ≤ six months after diagnosis. The median follow-up period from biopsy was 2.2 years. Only 0.4% of the 547 individuals who chose active surveillance experienced an adverse event and two-thirds of the individuals remained on active surveillance for more than 3 years. Only markers of tumor aggressiveness showed a significant difference between the two groups; individuals who underwent definitive treatment within 6 months of diagnosis had more aggressive pathological features than those who chose active surveillance. The authors determined that based on the collective data from the study, the use of the CCR score in evaluating PCa risk can safely increase selection of active surveillance when compared with the use of only clinical/pathological criteria and potentially allow more individuals to avoid unnecessary treatment of PCa and treatment-related side effects. Limitations included the lack of a control group to assess active surveillance selection and durability in men who did not receive a CCR score, a relatively short median

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follow-up time and cohort of individuals with low-risk PCa only. In addition, several study authors are employed by or have associations with the manufacturer of the test being evaluated in this study, creating the potential for bias.

The Prolaris test for use with biopsy and post-prostatectomy underwent assessment by Hayes in 2019. For the Prolaris Biopsy test, Hayes found insufficient evidence to support the analytical and clinical validity of this test to aid in prediction of PCa specific mortality and metastasis, and studies supporting clinical utility were limited as well (Hayes, Prolaris Biopsy Test [Myriad Genetic Laboratories Inc.], 2019, updated 2022). Regarding the use of Prolaris post-prostatectomy for determination of biochemical recurrence risk within ten years of prostatectomy, Hayes found minimal evidence of analytical validity and preliminary evidence for clinical validity, but no studies that provided evidence for clinical utility of Prolaris for post-prostatectomy use (Hayes, Prolaris Post-Prostatectomy [Myriad Genetic Laboratories Inc.], 2019, updated 2022).

In an effort to evaluate the current utility of GECs related to management of newly diagnosed PCa, Hu et al. (2018, included in Hayes 2024 Decipher Prostate Biopsy Genomic Classifier (Veracyte Inc.) conducted an observational study including individuals diagnosed with localized PCa. Three GECs results (Decipher Prostate Biopsy, Oncotype Dx Prostate and Prolaris), along with data on how the results were used, were collected to determine practice patterns, predictors of the use of GEC and the effect of GEC results on the management of PCa. Using the Michigan Urological Surgery Improvement Collaborative registry, the researchers determined that 18.8% of 3,966 individuals newly diagnosed with PCa underwent testing with a GEC. The rate of use of GEC varied in individual practice settings from 0% to 93% and individuals that that had GEC testing were more likely to have lower prostate specific antigen level, lower Gleason score, lower clinical T stage and fewer positive cores (all $p < .05$). For those individuals with clinically favorable cancer risk, rate of active surveillance was significantly different among individuals with GEC results above the threshold (46.2%), those with a GEC results below the threshold (75.9%) and individuals who did not have GEC testing (57.9%). Based on these results, the authors estimate that for every nine individuals with favorable cancer risk that participate in GEC testing, one additional individual may be managed with active surveillance. Individuals with favorable-risk PCa whose GEC results classified them as low risk were more likely to be managed with active surveillance than those who did not undergo testing, per the results of the multivariable analysis (odds ratio, 1.84; $p = .006$). The researchers concluded that that is currently high levels of variability among practices with regard to the use of GEC testing, but for individuals with clinically favorable risk, GEC can significantly increase the rate of active surveillance. Additional follow up to help determine whether the use of GEC testing should be included in the initial care of individuals with PCa to improve clinical outcomes is encouraged.

In a 2015 retrospective study, Cuzick et al. (included in Hayes, Post-Prostatectomy and Prolaris Biopsy Test, 2019 and the Boyer et al. 2024 systematic review, above) sought to validate a predefined prognostic score from a test using CCP to assist providers in choosing the most appropriate management for individuals with newly diagnosed, localized PCa. Study participants included individuals with localized PCa diagnosed using needle biopsy; all individuals were being managed conservatively. The primary endpoint of the study was death due to PCa. Validation was done using CCP score independently and in a prespecified linear combination with standardly used clinical information (CCR scores). Clinical information included baseline PSA, Gleason score, clinical stage, extent of disease and age, which were then combined into a sole risk assessment score (CAPRA). An independent validation cohort of 585 individuals, all of whom had full data available, made up the study. CCP score hazard ratio was s 2.08 (95% CI [1.76, 2.46], $p < 10\text{-}13$) per one unit change of the score in the independent validation. In the multivariate analysis which included CAPRA, CCP score hazard ratio was 1.76 (95% CI [1.44, 2.14], $p < 10\text{-}6$). In addition, the predefined CCR score was high predictive with a hazard ratio of 2.17 (95% CI [1.83, 2.57], $x2 = 89.0$, $p < 10\text{-}20$), thoroughly encompassing all prognostic information. The authors indicate that the prognostic value of the CCP score from needle biopsies was confirmed by this study; for individuals being managed conservatively, CCP scores were highly prognostic for death from PCa and provided data that was not available based on clinical information alone. They indicate that the CCP score can provide useful information for ascertaining which individuals with PCa can be safely treated with conservative methods and avoid radical treatment. A limitation of this study was that a large number of initial participants were excluded due to quality issues, inadequate tumor available or missing clinical data. In addition, all study participants were symptomatic with worse prognoses than contemporary cohorts of screen-detected cancers. Thus, the study population is not necessarily representative of current populations of individuals with PCa. In addition, for the majority of cases, changes in treatment greater than or equal to six months after diagnosis were not recorded. Lastly, several of the authors are employees of or otherwise associated with the test manufacturer, which could present risk of bias.

Other Prostate Cancer Assays

Although many additional genomic panel tests related to screening and stratifying risk in individuals with PCa are commercially available, the evidence to support the clinical validity and utility of these tests is currently lacking.

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In a Molecular Test Assessment, Hayes found a low-quality body of evidence addressing the clinical benefit of the ExoDx Prostate Test, which is proposed for use in individuals ≥ 50 years of age with PSA levels 2 to 10 ng/mL to aid in decision-making related to initial or repeat prostate biopsy. Although four studies addressing the clinical validity of test were reviewed, the evidence indicates low to acceptable ability to detect clinically significant PCa. No studies were found that compared ExoDx Prostate's clinical performance with other PSA derivatives, MRI, or other commercially available similar tests. Evidence for clinical utility was insufficient (Hayes, ExoDx Prostate Test [Exosome Diagnostics Inc.], 2023, updated 2024).

Another Molecular Test Assessment produced by Hayes (2024) focused on Select mdx. This gene expression test evaluates *HOXC6* and *DLX1*, along with the reference gene *KLK3* via urine sample. This result, combined with clinical risk factors such as age, PSA, digital rectal exam result, and prostate volume, leads to a test outcome indicating either an increased risk or a very low risk of clinically significant PCa upon biopsy. Hayes identified an overall very low-quality body of evidence which was inadequate to reach conclusions regarding the effectiveness of Select mdx testing for the prediction of clinically significant PCa risk and for informing clinical decision-making regarding biopsy. Some evidence suggests that Select mdx could lead to unnecessary biopsies in lower-risk individuals and comparative evidence was inconsistent and insufficient in quantity. Further study is required to clarify test accuracy and substantiate improvement in clinical outcomes though use of this test (Hayes, Select mdx [mdxhealth Inc.], 2024.)

Confirm mdx is an additional molecular test used to assess risk for PCa. This test uses tissue from a negative prostate biopsy to identify genetic biomarkers which can then be used to help determine if an individual may be ruled out for repeat biopsy or if the individual should undergo repeat biopsy or magnetic resonance imaging (MRI). In a Molecular Test Assessment (Confirm mdx [mdxHealth Inc.], 2024), Hayes found insufficient evidence to support use of Confirm mdx for ruling whether repeat biopsy is needed in individuals with prior negative biopsy. Although Confirm mdx appeared to be a significant predictor of PCa on repeat biopsy while other factors were not, no direct comparisons were performed and thus, no conclusions regarding comparative performance can be reached. No identified studies assessed clinical outcomes associated with use of Confirm mdx. Additional studies are required to evaluate whether Confirm mdx results in improved outcomes in individuals with PCa.

Tosoian et al. (2021) sought to validate an optimal threshold for the use of the MyProstateScore test in ruling out grade group ≥ 2 cancer in individuals referred for prostate biopsy. In this study, men who had not yet received prostate biopsy provided urine samples prior to biopsy and a MyProstateScore was generated using a model which leverages serum prostate specific antigen (PSA), urinary PCa antigen 3 and urinary TMPRSS2:ERG. The study enrolled individuals from academic and community settings for an overall population of 1,525 individuals. The researchers found that at a threshold of 10, MyProstateScore had 97% sensitivity and 98% negative predictive value for grade group ≥ 2 cancer. The authors concluded that MyProstateScore provided exceptional sensitivity and negative predictive value for ruling out grade group ≥ 2 in a large and pertinent population of individuals referred for prostate biopsy. Study limitations included the use of systematic biopsy as a reference standard, as biopsy appears to miss approximately 15-20% of cancers, which would include a proportion of grade group ≥ 2 cancers. In addition, not all grade group ≥ 2 cancers will ultimately be clinically significant. The authors encourage additional validation studies with longer term outcomes for this group. Furthermore, there were no individuals with a history of negative biopsy included in this study and the study was performed without use of multiparametric MRI, which is commonly used during diagnosis. Further data is needed to confirm the findings of this study and further assess clinical utility.

A prospective, randomized, blinded two-armed clinical utility study was conducted by Tutrone et al. (2020) to evaluate the impact of the ExoDx Prostate (IntelliScore) test (EPI) on the decision whether to perform a biopsy in a real-world clinical setting. EPI is designed to assess risk for high grade PCa. The study enrolled 1094 participants from 24 urology practices and a total of 72 urologists. All participants underwent EPI testing but were randomized into EPI vs Control. Only the EPI arm received results for the biopsy. In the EPI group (458) of the participants received negative EPI scores. Of these, 63% were recommended to defer biopsy and 74% of those did indeed defer the biopsy. Of those with positive EPI scores, 87% were recommended by urologist to proceed with biopsy and 72% of participants complied with that recommendation. Ultimately, this led to detection of 305 more high grade PCa in comparison with control group and the researchers estimated that 49% fewer high-grade cancers were missed due to deferred biopsy compared to standard of care. Sixty-eight percent of participating urologists indicated that the EPI influenced their decision regarding biopsy recommendation. The authors stated that this was the first report on a PCa biomarker utility study with a blinded control group and felt that the study showed that the EPI test influenced decision making regarding prostate biopsy and patient stratification. Despite these positive outcomes, there were limitations. In the EPI group, there was a 5.7% assay failure, and in the entire group of participants, there was a failure rate of 7.1%. Data is lacking regarding long-term outcomes of the participants who deferred biopsy after using EPI, and the large number of testing sites and urologists involved required the use of streamlined questionnaires, limiting feedback. Lastly, a small number of participants (< 5%) had undergone pre-biopsy

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MRI, which can help refine biopsy accuracy and provide additional information related to EPI test performance. The researchers suggest that future studies could include a larger percentage of individuals with MRI data available.

McKiernan et al. (2018) assessed the performance and utility of ExoDx Prostate IntelliScore (EPI) urine exosome gene expression assay versus SOC parameters for discriminating grades of PCa from benign disease. This study compared EPI results with biopsy outcomes in men with age ≥ 50 yr. and prostate-specific antigen (PSA) 2–10 ng/ml, scheduled for initial prostate biopsy. The results were that in a total of 503 participants with median age of 64 yr., median PSA 5.4 ng/ml, 14% African American, 70% Caucasian, 53% positive biopsy rate (22% GG1, 17% GG2, and 15% ≥ GG3), EPI was superior to SOC with an area under the curve (AUC) 0.70 versus 0.62, respectively, comparable with previously published results (n = 519 participants, EPI AUC 0.71). Using a validated cut-point 15.6 would have avoided 26% of unnecessary prostate biopsies and 20% of total biopsies, with NPV 89% and missing 7% of ≥ GG2 PCa. Setting a different cut-point 20 would avoid 40% of unnecessary biopsies and 31% of total biopsies, with NPV 89% and missing 11% of ≥ GG2 PCa. This study concluded that EPI has been validated in over 1000 individuals across two prospective validation trials for risk stratification of high-grade and low-grade from benign disease. The use of this test may improve identification of individuals with higher grade disease and could reduce unnecessary biopsies, although ten percent of PCa cases would be missed based on the test characteristics.

A study from McKiernan et al. (2016) evaluated the performance of the EPI urine exosome assay. The study compared individuals who received standard of care (SOC) alone to those who received SOC plus this novel exosome assay. SOC was defined as PSA levels, age, race, and family history. EPI urine exosome assay is a noninvasive, urinary three-gene expression assay that is designed to discriminate high-grade (> Gleason Score 7) from low-grade (Gleason Score 6) and benign disease. The researchers compared the urine exosome gene expression assay with biopsy outcomes in 499 participants with PSA levels of 2 to 20 ng/mL. After this first phase, the derived prognostic score was validated in 1064 participants that included PCA-free men, 50 years or older, scheduled for an initial or repeated prostate needle biopsy due to suspicious digital rectal examination (DRE) findings and/or PSA levels (limit range, 2.0-20.0 ng/mL). This study found that in 255 men in the training target population (median age 62 years and median PSA level 5.0 ng/mL, and initial biopsy), the urine exosome gene expression assay plus SOC was associated with enhanced discrimination between GS7 or greater and GS6 and benign disease (AUC 0.77 (95% CI, 0.71-0.83) vs SOC AUC 0.66 (95% CI, 0.58-0.72) ($p < .001$). The validation study found that in 519 participants urine exosome gene expression assay plus SOC AUC 0.73 (95% CI, 0.68-0.77) was superior to SOC AUC 0.63 (95% CI, 0.58-0.68) ($p < .001$). Using a predefined cut point, 138 of 519 (27%) biopsies would have been avoided, missing only 5% of individuals with dominant pattern 4 high-risk GS7 disease. This study concluded that the urine exosome gene expression assay was associated with improved identification of individuals with higher-grade PCa among men with elevated PSA levels and could reduce the total number of unnecessary biopsies.

In a review of tissue-based genomic biomarkers for PCa, Moschini et al. (2016), report that available genomic assays have improved the prognostic ability over clinicopathologic parameters of localized PCa. However, these assays should be prospectively applied, or even retrospectively applied to prospective studies, to 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.

Clinical Practice Guidelines

American Association of Clinical Urologists

In a 2018 position statement endorsed by the Large Urology Group Practice Association (LUGPA), the AACU states that they “support the use of tissue-based molecular testing as a component of risk stratification in PCa treatment decision making. We also support ongoing research to further refine the prognostic power of these tests.”

American Society of Clinical Oncology (ASCO)

Eggener et al. (2020) published the recent ASCO guideline on molecular biomarkers in localized PCa and summarized the evidence as follows:

- “Few biomarkers had rigorous testing involving multiple cohorts and only 5 of these tests are commercially available currently: Oncotype Dx Prostate, Prolaris, Decipher, Decipher PORTOS, and ProMark. With various degrees of value and validation, multiple biomarkers have been shown to refine risk stratification and can be considered for select men to improve management decisions. There is a paucity of prospective studies assessing short- and long-term outcomes of patients when these markers are integrated into clinical decision making.”

ASCO made four specific recommendations:

- Commercially available molecular biomarker tests (i.e., Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to

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affect management. Routine ordering of molecular biomarkers is not recommended. (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)
- Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered. (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)
- Consideration of a commercially available molecular biomarker test (e.g., Decipher Genomic Classifier) is recommended in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered. (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)
- In men with newly diagnosed PCa eligible for active surveillance, both magnetic resonance imaging and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another. (Type: Informal consensus; benefits/harms ratio unknown; Evidence quality: Low; Strength of recommendation: Weak)

American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)

The AUA and ASTRO published a three part updated guideline addressing clinically localized PCa in 2022 (Eastham et al.). This guideline was endorsed by the Society for Urologic Oncology (SUO) and provides the following recommendations regarding use of genomic testing:

- Clinicians may use tissue-based genomic biomarkers selectively when added risk stratification has the potential to impact clinical decision-making. (Expert Opinion)
- Clinicians should not use tissue-based genomic biomarkers routinely for risk stratification or to assist with clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)
- Patient and tumor risk factors should be fully assessed to guide decision regarding offering germline testing which would include mutations that are known to be associated with aggressive PCa types or are known to have implications for treatment. (Expert Opinion)

The guideline further states the use of genomic classifiers (GCs) to improve outcomes in individuals with clinically localized PCa has not been validated in high quality, prospective clinical trials to date. This is the reason the AUA/ASTRO guideline does not recommend routine use at this time. Existing published data supporting predictive ability of genomic classifiers have mostly been based on tissue analysis of radical prostatectomy samples; thus the impact of heterogeneity of tissue and under-sampling on the ability to prognosticate with GCs is still uncertain. Accumulating evidence has shown that GC scores based on biopsy specimens (specifically Decipher), do correlate with clinical outcomes.

American Urological Association (AUA)/Society for Urologic Oncology (SUO)

A 2023 AUA/SUO guideline (Wei et al.) includes the following recommendations:

- Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (Conditional Recommendation; Evidence Level: Grade C)
- After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (Conditional Recommendation; Evidence Level: Grade C)

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines for PCa (NCCN Prostate Cancer, v4.2023) state that Decipher, Oncotype DX Prostate (GPS) and Prolaris molecular assays may be considered in men with low or favorable intermediate risk PCa and a life expectancy greater than or equal to ten years during initial risk stratification to help guide decision-making regarding management. Individuals with unfavorable intermediate and high-risk disease may consider the use of Decipher and Prolaris molecular assays. Further, the Decipher test is recommended to inform adjuvant therapy when adverse features are found post prostatectomy and can be part of the discussion of risk stratification in patients with PSA persistence or recurrence after radical prostatectomy (category 2B evidence). NCCN has deemed the Decipher 22-gene genomic classifier an advanced tool with a high level of evidence for use as a GEP test for risk stratification in individuals with localized PCa and for use post-RP by NCCN.

The discussion section of the NCCN guideline states "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory

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pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that patients with low or favorable intermediate disease may consider the use of Decipher, Oncotype DX Prostate or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). 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."

Risk Group	Clinical/Pathological Features		
Very low	Has all of the following: • cT1c • Grade Group 1 • PSA < 10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤ 50% cancer in each fragment/core • PSA density < 0.15 ng/mL/g		
Low	Has all of the following but does not qualify for very low-risk: • cT1–cT2a • Grade Group 1 • PSA < 10 ng/mL		

Intermediate	Has all of the following:
	• No high-risk group features
	• No very high-risk group features
	• Has one or more intermediate risk factors (IRFs):
	  ○ cT2b–cT2c
	  ○ Grade Group 2 or 3
	  ○ PSA 10–20 ng/mL
		Favorable intermediate	Has all of the following:
			• 1 IRF
			• Grade Group 1 or 2
			• < 50% biopsy cores positive (e.g., < 6 of 12 cores)

		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (e.g., ≥ 6 of 12 cores)
High	• Has one or more high-risk features, but does not meet criteria for very high risk:cT3; or • Grade Group 4 or Grade Group 5; or • PSA > 20 ng/mL		
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA > 40ng/mL		

In its 2024 version 2 guideline addressing PCa early detection, the NCCN panel recommends "consideration of biomarker tests that have been validated in peer-reviewed, multi-site studies using an independent cohort of pts…" The panel indicates that various biomarker tests for improving specificity may be considered, including %fPSA, 4Kscore, Select mdx, ExoDx Prostate, PHI, MPS, and IsoPSA before biopsy in those with serum PSA levels of > 3 ng/mL who desire more specificity. In addition, PHI, %fPSA, 4Kscore, Confirm mdx, PCA3, MPS, and IsoPSA are also options in individuals thought to be higher risk despite a negative prostate biopsy. Validation of these tests in diverse populations has varied and it has not yet been determined how they could be optimally used in combination with MRI. The panel also states that no biomarker test can be recommended over any other for early PCa detection due to the quality and quantity of evidence available at this time and the optimal order of biomarker tests and imaging is unknown. Interpretation of multiple tests in individual patients is complex, and results are sometimes contradictory (NCCN Prostate Cancer Early Detection, v2.2024).

Thyroid Cancer/Indeterminate Thyroid Nodules

Vardarli et al. (2024) conducted a meta-analysis aimed at evaluating the performance of commercial molecular tests for thyroid nodules with indeterminate cytology (ITN). An electronic search was conducted using PubMed/Medline, Embase, and the Cochrane Library, selecting studies that assessed the diagnostic accuracy of the Afirma gene expression classifier (GEC), Afirma gene sequencing classifier (GSC), ThyroSeq v2 (TSv2), or ThyroSeq v3 (TSv3) in individuals with ITN (Bethesda category III or IV). Statistical analyses were performed using Stata. The study included 53 studies with 6490 fine needle aspirations (FNAs) and showed pooled estimates of sensitivity at 0.95 and specificity at 0.35. TSv3

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demonstrated the best overall performance, followed by TSv2, GSC, and GEC. GSC had the best rule-out performance, while TSv2 was superior for rule-in. The meta-regression analysis identified study design, Bethesda category, and type of molecular test as independent factors. The findings suggest that TSv3 has superior molecular diagnostic performance for ITN, with GSC and TSv2 excelling in specific diagnostic aspects. Limitations of the analysis included the following: 1) many of the included studies had a retrospective design, 2) not all ITNs with benign or negative molecular tests underwent surgery, thus the true false-negative rate is unknown, and 3) studies did not include head-to-head comparisons of the tests using the same cytological sample. Conducting additional studies with a prospective design, blinding, and surgical intervention (including histopathological diagnosis of ITNs) for all individuals undergoing molecular diagnostics would be beneficial to ascertain true false-negative results.

In a retrospective study, Potonnier et al. (2024) evaluated the diagnostic accuracy of a next-generation sequencing (NGS) panel on thyroid nodules with indeterminate cytology (Bethesda III, IV, V). The study included 121 participants with cytologically indeterminate thyroid nodules whose FNA samples were analyzed using the AmpliSeq cancer NGS panel. Results were then compared against final histological diagnoses. The panel's performance for Bethesda III and IV nodules revealed a sensitivity of 55.0%, specificity of 76.9%, positive predictive value (PPV) of 37.9%, and negative predictive value (NPV) of 87.0%. Although the results were promising, the authors indicate that the NPV was not sufficiently high to eliminate the need for diagnostic surgery in cases of indeterminate thyroid nodules.

Kim et al. (2023) conducted a single center RCT designed to determine the rate of delayed operation and false negative rate of the Afirma® GSC and ThyroSeq® v3 in participants with Bethesda III and IV thyroid nodules who underwent thyroid biopsy between August 2017 and November 2019. Of 176 indeterminate nodules with negative or benign molecular test results, 14 (8%) nodules underwent immediate resection, with no malignancies found on surgical pathology. Nonoperative management with active surveillance was pursued for 162 (92%) nodules with benign or negative test results. The median surveillance was 34 months (range 12-60 months), and 44 participants were lost to follow-up. Of 15 nodules resected during surveillance, one malignancy was found (overall false negative rate of 0.6%). This was a 2.7 cm minimally invasive Hürthle cell carcinoma that initially tested negative with ThyroSeq v3 and underwent delayed resection due to sonographic growth during surveillance. The authors concluded the majority of Bethesda III and IV thyroid nodules with negative or benign molecular test results are stable over three years of follow-up. Study limitations include short-term follow-up and randomization of participants to either Afirma GSC or ThyroSeq v3 which did not allow for a comparison of both molecular tests in the same nodule. The authors suggest longer term studies to verify durability of benign/negative molecular test results and to identify the length of time individuals need to remain under surveillance.

In 2022, Lee et al. conducted a systematic review and meta-analysis to appraise the diagnostic performance of second-generation molecular tests in diagnosing thyroid nodules with indeterminate fine-needle aspiration biopsy results. Included in the evaluation were 15 studies: seven Afirma GSC, six ThyroSeq v3, and two ThyGeNEXT®. Studies on ThyGeNEXT were excluded from the meta-analysis due to their small sample sizes. Pooled data for GSC studies on 472 thyroid nodules displayed a sensitivity of 96.6 (95% confidence interval: 89.7–98.9%), specificity of 52.9% (23.4–80.5%), PPV of 63% (51–74%), and NPV of 96% (94–98%). Pooled data for ThyroSeq studies on 530 thyroid nodules presented a sensitivity of 95.1% (91.1–97.4%), specificity of 49.6% (29.3–70.1%), PPV of 70% (55–83%), and NPV of 92% (86–97%). There was not a statistically significant variance in the diagnostic performances of GSC and ThyroSeq (p-values for sensitivity = 0.89, specificity = 0.82, PPV = 0.43, NPV = 0.17). Limitations to the study include the small number of studies contained within the meta-analysis, no long-term analysis of the utility of the tests, and only two studies evaluated on ThyGeNEXT. The authors concluded from the review that high sensitivity and NPV in GSC and ThyroSeq V3 may help rule out malignancy amid thyroid nodules with indeterminate cytology results. There was no difference in diagnostic performances between the two molecular tests displaying that either test is suitable for the malignancy of thyroid nodules. Publications by Livhits et al. (2021) and Endo et al. (2019), previously discussed in this policy, were included in this systematic review.

Babazadeh et al. (2022) reported on the clinical utility of Afirma XA testing during two years of clinical use. Afirma XA became available in 2018 and assesses 593 genes, including 905 potential variants and 235 fusions. Afirma XA was performed on 136 indeterminate nodules (103 of these met inclusion criteria). Forty-three of those had positive Afirma XA results, 83.7% of which were follicular cell-derived thyroid cancer on surgical histopathology. Overall PPV among Afirma GSC--suspicious indeterminate nodules during the same timeframe was 82.5%, similar to the Afirma XA results. Of the 60 nodules that tested negative with Afirma XA, 73.3% were follicular cell-derived thyroid cancer on surgical histopathology. The authors concluded that the Afirma XA positivity is predictive of follicular cell-derived thyroid cancer with PPV similar to that of GSC–suspicious results alone at the institution where the study took place. It is still uncertain whether Afirma XA results significantly increase the preoperative risk of malignancy for cytologically indeterminate nodules. More extensive studies on variants and fusions associated with varied risks of malignancy are needed. Longer-term data collection of

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Afirma XA results and related clinical variables is principal in standardizing how thyroid cancer specialists should use this molecular test.

Hu et al. (2021) investigated molecular findings across a large, real-world cohort of thyroid fine needle aspiration (FNA) samples through a retrospective analysis of RNA sequencing data files. Overall, there were a total of 50,644 consecutive Bethesda III-VI nodules included. The Afirma GSC, which uses whole transcriptome RNA sequencing to identify thyroid nodules as either benign or suspicious, confirmed that 66% of the 48,952 Bethesda III/IV FNA studied were benign. Among all Bethesda III/IV FNAs and 76% of Bethesda VI FNAs, the prevalence of BRAF V600E was 2%. Named were 130 different gene partners and fusions involving NTRK, RET, BRAF, and ALK, primarily prevalent in Bethesda V (10%). BRAF and ALK fusions were 81% and 67%, respectively; the PPV of an NTRK or RET fusion for carcinoma or noninvasive follicular thyroid neoplasm with papillary-like nuclear features was > 95% among small consecutive Bethesda III/IV sample cohorts with one of these fusions' available surgical pathology excision data. The expanded Afirma Xpression Atlas (XA) panel identified at least one genomic alteration in 70% of medullary thyroid carcinoma classifier positive FNAs, 44% of Bethesda III or IV Afirma GSC suspicious FNAs, 64% of Bethesda V FNAs, and 87% of Bethesda VI FNAs. Based on the results of this study, the authors felt the analytical and clinical validity of the Afirma GSC and XA assays were confirmed. However, the authors did not correlate the surgical pathology outcome with most of the FNA samples described or report surgical histology. There was no central blinded histopathologic review, and there is potential selection bias, especially among Bethesda V and VI samples.

A Hayes Molecular Test Assessment found limited but positive evidence supporting the Afirma GSC assay for identification of benign thyroid nodules in results deemed indeterminate by cytopathology so that individuals may avoid unnecessary surgical intervention. The evidence showed the GSC test has a high sensitivity and NPV, but the specificity and PPV varied between studies due to the lack of Afirma benign nodules resected to assess test performance. The Hayes report also indicates that the GSC test had better specificity and PPV than the previous version of the test (Genomic Expression Classifier), however studies could not confirm statistically significant differences in the values due to the limited number of resected nodules. Additional studies are required to report the follow up of individuals with Afirma benign outcomes, specifically around missed malignancies, to support the test performance. An updated review states the current Hayes rating is unlikely to change from the previous annual rating (Hayes, Afirma Genomic Sequencing Classifier [Veracyte Inc.], 2021, updated 2024).

Hayes assessed the use of the ThyGeNEXT® and ThyraMIR® tests in a Molecular Test Assessment. The assessment uncovered inadequate evidence supporting the use of the ThyGeNEXT and ThyraMIR tests to assist with reclassifying thyroid nodules with indeterminate cytology (Hayes, ThyGeNEXT and ThyraMIR [Interpace Diagnostics Group Inc.] 2021, updated 2022).

A Hayes Molecular Test Assessment addressing the ThyroSeq v3 Genomic Classifier (GC) test indicates that there is a very low-quality body of evidence supporting the ability of ThyroSeq v3 to predict malignancy in Bethesda III and IV thyroid nodules. Although the test appears to have high sensitivity and NPV, true accuracy is uncertain because there is a lack of reference standard testing in the majority of samples, especially when the results are negative. In addition, there was insufficient follow-up documented for individuals with ThyroSeq v3 negative results. No studies reporting on the improvement of health outcomes related to the use of ThyroSeq v3 were identified. Overall, Hayes found insufficient evidence for use of the ThyroSeq v3 GC in preoperative assessment of indeterminate thyroid nodules to measure cancer probability or provide prognostic data for clinical management (Hayes, ThyroSeq v3 Genomic Classifier [University of Pittsburgh Medical Center and Sonic Healthcare USA], 2023, updated 2024).

In a prospective blinded, multicenter study by Steward et al. (2019, included in the Lee et al. 2022 systematic review and the Hayes ThyroSeq v3 Genomic Classifier Molecular Test Assessment above), authors sought to find the diagnostic precision of a multigene classifier test (ThyroSeq v3) for cytologically indeterminate thyroid nodules. The study enrolled 782 individuals with a total of 1013 nodules. Of those, 286 FNA samples from 256 individuals met inclusion criteria and underwent molecular analysis with the multigene GC (ThyroSeq v3). The primary outcome of this study was the correct separation of benign histopathological nodules from cancer and noninvasive follicular thyroid neoplasms with papillary-like nuclei (NIFTP) in samples with Bethesda III and IV cytology. Of the 286 cytologically indeterminate nodules, 206 (72%) were benign, 69 (24%) were malignant, and 11 (4%) were noninvasive follicular thyroid neoplasms with papillary-like nuclei (NIFTP). Overall, 257 (90%) nodules (154 Bethesda III, 93 Bethesda IV, and 10 Bethesda V) had informative GC analysis, with 61% classified as negative and 39% as positive. The test collectively established a 94% (95% CI, 86%-98%) sensitivity and 82% (95% CI, 75%-87%) specificity in Bethesda III and IV nodules. With a cancer/NIFTP incidence of 28%, the NPV)was 97% (95% CI, 93%-99%), and the PPV was 66% (95% CI, 56%-75%). The detected 3% false-negative rate was comparable to benign cytology; the missed cancers were all low-risk tumors. Between nodules testing positive, precise groups of genetic variations had cancer likelihoods fluctuating from 59% to 100%. The authors concluded

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that ThyroSeq v3 showed high sensitivity/NPV and relatively high specificity/PPV, which could eliminate the need for diagnostic surgical procedures in up to 82% of all benign thyroid nodules with indeterminate cytology and 61% of individuals with Bethesda III to IV indeterminate nodules. The study, however, had limitations; study participants were not consecutively enrolled (they were chosen from a larger population undergoing testing), and approximately 20% of the original cohort was excluded due to no histological diagnosis. In addition, no ethnicity was reported and the study participants were from centers with significant clinical expertise and well-established thyroid nodule imaging, which limits the ability to generalize to larger populations of affected individuals, some of whom may be seen in general practices.

Angell et al. (2019) reported on their clinical and analytical validation of the Afirma XA, which uses whole transcriptome RNA-sequencing to detect gene variations and fusions from a panel of over 500 genes in thyroid fine needle aspiration (FNA) samples. From the same sample, DNA and RNA were purified using 943 blinded FNAs and multiple methodologies were used for comparison, including whole-transcriptome RNA-seq, targeted RNA-seq, and targeted DNA-seq. To define performance for fusions between whole transcriptome RNA-seq and targeted RNA-seq, 695 additional blinded FNAs were used. Of variants detected in DNA at 5 or 20% variant allele frequency, 74 and 88% were also detected by XA, respectively, and XA variant detection was 89% compared to another RNA-based detection method. Analytical validation studies showed high intra-plate reproducibility (89%-94%), inter-plate reproducibility (86–91%), and inter-lab accuracy (90%). Multiple variants and fusions formerly described across the spectrum of thyroid cancers were identified by XA, some of which have approved or investigational targeted therapies. The sensitivity of XA as a standalone test was 49% in 190 Bethesda III/IV nodules. Limitations of measuring variants in expressed RNA were identified, including the fact that some variants and fusions that were identified by an alternative method were not identified by XA; the researchers were not able to determine the reason for the difference, nor which tests was “correct.” The authors concluded that the data from this study supports the clinical and analytical validity of XA for GSC suspicious or for Bethesda V/VI nodules. The asserted that XA may also enhance genomic insight when the Afirma GSC is used first for Bethesda III/IV nodules as a rule-out test and results are GSC suspicious and may ultimately help to inform personalized clinical decision-making in individuals with thyroid nodules and thyroid cancer. Further studies addressing the clinical utility of this test are needed.

MicroRNAs (miRNA) are small noncoding RNAs that regulate gene expression. Research has demonstrated that a number of miRNAs are differentially expressed between benign and malignant thyroid nodules which have led to the development of miRNA based diagnostic lab tests, and in some cases, labs may offer miRNA testing in conjunction with gene variant and expression analysis. Wylie et al. (2016) conducted a study examining genetic variant and miRNA analysis on archived pathology samples from the University of Michigan. The samples consisted of an initial set of 235 aspirates representing 118 nodules with benign cytology, including 13 with surgical outcome (12 benign, 1 malignant), 73 with malignant cytology, including 51 with surgical outcome (1 benign, 50 malignant), and 44 with indeterminate cytology, all with available surgical outcome. The second set of aspirates consisted of 42 distinct nodules with indeterminate cytology and surgical outcome. Thirty-one miRNAs were analyzed as well as 17 genetic alterations in the BRAF, RAS, RET and PAX8 genes, considered standard mutation testing. Furthermore, 54 samples that were negative by the 17-mutation panel were interrogated using a miRNA classification algorithm, commercially available as the ThyraMIR Thyroid miRNA Classifier, which analyzes in parallel 20 genes through next generation sequencing and 46 messenger RNA (mRNA transcripts). The authors found that standard mutation testing alone had a sensitivity of 61%, consistent with the literature. Machine learning was utilized to group miRNA analysis into two groups of miRNAs, classifier A and classifier B. When miRNA classifier A was included in the analysis, the sensitivity rose to 78%, and 94% with classifier B. The authors calculated that this leads to a low residual risk of cancer (8%) among specimens negative by mutation and miRNA testing and corresponds to a calculated improvement from 78–90% NPV to 94–98% NPV at 20–40% cancer prevalence. These results contributed to the development of ThyraMIR. In the small cohort that underwent evaluation by ThyraMIR, the authors report a diagnostic sensitivity of 85% and specificity of 95%.

Clinical Practice Guidelines

American Thyroid Association (ATA)

The ATA (Bible et al., 2021) developed a guideline for anaplastic thyroid cancer (ATC) which indicates that no genetic alterations found in ATC are specific for ATC. However, in specific situations, molecular testing may aid with histopathologic diagnosis, which remains the gold standard. Genomic profiling of tumor tissue alone is not sufficient for diagnosing ATC, but the results of this testing may be helpful in differential diagnosis.
In a guideline on the clinical management of thyroid nodules, Haugen et al. (2016) provide the following recommendations regarding the use of molecular profiling:

- Nondiagnostic cytology: Some studies suggests that use of a thyroid core needle biopsy with *BRAF* testing, a gene panel, or a gene expression analysis may provide clinical guidance in these cases, but the full clinical impact of these approaches for nodules with nondiagnostic cytology remains unknown. If molecular testing is being considered,

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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.

- Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS): Investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making. The authors reviewed available data for multi-gene panels of *BRAF, NRAS, HRAS*, and *KRAS* point mutations, as well as *RET/PTC1* and *RET/PTC3*, with or without *PAX8/PPARγ* rearrangements, and a mRNA expression profile of 167 genes, and concluded that more data was needed to fully understand how such tests can impact clinical management. They conclude that there is currently no single optimal molecular test that can definitively rule in or rule out malignancy in all cases of indeterminate cytology.
- Follicular Neoplasm/Suspicious for Follicular Neoplasm Cytology: After consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery.
- Suspicious for Malignant Cytology: After consideration of clinical and sonographic features, mutational testing for *BRAF* or the seven-gene mutation marker panel *(BRAF*, *RAS*, *RET/PTC*, *PAX8/PPARγ)* may be considered in nodules with SUSP cytology if such data would be expected to alter surgical decision-making. Molecular testing using the 167 GEC has a PPV that is similar to cytology alone (76%) and a NPV of 85% and it is therefore not indicated in patients with this cytological diagnosis.
- Malignant cytology: While studies have been presented in the literature that suggest that *BRAF* and other multi-gene panels may be useful in prognosis and treatment decisions, more studies are needed to establish the impact of molecular profiling involving multiple mutations or other genetic alterations on clinical management of individuals with primary thyroid medullary cancer.
- Post-operative radioiodine (RAI) therapy: Molecular testing to guide postoperative RAI use is not recommended at this time.

American Association of Endocrine Surgeons (AAES)

The AAES (Patel et al., 2020) published evidence-based recommendations to aid clinicians in the optimal surgical management of thyroid disease, including the following statements which address molecular testing:

- If thyroidectomy is preferred for clinical reasons, then molecular testing is unnecessary (strong recommendation, moderate-quality evidence).
- When the need for thyroidectomy is unclear after consideration of clinical, imaging, and cytologic features molecular testing may be considered as a diagnostic adjunct for cytologically indeterminate nodules (strong recommendation, moderate-quality evidence).
- Accuracy of molecular testing relies on institutional malignancy rates and should be locally examined for optimal extrapolation of results to thyroid cancer risk (strong recommendation, moderate-quality evidence).
- For nodules that are cytologically categorized as Bethesda III, clinical factors, radiological features, and patient preference should inform decision-making regarding whether or not to proceed with repeat biopsy, molecular testing, diagnostic thyroidectomy, or observation (strong recommendation, moderate-quality evidence).
- Diagnostic thyroidectomy and/or molecular testing are accepted options for individuals with nodules cytologically categorized as Bethesda IV (strong recommendation, moderate-quality evidence).

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

The AACE/ACE/AME updated their guidelines on the management of thyroid nodules in 2016 (Gharib et al., 2016). They state that molecular profiling should be considered in nodules with indeterminate cytology, and not in those who are found to be clearly benign or malignant. They favor profiles that include *BRAF, RET/PTC, PAX8/PPARG* and *RAS* mutations. They find that there is insufficient evidence either for or against GECs. There is insufficient evidence to use molecular profiling to determine the extent of surgical interventions, or for use with low-risk indeterminate cytology cases.

National Comprehensive Cancer Network (NCCN)

The 2024 NCCN guidelines for thyroid carcinoma indicate that molecular diagnostics may be helpful to reclassify follicular lesions as more/less likely to be benign or malignant based on genetic profile. In addition, molecular testing may be useful for diagnosis of medullary thyroid cancer due to the difficulty of reaching a specific diagnosis with cytology in limited samples. Although past studies have shown that molecular diagnostics do not perform well for oncocytic carcinoma, formerly known as Hürthle cell neoplasms, modern genomic classifiers are promising with regard to these specimens. A requirement for the diagnosis of oncocytic carcinoma and follicular carcinomas is evidence of either vascular or capsular invasion, which fine needle aspiration cannot determine; use of molecular diagnostics may be considered in these

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situations but should be interpreted with caution and used in conjunction with individualized clinical, radiographic and cytologic features. The NCCN panel notes that molecular testing has been shown to have benefit for making targeted treatment decisions as well, especially those related to use of drug therapy or clinical trial participation. Some mutations may also have prognostic importance. Molecular testing of single genes or a GEC panel test may be considered and should be selected by the clinician based on the specific clinical question being asked (NCCN Thyroid Carcinoma, v4.2024).

Melanoma

Cutaneous Melanoma

Several molecular tests designed to assess severity of disease and risk of recurrence/metastases and assist with clinical decision-making regarding the need for biopsy in cases of cutaneous melanoma have been developed. At this time, further studies supporting the accuracy and clinical utility of these tests are needed.

In a prospective, multicenter study, Guenther et al. (2025) evaluated the accuracy of the integrated 31-gene expression profile (i31-GEP) for sentinel lymph node biopsy (SLNB) in predicting positive sentinel lymph node (SLN) results in 322 participants with T1-T2 tumors. This study expands on the original DECIDE study results (Yamamoto, 2023, discussed below). To ascertain whether incorporation of the i31-GEP into treatment decision-making led to fewer SLNBs, the researchers used propensity score-matching from a matched non-overlapping cohort (n = 322) where the i31-GEP was not utilized for decision-making regarding SLNB. Study results revealed that no participants with less than five percent i31-GEP predicted risk had a positive SLNB (0/35). Use of propensity matching showed an 18.5% reduction in SLNBs performed (43.7% vs 62.2%. $p < 0.001$). The researchers calculated that use of the i31-GEP could have reduced the volume of unneeded biopsies in 35/140 participants (25%); they assert that the performance and clinical utility of the i31-GEP for predicting positivity in SLNs was confirmed by this study and suggest that incorporation of this test into clinical decision-making could reduce the rate of SLNB and improve risk-related care of individuals with T1-T2 cutaneous melanoma. Noted limitations include the number of participants with SLNB results available; there was not a separate cohort for comparing SLNB procedure rates. Participants and physicians were also allowed to choose whether SLNB was performed with the individual's preference serving as the greatest influence, which may have introduced variability into clinical decision-making. Finally, the manufacturer of the GEP under evaluation provided funding for the study and several authors had affiliations with the manufacturer as well, which presents a potential risk of bias.

In an effort to quantify reductions in SLNB related to use of the 31-GEP and then monitor five-year clinical outcomes for each 31-GEP subclass, Yamamoto et al. (2023) performed a prospective, multicenter study (DECIDE) which enrolled 193 subjects with T1-T2 cutaneous melanoma tumors who had been deemed eligible for SLNB by expert physicians. Prior to performance of SLNB but after receipt of 31-GEP results, treating providers were queried regarding the clinical and pathological factors that influenced their decision regarding SLNB (n = 191). SLNB procedure rates from this study were compared to baseline SLNB rates from a contemporary study (Whitman et al., 2021) using the Exact binomial test, and logistic regression modeling was then used to pinpoint features associated with the rates of SLNB procedures. Results of the analyses showed that 52.4% (100/191) of clinical decisions to abstain from SLNB were impacted by 31-GEP test results, and in 70% of these instances (70/100) providers did not move forward with SLNB. Of the 30/100 SLNB that were performed in this group, all were negative. In addition, the 31-GEP contributed to 63 (33%) clinical decisions to perform SLNB; of these, 58/63 were performed (92.1%). These findings represented a 29.4% reduction of SLNBs completed in participants with Class 1A results when compared to the baseline rate of 78% ($p < .01$). In total, clinical decisions related to SLNB were impacted by 31-GEP results in 85.3% of cases. The results described led the authors to conclude that the 31-GEP test may provide clinically relevant information regarding the decision to forego or proceed with SLNB in individuals with T1-T2 tumors, which could in turn significantly decrease the rate of SLNB. The study, however, had limitations; the researchers did not include tumor location as a question with respect to its influence on SLNB performance decisions (previous studies have shown that tumors on the head/neck have lower rates of SLNB) which may have been a confounding factor in the analysis. In addition, this assessment did not include outcome data (that data is still accruing). The collection of various clinical and pathological data likely varied by site and could have contributed to bias. Lastly, the study was funded by Castle Biosciences, the test manufacturer, and several authors had affiliations with this manufacturer.

Bailey et al. (2023) conducted a registry study using data from the National Cancer Institutes (NCI) SEER Program to assess the effects of the DecisionDx-Melanoma 31-gene expression profile (31-GEP) test on survival outcomes in participants diagnosed with cutaneous malignant melanoma (CM). Individuals with stage I-III CM that had a 31-GEP result between 2016 and 2018 were associated to data from 17 SEER registries (n = 4687). The ability of the 31-GEP to stratify melanoma-specific survival (MSS) and overall survival (OS) were examined using Kaplan-Meier analysis and the log-rank test. The outcomes between 31-GEP tested participants were matched to those that did not receive the 31-GEP testing.

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Patients with a 31-GEP class 1A result had higher three-year MSS and OS than participants with a class 1B/2A or class 2B result (MSS: 99.7% *v* 97.1% *v* 89.6%, p < .001; OS: 96.6% *v* 90.2% *v* 79.4%, p < .001). A class 2B result was an independent predictor of MSS (HR, 7.00; 95% CI, 2.70 to 18.00) and OS (HR, 2.39; 95% CI, 1.54 to 3.70). 31-GEP testing was associated with a 29% lower MSS mortality (HR, 0.71; 95% CI, 0.53 to 0.94) and 17% lower overall mortality (HR, 0.83; 95% CI, 0.70 to 0.99) relative to untested participants. While the clinical use of the test may help providers deliver more personalized clinical management decisions for individuals with CM and identify their risk of dying, there were gaps and limitations. Study limitations/gaps included the following: mechanism of action related to better outcomes could not be identified, limited follow-up since the analysis was restricted to 2016-2018 and lack of data related comorbidities and specific treatments. Further robust studies are needed and/or ongoing collaboration with NCI/SEER to identify these gaps.

In a 2023 systematic review (including two Ferris studies [2017, 2018] that were previously discussed in this policy), Thomsen et al. attempted to determine the diagnostic accuracy of tape stripping (TS) for detecting cutaneous malignant melanoma (MM) in suspicious pigmented skin lesions. Ten studies were included. Sensitivity ranged from 68.8% (95% confidence interval [CI] 51.5, 82.1) to 100% (95% CI 91.0, 100). Specificity ranged from 69.1% (95% CI 63.8, 74.0) to 100% (95% CI 78.5, 100). A pooled analysis of five studies testing the RNA markers LINC00518 and PRAME found a sensitivity of 86.9% (95% CI 81.7, 90.8) and a specificity of 82.4% (95% CI 80.8, 83.9). This review had several limitations that included: a lack of information related to the characteristics of the study population, lack of histological examination for TS lesions, potential risk of overlap of participants and no randomized controlled trials that would determine the difference between TS and no-TS in terms of impact to prognosis. The authors indicate that in the studies evaluated, TS was used as a supplement to well-established diagnostic methods such as visual inspection, dermoscopy, and clinical photography. Since the overall quality of the studies was low, the reliability of sensitivity and specificity is questionable. Additional high-quality studies are needed to confirm the diagnostic accuracy of PLA testing in cutaneous malignant melanoma.

In their Molecular Test Assessment on the DecisionDX-Melanoma gene expression test, Hayes identified ten studies that met the defined criteria for their review. One study reported the reproducibility and technical reliability of the test and another reported failure rates for samples submitted from a single center. Seven of the studies focused on the clinical validity of the test to inform risk of recurrence or metastasis and the last study assessed the clinical validity of the test to predict the likelihood of sentinel lymph nodes. They did not identify any studies in peer-reviewed literature that met criteria and addressed the clinical utility of the test to improve clinical decision making and patient outcomes. Hayes concluded that there was a low-quality body of evidence for the analytical and clinical validity of this test to identify the risk of recurrence or metastasis or to predict sentinel lymph node positivity for individuals with American Joint Committee on Cancer (AJCC) stage I, II, or III cutaneous melanoma (Hayes, DecisionDx-Melanoma, 2022, updated February 2024).

Ludzik et al. (2022) conducted a retrospective case control study evaluating the use of the pigmented lesion assay (PLA). PLA is used to non-invasively detect the presence of three genes associated with melanoma (*LINC00518, PRAME*, and *TERT*) using adhesive patch testing. Patch testing has the potential to reduce the number of unnecessary biopsies. Currently, studies that evaluate the clinical usefulness of this test outside a research setting are lacking. The author's aim in this study was to identify possible barriers that reduce the clinical utility of PLA testing by dermatologists. Data was collected from April 2021 to April 2022 from an academic tertiary-level center evaluating a total of 472 lesions. Genetic analysis failure for *LINC00518* and *PRAME* occurred in 59 or 12.5% of cases and in 300 lesions or 70.9% of cases for TERT. In 38.5% of cases, PLA results were discrepant with histopathology. The additional time associated with PLA use independent from the participant's visit was 10-25 minutes. The authors note that this novel non-invasive PLA test for melanoma using an adhesive tape-stripping techniques and gene expression profiling may be a promising technique to reduce unnecessary biopsies and optimize the triage of pigmented lesions. Yet, studies evaluating the clinical value, and possible limitations of these tests in a real-world setting are limited. With the considerable number of discrepancies between PLA test results and histopathology and the number of non-actionable results, the use of this testing remains limited. Additional robust studies are needed to confirm the clinical utility of this test and prevent possible mismanagement of lesions associated with melanoma.

An Ontario Health Technology Assessment (2021) that evaluated the diagnostic accuracy, clinical utility, and budget impact of pigmented lesion assays (PLA) for people with suspected melanoma skin lesions. The systematic review included seven studies consisting of six cohort studies (including three Ferris studies [2017, 2018, and 2019] that were previously discussed in this policy) and one survey that were conducted in dermatology offices, examining adults (> 18 years old) with suspected melanoma lesions using the DermTech pigmented lesion assay. The authors stated that the risk of bias in the included studies was generally moderate to high, and the quality of evidence was very low. Limitations noted in the review included the potential bias from the industry sponsored studies, overestimation of the diagnostic accuracy of PLA, the diagnostic accuracy of visual assessment may have been underestimated when compared to published literature, and many parameters and assumptions used by the economic analysis were not reported in the study, which

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they stated had potentially serious limitations. They concluded that there was no evidence demonstrating the impact of PLA on patient outcomes and that the low-quality evidence for the diagnostic accuracy of PLA remains uncertain when compared to visual inspection alone. They also stated that the evidence is uncertain about whether PLA has an impact on clinical decision making and that the cost-effectiveness of this test compared with the standard care pathway is also uncertain.

Marchetti et al. (2020) completed a systematic review and meta-analysis to assess the performance of prognostic gene expression profile (GEP) tests in participants with American Joint Committee on Cancer (AJCC) stage I or stage II cutaneous melanoma. The review included seven studies with a total of 1450 participants. One study was determined to have a moderate risk of bias and the other six studies were determined to have a high risk of bias. There were 623 participants with stage I disease and 212 with stage II disease that were tested with DecisionDx-Melanoma. The authors found that DecisionDx-Melanoma correctly classified recurrence in 29% of the participants with stage I disease and 82% of those with stage II disease. It also found that the test correctly classified 90% with stage I disease and 44% with stage II disease among participants without recurrence. When they reviewed the data for MelaGenix, which had 88 participants with stage I disease and 245 with stage II disease, they found that the test correctly classified 32% with Stage I disease and 76% with stage II disease among those with recurrence. Among those participants tested with MelaGenix, the test correctly classified 77% with stage I disease and 43% with stage II disease. Limitations noted by the authors include the heterogeneity in study designs and data reporting, the lack of availability of individual participant data, short follow-up and significant censoring, the variability in the definitions used for melanoma recurrence, and the risk of bias and quality of the evidence. The authors concluded that the prognostic ability of DecisionDx-Melanoma and MelaGenix to predict recurrence among participants with localized melanoma varied by AJCC stage and appeared to be poor for participants with stage I disease. They recommend more rigorously structured studies be performed to better quantify the association of GEP tests with melanoma outcomes and to demonstrate clinical utility.

A 2020 meta-analysis (Greenhaw et al.) reported on the strength of the prognostic value of the 31-gene expression profile for cutaneous melanoma. To perform the assessment, meta-analysis was performed on 3 studies that met inclusion criteria. Clinical outcome for the 31 gene expression test were compared with the American Joint Committee on Cancer Staging. The 31-gene expression profile was able to identify the American Joint Committee on Cancer stage one to three categories with a high likelihood for distant metastases and recurrence. When the GEP and sentinel lymph node biopsy were evaluated in conjunction, sensitivity and negative predictive value related to distant metastasis-free survival both improved. The authors concluded that the 31-gene test accurately and consistently identified individuals with melanoma who were at increased risk of metastasis, functioned independently of other clinicopathologic factors, and improved accuracy of current risk stratification. Several limitations were noted, however. There is a possibility that unpublished negative-result studies exist that were not considered in this analysis. The studies included had different designs, which could impact the strength of the effect of gene expression profiling due to evolving treatments and population differences. Follow up time also varied across the studies, which is a consideration when interpreting overall survival estimates. Further studies are needed to evaluate most appropriate follow up and treatment of individuals identified as high-risk via the 31-gene expression in conjunction with other clinicopathologic factors.

A Molecular Test Assessment by Hayes (2019, updated 2022) focused on the Pigmented Lesion Assay (PLA) (DermTech), a gene expression test that is designed to help rule out melanoma and assist with decision-making regarding the need for biopsy. The assessment indicates that the initial evidence on the PLA test suggests that the use of PLA test results could inform clinical decision-making with respect to surgical biopsy, thereby reducing the number of benign lesions that undergo biopsy in individuals 18 years or older. However, published studies do not address full follow-up of individuals with negative results and most studies were retrospective or simulation design. Additional study is needed to establish whether the test performance is equivalent or superior to current standard of care methods (Hayes, Pigmented Lesion Assay [DermTech], 2019, updated 2022).

Hayes published a Molecular Test Assessment on the myPath Melanoma gene expression test as well. The test is intended to be used as an adjunct diagnostic tool to distinguish between benign nevi and malignant melanoma when histopathologic results of a patient are not clear. Their assessment included seven studies that consisted of one study looking at analytical validity, four studies on clinical validity, and two clinical utility studies. All seven studies were assessed to be of very low quality due to small sample sizes, study design, lack of test accuracy measurements, questionable study comparators and/or removal of challenging cases for clinical validity. Based on their review, Hayes concluded that there was limited evidence that supports the myPath Melanoma test as a diagnostic adjunct tool and that the evidence was insufficient to support the use of the test as a guide to manage treatment decisions. They also stated that the studies were limited in showing that test results have a positive impact on health outcomes. Hayes recommended more studies to evaluate the impact of myPath Melanoma for rare or challenging types of melanoma and on clinical practice along with studies that show how the test results are used in conjunction with other clinical information to develop

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a treatment plan (Hayes, myPath Melanoma [previously Myriad Genetics, test sold to Castle Biosciences in 2021] 2018, updated 2022).

Zager et al. (2018, included in Hayes DecisionDx-Melanoma Molecular Test Assessment, above) conducted a multi-center trial of archived primary melanoma tumors from 523 participants, using a 31 gene expression classifier (GEC) to classify tumors as Class 1 (low risk) and Class 2 (high risk). The five-year recurrence free survival (RFS) rates for Class 1 and Class 2 were 88% and 52%, respectively. DMFS were 93% for Class 1 versus 60% for Class 2. The GEC was a significant predictor of RFS and DMFS in univariate analysis in addition to with Breslow thickness, ulceration, mitotic rate, and sentinel lymph node (SLN) status. GEP, tumor thickness and SLN status were significant predictors of RFS and DMFS in a multivariate model that also included ulceration and mitotic rate. The authors concluded that the 31 gene GEC provided value to prognostication, and more prospective studies are needed.

Ardakani et al. (2017) assessed the ability of CGH to differentiate between melanocytic naevi and melanoma in cases where the two-show overlapping histological features. Melanomas are characterized by CNVs, while naevi are normal. The team used 19 formalin fixed, paraffin embedded (FFPE) unambiguous naevi and 19 melanomas and tested them using a SurePrint G3 Human CGH 8x60K array. CGH was able to differentiate between the naevi and the melanoma in 95% of cases. One naevus showed two large CNV. The authors concluded that CGH may be a good adjunctive test to resolve histologically equivocal melanocytic samples.

Uveal Melanoma

Miguez et al. (2023) conducted a retrospective analysis to assess and validate the prognostic value of GEP testing in individuals with uveal melanoma (UM). To date, no studies predicting metastasis by including tumor size have been performed. In this study, the researchers sought to determine the prognostic value of combining tumor size with the GEP classification to predict metastases. The results included 337 individuals from three different institutions with 87 demonstrated metastases. The mean follow-up time was 37.2 (standard deviation [SD], 40.2) months for subjects with metastases and 55.0 (SD, 49.3) months for those without metastases. Tumors of larger thickness and GEP class 2 (vs class 1) were associated significantly with increased risk of metastasis. Tumor thickness showed better prognostic usefulness than GEP classification (Wald statistic, 40.7 and 24.2, respectively). Class 2 tumors with a thickness of 7.0 mm or more were associated with increased risk of metastasis than tumors with a thickness of < 7.0 mm (hazard ratio [HR], 3.23; 95% confidence interval [CI], 1.61–6.51), whereas class 1 tumors with a thickness of 9.0 mm or more were associated with increased risk of metastasis than tumors with a thickness of < 9.0 mm (HR, 2.07; 95% CI, 0.86–4.99). No difference in metastasis-free survival (MFS) was found between individuals with class 1A tumors compared with those with class 1B tumors (p = .8). Subjects with class 2 tumors showed an observed five-year MFS of 47.5% (95% CI, 36.0%–62.8%). Study limitations included retrospective design, participants from three different institutions, and likely variation in tumor size and biopsy techniques among providers. Despite the limitations, the authors indicated that tumor size was the most significant predictor of metastasis; it provided additional prognostic value independent of GEP classification.

Singh et al. (2022) conducted a retrospective ten-year cohort study to assess the accuracy of the predicted MFS rate by a GEP test in individuals with UM by comparing the individual's GEP test results to what they found in their clinics. The authors reported that the test predicted worse outcomes for participants with UM than what occurred. The study included a retrospective record review of 352 consecutive patients from two clinics with a mean age at diagnosis of 59.4 years (+13.0 years) who were followed for a median interval of 38.0 months (19.0 - 57.0 months). All individuals had undergone a fine-needle aspiration biopsy GEP test of which, 43% showed class 1A (low risk) UM, 22% showed class 1B (intermediate risk) UM, and 35% showed class 2 (high risk) UM. The MFS was specified as time-to-metastasis for those who developed metastases, or the last follow-up date was used for those who did not develop metastatic disease. There were 48 participants who developed metastasis with 40 who had class 2 tumors, 5 with class 1A tumors and 3 with class 1B tumors. The authors found that the observed three-year MFS was 93% for all class 1 tumors and 67% for class 2 tumors while the five-year MFS was 87% for participants with class 1 tumors and 47% for those with class 2 tumors. Limitations of this cohort study included its retrospective design, small population size and small number of included study sites. The authors concluded that, in general, the MFS was better for smaller than larger tumors and that the predicted MFS for class 2 UM tumors appears to be worse than what they found to have actually occurred in the patient population. They recommended that future studies include the tumor size in the prediction model to enhance the accuracy of the GEP test.

Hayes completed a Molecular Test Assessment addressing the DecisionDx-UM test, a quantitative reverse transcriptase PCR-based profiling test intended to identify the likelihood of metastasis within 5 years in patients with UM. The evidence base examined in the assessment included one study each on analytical validity, clinical validity, and clinical utility (Plasseraud, 2016, discussed below). When reviewed together, the overall quality of the body of evidence was determined to be very low due to small sample sizes, short follow-up periods, the sensitivity and linearity of the test, and

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the ambiguity of the role of DecisionDx-UM in physician decisions. Hayes concluded that the evidence was insufficient to support the use of the DecisionDx-UM test to identify the likelihood of metastasis within 5 years in patients with UM because the validity of the test and the impact on patient management was unclear. The assessment stated that additional studies are needed to support the use of this test (Hayes, DecisionDx-UM [Castle Biosciences Inc.], 2020, updated 2023).

In a five-year clinical outcome report from a prospective registry of individuals tested with a prognostic 15-gene expression profile (15-GEP) test for UM and a meta-analysis with published cohorts, Aaberg et al. (2020) found that testing with the 15-GEP test guided management of individuals with UM. UM, a rare intraocular cancer, has a 30-50% risk of metastasis within 5 years of diagnosis. The prognostic 15-GEP was designed to predict five-year metastatic risk using three risk categories indicating low, intermediate, and high-risk groups. In this study, 89 participants who had undergone 15-GEP testing were prospectively enrolled at four separate locations. Clinical outcomes and management plans were tracked every six months. Eighty percent of class 1 (low-risk) participants received low-intensity management and all class 2 (high-risk) participants received high-intensity management ($p < 0.0001$). Five-year melanoma survival rates were 94% for class 1 and 63% for class 2. Five-year metastasis-free survival rates were 90% for class 1 and 41% for class 2. By meta-analysis performed on several prior studies to evaluate clinical outcomes of participants tested with15-GEP, class 2 was associated with an increased risk for both metastasis and mortality and was also the only independent predictor of metastasis.

Klufas et al. (2017) retrospectively reviewed the role of gene expression profile analysis (GEP) vs chromosome 3 specific analysis. Records of consecutive patients diagnosed with posterior UM who underwent intraoperative fine needle aspiration biopsy prior to placement of an iodine-125 radioactive plaque between 2012 and 2014 were reviewed. Two cohorts of participants were identified. Cohort 1 had 44 participants, and tumors had both GEP and FISH analysis. Cohort 2 had 43 participants, and those tumors had GEP, and multiplex ligation-dependent probe amplification (MLPA) results were obtained. Discordance between GEP and chromosome 3 status by FISH and MLPA occurred in the series at a rate of 15.9 and 16.3%, respectively. The authors concluded that caution must be advised when counseling an individual with a good-prognosis GEP "Class 1" result that the uveal tumor may actually harbor monosomy 3, which is associated with a poor prognosis for metastasis in nearly 20% of individuals.

Plasseraud et al. (2016, included in the Hayes DecisionDx-UM 2020 Molecular Test Assessment above) evaluated the clinical validity and utility of DecisionDx-UM in a prospective, multicenter, study (supported by Castle Biosciences, Inc.). Seventy participants were enrolled to document management differences and clinical outcomes associated with low-risk Class 1 and high-risk Class 2 results indicated by DecisionDx-UM testing. Thirty-seven participants in the prospective study were Class 1 and 33 were Class 2. Class 1 patients had 100% three-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 participants received significantly higher-intensity monitoring and more oncology/clinical trial referrals compared to Class 1 (Fisher's exact test $p = 2.1 \times 10^{-13}$ and $p = 0.04$, respectively). In the authors' opinion, the results of this study provided additional, prospective evidence through an independent cohort of individuals for which Class 1 and Class 2 patients were 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.

Clinical Practice Guidelines

American Academy of Dermatology (AAD)

Guidelines from the AAD, updated in 2019, included recommendations for diagnostic, prognostic, and therapeutic molecular testing (Swetter et al., 2019).

- Ancillary diagnostic molecular techniques (e.g., comparative genomic hybridization; fluorescence in situ hybridization, gene expression profiling [GEP]) may be used for equivocal melanocytic neoplasms.
- Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (e.g., sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial.
- Testing of the primary cutaneous melanoma for oncogenic mutations (e.g., *BRAF, NRAS*) is not recommended in the absence of metastatic disease.

National Comprehensive Cancer Network (NCCN)

NCCN Cutaneous Melanoma guidelines (v1.2025) indicate that for diagnostic testing, there is agreement that any ancillary testing (e.g., CGH, FISH, GEP, SNP arrays, NGS) to differentiate malignant from benign melanocytic neoplasms should be used as an adjunct to clinical and expert dermatopathological examination and that it should be interpreted within the context of their findings.

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The guideline further states the following regarding prognostic/predictive testing:

- "Despite commercially available GEP tests being marketed to risk stratify cutaneous melanomas, current GEP platforms do not provide clinically actionable prognostic information when combined or compared with known clinicopathologic (CP) factors (e.g., sex, age, primary tumor location, thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and/or [sentinel lymph node biopsy] SLNB status). Furthermore, the clinical utility of these tests to inform treatment recommendations and improve health outcomes by prompting an intervention has not been established.
- Various studies of prognostic GEP tests suggest their role as an independent predictor of worse outcome. However, GEP studies to date have not demonstrated added benefit beyond comprehensive CP variables, and it remains unclear whether available GEP tests are reliably predictive of outcome across the risk spectrum of cutaneous melanoma. Validation studies on prospectively collected, independent cohorts (similar to those performed in BC) are necessary to define the clinical utility of molecular prognostic GEP as an adjunct to AJCC staging and other known prognostically significant CP variables or as part of the multidisciplinary decision-making process to guide surveillance imaging, SLNB, and adjuvant therapy.
- Existing and emerging GEP tests and other molecular techniques (i.e., circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary models that incorporate readily available CP variables. Prospective study of the utility of predictive GEP for SLNB risk, in conjunction with well-established CP factors, is ongoing."

Regarding non-invasive patch testing for cutaneous melanoma, NCCN indicates that this testing may be helpful to guide biopsy decisions for melanocytic neoplasms that are dermoscopically and clinically suspicious for melanoma.

The NCCN Uveal Melanoma guidelines address the staging and management of uveal melanoma, stating that biopsy is not usually necessary for the initial diagnosis of uveal melanoma and selection of first line treatment, but it may be helpful when there is uncertainty regarding diagnosis and may also provide prognostic information that can help guide follow up. Risks/benefits of biopsy for prognostic purposes should be carefully considered and discussed at length.

Molecular/chromosomal testing for prognostic purposes is preferred over cytology alone if biopsy is performed. NCCN outlines tumor markers that have been shown to be associated with increased risk or shorter time to development of distant metastases and notes the development of gene expression profiling for prognostic purposes, which is recommended for stratification if biopsy is performed (NCCN Uveal Melanoma, v1.2024).

Cutaneous Squamous Cell Carcinoma

Gopal et al. discussed the integration of DecisionDx®-SCC, a 40-gene expression profile (40-GEP) testing into clinical recommendations for adjuvant radiation therapy (ART) in individuals with cutaneous squamous cell carcinoma (cSCC) in their 2024 Multidisciplinary Consensus Guidelines. These guidelines were developed by a panel of experts, including radiation oncologists and dermatologists, to enhance the precision of ART recommendations. The 40-GEP test classifies individuals into risk categories (Class 1, 2A, and 2B) based on their likelihood of metastasis, providing a more accurate prognostic tool compared to traditional clinicopathologic factors alone. The guidelines suggest that incorporating 40-GEP testing along with existing staging systems (e.g., AJCC-8) and management guidelines (e.g., NCCN) can better stratify individuals' risk and inform decisions regarding ART. This approach aims to improve outcomes by identifying high-risk individuals who would benefit most from ART while avoiding unnecessary treatment in lower-risk individual. The proper application of 40-GEP testing requires a collaborative decision-making process between the multidisciplinary team and the individual with cSCC. This approach takes into account various factors, including the individual's risk of metastasis, the characteristics of both the tumor and surrounding tissues, and the individual's personal preferences. The development of this article was funded by the 40-GEP test manufacturer and authors had had affiliations with the manufacturer as well, introducing potential risk of bias.

Ruiz et al. (2024) conducted a retrospective validation study evaluating the utility of the 40-GEP test in predicting the benefit of adjuvant radiation therapy (ART) for individuals with cSCC. The study focused on cSCC tumors received from two academic centers, examining associated five-year metastasis-free survival rates as well as projected time to metastasis. In random sampling of matched individual pairs (n = 52 ART-treated; 371 no ART), there was a median 50% decrease in five-year progression rate for ART-treated individuals (vs no ART) with 40-GEP Class 2B results. Class 2A results were associated with a small ART benefit; no differences were noted between ART treated and untreated tumors for participants with Class 1 results. Limitations of the study included the infrequent occurrence of Class 2B results, the study's retrospective design, and the inclusion of only two clinical sites, which may limit generalizability. In addition, the study was partially funded by the manufacturer of the GEP test and several authors had affiliations with this manufacturer, introducing potential risk of bias. Despite the limitations, the researchers assert that the study's statistical power was adequate due to the significant effect size observed. The authors concluded that in this study, the 40-GEP test effectively

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identified individuals with cSCC who were most likely to benefit from ART as well as those that may consider deferring treatment, which validates previously reported benefits of ART for Class 2B tumors and lack of benefit for Class 1 tumors.

In a 2024 expert panel consensus report, Zakria et al. discuss the integration of a prognostic 40-GEP test into the management of cutaneous squamous cell carcinoma (cSCC). The panel, comprised of eight dermatology/cSCC experts, reviewed existing literature and developed guidelines for incorporation of the 40-GEP test into clinical practice. The panel unanimously voted to adopt 7 consensus statements and recommendations, 6 of which were given a Strength of Recommendation Taxonomy (SORT) Level strength of "A" and 1 of which was given a strength of "C". The authors concluded that the 40-GEP test provided accurate and independent prognostic information beyond standard staging systems that only incorporate pathologic data and propose that incorporation of GEP testing into national guidelines may help further stratify individuals based on risk of metastasis and thereby improve morbidity and mortality. Of note, the study was partly funded by, and some of the authors have affiliations with, the manufacturer of the 40-GEP referenced in this consensus report.

The use of the 40-GEP test to improve metastatic risk assessment in cSCC was investigated by Ibrahim et al. (2022) in a multicenter study (33 sites). The researchers collected data from 420 primary tumors with known clinical outcomes and the 40-gene expression profile (40-GEP) test was used along with clinicopathological factors to stratify metastatic risk. The findings demonstrated that combining molecular profiling with traditional risk assessments significantly improved prognostic accuracy. Specifically, the 40-GEP test helped to better stratify individuals into risk categories, with Class 1 results showing metastasis rates similar to the general cSCC population and Class 2B results showing metastasis rates over 50%. The authors acknowledge potential limitations, such as the archival nature of samples and possible under-reporting of high-risk factors. This cohort, however, represented a high-risk cSCC population with a 15% metastasis rate and reflects current clinical pathology practices. Measures such as comprehensive monitoring and independent dermatopathologist review were implemented to mitigate potential under-reporting. Identifying the primary lesion among multiple cutaneous lesions was another limitation, but strict inclusion/exclusion criteria were used to address this. Lastly, potential for bias exists related to study funding (provided by the manufacturer of the 40-GEP test) and the affiliation of some study authors with the manufacturer. The researchers suggest that ongoing research will explore tissue testing from recurrent tumors and the use of the 40-GEP to predict risk of local recurrence as well. They propose that further study focused on the incorporation of molecular profiling with standard clinicopathologic assessments will ultimately enhance individual risk assessment and improve clinical decision-making, ultimately leading to better health outcomes and resource use for individuals with cSCC.

Wysong et al. (2021) directed a prospective study to develop and validate a 40-GEP test designed to predict metastatic risk in individuals with localized high-risk cutaneous squamous cell carcinoma (cSCC). Conducted across 23 independent centers, the study included testing of 586 archival primary cSCC tissue samples. Using a discovery cohort (n = 202), a GEP signature was developed; this was validated in a separate independent cohort with no overlap (n = 324). The 40-GEP test was designed to stratify individuals into three risk classes: Class 1 (low-risk), Class 2A (high-risk), and Class 2B (highest-risk). Results showed that the three-year metastasis-free survival (MFS) rates were 91.4% for Class 1 (low risk), 80.6% for Class 2A (high risk), and 44.0% for Class 2B (highest risk). The test demonstrated a positive predictive value (PPV) of 60% for Class 2B, surpassing traditional staging systems. Negative predictive value (NPV), sensitivity, and specificity were comparable to currently used staging modalities. The authors state that the 40-GEP test may prove to be a valuable tool for improving risk-directed management of individuals with high-risk cSCC. Study limitations include the potential under-staging of cases, which could affect metastasis rate accuracy, and risk of bias in specimen collection based on tissue availability from archival samples.

Clinical Practice Guidelines

No guidelines specifically discussing the DecisionDx-SCC/40-GEP or use of GEP for risk stratification in individuals with cSCC were identified.

Cancers of Unknown Primary (CUP)

Molecular tests intended to guide site-specific treatments in individuals with CUP have been developed. To date, peer-reviewed evidence supporting the use of these tests is insufficient. More high-quality studies addressing accuracy of these tests and data indicating whether they lead to improved outcomes is required.

In a 2023 prospective study (SUPER), Posner et al. assessed the diagnostic utility of RNA and DNA analysis in 215 participants with CUP in Australia. A retrospective analysis of clinicopathological information was performed; this revealed that 166/215 (77%) of the individuals with CUP did not have sufficient evidence to support a tissue of origin (TOO) diagnosis. The remaining participants had either sufficient evidence to support a likely TOO determination (13%), or a

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latent primary diagnosis (10%). Microarray analysis (CUPGuide) and/or a custom NanoString 18-class GEP test was performed for 191 CUP specimens and was found to be 91.5% accurate for high-medium confidence predictions in known metastatic cancers. In the cases where clinicopathological information resolved CUP, 80% had high-medium predictions and 94% agreed with pathology results. Of note, GEP use resulted in high-medium confidence in only 56% of clinicopathologically unresolved CUPs. In 201 CUP tumors, diagnostic markers were queried based on the cancer-type specific mutations found in 22 cancer types from the AACR Project GENIE database, which houses information on 77,058 tumors. Mutational signatures related to other factors, such as smoking were also explored. For CUPS unresolved by clinicopathological information, assessment of mutations and mutational signatures led to added diagnostic evidence in 31% of the cases; GEP classification, however, was only useful in 13% of those. Lung and biliary cancer were the most frequently identified cancers among CUPs where genomic information assisted with identifying TOO. The researchers determined that in this study, DNA and RNA tests help to resolve a third of CUP cases where clinicopathological data alone were not enough to establish TOO. While GEP is the most commonly studied molecular diagnostic test for CUP to date, this investigation found that DNA sequencing may be of greater diagnostic value, as many tumors appear to have an atypical transcriptional profile while maintaining identifiable and important diagnostic mutational features. Though DNA mutational profiling is not currently a guideline-recommended approach, the authors propose that the integration of this testing in cancer-type assessment and for use in identifying targeted treatments has potential high clinical value.

A study by Wang et al. (2023) sought to evaluate the use of rapid NGS to help identify CUP and associated therapeutic biomarkers that could be employed to guide site-specific therapies. Forty solid tumor samples were evaluated based on initial diagnosis of CUP and NGS testing was performed using the Oncomine Precision Assay GX. Genomic information was used to support a site-specific cancer diagnosis for 6 participants (15%). The most common genetic variations found were *KRAS* (35%), *CDKN2A* (15%), *TP53* (15%), and *ERBB2* (12%). Twenty-three individuals had results identifying actionable molecular-targeted treatments (variations in *BRAF, CDKN2A, ERBB2, FGFR2, IDH1*, and *KRAS*). An immunotherapy-sensitizing MMR deficiency was detected in one individual. The authors assert that this study supports the integration of rapid NGS into care for individuals diagnosed with CUP and the viability of using genomic profiling along with diagnostic histopathology and immunohistochemistry for these individuals. They recommend further study including the incorporation of diagnostic algorithms which include genomic profiling to better identify CUP. This study was limited by its retrospective design, small population, and analysis performed in a single institution only. In addition, a relatively small testing panel was used, which may not have captured some genome-wide biomarkers, and no survival or outcome data were evaluated.

Ding et al. (2022) conducted a systematic review and meta-analysis of studies investigating the efficacy of site-specific therapy guided by molecular profiling compared to empiric therapy for individuals with CUP. GEP was used to identify the tissue of origin in this study. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were assessed to compare the efficacy of site-specific therapy with empiric therapy in individuals with CUP. In addition, subgroup analyses were conducted. Five studies comprising 1114 participants were identified, of which 454 received site-specific therapy, and 660 received empiric therapy. Our meta-analysis revealed that site-specific therapy was not significantly associated with improved PFS (HR 0.93, 95% CI 0.74-1.17, p = 0.534) and OS (HR 0.75, 95% CI 0.55-1.03, p = 0.069), compared with empiric therapy. However, during subgroup analysis, significantly improved OS was associated with site-specific therapy in the high-accuracy predictive assay subgroup (HR 0.46, 95% CI 0.26-0.81, p = 0.008) compared with the low accuracy predictive assay subgroup (HR 0.93, 95% CI 0.75-1.15, p = 0.509). Additionally, when compared with participants with less responsive tumor types, more survival benefit from site-specific therapy was found in participants with more responsive tumors (HR 0.67, 95% CI 0.46-0.97, p = 0.037). The authors concluded that their results suggest that site-specific therapy is not significantly associated with improved survival outcomes; however, it might benefit individuals with CUP with more responsive tumor types. This is a non-randomized study and is limited due to a heterogeneous population. Further investigation is needed before clinical usefulness of this procedure is proven.

Ross et al. (2021) performed a retrospective analysis of CUP origin cases referred for comprehensive genomic profiling (CGP) to determine how many were potentially eligible for enrollment into an experimental CUPISCO arm, an ongoing randomized trial using CGP to assign individuals with CUP to targeted or immunotherapy treatment arms based on genomic profiling (NCT03498521). Centrally reviewed adenocarcinoma and undifferentiated CUP specimens in the FoundationCore database were analyzed using the hybrid capture based FoundationOne CDx assay (mean coverage, > 600×). Presence of genomic alterations, microsatellite instability (MSI), tumor mutational burden (TMB), genomic loss of heterozygosity (gLOH), and programmed death-ligand 1 (PD-L1) positivity were determined. A total of 96 of 303 participants (31.7%) could be matched to an experimental CUPISCO arm. Key genomic alterations included *ERBB2* (7.3%), *PIK3CA* (6.3%), *NF1* (5.6%), *NF2* (4.6%), *BRAF* (4.3%), *IDH1* (3.3%), *PTEN, FGFR2, EGFR* (3.6% each), *MET* (4.3%), *CDK6* (3.0%), *FBXW7, CDK4* (2.3% each), *IDH2, RET, ROS1, NTRK* (1.0% each), and ALK (0.7%). Median TMB was 3.75 mutations per megabase of DNA; 34 participants (11.6%) had a TMB ≥ 16 mutations per megabase. Three participants (1%) had high MSI, and 42 (14%) displayed high PD-L1 expression (tumor proportion score ≥ 50%). gLOH

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could be assessed in 199 of 303 specimens; 19.6% had a score of > 16%. The authors concluded that 32 percent of participants would have been eligible for targeted therapy in CUPISCO. Future studies, including additional biomarkers such as PD-L1 positivity and gLOH, may identify a greater proportion potentially benefiting from CGP-informed treatment. Clinical trial identification number: NCT03498521. The findings of this retrospective analysis of carcinoma of unknown primary origin (CUP) cases validate the experimental treatment arms being used in the CUPISCO study (NCT03498521) using comprehensive genomic profiling to assign participants with CUP to targeted or immunotherapy treatment arms based on the presence of pathogenic genomic alterations. The authors also concluded the findings suggest that future studies including additional biomarkers and treatment arms, such as programmed death-ligand 1 positivity and genomic loss of heterozygosity, may identify a greater proportion of individuals with CUP potentially benefiting from comprehensive genomic profiling-informed treatment. A limitation is that this study lacks detailed clinical data for each specimen, including whether any participants received specialized therapy and subsequently demonstrated therapeutic benefit. Further research is needed to validate these findings.

Lombardo et al. (2020) conducted a systematic review to describe genes and molecular pathways involved in cancer of unknown primary (CUP) pathogenesis and focus on available data of targeted genotype-directed treatment. This systematic review consisted of studies of individuals with CUP, whose tumor specimen was evaluated through NGS, according to PRISMA criteria from PubMed, ASCO meeting library and Clinicaltrial.gov identifying potentially targetable alterations for which approved/off-label/in clinical trials drugs are available. Case reports about individuals with CUP treated with targeted therapies driven by NGS results in order to explore the clinical role of NGS in this setting were identified. Fifteen publications of which eleven studies (9 full-text articles and 2 abstracts) have analyzed the genomic profiling of CUPs through NGS technology, with different platforms and with different cohorts, ranging from 16 to 1,806 participants were included. Among these studies, 85% of participants demonstrated at least one molecular alteration, the most frequent involving TP53 (41.88%), KRAS (18.81%), CDKN2A (8.8%), and PIK3CA (9.3%). A mean of 47.3% of participants harbored a potentially targetable alteration for which approved/off-label/in clinical trials drugs were available. Four case reports were identified in order to evaluate the clinical relevance of a specific targeted therapy identified through NGS. The authors concluded NGS may represent a tool to improve diagnosis and treatment of CUP by identifying therapeutically actionable alterations and providing insights into tumor biology. Potential limitations of a tissue-agnostic therapeutic approach include that extrapolating therapeutic actionability from one cancer histology to another might provide uncertain. Therefore, for individuals with CUP, it would be still important to consider putative primary sites even when candidate actionable driver mutations are found. In addition, redundancy in activation of pathways of resistance does often take place as a mechanism of primary as well as secondary resistance. Further research is needed to determine the clinical relevance of these findings.

A Hayes Molecular Test Assessment report concluded that there is insufficient evidence to draw conclusions regarding the effectiveness of the CancerTYPE ID gene expression test to aid in identifying the site of origin for cancers in patients with indeterminate, uncertain, or differential diagnoses. Peer-reviewed literature supporting the entire assay process as well as publications demonstrating that CancerTYPE ID provides accurate, clinically actionable information resulting in improved outcomes is needed. A 2022 update to the original 2018 assessment found no newly published studies meeting inclusion criteria for the Hayes report. (Hayes, CancerTYPE ID [biotheranostics Inc.], 2018, updated 2022). A 2023 Hayes research brief identified no new relevant publications evaluating clinical validity or utility of the CancerTYPE ID test (Hayes, CancerTYPE ID (Biotheranostics, Inc., 2023).

A systematic review conducted by Binder et al. (2018) to determine incidence and survival trends and to discuss the value of comprehensive genomic profiling (CGP) in individuals with CUP. Age-standardized incidence rates (ASR) per 100,000 were calculated for 2935 individuals with CUP from 1981 to 2014 using cancer registry data of the canton of Zurich, Switzerland. Kaplan-Meier survival curves were estimated for sex, age, and histological groups. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HR). A literature review was conducted to assess the current use of CGP in individuals with CUP. ASR of CUP increased from 10.3 to 17.6 between 1981 and 1997 and decreased to 5.8/100,000 in 2014. Mean overall survival remained stable. Mortality was lower for participants with squamous cell carcinoma (HR 0.48 [95% CI, 0.41-0.57]), neuroendocrine carcinoma (0.75 [0.63-0.88]), and higher for unclassified neoplasms (1.25 [1.13-1.66]) compared to adenocarcinomas. The literature review identified 10 studies using CGP of CUP tissue. Clinically relevant mutations were identified in up to 85% of individuals with CUP, of which 13%-64% may benefit from currently available drugs. The authors concluded that CUP incidence decreased most likely due to improved diagnostics, however, mortality did not improve over the last 34 years. CGP testing may help to identify molecular signatures in individuals with CUP and enable targeted treatment. Given poor prognosis and limited treatment options for individuals with CUP, genomic profiling using NGS technologies may meet a clinical need. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this procedure is proven.

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Clinical Practice Guidelines

European Society for Medical Oncology (ESMO)

A Clinical Practice Guideline addressing CUP was published by Krämer et al. in 2023. The authors state that pan-cancer NGS can be used in CUP, however, randomized trials assessing the clinical utility of such tests are not yet completed. To date, two randomized trials have failed to demonstrate that GEP-based site-specific therapy is superior to standard empiric therapy. Thus, no recommendation addressing the use of GEP for site-directed therapy in CUP is provided.

National Comprehensive Cancer Network (NCCN)

National Comprehensive Cancer Network (NCCN) clinical practice guidelines for occult primary state that while there may be a diagnostic benefit of GEP assays, it is similar to immunohistochemical staining in terms of accuracy of tumor classification, and a clinical benefit for GEP has not been demonstrated. The panel does not recommend gene sequencing for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors. Molecular profiling of tumor tissue using NGS or other techniques which identify gene fusions may be considered after initial determination of histology has been made. Testing on tumor tissue is preferred, but cell-free DNA can be considered if tumor tissue testing is not feasible. NCCN suggests that pathologists and oncologists collaborate on the judicious use of modalities including immunohistochemistry, GEP and NGS on a case-by-case basis, with the best individualized patient outcome in mind (NCCN Occult Primary/Cancer of Unknown Primary [CUP], v2.2025).

Colorectal Cancer (CRC)

Current evidence addressing the use of molecular testing for predicting risk of colorectal cancer (CRC) recurrence or for CRC screening purposes is insufficient. Additional high-quality studies supporting clinical utility are needed.

In a prospective, observational, multicenter study known as ECLIPSE (Evaluation of the ctDNA LUNAR Test in an Average Patient Screening Episode), Chung et al. (2024) assessed the performance of a cell-free DNA (cfDNA) blood-based test (Shield, Guardant Health) to identify asymptomatic and early-stage colorectal cancer in an average risk population. The study was sponsored by the test manufacturer, Guardant Health. The main outcomes evaluated were sensitivity for colorectal cancer detection and specificity for advanced neoplasia compared to colonoscopy. A secondary outcome assessed was sensitivity for advanced precancerous lesions. Initially, 10,258 participants were enrolled; 7861 of those met all eligibility criteria and were included in the final analysis. The study results revealed test sensitivity of 83.1% for detection of colorectal cancer (95% confidence interval [CI], 72.2 to 90.3), with 16.9% of participants who had documented colorectal cancer (detected via colonoscopy) showing a negative result. For stage I-III colorectal cancer, sensitivity was calculated to be 87.5% (95% CI, 75.3 to 94.1) Sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3 to 15.3). Almost 90% of participants who had no advanced colorectal neoplasia (either CRC or advanced precancerous lesions) detected on colonoscopy had a negative cfDNA blood test (10.4% had a positive cfDNA blood test) for an overall specificity for any advanced neoplasia of 89.6% (95% CI, 88.8 to 90.3). Specificity in participants whose colonoscopy results showed no colorectal cancer, no advanced precancerous lesions, and no nonadvanced precancerous lesions was 89.9% (95% CI, 89.0 to 90.7). Invalid cfDNA test results were received by 3.7% of participants. The authors recommend ongoing study evaluating participant adherence to cfDNA blood-based testing across various care settings as well as research regarding health economic and colorectal cancer-related outcomes. Additionally, studies that address impact of longitudinal testing on sensitivity for advanced neoplasia are advised.

The ColonSentry test uses quantitative real-time PCR to measure RNA transcript expression of 7 genes using a blood sample. The results are expressed as a ColonSentry score predicting an individual's risk of CRC related to risk in an average population. Hayes performed a Molecular Test Assessment addressing this technology in 2024.and found insufficient evidence to support use of the ColonSentry test for predicting CRC risk, citing limited studies and data and significant limitations in the existing evidence (Hayes, ColonSentry [StageZero Life Sciences], 2024).

In a 2024 Molecular Test Assessment, Hayes found insufficient evidence to support the use of the Oncotype Dx Colon Recurrence Score test. Overall, a very low-quality body of evidence exists for the use of this test in both stage II, mismatch repair proficient colon cancer and stage IIIA/B colon cancer (Hayes, Oncotype DX Colon Recurrence Score test [Exact Sciences.], 2024).

In 2023, Rokavec and associates sought to identify and validate a prognostic mRNA expression signature for the stratification of individuals with stage II CRC according to their risk for relapse. From 792 primary stage II CRCs, publicly available mRNA expression profiling data were analyzed to find genes consistently associated with relapse-free survival (RFS). Next, the gene expression signature was validated using NanoString technology and computationally refined on primary colorectal samples from 205 individuals with stage II CRC. Finally, validation of the refined signature was carried out in two independent, publicly available training cohorts comprising 166 individuals with stage II CRC. A 61-gene

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signature was identified and determined to be highly significantly associated with RFS (HR = 37.08, p = $2.68*10^{-106}$, sensitivity = 89.29%, specificity = 89.61%, and area under the curve [AUC] = 0.937). Experimental validation and refinement then identified a 15-gene signature that strongly predicted relapse in three separate cohorts: an in-house cohort (HR = 20.4, p = $8.73*10^{-23}$, sensitivity = 90.32%, specificity = 80.99%, AUC = 0.812), publicly available cohort GSE161158 (HR = 5.81, p = $3.57*10^{-4}$, sensitivity = 64.29%, specificity = 81.67%, AUC = 0.796), and publicly available cohort GSE26906 (HR = 7.698, p = $7.26*10^{-8}$, sensitivity = 61.54%, specificity = 78.33%, AUC = 0.752). Pooled cohort values showed that the 15-gene signature test (HR = 4.72, p = $7.76*10^{-25}$, sensitivity = 75%, specificity = 67.44%, AUC = 0.784) was superior to the Oncotype DX colon 7-gene signature test (HR = 2.698, p = $6.3*10^{-8}$, sensitivity = 62.16%, specificity = 55.5%, AUC = 0.633), which is currently the most widely used signature for prognostication of stage II colon cancer. The authors assert that they were able to identify and validate a new 15-gene expression signature for prognostication and stratification of individuals with stage II CRC which performed better in the evaluated validation cohorts than currently used clinico-pathologic biomarkers and signatures for stage II colon cancer prognostication. They speculate that this 15-gene expression signature has the potential to improve prognostication and therapy decisions for individuals diagnosed with stage II colon cancer. Further evaluation of the 15-gene signature in additional cohorts is recommended, including a combination of signature analysis and clinico-pathologic parameters, which may improve prognostic sensitivity and specificity. In addition, assessment of the signature and predictive value related to chemotherapy benefit in prospective, randomized controlled studies is required.

Yothers et al. (2022) conducted a patient-specific meta-analysis of 12-gene colon cancer recurrence score validation studies for recurrence risk assessment after surgery with or without fluorouracil (5FU) and oxaliplatin. Three validation studies of the 12-gene colon recurrence score assay were used with pre-specified patient-specific meta-analysis (PSMA) methods to integrate the 12-gene Oncotype DX Colon Recurrence Score result (RS) with the clinical and pathology risk factors stage, T-stage, mis-match repair (MMR) status, and number of nodes examined to calculate individualized recurrence risk estimates. Baseline risk estimation used the most recent studies, so the risk estimates reflect current medical practice. The effect of 5FU was estimated with a meta-analysis of two studies. The effect of oxaliplatin was estimated using one of the RS assay validation studies, in which participants were randomized to 5FU with or without oxaliplatin. The RS result and each of the clinical-pathologic factors provided independent prognostic information for recurrence. Among stage II, T3, MMR-proficient participants with ≥ 12 nodes examined (the most common scenario), those with RS ≤ 30 (approximately 48%) had estimated five-year recurrence risk ≤ 10% with surgery alone. Among stage IIIA/B, T3, MMR-deficient participants with ≥ 12 nodes examined, those with RS ≤ 19 (approximately 14%) had an estimated five-year recurrence risk ≤ 10% with surgery alone. Among stage IIIA/B, T3, MMR-proficient participants with ≥ 12 nodes examined, those with RS ≤ 14 (approximately 6%) had estimated five-year recurrence risk ≤ 10% with 5FU alone. The authors concluded that the PSMA integrates the 12-gene colon RS result with clinical and pathology factors to provide individualized recurrence risk estimates that reflect current medical practice. The risk estimates are in a range that may help inform treatment decisions for a substantial number of individuals with stage II and stage III cancer. Limitations include that the estimated effect of 5FU is from a meta-analysis of a randomized study and a non-randomized treatment comparison with covariate adjustment to reduce bias. The SUNRISE study was a retrospective analysis that selected participants who had not received adjuvant chemotherapy after resection for stage II or III colon cancer and this may have led to selection of participants whom clinicians had considered to be at lower risk of recurrence. Also, the PSMA risk assessment used a baseline risk assessment from the last two enrolling studies (NSABP C-07, enrolling from 2000–2002 and SUNRISE, enrolling from 2000–2005). If further improvements in clinical outcomes have occurred since this time, they are not reflected in the present recurrence risk estimates. Finally, the RS result is not predictive, that is, it is not associated with the relative treatment effect of chemotherapy with 5FU or oxaliplatin. Further research with randomized controlled trials is needed to validate these findings.

Daemen et al. (2021) conducted a retrospective study and review of randomized, open-label, prospective, parallel three-arm, phase three trial, sponsored by F. Hoffmann-La Roche, to improve high-risk classification by identifying biological pathways associated with outcome in adjuvant stage II/III CRC. A total of 1062 participants with stage III or high-risk stage II colon carcinoma from the three-arm randomized phase three AVANT trial were included in this retrospective study. The authors performed expression profiling to identify a prognostic signature. Data from validation cohort GSE39582, The Cancer Genome Atlas, and cell lines were used to further validate the prognostic biology. Retrospective analysis of the adjuvant AVANT trial uncovered a prognostic signature capturing three biological functions-stromal, proliferative, and immune-that outperformed the Consensus Molecular Subtypes (CMS) and recurrence prediction signatures like Oncotype Dx in an independent cohort. Importantly, within the immune component, high granzyme B (GZMB) expression had a significant prognostic impact while other individual T-effector genes were less or not prognostic. In addition, the authors found GZMB to be endogenously expressed in CMS2 tumor cells and to be prognostic in a T cell independent fashion. The authors concluded that this study furthers their understanding of the underlying biology that propagates stage II/III CRC disease progression and provides scientific rationale for future high-risk stratification and targeted treatment evaluation in biomarker defined subpopulations of resectable high-risk CRC. The results also shed light on an alternative

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GZMB source with context-specific implications on the disease's unique biology. A limitation to this study is that these results need to be clinically validated in a prospective study.

A 2020 (updated 2023) Hayes Molecular Test Assessment evaluated the use of Epi proColon (now known as ColoHealth™) for detecting methylated Septin 9 as cell-free circulating DNA. The test is intended as a screening tool for CRC in average-risk adults (50 or older) who have historically not completed their recommended CRC screening. Epi proColon uses real-time PCR to qualitatively identify DNA of methylated *SEPT9* in plasma obtained from the whole blood specimens of individuals undergoing testing. Hayes identified several studies addressing the use of Epi proColon, but the overall body of evidence is of low-quality. The accuracy of the test appears to increase in more advanced cancer stages (II-IV). Because this test is intended for individuals who would otherwise be noncompliant for colon cancer screening, there may be an impact on the management of these otherwise non-compliant individuals; however it does not replace standard screening tools and there is concern around the overall accuracy of the test to distinguish individuals with CRC and also a remaining need for identification of the population that would appreciate the greatest benefit from this test. Further study is recommended (Hayes, Epi proColon [Epigenomics Inc.], 2020, updated 2023.

In a meta-analysis, Hu et al. (2019) evaluated the diagnostic value of the methylated *SEPT9* (mSEPT9) gene for CRC detection. Twenty-two studies comprising 2271 individuals with CRC were included. The overall analysis of mSEPT9 showed a summary sensitivity of 0.69, specificity of 0.92, positive likelihood ratio (PLR) of 8.1, negative likelihood ratio (NLR) of 0.34, diagnostic odds ratio (DOR) of 24, and area under the curve (AUC) of 0.89. Subgroup and meta-regression analyses revealed that the diagnostic value was higher specific to the Epi proColon 2.0 assay, in individuals of Asian heritage, and when the mSEPT9 test was combined with fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT) when compared to other methods of methylated SEPT9 testing, white ethnicity, and mSEPT9 testing alone. The mSEPT9 positivity rate was higher in advanced CRC cases than in early-stage cases, and higher in CRC cases than in adenoma cases. No significant difference in mSEPT9 positivity was noted between left- and right-sided CRC. Per the authors, these findings suggest that plasma mSEPT9 has high diagnostic value for CRC, especially when newer methodologies are incorporated. Study limitations include the following: there was no consistent cut-off value when analyzing the diagnostic value, there was variability in control groups included in some of the studies, and heterogeneity related to sensitivity and specificity was significant across studies which could impact the reliability. In addition, risk factors for CRC were not accounted for and the analysis included only English and Chinese articles. Additional studies are needed to confirm the reliability of mSEPT9 for use as a biomarker in diagnosing CRC.

Zhang et al. (2017a) retrospectively reviewed the prognostic role of caudal-related homeobox transcription factor 2 (CDX2) expression in individuals with stage 1 and stage III metastatic CRC after complete surgical resection. The cohort (n = 145) included 66 participants with CDX2-negative metastatic CRC and a comparison cohort of 79 participants 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 participants 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 individuals 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 participants who either did or did not receive adjuvant chemotherapy. Reviewing a database of 669 individuals with stage II colon cancer and 1228 participants 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 participant 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 individuals 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 those 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.

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Yamanaka et al. evaluated the 12-gene Recurrence Score assay (Oncotype Dx Colon Recurrence Score) 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 1487 consecutive individuals with stage II to III disease who had surgery alone, 630 participants 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, participants with stage II disease in the high-risk group had a five-year risk of recurrence similar to individuals with stage IIIA to IIIB disease in the low-risk group (19% v 20%), whereas participants with stage IIIA to IIIB disease in the high-risk group had a recurrence risk similar to that of those 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.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

In their 2021 clinical guidelines for colorectal cancer screening (Shaukat et al.), the ACG recommends against Septin 9 testing for CRC screening (Conditional recommendation, very low-quality of evidence.) Given the evidence showing low sensitivity and the lack of long-term and comparative data on the Septin 9 test, the ACG states “it is not considered an optimal screening modality at this time.”

American Society of Clinical Oncology (ASCO)

In an update to their guideline addressing adjuvant therapy for stage II colon cancer, ASCO (Baxter et al., 2022) notes that their expert panel recognizes the development of tumor-based profiling tools that are designed to provide predictive/prognostic information which can potentially be used in treatment decision-making, but states that these types of tests are not yet ready for routine use. Further evidence of their effectiveness is needed before ASCO will endorse the use of these tools.

American Society for Clinical Pathology (ASCP)/College of American Pathologists (CAP)/ Association for Molecular Pathology (AMP)/American Society of Clinical Oncology (ASCO)

Together, the ASP, CAP, AMP, and ASCO convened an expert panel to create evidence-based guidelines for standard molecular biomarker testing in individuals diagnosed with CRC, which included a comprehensive search of the published literature including over 4,000 articles. Twenty-one recommendations were made, which include specifics regarding individual gene testing and requirements for laboratories. The guideline asserts that evidence supports testing for variations in specific genes in the EGFR signaling pathway because they may provide information that is clinically relevant for targeted therapy of CRC with anti-EGFR monoclonal antibodies. Some biomarkers, such as *BRAF* and DNA mismatch repair (MMR) have been shown to have clear value for prognostication and others (*KRAS* and *NRAS*) are evidence-backed for negative predictive value for benefit to anti-EGFR therapies. (Sepulveda et al., 2017)

National Comprehensive Cancer Network (NCCN)

NCCN Clinical Practice Guidelines for colon cancer recommend universal MMR or MSI testing for any individual with a personal history of colon or rectal cancer to 1) identify individuals with Lynch syndrome, 2) to assist with decision-making regarding use of immunotherapy for individuals with metastatic disease and 3) to inform clinical decisions for individuals with stage II disease. The guidelines summarize current data on multigene assays, Immunoscore testing and ctDNA, but the NCCN panel is uncertain regarding the value these tests add, noting insufficient data to recommend use of multigene test panels, Immunoscore or post-surgical ctDNA tests to either estimate risk of recurrence or make determinations regarding adjuvant therapy cancer. The panel encourages clinical trial enrollment to generate further data on these tests. Regarding the use of biomarker testing determining appropriate targeted therapies for treatment of advanced or metastatic CRC, the panel recommends determination of tumor gene status for *KRAS/NRAS* and *BRAF* mutations, as well as *HER2*amplifications and MSI/MMR status (if not previously done). Such testing may be performed for individual genes or as part of an NGS panel, with NGS being the preferred methodology (NCCN Colon cancer, v5.2024).

NCCN guidelines for colorectal cancer screening briefly address blood-based screening tests, noting that the septin9 gene (*SEPT9*) has demonstrated ability to distinguish CRC tissue from surrounding normal tissue; circulating methylated *SEPT9* is a biomarker for CRC. However several factors that may negatively impact the performance of the *SEPT9* tests have been suggested. These include early stage disease, diabetes, age over 65 years, arteriosclerosis, and arthritis. In

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addition, the interval for repeating the testing is undetermined; the panel will continue to review the evidence for this strategy as it is published.

United States Preventive Services Task Force (USPSTF)

The 2021 USPSTF recommendation statement for colorectal cancer screening indicates that because of limited evidence, the USPSTF recommendations do not include “serum tests, urine tests, or capsule endoscopy for colorectal cancer screening”.

Pancreatic Cancer and Ampullary Adenocarcinoma

There is currently insufficient evidence to support the use of molecular testing for risk assessment or diagnosis of pancreatic cancer. Additional large, high-quality studies are required to evaluate the clinical validity and utility of this technology.

In a prospective, multicenter study, Nicolle et al. (2024) investigated the use of molecular analysis of DNA and mRNA extracted from the products of ultrasound-guided fine needle aspiration biopsy of primary tumors in individuals with proven pancreatic adenocarcinoma to help distinguish between metastatic tumors and other tumor types. A total of 397 participants were included. Variant allele frequency of the *KRAS* mutation was leveraged to assess tumor cellularity, which ranged from 15 to 20% in all cells, regardless of the stage of the tumor. The researchers found that the molecular characteristics of metastatic primary tumors was significantly different from other types of tumors. In the metastatic tumors, *TP53* mutations were more common (p = 0.0002) and *RNF43* mutations were less common. Metastatic tumors were also found to have more basal-like tumor mRNA component (p = 0.001). Primary tumors in metastatic forms displayed transcriptomic characteristics that were related to worse outcomes when compared to other primary tumors, suggesting that their molecular profile may be important in the spreading of cancer cells beyond the pancreas. Some molecular markers were associated with better overall survival rates; these included mutations in homologous recombination deficiency genes in participants who received first-line platinum-based chemotherapy (p = 0.025) and wild-type *TP53* genes in participants with locally advanced tumors who received radio-chemotherapy (p = 0.01). A specific transcriptomic profile (known as *GemPred*) was associated with a significantly better overall survival level in participants with locally advanced or metastatic pancreatic cancer who received a gemcitabine-based first line of treatment (p = 0.019). The authors assert that the molecular analysis of both DNA and RNA can help to predict therapeutic response in individuals with pancreatic adenocarcinoma, which can impact overall survival outcomes in individuals undergoing platinum or gemcitabine-based therapies as well as radio-chemotherapy. This technology could also have potential benefit for the use in identifying targeted treatments. Though results appear promising, the study did have limitations, including findings of 6.4% of total samples that were negative for nucleic acids even though the core biopsy was of acceptable quality. Additionally, 45% of the samples tested did not reach RNA or DNA thresholds recommended by the sequencing facility (i.e., > 150 ng/sample). Additional high-quality studies are required to confirm these results and further investigate clinical utility.

A Hayes Precision Medicine Research Brief addressed PancreaSeq, a next generation sequencing-based test that analyzes 74 genes isolated from pancreatic cyst fluid to evaluate the risk of malignancy. Hayes concluded that there is currently not enough published peer-reviewed literature to evaluate the evidence related to PancreaSeq Genomic Classifier for characterization of pancreatic cysts in a full assessment (Hayes, PancreaSeq Genomic Classifier [University of Pittsburgh Medical Center], 2024).

In 2023, Paniccia and colleagues prospectively investigated the use of NGS of pancreatic cyst fluid in a real-time, multi-institutional group of individuals with pancreatic cysts. A total of 1887 specimens from 1832 individuals were tested with the earlier, 22-gene version of the PancreaSeq NGS panel. Follow up data was available for 66% (n = 1216) of participants. Of 251 individuals (21%) with surgical pathology available, mitogen-activated protein kinase/*GNAS* mutations had 90% sensitivity and 100% specificity for a mucinous cyst (PPV, 100%; NPV, 77%). When low-level variants were excluded, the combination of mitogen-activated protein kinase/*GNAS* and *TP53/SMAD4/CTNNB1*/mammalian target of rapamycin alterations had 88% sensitivity and 98% specificity for advanced neoplasia (PPV, 97%; NPV, 93%). With inclusion of cytopathologic evaluation along with PancreaSeq testing, sensitivity improved to 93% and high specificity of 95% (PPV, 92%; NPV, 95%) was preserved. Per the authors, lesser diagnostic performance is found when other methodologies or current pancreatic cyst guidelines (e.g., American Gastroenterology Association and International Association of Pancreatology/Fukuoka guidelines) are used. Out of 965 individuals who did not undergo surgery, none developed malignancy. Postoperative testing with Oncomine found mucinous cysts with *BRAF* fusions and *ERBB2* amplification and advanced neoplasia with CDKN2A alterations. The authors concluded that these results highlight the clinical utility of targeted NGS due to its high sensitivity and high specificity in the diagnosis of mucinous cysts and the detection of advanced neoplasia within a mucinous cyst. This study also expands the number of genomic alterations that

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are found not only in mucinous cysts but serous cystadenomas and cystic pancreatic neuroendocrine tumors. Although more high-quality studies are required, the data reported from this investigation adds to the existing support for integrating targeted NGS testing into evidence-based pancreatic cyst guidelines. Identified limitations include limited availability of surgical pathology for participants (14%) which represents surgical selection bias, testing selection bias (only pancreatic cyst fluid specimens that were satisfactory for targeted NGS testing were used), and limited follow-up period.

In a prospective, single-arm pilot study, Iwaya et al. (2023) analyzed viability and potential clinical utility of NGS using liquid-based cytology (LBC) samples obtained from endoscopic, ultrasound-guided fine-needle biopsy (EUS-FNB) performed on individuals with pancreatic cancer. Enrolled were 33 individuals with pancreatic cancer who underwent EUS-FNB; of these, samples from 31 individuals were included for DNA extraction/NGS and 30 of these (96.8%) had a sufficient quantity of DNA for analysis. The results of the study showed an overall success rate of 86.7% (n = 26) for use of formalin-fixed paraffin-embedded (FFPE), LBC, or frozen samples. When results were stratified using a variant allele frequency (VAF) > 10% tumor burden, the NGS success rate was 76.7% (n = 23) in FFPE, 83.3% (n = 25) in LBC, and 76.7% (n = 23) in frozen samples. Rates of detection for the primary gene variations were as follows: 86.7% for *KRAS*, 73.3% for *TP53*, 66.7% for *CDKN2A*, 36.7% for *SMAD4*, and 16.7% for *ARID1A*. The highest median value of VAF (23.5%) for *KRAS* and *TP53* was found with LBC. In this study, pancreatic cancer gene variant analysis via NGS was performed effectively using LBC in comparison with FFPE and frozen samples. The authors concluded that EUS-FNB samples are able to provide sufficient amounts of high-quality DNA for NGS analysis (when relatively small gene panels are used). Use of LBC specimens for NGS testing may be an option for genetic testing as a diagnostic or therapeutic approach for individuals with pancreatic cancer. Limitations of this study include the small sample size and inclusion of a single-center only, using a small number of experienced endoscopists. In addition, the individuals in this study were diagnosed by imaging only and no final pathology was performed on resected specimens. The gene panel used did not include *GNAS, VHL* or *RNF43*; as such, the possibility of intraductal papillary mucinous neoplasm (IPMN)-derived pancreatic cancer associated with these genes could not be ruled out.

Rift et al. (2023) evaluated the feasibility and diagnostic accuracy of molecular analysis and subtyping of pancreatic cystic lesions (PCLs) using EUS-guided “through the needle biopsy” (TTNB) sampling in a prospective study. In total, 101 individuals with PCLs > 15mm in the largest cross-section were included. NGS was used to analyze the EUS-guided TTNB samples for point mutations in tumor suppressors and oncogenes with a 51-gene customized hotspot panel. Histologic diagnosis was used to calculate sensitivity and specificity. A total of 91 participants had residual TTNB samples available for NGS after initial microscopic analysis of the specimens had been performed. Forty-nine of these revealed mutations, most often in *KRAS* and *GNAS*. This indicated an excess frequency of IPMNs in the study population. Sensitivity of 83.7% (95% CI, 70.3-92.7) and specificity of 81.8% (95% CI, 48.2-97.7) were established for the diagnosis of a mucinous cyst and sensitivity of 87.2% (95% CI, 74.2-95.2) and specificity of 84.6% (95% CI, 54.5-98.1) were demonstrated for the diagnosis of an IPMN. The authors concluded that molecular testing performed on TTNB samples yielded high sensitivity and specificity for the diagnosis of mucinous cysts and IPMN. Although TTNB has a risk of adverse effects of approximately 9.9% (which must be carefully considered for each individual’s clinical situation), the use of TTNB specimens is a solid alternative to use of cyst fluid for combined molecular and histologic diagnosis of PCLs. The study was limited by its single-center design and small sample size. In addition, the cohort included mostly low-grade lesions with a majority of IPMNs and a limited surgical cohort. Lastly, no cyst fluid was obtained for NGS analysis and comparison. Further studies focused on characterizing the subgroup of individuals with pancreatic cancer that would derive the greatest benefit from EUS-guided TTNB samples are recommended.

A Hayes Molecular Test Assessment concluded that there is insufficient evidence to support the use of the PancraGEN test to assess the risk of cancer in pancreatic cysts to help physicians choose appropriate surveillance strategies or surgical options for individuals with pancreatic cysts. No peer-reviewed articles were identified that assesses the analytical validity, clinical validity, or clinical utility of the current version of the PancraGEN test. In the 2023 annual review, 29 new abstracts were published; however, none met the inclusion criteria set out in the 2022 report. There has been no change in the current rating of D2 and no new application of the technology for the test. (Hayes, PancraGEN [Interpace Diagnostics], 2022, updated 2024).

A retrospective study was performed by Kandimalla et al. (2021) using a genome-wide DNA methylation analysis of multiple GI cancers to develop a pan-GI diagnostic assay and validate the tissue-specific differentially methylated regions (DMRs) in 300 cell-free DNA specimens for early detection and/or population screening of all GI cancers. The study design involved tissue discovery followed by plasma cell-free DNA (cfDNA) validation. Methylation data from 1,781 tumor and adjacent normal tissues and DMRs between individual GI cancers and adjacent normal were studied including CRC, hepatocellular carcinoma (HCC), esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), esophageal adenocarcinoma (EAC), and pancreatic ductal adenocarcinoma (PDAC). By comparing data from tumor versus normal tissues within each GI cancer, as well as across all GI cancers, a total of 67,832 regions of interest (ROI) were identified

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based on differentially methylated probes with a $p < 0.001$ and an absolute delta beta of 0.20 across all the comparisons. Three distinct categories of DMR panels were developed to include (i) cancer-specific biomarker panels with AUC values of 0.98 (CRC), 0.98 (HCC), 0.94 (ESCC), 0.90 (GC), 0.90 (EAC), and 0.85 (PDAC); (ii) a pan-GI panel that detected all GI cancers with an AUC of 0.88; and (iii) a multi-cancer (tissue of origin) prediction panel, EpiPanGI Dx, with a prediction accuracy of 0.85-0.95 for most GI cancers. The authors concluded that by using a novel biomarker discovery approach, they were able to provide the first evidence for a cfDNA methylation assay that offers strong diagnostic accuracy for multi-detection GI cancers in a non-invasive and cost-effective manner. This study is limited by its retrospective observations, limited sample size used to represent each stage, and lack of mutation profiles of cfDNA samples to be able to directly compare or combine the diagnostic performance of the methylation assay relative to genomic mutations. Further investigation with prospective evaluation is needed to determine the clinical relevance of these findings.

Singhi et al. (2018) studied the clinical validity of using pre-operative pancreatic cyst fluid (PCF) for NGS of *KRAS, GNAS, TP53, PIK3CA* and *PTEN* genes to predict benign vs malignant lesions. PCF samples from 595 participants (626 samples) were obtained through fine needle aspiration and subjected to NGS for the 5 genes. A different cohort of 159 PCF specimens was also evaluated for *KRAS/GNAS* mutations by Sanger sequencing. Of the 595 participants, 308 (49%) had *KRAS* or *GNAS* mutations and 35 had a mutation in *TP53, PIK3CA*, or *PTEN*. Follow up diagnostic pathology was available in 102 participants. For these 102, NGS testing of PCF for *KRAS/GNAS* had a 100% sensitivity (n = 56) and 96% specificity for an intraductal papillary mucinous neoplasm. In the separate cohort of participants for whom Sanger sequencing was used, *KRAS/GNAS* mutations detection had a 65% sensitivity and 100% specificity. By NGS, the combination of *KRAS/GNAS* mutations and alterations in *TP53/PIK3CA/PTEN* had an 89% sensitivity and 100% specificity for advanced cancer. The study concluded that in comparison to Sanger sequencing, preoperative NGS of PCF for *KRAS/GNAS* mutations is highly sensitive for IPMNs and specific for mucinous pancreatic cysts. In addition, the combination of *TP53/PIK3CA/PTEN* alterations is a useful preoperative marker for advanced cancer.

Wong et al. (2019) reported on ampullary cancer (AC) and germline alterations in *BRCA2, ERBB2*, and *ELF3*. Forty-five individuals with pathologically confirmed AC were tested with the Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) test (410-468 genes). Twenty-three individuals were also tested with GT with MSK-IMPACT (76-88 genes). Eight of 44 subjects (18%) were identified as harboring pathogenic mutations in *BRCA2, ATM, RAD50*, and *MUTYH*. Additionally, they found a wide spectrum of SAs in genes such as *KRAS, MDM2, ERBB2, ELF3*, and *PIK3CA*. Two individuals in the cohort underwent SA-targeted therapy, and one had a partial radiographic response.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

Elta et al. (2018) created clinical guidelines for the diagnosis and management of pancreatic cysts. The recommendation regarding molecular markers states: “Molecular markers can help identify IPMNs or MCNs. Their use may be considered in cases in which the diagnosis is unclear, and the results are likely to change management.” (Conditional recommendation, very low quality of evidence).

American Society of Clinical Oncology (ASCO)

Sohal et al. published an update to the ASCO Metastatic Pancreatic Cancer Guideline in 2020, noting that a complete discussion of molecular biomarker testing is outside the scope of the guideline, but a modification to the recommendations around molecular testing was made. This includes recommendation that all patients with pancreatic cancer should be offered information about biomarker testing and biomarker testing (specifically *NTRK* fusion testing) should be used in patient selection for targeted therapies.

In a provisional opinion, ASCO notes that despite considerable effort, no biomarkers obtained through non-invasive means (e.g., blood, stool, urine) have been proven effective for early identification of pancreatic cancer in individuals with no symptoms. In addition, there is no evidence supporting clinical utility or validity for the use of ctDNA for pancreatic cancer screening outside the context of clinical trials. ASCO advises that thorough testing and validation of possible biomarkers that could be used in high-risk individuals is needed. (Stoffel et al., 2019)

National Comprehensive Cancer Network (NCCN)

NCCN Pancreatic Adenocarcinoma guidelines include a recommendation for genetic testing for inherited mutations for individuals with confirmed pancreatic cancer and the use of tumor/somatic molecular profiling in cases of metastatic or locally advanced disease when an individual is a candidate for anti-cancer therapy. The use of molecular testing for diagnostics and risk assessment of pancreatic cyst fluid is not addressed. (NCCN Pancreatic Adenocarcinoma, version1.2025)

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Other Molecular Oncology Testing for Solid Tumor Cancers

Multi-Cancer Detection Tests [e.g., Galleri (Grail, Inc.)]

Multi-cancer detection (MCD) tests measure biological markers that cancer cells shed in body fluids. Current MCD assays are designed to find and measure the amount of a given substance in a sample (e.g., blood). These tests can check for many different types of cancer stemming from various organs. Currently, MCD tests are being studied in randomized controlled trials to determine the impact of this screening on occurrence of late-stage cancers and mortality. At present, there are no professional medical societies that have issued recommendations on the use of MCD tests for cancer screening (NCI, 2023) and published evidence does not support the use of MCD tests for screening for any type of cancer.

In a recent systematic review (2023), LeeVan & Pinsky evaluated the ability of cell-free-nucleic acid-based MCD tests to predict cancer status. Twenty relevant publications met all inclusion criteria and were evaluated in this review. Most of the included studies reported specificity along with overall sensitivity and many of the studies also reported sensitivity by stage/cancer type. Taken as a whole, the studies in this review reported specificities of 95% or higher and a median sensitivity of 73%. The authors note that the majority of cases of cancer in the studies reviewed were evaluated with MCD tests at diagnosis, which may lead to overestimates of test sensitivity when compared to samples for individuals who are asymptomatic. It was also noted that sensitivity varied by cancer type and typically increased with cancer stage. Ultimately, the researchers recognize the lack of published evidence supporting clinical validity (and clinical utility) of cell-free nucleic acid-based MCD testing and recommend further high-quality studies investigating MCD assay use in populations of asymptomatic individuals, which is the intended-use population for MCD testing.

Schrag et al. (2023) published the results of PATHFINDER, a study funded by GRAIL which examined the feasibility of using MCD for cancer screening. PATHFINDER was a prospective cohort study that was performed in primary care and oncology outpatient centers that were part of seven different United States health networks. The blood of adults aged 50 years or greater was collected and cfDNA was evaluated. If a methylation signature suggesting a cancer diagnosis was found, the predicted cancer origin was used to guide diagnostic assessment. The results were returned to the physicians overseeing each participants care. The chief outcome of this study was the time to further diagnostic testing and the extent of the testing performed that would confirm the presence or absence of cancer. A total of 6621 individuals had analyzable results and participated in the study. Of these, 1.4% (n = 92) had results which showed detection of a cancer signal. Of the 92 individuals with results showing detection of a cancer signal, 35 (38%) were subsequently diagnosed with cancer (true positives) and 57 (62%) were not diagnosed with cancer (false positives). Diagnostic resolution was achieved in a median of 79 days (interquartile range [IQR] 37–219): 57 days (33–143) in true-positive and 162 days (44–248) in false-positive participants. Two participants who began diagnostic evaluations prior to receiving MCD results were excluded. The majority of participants had both imaging (30 [91%] of 33 with true-positive results and 53 [93%] of 57 with false-positive results) and laboratory testing (26 [79%] of 33 with true-positive results and 50 [88%] of 57 with false-positive results) and participants with false-positive results had fewer procedures (17 [30%] of 57) than true positive results (27 [82%] of 33). Surgery was performed in only four participants (one false-positive and three true-positives). The authors assert that this study affords early substantiation to the feasibility of using a single blood test to screen for multiple cancer types. They recognize the need for further large studies demonstrating clinical utility and assessing the impact of MCD testing on cancer mortality. Several studies evaluating updated and refined versions of the MCD test originally used in PATHFINDER are in progress at this time.

Another recent study funded by GRAIL assessed the performance of MCD testing in symptomatic individuals who were referred to for specialty evaluation from primary care. Nicholson et al. (2023) conducted a multi-center prospective observational study (SYMPLIFY) in England and Wales. Participants were 18 years of age or older and had been referred from primary care with symptoms that were either non-specific or potentially related to gynecological, lung, or gastrointestinal cancers. A sample of blood was obtained from each participant when they presented for further investigation of their symptoms. A total of 5461 individuals were included in the final cohort after all exclusionary criteria had been applied (e.g., previous malignancy, cytotoxic or demethylating agents, participation in another trial of a GRAIL MCD test, test errors, lack of final diagnosis, participant withdrawal). Participants were tracked until a diagnosis was reached or for a maximum of nine months. MCD was performed on cfDNA and blinded to clinical outcome. Finally, predictions from the MCD test were compared to the diagnosis obtained via standard processes to determine primary outcomes including overall PPV and NPV, sensitivity and specificity. Final outcomes were measured only in participants who had both a valid MCD test and diagnostic resolution. A total of 368 individuals (6.7%) were found to have a cancer diagnosis and 5093 (93.3%) did not have a cancer diagnosis. MCD testing identified cancer signals in 323 cases; 244 of those cases were ultimately diagnosed with cancer, indicating a PPV of 75.5% (95% CI 70·5–80.1), NPV of 97.6% (97.1–98.0), sensitivity of 66.3% (61.2–71.1), and specificity of 98.4% (98.1–98.8). The researchers found that sensitivity increased with age and cancer stage (24.2% [95% CI 16.0–34.1] in stage I to 95.3% [88.5–98.7] in stage IV). When an

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individual had cancer and a cancer signal was detected by MCD testing, the MCD test's prediction of site of origin was accurate in 85.2% (95% CI 79.8–89.3) of cases. Individuals with symptoms indicating a potential upper gastrointestinal cancer were found to have the highest sensitivity and NPV for the MCD test at 80.4% (95% CI 66.1–90.6) and 99.1% (98.2–99.6), respectively. The authors assert that this study was the first large-scale prospective evaluation of an MCD in a symptomatic population, and its results indicate that the use of MCD testing to assist clinical providers with decision-making regarding the urgency of follow-up and route of referral from primary care is viable. In addition, they feel that data from this study may be used as a foundation for further prospective study on individuals who present to primary care clinics with non-specific symptoms. Further study is recommended to evaluate the impact of MCD testing on use of resources, clinical decision-making and clinical outcomes.

Klein et al. (2021) documented the results of an observational study to validate a multi-cancer early detection test designed to complement existing screening methods and potentially increase the number of cancers found through population screening, potentially impacting, and improving clinical outcomes. Including 4077 participants in an independent validation set (cancer n = 2823, non-cancer n = 1254), sensitivity, specificity, and cancer signal origin (CSO) were measured. This population was a pre-specified sub-study of the Circulating Cell-free Genome Atlas Study, a prospective, multi-center, observational study designed to collect biological samples (blood and tumor tissue) both from participants with newly diagnosed cancer and from participants without a diagnosis of cancer to characterize population heterogenicity in cancer and cancer-free participants so that models for distinguishing between cancer and non-cancer could be developed. According to the authors, the Atlas study demonstrated that MCED testing using cfDNA in combination with machine learning could detect cancer signals across various cancer types and predict cancer signal origin with high accuracy. The objective of the current study is to further validate an MCED test that has been refined for use as a screening tool. Overall sensitivity for cancer signal detection was 51.5% and showed increasing sensitivity with stage of cancer. Cancer signal detection specificity was 99.5% (95% confidence interval). Cancer signals were detected across more than 50 cancer types. CSO prediction in true positives was 88.7% overall. The researchers concluded that the MCED test showed high specificity and accuracy in prediction of CSO and detected signals across multiple cancer types. A noted limitation is that blood sample collection from participants with cancer done after biopsies had been performed could increase the possibility that tumor cfDNA fraction could also increase relative to pre-biopsy. In addition, CCGA is a case-control study, so would not reflect performance in a screening population. Further studies evaluating test performance and clinical utility in target-use population are needed. This study was included in the LeeVan & Pinsky systematic review discussed above.

In a prospective case-control sub-study of the Atlas and STRIVE studies (NCT02889978 and NCT03085888), the performance of targeted methylation analysis of cfDNA in detecting and localizing multiple cancer types across all stages, with high specificity, was assessed. A total of 6689 participants (2482 with cancer [over 50 types], 4207 without cancer) were grouped into training or validation sets. Cell-free DNA was sequenced, targeting a panel of over 100,000 informative methylation areas. From this, a classifier was developed and validated for detection of cancer and localization of tissue of origin. The publication (Liu et al., 2020) documented consistent performance in both the training and validation sets. In the validation set, specificity was 99.3%. Stage I-III sensitivity was 67.3% in a pre-selected set of 12 cancer types (head and neck, esophagus, liver/bile-duct, anus, colon/rectum, bladder, plasma cell neoplasm, stomach, pancreas, ovary, lung, and lymphoma), which make up approximately 63% of annual cancer deaths in the US. Stage I-III sensitivity was 43.9% in all cancer types, with increase in detection as cancer stage increased. Tissue of original was predicted in 96% of samples with cancer-like signals and of that group, the tissue of origin localization was accurate in 93%. In conclusion, the researchers indicate that cfDNA sequencing using informative methylation patterns warrants further evaluation in prospective, population-level studies. This study was included in the LeeVan & Pinsky systematic review discussed above.

NavDx®

NavDx is a blood test that is meant to detect and measure tumor tissue-modified viral (TTMV) human papillomavirus (HPV) DNA in individuals diagnosed with an HPV-related cancer to confirm tumor HPV genotype, evaluate current treatment response, identify MRD after treatment and potentially detect cancer recurrence earlier than standard follow up surveillance (Naveris, 2023). At present, there is insufficient evidence to support the use of NavDx for use in individuals with HPV-related cancers.

In a 2024 systematic review and meta-analysis, Campo et al. evaluated the sensitivity, specificity, and accuracy of circulating tumor HPVDNA (ctHPVDNA) and TTMV-HPVDNA by digital drop PCR (ddPCR) to determine the efficacy and limitations for its use in post-treatment surveillance of HPV+ oropharyngeal squamous cell carcinoma (OPSCC). Twelve studies comprising 1311 participants were included in the meta-analysis. In 398 individuals, HPVDNA was evaluated by ctHPVDNA, and TTMV-HPVDNA was used to evaluate 913. The results showed pooled sensitivity and specificity of 86% (95% CI: 78%-91%) for ctHPVDNA and 96% (95% CI: 91%-99%) for TTMV-HPVDNA. Pooled diagnostic odds ratio

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(DOR) was 371.66 and the area under the curve (AUC) was 0.81 (95% CI, 0.67–0.91). The authors concluded that the use of cell-free DNA may be helpful for detecting earlier recurrence in individuals with HPV+OPSCC; however, these testing methodologies and protocols require standardization before they can be routinely used in clinical setting. Further research including prospective studies with larger numbers of participants and improvement in the test sensitivity are needed. Publication by Berger et al. (2022), previously discussed in this policy, was included in the Campo et al. systematic review and meta-analysis.

Hayes published a Molecular Test Assessment in 2023 addressing the use of NavDx for the detection and measurement of circulating TTMV HPV DNA in HPV-related cancer. The assessment found that the overall body of evidence for the NavDx test is limited. Only one poor-quality study (Berger et al., 2022) meeting inclusion criteria assessed the currently marketed NavDx test. This study evaluated a single use of the test (monitoring for recurrence); it reported limited data for clinical performance, did not compare the NavDx test with the current standard care surveillance schedule or another assessment method, and lacked follow-up for patients with negative tests. No studies evaluated the clinical utility of the NavDx test to impact treatment decision-making or patient clinical outcomes for any use. No studies evaluated the clinical validity of the NavDx test to confirm tumor HPV genotype, assess current treatment response, or identify MRD posttreatment. The 2024 annual review of the NavDx Molecular Test assessment indicates that evidence newly published since the prior assessment is unlikely to change the current Hayes rating. (Hayes, NavDx [Naveris], 2023, updated 2024).

An ECRI clinical evidence assessment evaluating NavDx for detecting recurrence of HPV-associated cancers concluded that based on evidence from two diagnostic cohort studies, NavDx may add incremental value for identifying HPV-associated oropharyngeal squamous cell cancer (SCC) recurrence when used in addition to standard surveillance. However, available studies primarily focused on HPV-16 which makes in unclear how well it works for other HPV subtypes. Furthermore, there are no published data on the clinical utility of the NavDx on patient management or outcomes (ECRI, 2023).

In a 2023 publication, Ferrandino et al. reported on the accuracy of TTMV HPV DNA testing via liquid biopsy for the diagnosis and monitoring of individuals with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). In this retrospective, observational cohort study including 399 participants, 163 were in the diagnostic cohort and 290 were in the surveillance cohort. In the diagnostic cohort, 152/163 participants had HPV-associated OPOSCC and 11/163 had HPV-negative OPSCC. For this group, sensitivity of TTMV HPV DNA in pretreatment diagnosis was 91.5% (95% CI, 85.8%-95.4% [139 of 152 tests]), and specificity was 100% (95% CI, 71.5%-100% [11 of 11 tests]). In the surveillance cohort, 593 tests were conducted in the 290 participants. Molecularly confirmed pathological recurrences occurred in 23 individuals. The TTMV HPV DNA test exhibited a sensitivity of 88.4% (95% CI, 74.9%-96.1% [38 of 43 tests]) and specificity of 100% (95% CI, 99.3%-100% [548 of 548 tests]) in identifying recurrences. The PPV was 100% (95% CI, 90.7%-100% [38 of 38 tests]), and the NPV was 99.1% (95% CI, 97.9%-99.7% [548 of 553 tests]). Median time from positive TTMV HPV DNA test to pathologic confirmation was 47 (0-507) days. The authors concluded that this cohort study revealed a 100% specificity of the TTMV HPV DNA assay when used in a clinical setting for both diagnosis and surveillance. Sensitivity, however, was 91.5% for the diagnosis cohort and 88.4% for the surveillance cohort, indicating false negatives in nearly 1 in 10 negative results. Further research in high-quality studies is needed to validate the performance of this assay, after which appropriate use of the assay and clinical usefulness will also need to be established. (This study is included in the systematic review and meta-analysis by Campo et al., 2024.)

In a 2022 cross-sectional study, Rettig et al. analyzed plasma from 110 individuals with initial or recurrent HPV positive OPSCC (without distant metastases) using a digital droplet polymerase chain reaction (PCR)-based assay (NavDx®, Naveris Inc., Waltham, MA). This assay assesses tumor tissue–derived HPV DNA in plasma. The objective was to describe the clinical, pathologic, and imaging features associated with TTMV-HPV DNA. Circulating TTMV-HPV DNA was found in 98 individuals and was most strongly associated with clinical N stage. Few individuals (n = 11) had N0 stage disease and only four of these (36%) had detectable DNA. In subjects with clinical stage N1-N3 disease, 94/99 (95%) had detectable DNA. Of subjects with undetectable TTMV-HPV DNA, over half (seven of twelve) had clinical stage N0 disease. The majority of individuals had computerized tomography (CT) and positron emission tomography (PET) scans available; TTMV-HPV DNA prevalence and score increased with progressively higher clinical nodal stage, diameter of largest lymph node, and higher nodal maximum standardized uptake value on PET/CT. In addition, the size of the largest cervical lymph node was more closely associated with the circulating TTMV-HPV DNA than it was with the size of the primary tumor. The authors concluded that circulating TTMV-HPV DNA detection and score were strongly associated with nodal disease in individuals with HPV-positive OPSCC, and the cause of this association as well as the use of this assay for surveillance merit further investigation. This study is limited by a relatively small number of participants, especially in certain subgroups, and potential author biases.

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Tumor-Informed and Tumor-Naive MRD Assays (e.g., Signatera)

Signatera is an individualized molecular test that detects circulating tumor DNA (ctDNA) in the blood of individuals who have been diagnosed with cancer. The test assesses molecular residual disease (MRD) following definitive treatment to monitor response and/or detect recurrence after remission. Signatera uses a whole exome sequencing-based, tumor-informed approach to target specific mutations present in tumor tissue (Natera Inc., 2024). Currently, evidence to support clinical utility of Signatera use for monitoring response to treatment or for surveillance after treatment is lacking.

A retrospective analysis of the effect of ctDNA monitoring on the identification and subsequent management of recurrence in 108 individuals with resected early-stage non-small cell lung cancer (NSCLC) was performed by Martin et al. in 2024. Signatera was used to detect and measure ctDNA at three-month intervals after cancer resection with curative intent had been performed. The study took place between October 2021 and March 2023 and at least one ctDNA measurement post-operatively and one CT scan report post-operatively were required for inclusion in the analysis. ctDNA-positive test results were the primary outcome measured. A secondary outcome assessed was change in treatment plan after ctDNA-positive result. A total of 11.1% (n = 12) of the study participants were found to have ctDNA-positive results at one or more measurement intervals after surgery. Of these, eight participants (66.7%) had a clinically identifiable recurrence. The remaining four participants had limited clinical follow-up assessments. Overall, ten of the study participants developed recurrent disease and eight of these participants had ctDNA positivity. Brain-only metastases were found in the remaining two participants with recurrence. Of the 12 participants with ctDNA-positivity, 100% had a change in post-operative clinical care; all twelve participants with ctDNA-positive results underwent an early positron emission tomography scan with 66.6% found to be positive for characteristics of malignancy. The authors concluded that routine monitoring of ctDNA after curative intent therapy may improve risk stratification and prognostic ability in this population. However, the small number of participants in this study coupled with its retrospective design limit its quality. In addition, some participants were not compliant with the regularly scheduled testing intervals and the providers involved in care of the participants were not blinded to ctDNA results when making decisions regarding their surveillance and adjuvant treatments. Lastly, several of the authors were employees of the company that manufactures the assay used in this study. Further high-quality, prospective studies with larger cohorts and longer follow up times are needed to validate these early results and help develop best-practice strategies.

Another retrospective analysis focused on the use of Signatera to detect MRD in ctDNA was performed by Emiloju et al. in 2024, this time in individuals with stage II-IV colorectal cancer (CRC). The researchers examined the clinical records of 120 individuals with CRC who had undergone at least one tumor-informed ctDNA assay. A total of 476 ctDNA assays were performed on the 120 subjects. Seventy percent of the assays were administered for individuals who had recurrent disease, most often to monitor effectiveness of treatments provided. Only 16% of the total assays performed led to a change in clinical decision-making. Overall, 62 individuals experienced a total of 110 recurrences (some subjects had more than one recurrence). The authors determined that the results of this study show that although ctDNA for MRD detection may be helpful for certain individuals with CRC, 84% of the total assays included in this analysis resulted in no change to clinical decision-making, which highlights the need for additional study in high-quality clinical trials.

In a Molecular Test Assessment (Hayes, Signatera [Natera Inc.], 2023, updated 2024) Signatera was evaluated for use in both monitoring response during treatment and monitoring for recurrence after treatment in individuals with solid tumor cancers. Hayes identified nine studies which assessed the clinical validity of Signatera, but no peer-reviewed articles that reported impact on clinical decision-making or an improvement in outcomes related to the use of Signatera, Significant questions exist regarding appropriate selection of individuals for testing and most effective timing of testing. In addition, the studies identified by Hayes had a wide variation in cancer types and treatments and overall quality was poor. At this time, evidence is insufficient to support the use of Signatera for both monitoring response and detecting recurrence. Hayes notes, however, that there are multiple ongoing clinical trials evaluating these outcomes. The 2024 annual review of this Hayes assessment indicates that recently published evidence is unlikely to change the current Hayes rating for this test.

In a retrospective, single-center cohort study, Fakih et al. (2022, included in the 2023 Hayes Signatera Molecular Test Assessment) evaluated the comparative surveillance strategies of ctDNA assay (Signatera) with standard radiographic imaging and carcinoembryonic antigen (CEA) levels per NCCN guidelines in individuals with resected CRC. Out of 48 individuals with curatively resected CRC, 15 had disease recurrence during surveillance. Confirmation via imaging was made on nine individuals, and positive ctDNA confirmed disease recurrent in 8, CEA levels in 3 individuals and combined imaging with CEA levels in 11 individuals. According to the numbers, ctDNA did not perform better than imaging in detecting recurrence, as sensitivity results were 53.3% (95% CI, 27.4%-77.7%) and 60% (95% CI, 32.9%-82.5%), respectively (p > .99). The combination of imaging plus measurement of CEA levels (sensitivity, 73.3% [95% CI, 44.8%-91.1%]) had a numerical advantage compared with ctDNA in identifying recurrence (p = .55). In addition, authors noted no significant difference among ctDNA (median, 14.3 months), imaging (median, 15.0 months), or imaging plus measurement

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of CEA levels (median, 15.0 months) in the time to identify disease recurrence. The study is limited by its small size, a small number of reoccurrences, and short follow-up. The authors concluded that the findings show that ctDNA assay (Signatera) may not supply definitive advantages as a surveillance strategy compared to standard imaging combined measurement of CEA levels when performed per NCCN guidelines. Additional prospective studies focusing on the correlation between low-burden lung recurrence and negative ctDNA findings should be investigated further.

The use of ctDNA as a prognostic biomarker for relapse of metastatic colorectal cancer (mCRC) was the subject of a cohort study by Loupakis et al. (2021, included in the 2023 Hayes Signatera Molecular Test Assessment). In this study, 112 individuals with mCRC were evaluated. These participants were part of the PREDATOR clinical trial and had undergone resection of metastases with curative intent. In this study, evaluation of the prognostic value of ctDNA was performed by correlating clinical outcomes with molecular residual disease (MRD) status after surgery using a tumor-informed, personalized ctDNA assay (Signatera). MRD positive results were found in 54.4% of the participants after surgery. Of those, 96.7% progressed at the time data collection ended. Positive results were also associated with lower overall survival. At the time of data analysis, 96% of all study participants in the MRD-negative arm of the study were living, compared with only 52.4% in the MRD-positive arm. For individuals who were MRD-negative in the combined ctDNA analysis at both points in time and did not receive systemic therapy, overall survival rate was 100%. When multivariate analysis was performed, the most significant prognostic factor associated with disease -free survival was ctDNA based MRD status. The researchers concluded that post-operative MRD evaluation is a strong biomarker in individuals with mCRC undergoing metastatic resection and feel that it has potential use in clinical decision-making. Further clinical studies will be needed to support use of this technology in the future.

Magbanua et al. (2021, included in the 2023 Hayes Signatera Molecular Test Assessment) evaluated the clinical utility of ctDNA to test for risk of metastatic recurrence and predictive ability of pathologic complete response (pCR) for individuals with early BC. A retrospective ancillary ctDNA study was performed on samples that had been prospectively collected from high-risk individuals with early BC that were part of the multicenter neoadjuvant I-SPY2 TRIAL. Eligibility requirements included tumor size ≥ 2.5-cm and stage II/III BC. Participants with *de novo* metastatic disease were not included in the study. In addition, eligibility was limited to individuals who had received a MammaPrint high score. On pretreatment testing, 73% of participants were ctDNA positive. Those participants who continued to be ctDNA positive 3 weeks after initiation of paclitaxel were significantly more likely to have residual disease after neoadjuvant chemotherapy (NAC) when compared to those who were no longer ctDNA positive. All individuals who achieved pCR after NAT were ctDNA negative. For participants who did not achieve pCR, ctDNA positive results had a significantly increased risk of metastatic recurrence. Notably, participants who were ctDNA negative but who did not achieve pCR still had excellent outcomes. In this study, lack of ctDNA clearance significantly predicted poor response and metastatic recurrence of cancer. Clearance of ctDNA was associated with improved survival. The researchers concluded that personalized testing of ctDNA during NAC may assist with clinical assessment and treatment in early BC. Noted limitations include the inability of the Signatera test to detect new second primary cancers and novel somatic variants that may have arisen during tumor evolution. Further studies are required, including those that simultaneously evaluate ctDNA and circulating tumor cells in the neoadjuvant setting.

Reinert et al. (2019, included in the 2023 Hayes Signatera Molecular Test Assessment) reported results of a prospective, multi-center cohort study designed to analyze how ctDNA is associated with CRC recurrence. Ultradeep sequencing of plasma cell-free DNA was performed in study participants with CRC before pre- and post-surgery, during and after adjuvant chemotherapy (ACT), and during the surveillance period. The study took place in Demark and evaluated 125 individuals with stages I to III CRC. Plasma samples were obtained prior to surgery, after surgery (day 30) and ongoing every third month for up to 3 years. In the pre-surgery period, ctDNA was detected in 88.5% of participants. Post definitive treatment, ctDNA analysis identified 87.5% of relapses and at post-op day 30, ctDNA-positive participants were 7 times more likely to suffer relapse that those with negative ctDNA results. After ACT, ctDNA participants with positive results were 17 times more likely to relapse. During and after undergoing ACT, monitoring of participants found that 30% of the ctDNA positive individuals were cleared of disease. In the post-therapy period, ctDNA-positive participants were more than 40 times more likely to have a recurrence of their disease than the ctDNA-negative participants. Actionable mutations were found in 81.8% of the relapse samples that were ctDNA-positive. The researchers concluded that ctDNA analysis has potential to be helpful with postoperative management of CRC, in terms of early relapse detection, ACT monitoring and risk stratification. However, the sample size of participants with recurrent CRC in this study was small and analysis was done on multiple different subsets. This study provides a base for further clinical trials investigation the use of ctDNA in management of CRC and other diseases.

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Solid Tumor Profiling Including Whole Exome, Whole Genome, and/or Whole Transcriptome Sequencing

Molecular assays using whole exome, whole genome, and/or whole-transcriptome sequencing to detect clinically meaningful somatic variations in tumor tissue have been developed. There is currently insufficient evidence in the peer-reviewed clinical literature to support the use of these tests to provide molecular information intended to inform clinical decision-making for individuals with cancer.

To explore the use of RNA next-generation sequencing (NGS) for the detection of fusions and splicing variations in individuals with non-small cell lung cancer (NSCLC), Owen et al. (2024) performed a multisite, retrospective cohort study using the Tempus xR assay (tissue-based whole transcriptome RNA sequencing) and the Tempus xT assay, version 4 (tissue-based DNA sequencing). The primary outcome assessed was detection rates of NCCN guideline-based structural variants that were uniquely identified by RNA-NGS. Included participants (n = 5570) had sufficient tissue quantity for both RNA-NGS and DNA-NGS testing. Overall, the frequency of actionable structural variant detection was 8.8% (n = 491) with 86.7% of those variants detected via DNA-NGS. Performing concurrent DNA-NGS and RNA-NGS led to the detection of 15.3% more participants with actionable structural variants (aSV) compared to use of only DNA-NGS (491 vs 426 participants, respectively). No significant association was found between the assay that was used for aSV identification and aSV-targeted therapeutic adoption or clinical outcome. These results suggest that the identification of aSV through the use of concurrent RNA-NGS and DNA-NGS is higher across NCCN guideline-recommended biomarkers than the use of DNA-NGS alone, leading the authors to conclude that RNA-NGS should be considered for routine use in the clinical care of individuals with advanced NSCLC. The study was limited by the use of just one commercial NGS platform, and since the study was retrospective, there was incomplete longitudinal data regarding therapy selection and time-to-next-treatment analyses which led to small cohort sizes and thus, potential difficulty detecting statistical differences between DNA-NGS and RNA-NGS. In addition, differences in assay failure rates between DNA-NGS and RNA-NGS were not accounted for in this study. Further high-quality, prospective studies are recommended to validate these findings and further investigate the use of RNA-NGS use as a companion diagnostic test.

Pleasance et al. (2022) performed whole-genome and transcriptome sequencing and analysis (WGTA) on samples from 570 individuals with various types of advanced or metastatic cancer to identify and prioritize clinically actionable genomic variations and potentially inform treatment decisions. Participants were enrollees in the Personalized OncoGenomics (POG) program (NCT02155621), a single-arm prospective trial with primary objectives of: 1) determining the feasibility of integrating WGTA in advanced cancer populations, 2) understanding the frequency of clinically actionable findings using WGTA and the potential rate of WGTA-informed therapy, and 3) obtaining better understanding of the genomics involved in advanced and pre-treated cancers. In the Pleasance study, DNA-based information was combined with RNA-based information to produce comprehensive WGTA profiles which were then reviewed by a multidisciplinary team. A total of 83% of participants had clinically actionable targets, and of those, 37% went on to receive WGTA-informed treatment. The researchers found RNA expression data to be the most informative, with contributions to 67% of WGTA-informed treatments. Twenty-five percent of treatments were guided by RNA expression only. Forty-six percent of WGTA-informed treatments resulted in a clinical benefit. Based on these results, the authors contend that their study exhibits the potential benefit of using whole genome and transcriptome sequencing in the individualized care of persons affected with cancer. A noted barrier in the study was limited access to drugs that were related to WGTA results obtained; this underscores the need for access to approved off-label treatments and clinical trials to enhance potential for clinical action. An additional limitation was the lack of evaluation of impact of WGTA on overall survival.

A 2022 prospective precision medicine trial (Summers et al.) used whole exome sequencing (WES) of tumor and germline tissue and whole transcriptome RNA sequencing of tumor tissue to assess genomic variations in 127 tumors from 126 unique pediatric participants. The researchers identified somatic tumor variations in 95.3% of the participants. Cancer predisposition syndromes based on known pathogenic or likely pathogenic germline mutations were detected in 7.1% of the participants. In addition, they created a scoring system for measuring the impact of tumor and germline testing; at least one impactful finding from genomic testing was found in 85% of samples sequenced (108/127z). In 65.1% (82/126) of participants, recommendation for consideration of a targeted agent was made and 20 participants went on to receive targeted therapy based on their results (24% of those receiving a recommendation and 16% of the total cohort). The authors concluded that paired tumor/normal WES and tumor whole transcriptome sequencing of de novo or relapsed/refractory tumors was possible and could have a significant clinical impact in individuals with high-risk pediatric cancers. Limitations included small sample size and lack of long term outcome data.

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Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

ASCO's 2022 publication (Henry et al.) updating to their Biomarkers for Systemic Therapy in Metastatic Breast Cancer guideline (Henry et al., 2022) indicates that there are "insufficient data to recommend routine use of ctDNA or circulating tumor cells to monitor response to therapy among patients with metastatic breast cancer" (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

In a 2022 ASCO provisional opinion addressing somatic testing for individuals with metastatic or advanced cancer, Chakravarty et al. note that there is substantial interest in the detection of MRD for individuals whose recurrent cancer is not yet detectable by imaging. Studies evaluating several types of tumors have shown potential for the use of ctDNA to identify individuals who may be at higher risk for recurrence. However, no specific recommendations regarding the use of ctDNA for detection of MRD are made in this document.

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

Merker et al. (2018) published a joint review from ASCO and CAP assessing the clinical use of ctDNA. The researchers performed a literature review and identified 1339 references. Of these references, 390 plus an additional 31 supplied by the researchers were evaluated. The literature review ultimately included 77 references and stated that while some ctDNA tests have demonstrated clinical validity and utility with specific advanced stage cancer, overall, there is insufficient evidence of clinical validity and utility for the majority of these assays in this stage of cancer. The researchers also noted that there is no evidence of clinical utility and little evidence of clinical validity of ctDNA tests in early-stage cancer, treatment monitoring, or residual disease detection. Likewise, no evidence of clinical validity and utility was demonstrated in the literature review for the use of ctDNA in cancer screening.

European Society for Medical Oncology (ESMO)

A 2022 ESMO publication (Pascual et al.) made recommendations specific to the use of ctDNA for individuals with cancer. Regarding the detection of MRD, the authors indicates that for individuals treated for early-stage cancers, there is strong evidence of validity for the prediction of future relapse for several cancer types, however MRD detection cannot be recommended for routine clinical practice as there is insufficient evidence for clinical utility in terms of directing treatment. The authors go on to state that for advanced cancer monitoring, there is "insufficient evidence to use regular monitoring of ctDNA during therapy. Although early ctDNA dynamics associate strongly with outcome, and resistance mutations may be identified many months before clinical progression, there is insufficient evidence that acting on such findings improves outcome". Lastly, with respect to the use of ctCNA for other purposes such as multi-cancer screening, ESMO states that "at this point, screening cannot be considered as a validated use for ctDNA assays."

National Institute for Health and Care Excellence (NICE)

In 2022, NICE published a Medtech innovation briefing on Signatera for detecting MRD from solid tumor cancers. In summary, the briefing outlines the lack of prospective evidence on the utilization of Signatera in clinical practice or its effect on treatment decisions or clinical outcomes. Additionally, experts advised there is insufficient evidence to support the use of the technology routinely in the NHS. The experts point out their advice is in line with the recommendations from the ESMO on the use of ctDNA. Many ongoing trials may address the gaps in the evidence in the future.

National Comprehensive Cancer Network (NCCN)

Head and Neck Cancers

In Head and Neck Cancers (version 2.2025), NCCN states "the performance of various plasma cell-free HPV DNA detection assays (preferably validated per CLIA and CAP regulatory guidelines) for a diagnosis of HPV-positive oropharyngeal cancer against a gold standard of E6/E7 mRNA detection is unknown. Sensitivity and specificity against p16-IHC are approximately 90% and 94%, respectively. At this time, persistent cell-free oncogenic HPV DNA detection in plasma (among those positive and quantifiable at diagnosis) may identify patients at increased risk for progression after completion of curative intent therapy. However, without concurrent clinical, radiographic, or pathological correlates represents an outcome without actionable therapeutic implications outside of clinical trials."

Breast Cancer

NCCN addresses the clinical use of circulating tumor cells (CTC) or ctDNA for monitoring of metastatic disease in its Breast Cancer (version 6.2024) guidelines, stating, "the clinical use of Circulating Tumor Cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring"). This guideline does not discuss or make recommendations regarding testing for MRD.

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Colon Cancer

Per NCCN (Colon Cancer, version 5.2024), post-surgical ctDNA assessment has been studied as a potential predictor for increased risk of recurrence in stage I-III colon cancer, however the value of this information has not been fully determined. Evidence substantiating predictive capabilities related to the benefit of chemotherapy is insufficient. NCCN's colon cancer expert panel finds a lack of data to recommend the use of multigene assays, Immunoscore, or use of post-surgical ctDNA to estimate risk of recurrence or to assist with decision-making regarding adjuvant therapy. The panel highlights the importance of ongoing clinical trials to further expand knowledge and provide data on these tests.

Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate

In its 2.2025 guidelines, NCCN briefly mentions pre-symptomatic ctDNA cancer detection assays, stating that these assays "should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical

utility and determine clinical validity, are not fully defined. The psychological impact of ctDNA testing remains unknown. For these reasons, ctDNA should not be used, outside of the clinical trial setting, to replace well-established methods of cancer screening (e.g., mammography).

Rectal Cancer

For adjuvant treatment or surveillance following operative management of rectal cancer, NCCN (Rectal Cancer, version 4.2024) states, "Circulating tumor DNA (ctDNA) is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial." The guideline also indicates that ctDNA has no proven role in the nonoperative management of rectal cancer.

Melanoma: Cutaneous

In NCCN's Cutaneous Melanoma guidelines (version 3.2024), it is noted that existing and emerging molecular techniques such as ctDNA tests should be prospectively compared to determine clinical utility. No recommendations regarding ctDNA are made in this guideline.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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 22, 2025)

A list of nucleic acid-based tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed January 24, 2025)

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Policy History/Revision Information

Date	Summary of Changes
02/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect annual edits; added 0611U, 0612U, 0613U, and 81524 **Supporting Information** • Archived previous policy version CS152NJ.AD

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