Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Policy Number: MMP210.35
Last Committee Approval Date: May 13, 2026
Effective Date: June 1, 2026

Instructions for Use

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Related Medicare Advantage Medical Policies

- Clinical Diagnostic Laboratory Services
- Molecular Pathology/Genetic Testing Reported with Unlisted Codes
- Pharmacogenomics Testing
- Tier 2 Molecular Pathology Procedures
- Urogenital/Anogenital (UG/AG) Panels

Related Reimbursement Policies

- Clinical Laboratory Improvement Amendments (CLIA) ID Requirement Policy, Professional
- Laboratory Services Policy, Professional
- Molecular Pathology Policy, Professional and Facility

Related Commercial Policy

- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions

Coverage Rationale

Overview

A molecular diagnostic test (MDT) is any test that involves the detection or identification of nucleic acid(s) deoxyribonucleic acid/ribonucleic acid (DNA/RNA), proteins, chromosomes, enzymes, cancer chemotherapy sensitivity and/or other metabolite(s). The test may or may not include multiple components. A MDT may consist of a single mutation analysis/identification, and/or may or may not rely upon an algorithm or other form of data evaluation/derivation.

A laboratory developed test (LDT) is any test developed by a laboratory developed without Food and Drug Administration (FDA) approval or clearance.

CMS National Coverage Determinations (NCDs)

For the tests in this policy that utilize the Next Generation Sequencing technology, Medicare does not have an NCD. NCD 90.2 *Next Generation Sequencing (NGS)* is applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancer. For coverage guidelines of those tests, refer to NCD 90.2 Next Generation Sequencing (NGS). Medicare Administrative Contractors (MACs) may determine coverage of diagnostic lab tests using NGS for ribonucleic acid (RNA) sequencing and protein analysis.

CMS Local Coverage Determinations (LCDs) and Articles

Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) exist for tests in this policy that utilize the Next Generation Sequencing technology and compliance with these policies is required where applicable. LCDs/LCAs also exist for molecular tests in this policy that do not utilize the Next Generation Sequencing technology. For specific molecular testing LCDs/LCAs, refer to the table for Molecular Pathology/Molecular Diagnostics/Genetic Testing.

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For coverage guidelines for states/territories with no LCDs/LCAs, or when the LCDs/LCAs are silent on coverage criteria, refer to the covered and non-covered indications below.

Covered Indications

ABL1 (ABL Proto-Oncogene 1, Non-Receptor Tyrosine Kinase) Kinase Domain

ABL1 gene analysis, variants in the kinase domain is considered reasonable and necessary in patients with acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML) to guide therapeutic decision making.

ASXL1 (Additional Sex Combs Like 1, Transcriptional Regulator)

ASXL1 gene analysis is considered reasonable and necessary for prognosing patients with acute myeloid leukemia, myeloproliferative disease [MPD - essential thrombocytosis (ET), myelofibrosis & polycythemia vera (PV)], and myelodysplastic syndrome (MDS).

BDX-XL2 (Oncology Lung)

BDX-XL2 test (Biodesix, Seattle, WA) is reasonable and necessary for the management of a lung nodule, between 8 and 30 mm in diameter, in patients 40 years or older, and with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less. The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.

JAK2 (Janus Kinase 2) and MPL (MPL Proto-Oncogene, Thrombopoietin Receptor) (Myeloproliferative Disorders)

Genetic testing of *JAK2* exon 12 is reasonable and necessary in the initial work-up of *JAK2* (V617F variant) negative adults with clinical, laboratory, or pathological findings suggesting polycythemia vera.

Genetic testing of the *MPL* gene is reasonable and necessary in the initial work-up of *BCR-ABL* negative and *JAK2* (V617F variant) negative adults with clinical, laboratory, or pathological findings suggesting thrombocytosis, essential thrombocythemia (ET), or primary myelofibrosis (PMF).

KIT (V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog)

KIT gene analysis is considered reasonable and necessary in patients who have gastrointestinal stromal tumor (GIST), acute myeloid leukemia (AML), melanoma, and myeloproliferative disease [MPD-essential thrombocytosis (ET), myelofibrosis & polycythemia vera (PV)] to guide therapeutic decision making.

myPath Melanoma

The purpose of this test is to assist dermatopathologists to arrive at the correct diagnosis of melanoma vs non-melanoma when examining skin biopsies. Molecular deoxyribonucleic acid (DNA)/ribonucleic acid (RNA) assays that aid in the diagnosis or exclusion of melanoma from a biopsy are reasonable and necessary when **all** of the following clinical conditions are met:

- The test is ordered by a board-certified or board-eligible dermatopathologist
- The specimen is a primary (non-metastatic, non-re-excision specimen) cutaneous melanocytic neoplasm for which the diagnosis is equivocal/uncertain (i.e., clear distinction between benign or malignant cannot be achieved using clinical and/or histopathological features alone) despite the performance of standard-of-care test procedures and relevant ancillary tests (i.e., immunohistochemical stains)
- The specimen includes an area representative of the lesion or portion of the lesion that is suspicious for malignancy
- The patient may be subjected to additional intervention, such as re-excision and/or sentinel lymph node biopsy, as a result of the diagnostic uncertainty
- The patient has not been tested with the same or similar assay for the same clinical indication
- The test is validated for use in the intended-use population and is performed according to its stated intended-use

Oncotype DX Breast Cancer Assay [Oncology Breast Messenger Ribonucleic Acid (mRNA)]

Oncology (breast), mRNA, gene expression profiling by real-time reverse transcription polymerase chain reaction (RT-PCR) of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score is considered reasonable and necessary to guide therapeutic decision-making in patients with the following findings:

- Estrogen-receptor positive, node-negative carcinoma of the breast
- Estrogen-receptor positive micrometastases of carcinoma of the breast

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- Estrogen-receptor positive breast carcinoma with 1-3 positive nodes

Oncotype DX Breast DCIS Score Test (Ductal Carcinoma In Situ)

Oncotype DX® DCIS assay (Genomic Health, Inc., Redwood City, CA) is reasonable and necessary for women diagnosed with DCIS who are planning on having breast conserving surgery and considering adjuvant radiation therapy.

PDGFRA (Platelet-Derived Growth Factor Receptor, Alpha Polypeptide)

PDGFRA gene analysis is considered reasonable and necessary in patients with *PDGFRA*-associated chronic eosinophilic leukemia or gastrointestinal stromal tumor (GIST) caused by mutations in the *PDGFRA* gene to guide therapeutic decision making.

Pigmented Lesion Assay (PLA) (Oncology Melanoma)

The PLA is reasonable and necessary for use on melanocytic skin lesions with one or more clinical or historical characteristics suggestive of melanoma, including one or more ABCDE (Asymmetry, Border, Color, Diameter, Evolving) criteria when a clinician trained in the clinical diagnosis of skin cancer is considering the need for biopsy to rule out melanoma. The PLA should not be used on clinically obvious melanoma. The PLA result is one element of the overall clinical assessment, and should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.

PIK3CA (Phosphatidylinositol-4, 5-Biphosphate, 3-Kinase, Catalytic Subunit Alpha)

The United States Food and Drug Administration (U.S. FDA) has approved Piqray (alpelisib) tablets, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression on or after an endocrine-based regimen. *PIK3CA* testing is reasonable and necessary for this indication.

In addition to utilizing the coverage rationale referenced above in states/territories with no LCDs/LCAs, UnitedHealthcare also uses the criteria above to supplement the general Medicare criteria within the National Government Services (NGS) jurisdiction regarding when *PIK3CA* testing is reasonable and necessary. UnitedHealthcare uses the criteria noted above in order to ensure consistency in reviewing the conditions to be met for coverage of *PIK3CA* testing. Use of these criteria to supplement the coverage criteria noted above provides clinical benefits by identifying *PIK3CA*-mutated breast cancer, which has shown a clinical benefit in individuals taking alpelisib with fulvestrant for treatment of HR +, HER2-, *PIK3CA*-mutant advanced breast cancer after CDK4/6i treatment. Specifically, there was a 7.9-month numeric improvement in median overall survival when alpelisib was added to fulvestrant treatment of individuals with *PIK3CA*-mutated, HR +, HER2- advanced breast cancer. The added criteria will also provide numerous clinical benefits by guiding the treatment plan and medication regimen for this specific type of breast cancer. The potential clinical harms of using these criteria may include denying claims in the NGS jurisdiction since there are no concrete clinical guidelines. However, with no specific clinical guidelines for this test, claims may be inappropriately allowed for indications other than the Food and Drug Administration (FDA) approved indications for Piqray. The clinical benefits of using these criteria are highly likely to outweigh any clinical harms because the criteria will ensure this test is being used when reasonable and necessary, based on the clinical studies shown in this policy including a study of individuals with *PIK3CA*-mutant disease with prior CDK4/6i plus hormone therapy. In post matching and unadjusted results, primary and secondary endpoints were in favor of treatment with alpelisib with fulvestrant over standard treatments. For other indications such as colorectal cancer, prostate cancer, and borderline ovarian tumors, there is insufficient evidence to support *PIK3CA* testing.

RiskReveal (Formerly DetermaRx) (Oncology Lung)

Molecular classifiers for non-small cell lung cancer (NSCLC) are considered reasonable and necessary when members meet all of the following criteria:

- The individual has a non-squamous NSCLC with a tumor size < 5 cm, and there are no positive lymph nodes (i.e., American Joint Committee on Cancer (AJCC) Eighth Edition Stages I and IIa)
- The individual is sufficiently healthy to tolerate chemotherapy
- Adjuvant platinum-containing chemotherapy is being considered for the individual
- The test is ordered by a physician who is treating the individual for NSCLC (generally a medical oncologist, surgeon, or radiation oncologist) to help in the decision of whether or not to recommend adjuvant chemotherapy

TERT (Telomerase Reverse Transcriptase)

TERT gene analysis is considered reasonable and necessary in patients with malignant neoplasm of the brain.

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Thyroseq Genomic Classifier, ThyGeNEXT, ThyraMIR, and Afirma

ThyroSeq® is a test utilized to better define the need for thyroid surgery and the type of such surgery. ThyraMIR® is used as a companion test to ThyGeNEXT® when ThyGeNEXT results are inconclusive. ThyroSeq, ThyraMIR, ThyGeNEXT and Afirma® services are reasonable and necessary for patients with any of the following conditions:

- An indeterminate pathology on fine needle aspiration
- Patients with one or more thyroid nodules with a history or characteristics suggesting malignancy such as:
  - Nodule growth over time
  - Family history of thyroid cancer
  - Hoarseness, difficulty swallowing or breathing
  - History of exposure to ionizing radiation
  - Hard nodule compared with rest of gland consistency
  - Presence of cervical adenopathy

Non-Covered Indications

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death (e.g., Canavan disease) are not reasonable and necessary since these tests are generally not relevant to a Medicare member.

The following types of genetic tests are examples of services that are not relevant to a Medicare member, are not considered a Medicare benefit (statutorily excluded), and therefore will be denied as Medicare excluded tests:

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law
- Tests performed to determine carrier screening
- Prenatal diagnostic testing
- Tests performed on patients without signs or symptoms to determine risk for developing a disease or condition
- Tests without diagnosis specific indications

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition are not a Medicare benefit and are not covered.

In accordance with the Code of Federal Regulations, Title 42, Subchapter B, Part 410, Section 410.32, the referring/ordering practitioner must have an established relationship with the patient, and the test results must be used by the ordering/referring practitioner in the management of the patient's specific medical problem.

Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states "...no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis and treatment of illness or injury...".

Therefore, the following tests will be denied:

- **AFF2 [ALF transcription elongation factor 2 (FMR2)]** [e.g., fragile X intellectual disability 2 (FRAXE)]
- **AR (androgen receptor)** (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation)
- **Ashkenazi Jewish Associated Disorders Carrier Screening Panel** (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease)
- **ASPA (aspartoacylase)** (e.g., Canavan disease)
- **BCKDHB (branched - chain keto acid dehydrogenase E1, beta polypeptide)** (e.g., maple syrup urine disease)
- **Cytogenomic (Genome-Wide) Analysis for Constitutional Chromosomal Abnormalities**
- **DMPK (DM1 protein kinase)** (e.g., myotonic dystrophy type 1)
- **F9 (coagulation factor IX)** (e.g., hemophilia B)
- **FANCC (Fanconi anemia, complementation group C)** (e.g., Fanconi anemia, type C)
- **Fetal Chromosomal Aneuploidy** (e.g., trisomy 21, 18, and 13, monosomy X)
- **Fetal Chromosomal Microdeletions** (e.g., DiGeorge syndrome, Cri-du-chat syndrome)
- **FMR1 (fragile X messenger ribonucleoprotein 1)** [e.g., fragile X syndrome, X-linked intellectual disability (XLID)]
- **FXN (frataxin)** (e.g., Friedreich ataxia)
- **G6PD (glucose-6-phosphate dehydrogenase)** (e.g., hemolytic anemia, jaundice)
- **Genetic Testing for Severe Inherited Conditions Carrier Screening Panel** [e.g., cystic fibrosis, Ashkenazi Jewish - associated disorders (e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease), beta hemoglobinopathies, phenylketonuria, galactosemia]
- **Genome Sequencing** (e.g., unexplained constitutional or heritable disorder or syndrome)

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- **HBA1/HBA2 (alpha globin 1 and alpha globin 2)** (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease)
- **HBB (hemoglobin, subunit beta)** (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy)
- **Hearing Loss Panel** (e.g., non-syndromic hearing loss, Usher syndrome, Pendred syndrome)
- **Hereditary Peripheral Neuropathies Panel** (e.g., Charcot-Marie-Tooth, spastic paraplegia)
- **Hereditary Retinal Disorders Panel** (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy)
- **HTT (huntingtin)** (e.g., Huntington disease)
- **IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)** (e.g., familial dysautonomia)
- **MCOLN1 (mucolipin 1)** (e.g., Mucolipidosis, type IV)
- **MECP2 (methyl CpG binding protein 2)** (e.g., Rett syndrome)
- **Nuclear Encoded Mitochondrial Genes Panel** (e.g., neurologic or myopathic phenotypes)
- **PMP22 (peripheral myelin protein 22)** (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies)
- **SMN1 (survival of motor neuron 1, telomeric)** (e.g., spinal muscular atrophy)
- **SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal)** (e.g., Niemann-Pick disease, Type A)
- **SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide n and ubiquitin protein ligase E3A)** (e.g., Prader-Willi syndrome and/or Angelman syndrome)
- **Whole Mitochondrial Genome** [e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERFF), neuropathy, ataxia, and retinitis pigmentosa (NARP), Leber hereditary optic neuropathy (LHON), Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia]
- **X-linked Intellectual Disability (XLID) Panel** (e.g., syndromic and non-syndromic XLID)

Note: In the instance where the tests above are used for symptomatic adults, testing is unlikely to impact therapeutic decision-making in the clinical management of the patient and therefore not reasonable and necessary.

DecisionDx-SCC

Current molecular biomarker tests that risk stratify individuals with cutaneous squamous cell carcinoma (cSCC) are not reasonable and necessary.

Medicare does not have a National Coverage Determination (NCD) for DecisionDx®-SCC. Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) exist and compliance with these policies is required where applicable. For specific LCDs/LCAs, refer to the table for Molecular Pathology/Molecular Diagnostics/Genetic Testing.

For coverage guidelines for states/territories with no LCDs/LCAs or when the LCDs/LCAs are silent on coverage criteria, refer to the UnitedHealthcare Commercial Medical Policy titled Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions.

MTHFR (5,10-Methylenetetrahydrofolate Reductase)

MTHFR genetic testing, which encodes the 5,10-methylenetetrahydrofolate reductase enzyme, for thrombophilia for all risk factors, signs, symptoms, diseases, or conditions, including cardiovascular risk assessment, is not reasonable and necessary. *MTHFR* is not considered to be clinically efficacious; therefore, testing is not reasonable and necessary.

OVERA and ROMA

These multi marker serum tests related to ovarian cancer testing are not reasonable and necessary.

Resolution ctDX Lung

Resolution ctDX Lung™ is not reasonable and necessary for non-small cell lung cancer (NSCLC).

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; however, language may be included in the listing below to indicate if a code is non-covered. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may

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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
Non-Covered	
0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score (Overa®)
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) (Resolution ctDx Lung)
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) (DecisionDx-SCC)
81171	AFF2 [ALF transcription elongation factor 2 (FMR2)] [e.g., fragile X intellectual disability 2 (FRAXE)] gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81172	AFF2 [ALF transcription elongation factor 2 (FMR2)] [e.g., fragile X intellectual disability 2 (FRAXE)] gene analysis; characterization of alleles (e.g., expanded size and methylation status)
81173	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
81174	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
81204	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (e.g., expanded size or methylation status)
81205	BCKDHB (branched - chain keto acid dehydrogenase E1, beta polypeptide) (e.g., maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278S, E422X)
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization (CGH) microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81234	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81238	F9 (coagulation factor IX) (e.g., hemophilia B), full gene sequence
81239	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; characterization of alleles (e.g., expanded size)
81242	FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A > T)
81243	FMR1 (fragile X messenger ribonucleoprotein 1) [e.g., fragile X syndrome, X-linked intellectual disability (XLID)] gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) [e.g., fragile X syndrome, X-linked intellectual disability (XLID)] gene analysis; characterization of alleles (e.g., expanded size and promoter methylation status)
81248	G6PD (glucose - 6 - phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; known familial variant(s)
81249	G6PD (glucose - 6 - phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; full gene sequence

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CPT Code	Description
Non-Covered	
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T > C, R696P)
81271	HTT (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; known familial variant(s)
81290	MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A > G, del6.4kb)
81291	MTHFR (5,10 - methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
81302	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
81324	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide n and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81336	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81361	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (e.g., HbS, HbC, HbE)

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CPT Code	Description
Non-Covered	
81362	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81412	Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81420	Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81430	Hearing loss (e.g., non-syndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (e.g., non-syndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81434	Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81443	Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
81448	Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (e.g., BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81460	Whole mitochondrial genome [e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERFF), neuropathy, ataxia, and retinitis pigmentosa (NARP), Leber hereditary optic neuropathy (LHON)], genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection

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CPT Code	Description
Non-Covered	
81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
81470	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (ROMA™)
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
Provisional Coverage	
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 (ThyraMIR)
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") (Thyroseq® Genomic Classifier)
0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
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 (Oncotype DX Breast DCIS Score® test)
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 [Genomic Prostate Score (GPS)] (Deleted 05/13/2026)
0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy (BDX-XL2)
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) [Pigmented Lesion Assay (PLA)]
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) (myPath® Melanoma)
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (e.g., breast cancer) gene analysis [i.e., p.C420R, p.E542K, p.E545A, p.E545D (g.1635G > T only), p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y], utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status
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 (ThyGeNEXT)
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) (ThyroSeq CRC) (Deleted 04/23/2025)

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CPT Code	Description
Provisional Coverage	
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 (RiskReveal™, formerly DetermaRx™)
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (e.g., exon 12)
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) [e.g., gastrointestinal stromal tumor (GIST), acute myeloid leukemia, melanoma], gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)
81279	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
81314	PDGFRA (platelet derived growth factor receptor, alpha polypeptide) [e.g., gastrointestinal stromal tumor (GIST)], gene analysis, targeted sequence analysis (e.g., exons 12, 18)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81345	TERT (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (e.g., promoter region)
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 (Oncotype DX Breast Cancer Assay)
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) (Afirma)
88120	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual (UroVysion®) (Deleted 04/23/2025)
88121	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology (UroVysion) (Deleted 04/23/2025)

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Diagnosis Codes
Refer to Molecular Pathology/Molecular Diagnostics/Genetic Testing: Diagnosis Code List for diagnosis codes for CPT codes 0018U, 0026U, 0027U, 0045U, 0047U, 0080U, 0089U, 0090U, 0155U, 0245U, 0287U, 0288U, 81170, 81175, 81176, 81272, 81279, 81309, 81314, 81338, 81339, 81345, 81519, 81546, 88120, and 88121.

Definitions

Analytical Validity (AV): A process intended to determine if a test, tool, or instrument has acceptable technical performance (sensitivity, specificity, accuracy, precision, etc.). Analytical validation is an assessment of the test's technical performance (the test measures what it was designed to measure), not its usefulness or clinical significance. Analytical Validity includes the ability of the test to accurately and reliably detect the mutation and/or variant.

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Clinical Utility (CU): The ability of a test to provide information related to the patient's care and management, and thus, its ability to inform treatment decisions. Centers for Medicare and Medicaid Services (CMS) is most focused on assessing Clinical Utility in the context of whether or not a test is used to guide patient management and whether or not use of the test results leads to treatment that improves health outcomes.

Clinical Validity (CV): The ability of a test to classify a patient's specific circumstance into a diagnostic, prognostic, or predictive functional category. It should be noted that Clinical Validity is not a fixed value. Clinical Validity includes the ability of the test to accurately and reliably detect the disease of interest in the defined population.

(L39365, L39367 Genetic Testing in Oncology: Specific Tests)

Centers for Medicare and Medicaid Services (CMS) Related Documents

After checking the table below and searching the Medicare Coverage Database, if no NCD, LCD, or LCA is found, refer to the criteria as noted in the Coverage Rationale section above.

Molecular Pathology/Molecular Diagnostics/Genetic Testing

NCD	LCD	LCA	Contractor Type	Contractor Name
ABL1 Kinase Domain				
N/A	L36117 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A54686 Billing and Coding: MolDX: BCR-ABL	Part A and B MAC	CGS
	L40000 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms			
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L36180 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A55595 Billing and Coding: MolDX: BCR-ABL	Part A and B MAC	Noridian
	L39923 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms			
N/A	L36186 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A55600 Billing and Coding: MolDX: BCR-ABL **Retired 02/19/2026**	Part A and B MAC	Noridian

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NCD	LCD	LCA	Contractor Type	Contractor Name
ABL1 Kinase Domain				
N/A	L39927 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms **Retired 02/05/2026**			
N/A	L38123 MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	A57891 Billing and Coding: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	Part A and B MAC	Noridian
N/A	L38125 MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies **Retired 02/05/2026**	A57892 Billing and Coding: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Part A and B MAC	Novitas**
N/A	L36044 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025** L39919 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	A53531 Billing and Coding: MolDX: BCR-ABL	Part A and B MAC	Palmetto**
N/A	L38047 MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	A57837 Billing and Coding: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	Part A and B MAC	Palmetto**
N/A	L36815 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/16/2025** L36807 MolDX: Molecular Diagnostic Tests (MDT)	A55233 Billing and Coding: MolDx: BCR-ABL	Part A and B MAC	WPS*

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NCD	LCD	LCA	Contractor Type	Contractor Name
ABL1 Kinase Domain				
N/A	L38176 MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	A57878 Billing and Coding: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies	Part A and B MAC	WPS*
AFF2, AR, ASPA, BCKDHB, Cytogenomic (Genome-Wide) Analysis for Constitutional Chromosomal Abnormalities, DMPK, F9, FANCC, FMR1, FXN, G6PD, HBA1/HBA2, HBB, HTT, MCOLN1, PMP22, SMN1, SMPD1, SNRPN/UBE3A				
N/A	L34519 Molecular Pathology Procedures	A57451 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	First Coast
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**
Afirma				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54185 Billing and Coding: MolDX: Afirma™ Assay by Veracyte Update **Retired 06/05/2025**	Part A and B MAC	CGS
N/A	L39650 MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	A59474 Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	Part A and B MAC	CGS
N/A	L38968 Thyroid Nodule Molecular Testing	A58656 Billing and Coding: Thyroid Nodule Molecular Testing	Part A and B MAC	NGS
N/A	L39682 MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	A59509 Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	Part A and B MAC	Noridian
N/A	L39684 MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules **Retired 02/05/2026**	A59511 Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Part A and B MAC	Novitas**

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NCD	LCD	LCA	Contractor Type	Contractor Name
Afirma				
N/A	L39646 MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	A59470 Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	Part A and B MAC	Palmetto**
N/A	L39720 MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	A59560 Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules	Part A and B MAC	WPS*
Ashkenazi Jewish Associated Disorders Carrier Screening Panel				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54270 Billing and Coding: MolDX: IKBKAP Genetic Testing	Part A and B MAC	CGS
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**
ASXL1, KIT, PDGFRA, TERT				
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Part A and B MAC	Novitas**
BDX-XL2				
N/A	L37054 BDX-XL2	A57356 Billing and Coding: BDX-XL2	Part A and B MAC	Noridian
N/A	L37062 BDX-XL2 **Retired 10/23/2025**	A57357 Billing and Coding: BDX-XL2 **Retired 10/23/2025**	Part A and B MAC	Noridian
N/A	L37031 BDX-XL2	A56929 Billing and Coding: BDX-XL2	Part A and B MAC	Palmetto**
N/A	L37216 BDX-XL2	A57558 Billing and Coding: BDX-XL2	Part A and B MAC	WPS*
DecisionDx-SCC				
N/A	L39585 MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	A59382 Billing and Coding: MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	Part A and B MAC	CGS

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NCD	LCD	LCA	Contractor Type	Contractor Name
DecisionDx-SCC				
N/A	L39367 Genetic Testing in Oncology: Specific Tests	A59123 Billing and Coding: Genetic Testing in Oncology: Specific Tests	Part A and B MAC	First Coast
N/A	L39589 MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	A59386 Billing and Coding: MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	Part A and B MAC	Noridian
N/A	L39594 MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma **Retired 01/22/2026**	A59401 Billing and Coding: MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma **Retired 01/22/2026**	Part A and B MAC	Noridian
N/A	L39365 Genetic Testing in Oncology: Specific Tests	A59125 Billing and Coding: Genetic Testing in Oncology: Specific Tests	Part A and B MAC	Novitas**
N/A	L39583 MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	A59380 Billing and Coding: MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	Part A and B MAC	Palmetto**
N/A	L39614 MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	A59429 Billing and Coding: MolDX: Molecular Biomarker Testing for Risk Stratification of Cutaneous Squamous Cell Carcinoma	Part A and B MAC	WPS*
Fetal Chromosomal Aneuploidy and Microdeletions, Genome Sequencing (unexplained constitutional or heritable disorder or syndrome), Hearing loss Panel, Hereditary Retinal Disorders Panel, Hereditary Peripheral Neuropathies Panel, Nuclear Encoded Mitochondrial Genes Panel, Whole Mitochondrial Genome				
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**
Genetic Testing for Severe Inherited Conditions Carrier Screening Panel, IKBKAP				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54270 Billing and Coding: MolDX: IKBKAP Genetic Testing	Part A and B MAC	CGS
N/A	L34519 Molecular Pathology Procedures	A57451 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	First Coast

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NCD	LCD	LCA	Contractor Type	Contractor Name
Genetic Testing for Severe Inherited Conditions Carrier Screening Panel, IKBKAP				
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**
JAK2, MPL				
N/A	L40000 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	A59919 Billing and Coding: MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	Part A and B MAC	CGS
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L39923 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	A59835 Billing and Coding: MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	Part A and B MAC	Noridian
N/A	L39927 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms **Retired 02/05/2026**	A59837 Billing and Coding: MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L39919 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	A59827 Billing and Coding: MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	Part A and B MAC	Palmetto**
N/A	L40022 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	A59939 Billing and Coding: MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms	Part A and B MAC	WPS*

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NCD	LCD	LCA	Contractor Type	Contractor Name
JAK2, MPL				
N/A	L36117 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A56999 Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	Part A and B MAC	CGS
N/A	L36180 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A57421 Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	Part A and B MAC	Noridian
N/A	L36186 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A57422 Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	Part A and B MAC	Noridian
N/A	L36044 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	A56959 Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/17/2025**	Part A and B MAC	Palmetto**
N/A	L36815 MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/16/2025**	A57570 Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease **Retired 08/16/2025**	Part A and B MAC	WPS*
MECP2				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54278 Billing and Coding: MolDX: MECP2 Genetic Testing **Retired 06/05/2025**	Part A and B MAC	CGS
N/A	L34519 Molecular Pathology Procedures	A57451 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	First Coast
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**

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NCD	LCD	LCA	Contractor Type	Contractor Name
MTHFR				
N/A	L35984 MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	A56980 Billing and Coding: MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	Part A and B MAC	CGS
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L36155 MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	A57423 Billing and Coding: MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	Part A and B MAC	Noridian
N/A	L36159 MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) **Retired 01/22/2026**	A57424 Billing and Coding: MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) **Retired 01/22/2026**	Part A and B MAC	Noridian
N/A	L36089 MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	A56899 Billing and Coding: MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	Part A and B MAC	Palmetto**
N/A	L36400 MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	A57571 Billing and Coding: MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	Part A and B MAC	WPS*
myPath Melanoma				
N/A	L39389 MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	A59163 Billing and Coding: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	Part A and B MAC	CGS
N/A	L39373 MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	A59179 Billing and Coding: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	Part A and B MAC	Noridian
N/A	L39375 MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma **Retired 01/22/2026**	A59181 Billing and Coding: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma **Retired 01/22/2026**	Part A and B MAC	Noridian

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NCD	LCD	LCA	Contractor Type	Contractor Name
myPath Melanoma				
N/A	L39345 MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	A59109 Billing and Coding: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	Part A and B MAC	Palmetto**
N/A	L39479 MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	A59261 Billing and Coding: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma	Part A and B MAC	WPS*
Oncotype DX Breast Cancer Assay				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54195 Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay	Part A and B MAC	CGS
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L35160 MolDX: Molecular Diagnostic Tests (MDT)	A54480 Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay	Part A and B MAC	Noridian
N/A	L36256 MolDX: Molecular Diagnostic Tests (MDT) **Retired 02/05/2026**	A54482 Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay **Retired 02/19/2026**	Part A and B MAC	Noridian
N/A	L35025 MolDX: Molecular Diagnostic Tests (MDT)	A53105 Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay	Part A and B MAC	Palmetto**
N/A	L36807 MolDX: Molecular Diagnostic Tests (MDT)	A55230 Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay	Part A and B MAC	WPS*
Oncotype DX Breast DCIS Score Test				
N/A	L36951 MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	A56887 Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	Part A and B MAC	CGS
N/A	L36941 MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	A57619 Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	Part A and B MAC	Noridian
N/A	L36947 MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) **Retired 02/05/2026**	A57620 Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L36912 MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	A56870 Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	Part A and B MAC	Palmetto**
N/A	L37199 MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	A57583 Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™)	Part A and B MAC	WPS*

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NCD	LCD	LCA	Contractor Type	Contractor Name
OVERA				
N/A	L38371 Multimarker Serum Tests Related to Ovarian Cancer Testing	A57020 Billing and Coding: Multimarker Serum Tests Related to Ovarian Cancer Testing	Part A and B MAC	NGS
Pigmented Lesion Assay (PLA)				
N/A	L38111 MolDX: Pigmented Lesion Assay	A57915 Billing and Coding: MolDX: Pigmented Lesion Assay	Part A and B MAC	CGS
N/A	L38151 MolDX: Pigmented Lesion Assay	A58052 Billing and Coding: MolDX: Pigmented Lesion Assay	Part A and B MAC	Noridian
N/A	L38153 MolDX: Pigmented Lesion Assay **Retired 02/05/2026**	A58053 Billing and Coding: MolDX: Pigmented Lesion Assay **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L38051 MolDX: Pigmented Lesion Assay	A57868 Billing and Coding: MolDX: Pigmented Lesion Assay	Part A and B MAC	Palmetto**
N/A	L38178 MolDX: Pigmented Lesion Assay	A57983 Billing and Coding: MolDX: Pigmented Lesion Assay	Part A and B MAC	WPS*
PIK3CA				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54295 Billing and Coding: MolDX: PIK3CA Gene Tests	Part A and B MAC	CGS
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A55597 Billing and Coding: MolDX: PIK3CA Gene Tests	Part A and B MAC	Noridian
N/A	N/A	A55602 Billing and Coding: MolDX: PIK3CA Gene Tests **Retired 02/19/2026**	Part A and B MAC	Noridian
N/A	L35025 MolDX: Molecular Diagnostic Tests (MDT)	A53558 Billing and Coding: MolDX: PIK3CA Gene Tests	Part A and B MAC	Palmetto**
N/A	L36807 MolDX: Molecular Diagnostic Tests (MDT)	A55200 Billing and Coding: MolDX: PIK3CA Gene Tests	Part A and B MAC	WPS*
Resolution ctDx Lung				
N/A	L38065 MolDX: Plasma-Based Genomic Profiling in Solid Tumors	A57917 Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors	Part A and B MAC	CGS
N/A	L39230 MolDX: Plasma-Based Genomic Profiling in Solid Tumors	A58973 Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors	Part A and B MAC	Noridian

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NCD	LCD	LCA	Contractor Type	Contractor Name
Resolution ctDx Lung				
N/A	L39232 MolDX: Plasma-Based Genomic Profiling in Solid Tumors **Retired 02/05/2026**	A58975 Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L38043 MolDX: Plasma-Based Genomic Profiling in Solid Tumors	A57867 Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors	Part A and B MAC	Palmetto**
N/A	L38168 MolDX: Plasma-Based Genomic Profiling in Solid Tumors	A57936 Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors	Part A and B MAC	WPS*
RiskReveal (Formerly DetermaRx)				
N/A	L38284 MolDX: Predictive Classifiers for Early Stage Non-small Cell Lung Cancer	A58038 Billing and Coding: MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	Part A and B MAC	CGS
N/A	L38327 MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	A57329 Billing and Coding: MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	Part A and B MAC	Noridian
N/A	L38329 MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer **Retired 02/05/2026**	A57330 Billing and Coding: MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer **Retired 02/05/2026**	Part A and B MAC	Noridian
N/A	L38238 MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	A58031 Billing and Coding: MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	Part A and B MAC	Palmetto**
N/A	L38443 MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	A57112 Billing and Coding: MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer	Part A and B MAC	WPS*
ROMA				
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	L38371 Multimarker Serum Tests Related to Ovarian Cancer Testing	A57020 Billing and Coding: Multimarker Serum Tests Related to Ovarian Cancer Testing	Part A and B MAC	NGS
ThyraMIR, ThyroSeq Genomic Classifier				
N/A	L38968 Thyroid Nodule Molecular Testing	A58656 Billing and Coding: Thyroid Nodule Molecular Testing	Part A and B MAC	NGS

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NCD	LCD	LCA	Contractor Type	Contractor Name
ThyraMIR, ThyroSeq Genomic Classifier				
N/A	L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Part A and B MAC	Novitas**
ThyGeNEXT				
N/A	L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Part A and B MAC	Novitas**
X-Linked intellectual disability (XLID) Panel				
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54274 Billing and Coding: MolDX: L1CAM Gene Sequencing Guidelines **Retired 06/05/2025**	Part A and B MAC	CGS
N/A	L36021 MolDX: Molecular Diagnostic Tests (MDT)	A54278 Billing and Coding: MolDX: MECP2 Genetic Testing **Retired 06/05/2025**	Part A and B MAC	CGS
N/A	N/A	A58918 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	First Coast
N/A	L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	Part A and B MAC	NGS
N/A	N/A	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	Part A and B MAC	Novitas**

Medicare Administrative Contractor (MAC) With Corresponding States/Territories	
MAC Name (Abbreviation)	**States/Territories**
CGS Administrators, LLC (CGS)	KY, OH
First Coast Service Options, Inc. (First Coast)	FL, PR, VI
National Government Services, Inc. (NGS)	CT, IL, ME, MA, MN, NH, NY, RI, VT, WI
Noridian Healthcare Solutions, LLC (Noridian)	AS, AK, AZ, CA, GU, HI, ID, MT, NV, ND, Northern Mariana Islands, OR, SD, UT, WA, WY
Novitas Solutions, Inc. (Novitas)	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX, VA**
Palmetto GBA (Palmetto)	AL, GA, NC, SC, TN, VA**, WV
Wisconsin Physicians Service Insurance Corporation (WPS)*	IA, IN, KS, MI, MO, NE
Notes	
*Wisconsin Physicians Service Insurance Corporation: Contract Number 05901 applies only to WPS Legacy Mutual of Omaha MAC A Providers. **For the state of Virginia: Part B services for the city of Alexandria and the counties of Arlington and Fairfax are excluded for the Palmetto GBA jurisdiction and included within the Novitas Solutions, Inc. jurisdiction.	

CMS Benefit Policy Manual

Chapter 15, § 80.1; 80.1.3, Clinical Laboratory Services

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CMS Claims Processing Manual

Chapter 12, § 60, Payment for Pathology Services
Chapter 16, §§ 10.2, General Explanation of Payment; 20, Calculation of Payment Rates – Clinical Laboratory Test Fee Schedules; 40, Billing for Clinical Laboratory Tests

CMS Transmittal(s)

Transmittal 11460, Change Request 12705, Dated 06/17/2022 (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determination (NCDs) – October 2022 Update)
Transmittal 11461, Change Request 12483, Dated 06/21/2022 (National Coverage Determination (NCD) 90.2, Next Generation Sequencing (NGS))
Transmittal 12355, Change Request 13278, Dated 11/09/2023, (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determinations (NCDs) – January 2024 Update)
..Transmittal 12440, Change Request 13391, Dated 01/03/2024 (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determinations (NCDs) – April 2024 Update--CR 2 of 2)
Transmittal 12444, Change Request 13278, Dated 01/04/2024 (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determinations (NCDs) – January 2024 Update)
Transmittal 12626, Change Request 13596, Dated 05/09/2024 (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determinations (NCDs) – October 2024)
Transmittal 13375, Change Request 14197, Dated 08/21/2025 (International Classification of Diseases, 10th Revision (ICD-10) and Other Coding Revisions to National Coverage Determinations (NCDs) – January 2026 Update – CR 1 of 2)

Others

L35062 Biomarkers Overview
A56541 Billing and Coding: Biomarkers Overview
A58917 Billing and Coding: Molecular Pathology and Genetic Testing
A58918 Billing and Coding: Molecular Pathology and Genetic Testing
L36021 MolDX: Molecular Diagnostic Tests (MDT)
A56973 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L35160 MolDX: Molecular Diagnostic Tests (MDT)
A57526 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L36256 MolDX: Molecular Diagnostic Tests (MDT) **Retired 02/05/2026**
A57527 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) **Retired 02/05/2026**
L35025 MolDX: Molecular Diagnostic Tests (MDT)
A56853 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L36807 MolDX: Molecular Diagnostic Tests (MDT)
A57772 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)
L34519 Molecular Pathology Procedures
A57451 Billing and Coding: Molecular Pathology Procedures
L35000 Molecular Pathology Procedures
A56199 Billing and Coding: Molecular Pathology Procedures
L38288 MolDX: Repeat Germline Testing
A57141 Billing and Coding: MolDX: Repeat Germline Testing
L38351 MolDX: Repeat Germline Testing
A57331 Billing and Coding: MolDX: Repeat Germline Testing
L38353 MolDX: Repeat Germline Testing **Retired 02/05/2026**
A57332 Billing and Coding: MolDX: Repeat Germline Testing **Retired 02/05/2026**
L38274 MolDX: Repeat Germline Testing
A58017 Billing and Coding: MolDX: Repeat Germline Testing
L38429 MolDX: Repeat Germline Testing
A57100 Billing and Coding: MolDX: Repeat Germline Testing
A59646 Billing and Coding: MolDX: Proteomics Testing
A59641 Billing and Coding: MolDX: Proteomics Testing
A59642 Billing and Coding: MolDX: Proteomics Testing **Retired 02/19/2026**
A59636 Billing and Coding: MolDX: Proteomics Testing
A59649 Billing and Coding: MolDX: Proteomics Testing

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CMS Clinical Laboratory Fee Schedule, CMS Website
Code of Federal Regulations, Title 42, § 410.32, Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions
Palmetto GBA MolDx Website
Palmetto GBA MolDx Manual, Palmetto GBA MolDx Website
Social Security Act, Title XVIII Section 1862(a)(1)(A)

Clinical Evidence

ABL1 (ABL Proto-Oncogene 1, Non-Receptor Tyrosine Kinase) Kinase Domain

The *ABL1* gene provides directions for making a protein involved in various functions in cells throughout the body. The ABL1 protein operates as a kinase, which is an enzyme that changes the activity of other proteins by adding a cluster of oxygen and phosphorus atoms (a phosphate group) at specific positions. The ABL1 kinase is normally turned off (inactive) and must be turned on (activated) to perform its tasks. The ABL1 kinase can be activated by a several various triggers and can add a phosphate group to many different proteins (also called substrates). This diversity allows *ABL1* to be involved in a wide variety of cellular processes, including cell growth and division (proliferation), maturation (differentiation), and movement (migration). It can either aid in cell survival or trigger-controlled cell death (apoptosis), depending on cellular conditions. The *ABL1* gene is a part of a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. A genetic rearrangement (translocation) involving the *ABL1* gene induces a type of cancer of blood-forming cells called chronic myeloid leukemia. This slow-growing cancer leads to an overproduction of abnormal white blood cells (MedlinePlus, 2016a).

Raza et al. (2025) performed a systematic review and bias-corrected meta-analysis to compare third-generation tyrosine kinase inhibitor (TKI) ponatinib with first- and second-generation TKIs for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. The comparison was done in terms of complete molecular response (CMR), overall survival (OS), and event-free survival (EFS). TKIs bind to the adenosine triphosphate (ATP)-binding site of the *ABL* kinase domain. TKIs effectively inhibit the proliferative activity of leukemic cells by disrupting the ATPase activity of the kinase. Twelve studies were included in the review. In the uncorrected analysis, ponatinib showed a significant advantage for complete molecular response (CMR). However, this effect was insignificant after bias correction. For EFS and OS eponatinib showed superior outcomes in both bias-corrected and uncorrected analyses. Bias correction showed an 80.2% lower risk in OS and a 94.2% lower risk in EFS with ponatinib. In six studies that reported treatment-related adverse events, there were no significant differences found between ponatinib and other TKIs. The authors concluded that ponatinib is correlated with substantially better survival outcomes compared to other TKIs. However, due to limited safety data, the authors acknowledge that future randomized controlled trials are needed to robustly evaluate its safety profile compared to other TKIs. Study limitations reported by the authors included that the effective number of studies calculated using P.bias was very low mostly due to the meta-analysis being dominated by one randomized controlled trial. Also, only six studies reported the adverse event profiles of the TKIs used, preventing its inclusion as a primary outcome and making bias correction unfeasible and the included studies combined non-resistant and resistant cases, with resistance profiles unspecified.

Garcia-Gutierrez et al. (2024) performed a systematic review of clinical trials and matching-adjusted indirect comparison (MAIC) analysis on asciminib vs ponatinib in post-second-generation tyrosine kinase inhibitor (TKI) therapy for chronic-phase chronic myeloid leukemia (CML). TKIs for CML bind to the adenosine triphosphate (ATP) site of the BCR::ABL1 oncoprotein to prevent abnormal kinase activity. Four clinical trials were included in the analysis (ponatinib: NCT01207440, NCT02467270 and asciminib: NCT03106779, NCT02081378). In patients without baseline response of BCR::ABL1^{IS} ≤ 1%, the adjusted BCR::ABL1^{IS} ≤ 1% rate difference with ponatinib vs asciminib was 9.33% by 12 months in favor of ponatinib. In patients with the *T315I* mutation, adjusted BCR::ABL1^{IS} ≤ 1% rate difference with ponatinib vs asciminib was 43.54% by 12 months. The authors concluded that after key baseline characteristics adjustment, cumulative BCR::ABL1^{IS} ≤ 1% and MMR rates were greater with ponatinib than asciminib in patients without a baseline response in the majority of the comparisons by 12 months. Favorable efficacy outcomes observed in asciminib vs ponatinib were consistently stronger in the *T315I* mutation subgroup. Study limitations reported by the authors included the inability to include intolerance and resistance variables due to the ponatinib trials having a larger proportion of patients with resistance disease and did not have a number of patients with intolerance to match those in the asciminib trials. The comparison between asciminib and ponatinib was limited by the availability of the published data and the MAIC was also limited by the available baseline measures.

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Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Chronic Myeloid Leukemia (v1.2026) make the following recommendations for the initial diagnosis and workup of Chronic Myeloid Leukemia:

- History & Physical, including palpation of the spleen.
- CBC with differential.
- Chemistry profile.
- Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation.
- Quantitative reverse transcription polymerase chain reaction (qPCR) to establish the presence of quantifiable *BCR:ABL1.*
- Hepatitis B panel.
- Assess for distress.

NCCN also provides the following treatment recommendations based on *BCR:ABL1* mutation profile:

- Patients with disease resistant to primary treatment with imatinib should be treated with an alternate tyrosine kinase inhibitor (TKI), taking into account *BCR:ABL1* kinase domain mutation status.
- Patients with disease resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib), taking into account *BCR:ABL1* kinase domain mutation status. Subsequent therapy with an alternate TKI would be effective only in patients with identifiable *BCR:ABL1* mutations that confer resistance to TKI therapy. Ponatinib is preferred for patients with no identifiable *BCR:ABL1* mutations.
    - Ponatinib is the preferred treatment option for patients with a *T315I* mutation in accelerated phase chronic myeloid leukemia (AP-CML) or blast phase chronic myeloid leukemia (BP-CML). It is also a treatment option for chronic phase chronic myeloid leukemia (CP-CML) with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated.
    - Asciminib is a treatment option for CP-CML patients with the *T315I* mutation and/or CP-CML and AP-CML that was previously treated.
    - Certain *BCR:ABL1* kinase domain mutations may have a greater sensitivity to certain TKIs.

For acute lymphoblastic leukemia, NCCN states consolidation therapy options in the setting of minimal residual disease (MRD) positivity or negativity may include blinatumomab in combination with a tyrosine kinase inhibitor (TKI), continuation of corticosteroid or multiagent therapy in combination with a TKI, or single agent TKI. For MRD positivity, NCCN recommends using an alternative/broader acting TKI and *ABL1* kinase domain mutation testing. However, they note that mutations associated with asciminib resistance can occur outside the kinase domain. For progressive, persistent, or emergent MRD, marrow progression, or development of extramedullary disease following consolidation therapy, NCCN recommends *ABL1* kinase domain mutation testing, followed by treatment for relapsed/refractory (R/R) disease. For Ph+ B-ALL that experience relapse after or have disease refractory to initial TKI-containing therapy, NCCN recommends *ABL1* kinase domain mutation testing (NCCN Acute Lymphoblastic Leukemia, v2.2025).

AFF2 [ALF Transcription Elongation Factor 2 (FMR2)] [e.g., Fragile X Intellectual Disability 2 (FRAXE)]

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Carrier screening is not a Medicare benefit.

Fragile XE syndrome is a genetic disorder caused by mutations in the *AFF2* gene. It impairs cognitive functioning and thinking ability. Most affected individuals have mild intellectual disabilities. Some have borderline cognitive function, meaning that it is below average but not low enough to be classified as an intellectual disability. Individuals with two X chromosomes (typical for females) are seldomly diagnosed likely due to very mild signs and symptoms, if present at all. The most common sign of impaired cognitive function is learning disabilities, which are probably a result of behavioral and communication problems, which include delayed speech, hyperactivity, poor writing skills, and a short attention span. Some individuals show autistic behaviors like repetitive behaviors, hand flapping, and intense interest in a particular subject. Cognitive functioning remains steady and does not get worse with age (MedlinePlus, 2024a). It is also used for carrier screening (NIH, 2023).

Golding et al. (2025) performed a comparison study on the behavioral, cognitive, and psychiatric phenotypes associated with numbers of repeats of the FRAXE allele on the *FMR2* gene. Using a phenome scan, the authors compared 1,951 behavioral, cognitive, and psychiatric outcomes of 5,060 boys from the Avon Longitudinal Study of Parents and Children (ALSPAC). The findings uncovered that boys with relatively high levels of repeats (> 24) had an increased risk of certain

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neurocognitive outcomes ($p < 0.01$). Boys with > 24 repeats were more likely to report psychosis-like experiences, increased ability to recognize facial signs of anger, increased risk of eating disorders, and increased likelihood of smoking cigarettes and using illicit drugs during adolescence than would be expected by chance. There were no signs of associations with cognitive abilities. The authors concluded that there was little evidence that higher levels of the normal range of FRAXE repeats were associated with a difference in cognitive abilities. However, there was evidence of increased reports of psychotic-like experiences and other behavior problems in this group. There was no evidence of evolutionary neurocognitive advantage. Study limitations reported by the authors included that apart from the possible findings with schizophrenia, they were unable find any evidence in the literature to confirm (or deny) the other findings in regard to FRAXE repeat size since no studies, to their knowledge, looked at features such as self-esteem, eating disorders, or use of substances prone to induce addiction. Another limitation was the methodology used may result in increased or decreased expected numbers as the assumption is that all the items considered are mutually independent (which they are not). However, the authors suggest that the results should be valid hypothesis raisers for testing in other large datasets.

There is no cure for fragile XE syndrome. Early intervention and support services can help. Special education classes, occupational therapy, speech therapy, and behavioral therapies may be beneficial to children (Weissman, 2024).

AR (Androgen Receptor) (e.g., Spinal and Bulbar Muscular Atrophy, Kennedy Disease, X Chromosome Inactivation)

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

The *AR* gene provides instructions for making a protein called an androgen receptor. Androgens are hormones (such as testosterone) that are important for normal male sexual development before birth and during puberty. By turning the genes on or off as necessary, the androgen receptor complex helps direct the development of male sex characteristics. Androgens and androgen receptors also have other important functions in both males and females, such as regulating hair growth and sex drive. Hundreds of different mutations in the *AR* gene have been identified in people with androgen insensitivity syndrome, spinal and bulbar muscular atrophy (Kennedy's disease), androgenic alopecia (also known as male pattern baldness, and in women it is known as female pattern hair loss), polycystic ovarian syndrome and prostate cancer (MedlinePlus, 2024e).

Kennedy disease is a rare, slowly progressive neuromuscular disorder in which symptoms present mainly between the ages of 20 and 50. It affects approximately 1 in 200,000 people worldwide and mostly occurs in males. Treatment is for symptoms and life expectancy is normal, though a small percentage of patients may succumb to the disease in their 60's or 70's due to swallowing complications. The diagnosis is suspected based on physical signs and symptoms, and sometimes family history and there is currently no known treatment or cure (NORD, 2023a).

Genetic testing is performed for carrier screening (ACOG, 2017, reaffirmed 2025).

Studies of the number of cytosine, adenine, and guanine (CAG) repeats in *AR* alleles in males with Kennedy disease have established a correlation between number of CAG repeats and disease severity. Males whose alleles have a larger number of CAG repeats tend to have earlier disease onset and more rapid progression. Clinical trials of anti-androgen drugs did not consistently reveal significant efficacy, but leuprorelin was efficacious as a treatment for dysphagia in a follow-up clinical trial in Japan, leading to its approval in Japan but not elsewhere. Supportive care involving physical, occupational and speech/language therapy to improve quality of life, maximize function, and reduce complications is recommended (La Spada, 2026).

Hayes Molecular Test Assessment of Spinal and Bulbar Muscular Atrophy (SBMA; Kennedy Disease) states that SBMA is caused by the expansion of a cytosine, adenine, and guanine (CAG) trinucleotide repeat in the androgen receptor (*AR*) gene, which is located on the X chromosome at bands q11 to q12. Analytical validity studies of SBMA testing are rare. However, the available studies suggest that the analysis is both accurate and reproducible. For the diagnosis of SBMA in patients with symptoms of lower motor neuron disease, bulbar dysfunction, and/or signs of androgen insensitivity, Hayes assigns a rating of C (potential but unproven benefit). For the diagnosis of SBMA in patients with suspected ALS, Hayes assigns a rating of D2 (insufficient evidence). For predictive testing in asymptomatic adults with an established family history of SBMA, Hayes assigns a rating of C. For carrier testing in the female relatives of known SBMA patients or carriers, Hayes assigns a rating of C. For the prenatal or preimplantation genetic diagnosis of SBMA, Hayes assigns a rating of D2 [Hayes, Spinal and Bulbar Muscular Atrophy (SBMA; Kennedy Disease), 2010, updated 2014].

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Ashkenazi Jewish Associated Disorders Carrier Screening Panel (e.g., Bloom Syndrome, Canavan Disease, Cystic Fibrosis, Familial Dysautonomia, Fanconi Anemia Group C, Gaucher Disease, Tay-Sachs Disease)

Carrier screening is not a Medicare benefit.

Genetic testing is performed for carrier screening of conditions in people of Ashkenazi Jewish descent (ACOG, 2017, reaffirmed 2025).

ASPA (Aspartoacylase) (e.g., Canavan Disease)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Carrier screening is not a Medicare benefit.

Genetic testing is used to diagnose Canavan disease in newborns who typically present symptoms in the first few months of life with delayed motor milestones (e.g., head control and sitting). They will manifest macrocephaly, hypotonia, and intellectual disability. Life expectancy is variable, but many individuals die in childhood or adolescence. It is also used for carrier screening (ACOG, 2017, reaffirmed 2025).

There is no cure for Canavan disease. Treatment is to manage symptoms (NORD, 2024).

ASXL1 (Additional Sex Combs Like 1, Transcriptional Regulator)

Sheikhi et al. (2024) conducted a systematic review and meta-analysis on the prognostic significance of *ASXL1* mutations in acute myeloid leukemia (AML). Twenty-seven studies which included 8,953 participants were included in the review. The authors extracted the hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS), event-free survival (EFS), and relapse-free survival (RFS) from these studies. The pooled HR for OS in multivariable analysis showed that *ASXL1* considerably reduced survival in patients with AML (pooled HR: 1.67; 95% CI: 1.342-2.091). The authors concluded that *ASXL1* mutations may confer a poor prognosis in AML, which may be seen as potential prognostic factors. However, the authors recommend more detailed studies with different *ASXL1* mutations to give more insight on this issue. The authors reported some study limitations including the presence of additional genetic mutations other than *ASXL1* that may have resulted in heterogeneity of the study, the impact of other possible sources of heterogeneity were not assessed due to additional data needed, and while some studies reported multivariate HRs, others used univariate HRs, which may have led to heterogeneity.

Zhang et al. (2023) performed a meta-analysis on the prognostic value of *ASXL1* mutations in patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Included in the meta-analysis were 5,816 patients from 10 studies. The combined hazard ratios (HRs) and their 95% confidence intervals (CIs) for overall survival (OS) and AML transformation were calculated. Findings showed that *ASXL1* mutations have an adverse prognostic impact on OS (HR = 1.68, 95% CI:1.45–1.94, p < 0.0001) and AML transformation (HR = 2.20, 95% CI:1.68–2.87, p < 0.0001). The results for different age groups had no significant differences (HR = 1.87, 95% CI: 1.31–2.67; HR = 1.62, 95% CI:1.35–2.07). The pooled HR for OS was 1.37 (95% CI:1.20–1.56, p < 0.0001). *ASXL1* mutations were particularly correlated with a poorer OS in the subgroup aged ≥ 60 years (HR = 2.86, 95% CI:1.34–6.08, p = 0.006). When considering cytogenetically normal AML (CN-AML), the HR was 1.78 (95% CI:1.27–2.49, p = 0.001). The authors concluded that their analysis indicated an independent, adverse prognostic impact of *ASXL1* mutations in MDS and AML, which is also applicable to CN-AML. Age was a risk factor for AML and *ASXL1* mutations but not for MDS. Limitations reported by the authors included that univariate HRs were separated from multivariate HRs to decrease heterogeneity. However, the adjustment factors from the multivariate Cox proportional hazards model differed in each eligible study, which is something that was uncontrollable. Another limitation reported by the authors was that due to insufficient data, the authors did not evaluate other clinical features that could likely explain the heterogeneity. Also, the authors reported that *ASXL1* mutations frequently coexist with other gene mutations, and the impact of gene interactions on disease prognosis was not measurable. The authors also acknowledged there was clear publication bias.

Hu and Wang (2022) conducted a meta-analysis to explore the effect of gene mutations on overall response rate (ORR) and overall survival (OS) in myelodysplastic syndrome (MDS) treated with hypomethylating agents (HMAs). The results of the meta-analysis demonstrated a pooled odds ratio (OR) and 95% confidence interval (CI) for ORR, and the pooled hazard ratio (HR) and 95% CI for OS were chosen to estimate the effect. The pooled OR of *TET2* was 0.73 (95% CI: 0.59-0.91, p = 0.005), and the pooled OR of *ASXL1* was 1.38 (95% CI: 1.12-1.71, p = 0.003). As for prognosis, the pooled HR of *RUNX1* was 1.45 (95% CI: 1.15-1.85, p = 0.002). The pooled HR of *TP53* was 2.30 (95% CI: 1.83-2.90, p < 0.001), and the pooled HR of *U2AF1* was 1.41 (95% CI: 1.15-1.74, p = 0.001). There was no statistical difference shown in other genes. Therefore, the authors concluded that *TET2* mutation and *ASXL1* wild type were the predictors of better

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response to HMAs. *TP53*, *RUNX1*, and *U2AF1* mutations were associated with poor prognosis in MDS. The authors reported that a limitation of the meta-analysis was that patients with MDS that were included were treated with hypomethylating agents and those patients are mostly higher-risk MDS, which leads to certain selection bias.

Sutandyo et al. (2022) performed a systematic review and meta-analysis aimed to explore adults with myelodysplastic syndrome (MDS) to elucidate the role of these genes in acute myeloid leukemia (AML) transformation risk. The outcome of this review was measured using the hazard ratio (HR). The results of the exploration were no statistically significant difference in AML transformation risk between *U2AF1* mutant and *U2AF1* wildtype MDS [HR: 1.41; 95% confidence interval (CI): 0.95-2.07, p = 0.08, Cochrane standard statistical I^2 = 0%]. Pooled HR showed that patients with *SRSF2* mutation had a higher risk of AML transformation (HR 2.62; 95% CI: 1.54-4.45; p = 0.0004; I^2 = 55%). The pooled HR for *SF3B1* was 0.48 (95% CI: 0.22-1.06, p = 0.07, I^2 = 55%). *TET2*, *ASXL1*, and *EZH2* mutations were not associated with AML transformation. Meanwhile, *DNMT3A* mutations were associated with AML transformation with pooled HR of 2.73 (95% CI: 1.43-5.21; p = 0.08; I^2: 67%). The pooled HR for *IDH* genes was smaller (HR: 2.92; 95% CI: 1.21-7.06; p = 0.02; I^2:65%). Patients with *RUNX1* mutation were associated with AML transformation (HR: 1.85; 95% CI: 1.11-3.09; p = 0.02; I^2:38%). The authors concluded that individuals with mutations of *SRSF2*, *DNMT3A*, *IDH*, and *RUNX1* have a higher HR for AML transformation. The authors reported study limitations including that the interaction of gene mutations with each other was not evaluated. Therefore, it is unknown if the AML progression was due to the combination of some mutations or independently. Also, the authors reported that there were different definitions of outcomes measured.

Zhao et al. (2022) created a meta-analysis that evaluated the prognostic efficacy of *ASXL1* and *TET2* mutations in the chronic myelomonocytic leukemia (CMML) population. Sixteen studies were included in the meta-analysis using overall survival rate (OS) with hazard ratios (HRs). The results of the meta-analysis demonstrated that the total HR of OS was 0.74, 95% confidence interval (CI) = 0.61-0.91, p = 0.005, compared with patients with CMML without *TET2* mutations (*TET2*MT), and the total HR of OS was 1.56, 95% CI = 1.34-1.80, p = 0.000, compared with patients with CMML without *ASXL1* mutation (*ASXL1*WT), indicating that *TET2*MT *and ASXL1*WT *were* favorable for prognosis of CMML. Whether the gene is mutated or not, the acute transformation rate of disease and mortality rate were further considered for assessment. Compared with the patients with CMML with *TET2*MT *and ASXL1*WT, the HR of patients within both *TET2*MT *and ASXL1*MT *was* 1.51 (95% CI = 1.14-1.99; p = 0.004), the HR of patients with neither *TET2*MT nor *ASXL1*MT *was* 1.49 (95% CI = 1.12-1.98; p = 0.007), and the HR of *TET2*WT and *ASXL1*MT *patients* was 1.88 (95% CI = 1.21-2.94; p = 0.005).The authors concluded that the presence of *TET2*MT and *ASXL1*WT genotype was the most beneficial for the survival of individuals with CMML. Study limitations reported by the authors included that they could not evaluate other clinical parameters except OS due to lack of data, all included studies were observational, and the number of studies included were relatively small.

Wang et al. (2021) performed a meta-analysis to evaluate the prognostic value and clinical characteristics of *ASXL1* mutations in patients with primary myelofibrosis (PMF). Hazard ratios (HRs) and their 95% confidence intervals (CIs) of overall survival (OS) and leukemia-free survival (LFS), the number of patients transformed to acute leukemia, and clinical characteristics to carry out a meta-analysis by fixed effect model or random effect model according to the heterogeneity between studies were extracted. Fourteen studies consisting of 4,501 patients with PMF were included in the analysis. The results showed that *ASXL1* mutations may predict a shorter overall survival (HR = 2.30, 95% CI: 1.79–2.94) and a higher likelihood of transforming into acute leukemia [leukemia-free survival (LFS): HR = 1.77, 95% CI: 1.30–2.42; the rate of acute leukemia transformation: odds ratio (OR) = 2.06, 95% CI: 1.50–2.83]. *ASXL1* mutations were also correlated with men over 65 years old, lower platelet counts levels, and a greater risk of the international prognostic score system. The authors concluded that *ASXL1* mutations have a substantial adverse effect on the prognosis of patients with PMF and may aid in prognostic assessment and risk stratification for patients with PMF. Study limitations reported by the authors included that all articles were retrospective observational studies and that the studies were all published in English which potentially allow for some publication bias.

Guglielmelli et al. (2021) performed a retrospective, observational, multicenter study to evaluate specific gene mutations and thrombosis in essential thrombocythemia (ET). Five hundred two patients with World Health Organization (WHO)-defined ET and an average age of 55 years old were included in the study. The most frequent mutation, other than *JAK2/CALR/MPL*, was *ASXL1* (7–20%). Leukocytosis (≥ 11 × 109/L) was noted in 22% of patients, abnormal karyotype in 9%, and extreme thrombocytosis (≥ 1000 × 109/L) in 27%. Treatment plan included antiplatelet therapy for low-risk disease and cytoreductive drugs for high-risk disease. The authors concluded that there was favorable influence of harboring *ASXL1*/*RUNX1*/*EZH2* mutations on arterial thrombosis in the context of arterial events that occurred both before and after diagnosis. Study limitations included that patients were selected based on the availability of next-generation sequencing data which may exclude patients without molecular profiling. This could skew the mutation prevalence and associations. Also, there was no control group.

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Andréasson et al. (2020) performed a cohort study to identify gene mutations that could be used together with clinical data as prognostic markers to guide treatment decisions in patients with polycythemia vera (PV). Eighty-five patients were included in the study with a mean age of 71. An increased number of mutations found by the selected gene panel was substantially linked to inferior overall survival. Only mutations in the *ASXL1* gene (found in 8.2% of the patients, n = 7) had a significant impact on survival, when correlating individual mutations to overall survival. The projected 5-year survival for *ASXL1*-mutated patients was 43%, whereas the projected 5-year survival was 74% for non-mutated patients. The authors concluded that *ASXL1* is a marker for poor prognosis and targeted testing of a few clinically significant genes such as the *ASXL1* gene should be done and interpreted together with fundamental clinical data. The study was limited by the sample size.

Wan and Han (2020) conducted a meta-analysis to obtain the myeloid tumors in myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN)'s mutational profiles and explore possible similarities and differences. Fifty-three articles were eligible for the meta-analysis; at most, 9,809 cases were involved for any gene. The top mutant genes and their pooled mutation rates were as follows: *SF3B1* [20.2% (95% CI 11.6-30.5%)] in MDS, *TET2* [39.2% (95% CI 21.7-52.0%)] in MDS/MPN, and *JAK2* [67.9% (95% CI 64.1-71.6%)] in MPN. Subgroup analysis revealed that leukemic transformation-related genes were more commonly mutated in high-risk MDS (MDS with multilineage dysplasia and MDS with excess blasts) than in other MDS entities. Thirteen genes, including *ASXL1, U2AF1, SRSF2, SF3B1*, and *ZRSR2*, had significantly higher mutation frequencies in primary myelofibrosis (PMF) compared with essential thrombocythemia and polycythemia vera this difference distinguished PMF from MPN and likened it to MDS. Chronic myelomonocytic leukemia and atypical chronic myeloid leukemia were similar entities but showed several mutational differences. A heat map demonstrated that juvenile myelomonocytic leukemia and MDS/MPN with ring sideroblasts and thrombocytosis were distinct entities, whereas MDS/MPN-unclassifiable was closest to high-risk MDS. The authors concluded that such genetic closeness or difference reflected features in these conditions' pathogenesis, diagnosis, treatment, and progression and could inspire future genetic studies. Study limitations reported by the authors included that significant heterogeneity was found among studies but in those cases, a randomized effects model was chosen to obtain the pooled proportions.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN notes that identification of mutations that carry therapeutic and prognostic impact is rendering molecular profiling for all acute myeloid leukemia (AML) cases a standard for diagnostic workup. On top of basic cytogenetic analysis, new molecular markers can aid in refining prognostics groups, especially in the setting of a normal karyotype. These markers include *ASXL1* gene mutations (NCCN Acute Myeloid Leukemia, v3.2026).

Identification of high-molecular-risk mutations (*ASXL1*, *EZH2*, *IDH1*, *IDH2, SRSF2*, or *TP53* mutations) may be helpful in decision-making regarding allogeneic hematopoietic cell transplant (HCT) in patients with myelofibrosis (MF). In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*, and *SF3B1* mutations) may be of help in determining the clonal nature of the disease. *ASXL1* is associated with inferior overall survival (OS) and leukemia-free survival (LFS) and LFS following HCT. *ASXL1* mutation retains prognostic significance for inferior OS independent of International Prognostic Scoring System (IPSS) or Dynamic International Prognostic Scoring System (DIPSS)-Plus risk score. *ASXL1*, *EZH2*, *SRSF2*, *TP53*, *IDH1*, *IDH2*, or *U2AF1* mutations are considered high-molecular-risk (HMR) mutations and are correlated with substantially shorter OS and leukemia-free survival (LFS) in primary myelofibrosis (PMF). *ASXL1*, *EZH2*, *SRSF2*, and *RAS* mutations are predictive of OS, and *ASXL1*, *SRSF2*, and *IDH1* or *IDH2* are predictive of leukemic transformation in PMF (NCCN Myeloproliferative Neoplasms, v2.2025).

ASXL1 is independently associated with a poor prognosis in chronic myelomonocytic leukemia (CMML) and myelodysplastic syndromes (MDS). For CMML-1 treatment consideration is hypomethylating agent (HMA) or hydroxyurea. For CMML-2 treatment is HMA ±venetoclax and/or allogeneic hematopoietic cell transplant (HCT). For MDS/myeloproliferative neoplasm (MPN) not otherwise specified treatment consideration is HMA and/or allogeneic HCT (NCCN Myelodysplastic Syndromes v1.2026).

BCKDHB (Branched-Chain Keto Acid Dehydrogenase E1, Beta Polypeptide) (e.g., Maple Syrup Urine Disease)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Carrier screening is not a Medicare benefit.

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Genetic testing is used to diagnose maple syrup urine disease (MSUD) in infants whose urine has a distinctive sweet odor. Affected individuals manifest poor feeding, lethargy, and developmental delays. It is also used for carrier screening (ACOG, 2017, reaffirmed 2025).

BDX-XL2 (Oncology Lung)

Pritchett et al. (2023) reported on the results of the ORACLE prospective, multicenter, observational clinical trial (NCT03766958) to assess the clinical utility of Nodify XL2 (also known as BDX-XL2) and its ability to reduce invasive procedures in patients with benign lung nodules. The test comprises measurement of two plasma proteins, Galectin-3 Binding Protein (LG3BP) and Scavenger Receptor Cysteine-Rich Protein Type 1 Protein M130 (C163A), by liquid chromatography-multiple reaction monitoring (MRM) mass spectroscopy and integration with five clinical risk factors in an algorithm to determine a post-test probability result of likely benign. A prospective, multicenter observational trial (PANOPTIC, NCT01752114) of patients with indeterminate pulmonary nodules with a pre-test pCA ≤ 50% (8–30 mm in largest diameter) showed the blood-based integrated classifier's (IC's) sensitivity to be 97% and the negative predictive value to be 98%, indicating that tested nodules are characterized as likely benign. Study inclusion criteria for the ORACLE study were pre-test probability of cancer (pCA) ≤ 50%, ≥ 40 years of age, nodule 8–30 mm in diameter, and no history of lung cancer and/or active cancer (except for non-melanomatous skin cancer) within 5 years, which is the intended use population of the test. A total of 280 tested with the IC, and 278 control patients met eligibility and analysis criteria and 197 were in each group after propensity score matching (PSM) (IC and control groups). Patients in the IC group were 74% less likely to undergo an invasive procedure in comparison to the control group (absolute difference 14%, $p < 0.001$). This indicates that for every seven patients tested, one unnecessary invasive procedure was avoided. A decrease in invasive procedures corresponded to a decrease in risk classification, with 71 patients (36%) in the IC group classified as low risk (pCA < 5%). The proportion of IC group patients with malignant pulmonary nodules (PNs) sent to surveillance were not statistically different than the control group, 7.5% vs 3.5% for the IC vs control groups, respectively (absolute difference 3.91%, $p = 0.075$). The authors concluded that IC for patients with a newly discovered PN has shown valuable clinical utility in a real-world setting. Use of this biomarker can alter physicians' practice and decrease invasive procedures in patients with benign PNs. Study limitations reported by the authors included that definitive diagnoses for nodules were based on one year of follow-up and the observational and non-randomized nature of the study. A large randomized controlled trial (ALTITUDE trial NCT04171492) is underway to address these limitations.

Kheir et al. (2023) performed a retrospective, multicenter study across several geographical locations on the impact of Nodify XL2 integrated classifier (IC) (also known as BDX-XL2) and clinical decision making for lung nodules. The study included 231 patients, of which 102 (44.2%) were tested with the IC and 129 (55.8%) were not. The median number of chest imaging studies was two [interquartile range (IQR), 1–2] in the IC arm and two [IQR, 1–3] in the non-IC arm ($p = 0.09$). The median outpatient clinic visit was 2.00 (IQR, 1.00–3.00) in the IC arm and 2.00 (IQR, 2.00–3.00) in the non-IC ($p = 0.004$). Fewer invasive procedures were pursued in the IC arm as compared to non-IC respectively (26.5% vs 79.1%, $p < 0.001$). All patients in the IC arm with post-pCA (likely benign n = 39) had designated benign diagnosis at follow up of one year. The authors concluded that patients with lung nodules with a pre-test probability of cancer (pCA) ≤ 50%, use of the IC was associated with less invasive procedures and clinic visits without misclassifying patients with likely benign lung nodules results at follow-up of one year. Study limitations reported by the authors included its retrospective design and that patients were followed up at one year instead of the traditional two years surveillance for nodule stability.

Long et al. (2023) pooled two cohorts from the Pulmonary Nodule Plasma Proteomic Classifier (PANOPTIC) clinical trial and the Observational Registry Study to Evaluate the Performance of BDX-XL2 in Routine Clinical Use (ORACLE) clinical trial to analyze the clinical usefulness of BDX-XL2 (Nodify XL2). One hundred fifty patients from PANOPTIC and 280 patients from ORACLE totaling 430 patients were included in the study. Two hundred eleven incidental vs 69 screen-detected nodules were included and no difference in performance of the proteomic integrated classifier (IC) was found [negative predictive value (NPV), 94% vs 100%; $p = 0.58$]. Fourty-six percent were male and 54% female and sex did not impact performance (NPV, 97% male vs 95% female; $p = 0.7023$). One hundred three patients were current tobacco users, 216 were former tobacco users, and 111 never used tobacco. Higher sensitivity and lower specificity was discovered in patients who ever used tobacco compared to those who never used tobacco [94% vs 67% ($p = 0.0218$) and 39% vs 68% ($p < 0.001$), respectively]. However, NPV did not differ between groups (97% vs 94%; $p = 0.43$). Median nodule diameter was 11 mm. Based on size of ≤ vs > 11 mm, evaluation of the IC demonstrated similar sensitivity (92% vs 87%; $p = 0.69$). Specificity was higher for nodules of ≤ 11 mm (57% vs 35%; $p < 0.001$). NPV was similar between the two groups (98% vs 93%; $p = 0.105$). The authors concluded that the results showed a high NPV for the IC that was not different based on sex, screen detection, smoking status, or nodule size. Including the ORACLE cohort allowed the authors to analyze test performance in a screen-detected population. The analysis suggests that the IC may be effectively used in a broader range of patient populations than previously reported. Study limitations reported by the authors included that many of the subgroups included fairly small numbers to analyze and benign status was established based on 12 months of CT scans instead of the standard 24 months. However, extended follow-up of the PANOPTIC cohort showed that all nodules that were determined to be benign at 12 months were still benign at 24 months.

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BDX-XL2 was retrospectively validated on the prospective observational PANOPTIC study (NCT01752114) of lung nodule management. Silvestri et al. (2018) analyzed the results of the PANOPTIC trial which enrolled 685 subjects across 33 sites in the US and Canada. Validation of BDX-XL2 followed the National Academy of Medicine's guidelines for rigorous test development (Micheel et al., 2012). In the PANOPTIC study, 178 subjects met the intended use population of BDX-XL2. This consisted of 149 benign lung nodules (as determined by histopathology after biopsy or surgery, or by stable CT surveillance of a lung nodule after at least one year) and 29 malignant lung nodules (as determined by histopathology after biopsy or surgery), yielding a cancer prevalence of 16.3%. Per protocol, this cohort of patients was split into separate verification (n = 69) and validation (n = 109) subsets, with pre-specified interim and final analyses on each subset, respectively, to determine the performance characteristics of the test. Since the test system and clinical endpoints were unchanged between the interim and final analyses, all analyses were blinded, and the two patient cohorts were mutually exclusive, the 69 and 109 patients are combined below.

For these 178 subjects, BDX-XL2 yielded a sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of 97% [confidence interval (CI): 82%-100%], 44% (CI: 36%-52%), 98% (CI: 92%-100%), and 25% (CI: 17%-34%), respectively. It was noted that the post-test probability of BDX-XL2 is equivalent to its NPV. Procedure use and clinical factors were collected in the PANOPTIC study permitting the comparison of BDX-XL2 performance to (1) current practice, as characterized by physician pre-test risk assessment, denoted as probability of malignancy (pCA), which is based on the physician's clinical assessment of risk using a clinical risk model and/or clinical judgement; (2) positron emission tomography (PET); and (3) clinical risk factor models including the 'Mayo', 'Veterans Association (VA)', 'Brock' and 'Herder' models. Using area under the curve (AUC) as a general performance measure, the respective AUCs for BDX-XL2, pCA, PET, and these 4 clinical factor models were: 76% (CI: 69%-82%), 69% (CI: 62% - 76%), 58% (CI: 46%-69%), 69% (CI: 62%-76%), 60% (CI: 53%-67%), 71% (CI: 63%-77%), and 67% (CI: 56%-78%). BDX-XL2 had statistically significant improved performance over all above diagnostic modalities with p-values 2.1xE-11 (pCA), 0.001 (PET), 0.0009 (Mayo), 2.7xE-7 (VA), 0.005 (Brock) and 0.02 (Herder). Limitations of the study reported by the authors included that the effect the plasma protein test might have had on testing ordering was analyzed retrospectively, community practices were underrepresented, and usually two years of nodule stability is required to determine a nodule being benign.

Summary of Analytical and Clinical Performance

General

- **Intended Use**: BDX-XL2 is intended for the evaluation of 8-30 mm lung nodules in patients 40 years or older with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less.
- **Validated Specimen Type(s)**: Plasma from K2 ethylenediaminetetraacetic acid (EDTA) vacutainer tubes.

Analytical Performance

Description	Results (With 95% Confidence Intervals, if Applicable)
Repeatability (within run precision) Eight samples tested three times within a run, one instrument, two operators, three runs, three non-consecutive days, one manufacturing reagent lot for critical reagents. Qualitative results represent only two possible final results (i.e., indeterminate and likely benign) with post-test probabilities for the latter from 90 to 98%.	Analytes (analytical repeatability): • ARRLG3BP CV = 7.0% (3.6%-10.3%) • ARRC163A CV = 5.9% (3.6%-8.2%) Score (analytical repeatability): Score CV = 9.0% (3.4%-14.6%) Qualitative (clinical concordance): 62.5% (5/8; 24.5%-91.5%) ARR is defined as the ratio between the peak area for the endogenous quantifier peak and the peak area of the corresponding SIS peptide, multiplied by a calibration factor that is specific for each SIS lot. Score is defined as Log2 (ARRLG3BP/ ARRC163A)

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Description	Results (With 95% Confidence Intervals, if Applicable)
Intermediate precision (between run precision) Seven samples tested once in three different runs, one instrument, two operators, three runs, three non-consecutive days, one manufacturing reagent lot for critical reagents. Qualitative results represent only two possible final results (i.e., indeterminate and likely benign) with post-test probabilities for the latter from 90 to 98%.	Analytes (analytical repeatability): • ARRLG3BP CV = 14.5% (10.1%-18.9%) • ARRC163A CV = 12.8% (9.1%-16.6%) Score (analytical repeatability): Score CV = 6.0% (3.7%-8.4%) Qualitative (clinical concordance): 85.7% (6/7; 42.1%-99.6%)
Reproducibility (between sites)	Not applicable
Minimum input quantity	20 µL plasma
Limit of blank (LOB)	Defined as the upper 99.5% confidence interval (CI) for the response ratio (ARR) observed in negative controls.
Limit of detection (LOD)	The lower limit of response for each analyte in samples and positive controls is defined as the lower limit of quantification.
Limits of quantitation (LOQ)	The lower limit of quantification (LLOQ) is defined as the lowest response ratio within the linear range where the coefficient of variation (CV) was equal to or below 0.20, where linearity was established using five replicate measures at each concentration. The upper limit of quantification (ULOQ) is defined as the highest response ratio within the linear range where the coefficient of variation (CV) was equal to or below 0.20, where linearity was established using five replicate measures at each concentration. LG3BP: • ULOQ = 42 • LLOQ = 0.043 C163A: • ULOQ = 71 • LLOQ = 0.053
Linearity	Not applicable for qualitative interpretation (i.e., likely benign or indeterminate). For individual analytes, the linear response range was established between the LLOQ and ULOQ.
Interfering substances	Visual inspection to detect hemolysis (i.e., 100 mg/dL of hemoglobin rejected). MRM-MS chromatograms for each analyte in every sample are inspected for interference, with any interference resulting in QC failure.
Specimen stability, primary (EDTA whole blood)	Three hours at 2-8 °C based on validation study (manuscript in preparation).
Specimen stability, intermediate (plasma)	24 months at -70 °C based on validation study (manuscript in preparation).
Reagent closed/shelf-life stability	24 months at -70 °C for two critical reagents (i.e., Human Plasma Samples (HPS) and SIS peptides). ARR for 623 samples evaluated with slope not significantly different from zero (p = 0.77). Non-critical (general purpose) reagents are stored and expired per manufacturer recommendations.
Reagent open/in use stability	Critical reagents: Not applicable since single use aliquots. Non-critical reagents are stored and expired per manufacturer recommendations.

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Clinical Performance: Validity

BDX-XL2 integrates the relative abundance of two plasma proteins (LG3BP and C163A) with five clinical risk factors (age, smoking status, nodule diameter, nodule spiculation status and nodule location). From these seven markers, a numerical value, XL_2(k), for a patient k, is calculated.

XL_2(k) ranges between 0 and 1 and its value is used to index the post-test probability (i.e., NPV) validated in the PANOPTIC study (see Table 1 below).

XL_2(k) Value	Post-Test Benign Probability (i.e., NPV) (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	Test Report
0 to 0.131	98% (92-100%)	97% (82-100%)	44% (36-52%)	25% (17% - 34%)	Likely Benign
> 0.131 to 0.1613	97% (91-100%)	93% (77-99%)	49% (41-57%)	26%(18-36%)	Likely Benign
0.1613 to 0.172	96% (90-99%)	90% (73-98%)	54% (45-62%)	27% (19-37%)	Likely Benign
> 0.172 to 0.176	95% (89-99%)	86% (68-96%)	55% (47-63%)	27% (18-37%)	Likely Benign
> 0.176 to 0.1785	94% (87-98%)	83% (64-94%)	56% (47-64%)	27% (18-37%)	Likely Benign
> 0.1785 to 0.193	93% (86-98%)	79% (60-92%)	57% (44-65%)	26% (18-37%)	Likely Benign
> 0.193 to 0.195	92% (85-96%)	76% (56-90%)	58% (49-66%)	26% (17-37%)	Likely Benign
> 0.195 to 0.2306	91% (84-96%)	69% (49-85%)	64% (56-72%)	27% (18-39%)	Likely Benign
> 0.2306 to 0.354	90% (84-95%)	55% (36-74%)	83% (75-88%)	38% (24-54%)	Likely Benign
> 0.354	-	-	-	-	Indeterminate

Clinical Performance: Utility

PANOPTIC was a non-interventional study; however, the potential clinical utility of BDX-XL2 can be estimated by evaluating how many benign (benefit) and malignant (harm) nodules would have been routed away from invasive procedures into computed tomography (CT) surveillance if BDX-XL2 had been used to guide patient management in the study (and assuming complete compliance). Table 2 summarizes the potential clinical utility of BDX-XL2 at each post-test probability.

Probability of Being Benign	Of Benign Nodules (95% CI)	CT Surveillance (95% CI)
98%	15/42 = 36% (22% - 52%)	1/29 = 3% (0% -18%)
97%	17/42 = 40% (26% - 57%)	2/29 = 7% (1% -23%)
96%	19/42 = 45% (30% - 61%)	2/29 = 7% (1% -23%)
95%	20/42 = 48% (32% - 64%)	2/29 = 7% (1% -23%)
94%	20/42 = 48% (32% - 64%)	2/29 = 7% (1% -23%)
93%	22/42 = 52% (36% - 68%)	3/29 = 10% (2% -27%)
92%	22/42 = 52% (36% - 68%)	4/29 = 14% (4% -32%)
91%	25/42 = 60% (43% - 74%)	4/29 = 14% (4% -32%)
90%	32/42 = 76% (61% - 88%)	7/29 = 24% (10% -44%)

Table 2: Potential Clinical Utility of BDX-XL2

In the PANOPTIC study, there were 178 intended use subjects (when the verification and validation sets are combined) of whom 29 had malignant lung nodules and 149 had benign lung nodules. Of the 149 benign lung nodules, 42 had at least one invasive procedure. Hence the denominator of “42” in column two of Table two. Of the 29 malignant lung nodules, 13 were routed to computed tomography (CT) surveillance. That is, 13/29 = 45% of malignant nodules were routed to CT surveillance in PANOPTIC. This is substantially larger than the largest corresponding value in Table two (i.e., 24%).

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In summary, the BDX-XL2 assay is reasonable and necessary to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. This assay is only covered when the following conditions are met:

- Patient is at least 40 years of age and has a lung nodule of diameter 8 to 30 mm, and
- The pre-test risk of cancer as determined by the Mayo risk prediction algorithm is 50% or less.

Note: The BDX-XL2 test should not be ordered if a physician does not intend to act upon the test result. It is expected that physicians will advise nodule surveillance for at least 80% of patients with a post-test probability of 98% or higher.

Cytogenomic (Genome-Wide) Analysis for Constitutional Chromosomal Abnormalities

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition and prenatal diagnostic testing are not a Medicare benefit.

Routine chromosome analysis has been used historically to identify chromosome abnormalities during pregnancy when risk factors are present, such as advanced maternal age and chromosome abnormalities. Chromosome microarray analysis (CMA) does not require cell culture or dividing cells, so it provides an advantage in turn-around time for time sensitive analysis, as is often the case during pregnancy. In addition, CMA can identify smaller chromosomal abnormalities than a routine chromosome analysis and is able to identify chromosomal breakpoints that are unbalanced but may appear balanced on a conventional karyotype. CMA does have limitations; it cannot detect totally balanced chromosomal material or low-level mosaicism. Some arrays may not detect triploidy. Clinicians may use CMA as a first line test, or only when fetal abnormalities are identified (Society for Maternal-Fetal Medicine, 2016).

DMPK (DM1 Protein Kinase) (e.g., Myotonic Dystrophy Type 1)

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

The *DMPK* gene provides instructions for making a protein called myotonic dystrophy protein kinase. This protein appears to play an important role in muscle, heart, and brain cells. The protein may be involved in communication within cells. It also appears to regulate the production and function of important structures inside muscle cells by interacting with other proteins. For example, myotonic dystrophy protein kinase has been shown to turn off part of a muscle protein called myosin phosphatase. Myosin phosphatase is an enzyme that plays a role in muscle contraction and relaxation. Mutations in the *DMPK* gene cause a form of myotonic dystrophy known as myotonic dystrophy type 1 (MedlinePlus, 2020a). Myotonic dystrophy type 1 is the most common form of muscular dystrophy. The diagnosis is based on a patient's medical history, family history, physical examination findings, and genetic studies; the diagnostic standard is genetic testing to identify cytosine-thymine-guanine (CTG) repeat expansions. Treatments may focus on specific symptoms such as muscle weakness and/or atrophy, cardiac arrhythmias, fatigue, and myotonia. Currently, there are no cures for myotonic dystrophy type 1 (Hartman et al., 2024).

Hayes Molecular Test Assessment for Myotonic Dystrophy Types 1 and 2 states that myotonic dystrophy (DM) is a neuromuscular condition which manifests as progressive weakness, muscle abnormalities, and a multisystemic phenotype, with involvement of cardiac, endocrine, respiratory, and other systems. Myotonic dystrophy type 1 (DM1) and the milder, but phenotypically similar, myotonic dystrophy type 2 (DM2) are caused by genetic variants in 2 separate genes. Both genes display an autosomal dominant mode of inheritance. A severe form of DM1, congenital myotonic dystrophy (CDM1), can occur in the neonatal period with early mortality, as well as various physical and mental disabilities. The cause of DM1 is an expansion of a trinucleotide (CTG) repeat in the dystrophia myotonica protein kinase (*DMPK*) gene. The cause of DM2 is an expansion of a tetranucleotide repeat (CCTG) in the zinc finger protein 9 (*ZFP9*) gene. There is no treatment to prevent DM1 or DM2, or to change prognosis. For confirmation of a diagnosis of DM1 or DM2 in symptomatic patients in the absence of classical symptoms or a family history of the disorder, Hayes assigns a rating of C (potential but unproven benefit). For confirmation of a diagnosis of DM1 or DM2 in symptomatic patients who have classic symptoms and/or a family history of the disorder, Hayes assigns a rating of D2 (insufficient evidence). For diagnosis of DM1 or DM2 in asymptomatic adults who are at an increased risk of DM1 or DM2 through a positive family history, Hayes assigns a rating of D2. For diagnosis of DM1 in asymptomatic adults who are at an increased risk of DM1 through a positive family history, and are considering reproductive options, Hayes assigns a rating of C. For diagnosis of DM2 in asymptomatic adults who are at an increased risk of DM2 through a positive family history, and are considering reproductive options, Hayes assigns a rating of D2. For prenatal diagnosis or preimplantation genetic diagnosis (PGD) of DM1 in couples in which 1 or both members has been confirmed to be affected with, or is a presymptomatic carrier of, DM1 through genetic testing, Hayes assigns a rating of B (some proven benefit). For prenatal diagnosis or PGD of DM2, Hayes assigns a rating of D2 (Hayes, Myotonic Dystrophy Types 1 and 2, 2009, updated 2013).

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F9 (Coagulation Factor IX) (e.g., Hemophilia B)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Hemophilia B is caused by deficiency in factor IX clotting activity which causes prolonged oozing after surgery, injuries, or tooth extractions, and recurrent or delayed bleeding before a wound is completely healed. The age of diagnosis and frequency of bleeding episodes depends on the level of factor IX clotting activity. In any individual, bleeding episodes can be more frequent in children and adolescents than in adults. Severe hemophilia B is often diagnosed by age two and can have on average, 2-5 spontaneous bleeding episodes every month. Moderate hemophilia B has less frequent spontaneous bleeding, although this depends on the individual, with frequency of bleeding episodes varying from once/month to once/year from prolonged or delayed oozing after relatively minor trauma. Moderate hemophilia B is usually diagnosed before 5-6 years old. Mild hemophilia B usually does not have spontaneous bleeding episodes with frequency of bleeding ranging from once/year to once/decade. Individuals with mild hemophilia B are usually not diagnosed until later in life when they undergo surgery, tooth extractions, or there is major trauma. Hemophilia B diagnosis is established by low factor IX clotting activity. *F9* molecular testing confirms the diagnosis. Depending on the *F9* sequencing method used, single-exon, multi-exon, or whole-gene deletions/duplications may not be detected. It is also used for prenatal/preimplantation testing and carrier screening (Konkle and Nakaya Fletcher, 2025).

Tests to diagnose hemophilia B include partial thromboplastin time, prothrombin time, and serum factor IX activity (MedlinePlus, 2024b).

FANCC (Fanconi Anemia, Complementation Group C) (e.g., Fanconi Anemia, Type C)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose Fanconi anemia (FA) in individuals with prenatal and/or postnatal short stature, skeletal malformations, abnormal skin pigmentations, microcephaly, ophthalmic anomalies, and genitourinary tract anomalies with macrocytosis, increased fetal hemoglobin, and cytopenia. It is also used for prenatal testing, preimplantation genetic testing, and carrier screening (Mehta and Ebens, 2026).

Fetal Chromosomal Aneuploidy (e.g., Trisomy 21, 18, and 13, Monosomy X)

Prenatal diagnostic testing is not a Medicare benefit.

Cell-free deoxyribonucleic acid (DNA) testing is used for noninvasive prenatal testing that mainly looks for Down syndrome (trisomy 21, 18, 13, and extra or missing copies of the X and Y chromosome) (MedlinePlus, 2021b).

Fetal Chromosomal Microdeletions (e.g., Digeorge Syndrome, Cri-Du-Chat Syndrome)

Prenatal diagnostic testing is not a Medicare benefit.

Noninvasive prenatal testing (NIPT) is used in the clinical detection of fetal autosomal deletions (Yin et al., 2019).

FMR1 (Fragile X Messenger Ribonucleoprotein 1) [e.g., Fragile X Syndrome, X-Linked Intellectual Disability (XLID)]

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

In a Hayes Clinical Utility Evaluation on Fragile X Syndrome, it is noted that genetic testing is used to diagnose Fragile X Syndrome (FXS), the most common cause of inherited intellectual disability (ID) and is caused by changes in the *FMR1* gene. There is no cure for FXS. For use of FXS genetic testing to diagnose individuals with intellectual disability (ID) and/or autism spectrum disorder (ASD) of unknown cause, and/or other features of FXS, Hayes assigns a rating of C (potential but unproven benefit). For use of FXS genetic testing for carrier screening in women to be used for family planning/reproductive decision making related to having a pregnancy/child with FXS, Hayes a assigns a rating of C. For use of FXS genetic testing for prenatal diagnosis in an at-risk pregnancy, Hayes assigns a rating of C. For use of FXS

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genetic testing for newborn screening, Hayes assigns a rating of D2 (insufficient evidence) (Hayes, Genetic Testing for Fragile X Syndrome, 2017, updated 2021).

The average age of FXS diagnosis is 42 months for girls and 35-37 months for boys (CDC, 2024).

FXN (Frataxin)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose Friedreich ataxia which presents as muscle weakness impacting gait, dysarthria, dysphagia, peripheral motor and sensory neuropathy, spasticity, autonomic disturbance, optic atrophy, and abnormal eye movements. Onset is usually at 10-15 years of age. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Bidichandani et al., 2025).

Lima et al. (2025) performed an observational study on omaveloxolone in adult patients with Friedreich's ataxia (FRDA), an autosomal recessive neurodegenerative spinocerebellar ataxia caused by a homozygous GAA triplet repeat expansion in the frataxin (*FXN*) gene. Patients were assessed with an anamnestic profile, general and neurological examination, clinical scales, and blood tests, at baseline, at 12 weeks and after 24 weeks of treatment with omaveloxolone. Primary outcomes included assessing neurological severity and functional status using mFARS (modified Friedreich's Ataxia Rating Scale), SARA (Scale for the Assessment and Rating of Ataxia), FA-ADL (Friedreich's Ataxia Activities of Daily Living), 9-Hole Peg Test (9HPT) for upper limb dexterity, interleukin-6 (IL-6) levels and routine lab tests. Patients were given oral omaveloxolone 150 mg daily. Twenty patients were included in the study. The drug was safe with no significant adverse events during the first 24 weeks and without discontinuations. Asymptomatic and transient liver transaminase elevation occurred in half the patients. Cardiac function was stable, as well as NT-proBNP and lipids. Clinical scales did not show any significant difference during follow-up, but a significant decreased in IL-6 was reported. The authors concluded that the drug appears to be safe and well-tolerated in adult patients with FRDA in the real-life setting. There were no significant worsening of symptoms observed and no signs of progression. After 24 weeks, improvement of inflammatory biomarkers was observed but no predictive factors for the disease response were identified. The authors note due to the small sample size and short duration of the study, this limits the generalizability of the findings. The authors concluded that further studies with longer duration are needed to clearly show the efficacy of the drug in FRDA.

In a Hayes Molecular Test Assessment for Friedreich Ataxia (FRDA), it is noted that FRDA is caused by expansion of a GAA trinucleotide repeat in the frataxin (*FXN*) gene. *FXN* gene testing can be considered in adults or children with symptoms consistent with FRDA, Friedreich ataxia with retained reflexes (FARR), late-onset Friedreich ataxia (LOFA), or in patients with apparently recessive or sporadic ataxia. Carrier testing can be performed in first-degree relatives of individuals with genetically confirmed FRDA. Prenatal or preimplantation genetic diagnosis can be performed in families where both parents carry *FXN* repeat expansions. Genetic testing for confirmation of diagnosis of FRDA in patients with symptoms compatible with FRDA earned a Hayes rating D1 (no proven benefit and/or not safe). Hayes rating D2 (insufficient evidence) was assigned for confirmation or exclusion of diagnosis of FRDA in patients with idiopathic or apparently recessive ataxia. Hayes rating C (potential but unproven benefit) was assigned for confirmation or exclusion of diagnosis of FRDA in patients with idiopathic or apparently recessive ataxia to provide information to relatives at risk. Hayes rating D2 was assigned for carrier testing in relatives of individuals with genetically confirmed FRDA to facilitate reproductive decision making. Hayes rating D2 was assigned for prenatal or preimplantation genetic diagnosis in families with genetically confirmed FRDA [Hayes, Friedreich Ataxia (FRDA), 2011, updated 2014].

G6PD (Glucose-6-Phosphate Dehydrogenase)

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

The *G6PD* gene provides instructions for making an enzyme called glucose-6-phosphate dehydrogenase. More than 200 mutations in this gene cause glucose-6-phosphate dehydrogenase (G6PD) deficiency, a disorder that affects red blood cells, which carry oxygen from the lungs to tissues throughout the body and is most common in males. The most common medical problem associated with glucose-6-phosphate dehydrogenase deficiency is hemolytic anemia. An estimated 400 million people worldwide have glucose-6-phosphate dehydrogenase deficiency. This condition occurs most frequently in certain parts of Africa, Asia, the Mediterranean, and the Middle East. It affects about 1 in 10 African American males in the United States (MedlinePlus, 2023a, 2024d).

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The diagnosis of G6PD deficiency is made by a quantitative spectrophotometric analysis which is a rapid fluorescent spot test. If the blood spot fails to fluoresce under ultraviolet light the diagnosis is positive. Genetic tests may be used for population screening, family studies, or prenatal diagnosis (Frank, 2005). The presence of acute hemolytic anemia (AHA) will prompt testing for G6PD deficiency which is done via the standard spectrophotometric assay which is highly reliable. In most cases, the result will be clear cut and below the normal range (Luzzatto et al., 2016).

Genetic Testing for Severe Inherited Conditions Carrier Screening Panel [e.g., Cystic Fibrosis, Ashkenazi Jewish-Associated Disorders (e.g., Bloom Syndrome, Canavan Disease, Fanconi Anemia Type C, Mucolipidosis Type VI, Gaucher Disease, Tay-Sachs Disease), Beta Hemoglobinopathies, Phenylketonuria, Galactosemia]

Carrier screening is not a Medicare benefit.

Genome Sequencing (Unexplained Constitutional or Heritable Disorder Syndrome)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition and prenatal diagnostic testing are not a Medicare benefit.

Hayes published a Clinical Utility Evaluation (2023, updated 2025) addressing the use of genetic testing, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), for individuals with clinically diagnosed autism spectrum disorder (ASD). Overall, Hayes found evidence from few very poor-quality studies supporting the use of genetic testing for in individuals with this disorder. Although limited evidence indicates that results of genetic testing may lead to additional testing and treatment recommendations in a portion of individuals tested, it is not clear if there are improved outcomes or any benefit in comparison with standard evaluation protocols.

In a 2022 (updated 2025) Clinical Utility Evaluation, Hayes found insufficient evidence for use of whole-exome sequencing (WES) or whole-genome sequencing (WGS) to assist with clinical decision-making and improve overall outcomes in adults with suspected neuromuscular disease or movement disorders. Limited, very low-quality evidence was found for WES; larger prospective studies investigating impact on clinical management and outcomes are required. For WGS, no studies investigating use in adults suspected to have neuromuscular or movement disorders were identified. Studies evaluating WGS data and its relationship to management and outcomes in individuals with these disorders are needed.

A Hayes Clinical Utility Evaluation (2021a, updated 2023) indicates uncertain clinical utility for whole-exome sequencing (WES) and insufficient clinical utility for whole-genome sequencing (WGS) when these technologies are used to inform clinical action and/or improve outcomes in children 18 years or younger with neurological phenotypes for whom a diagnosis has not been determined after standard diagnostic tests. In the case of WES, included studies (n = 12) documented changes in treatment and improved outcomes in a small portion of individuals tested (2-22%). For WGS, outcomes are from a small and narrowly defined population group focused on infants with neurological phenotypes; Hayes notes that additional studies evaluating both larger numbers and a broader range of children with neurological symptoms are required.

An additional Clinical Utility Evaluation (Hayes, 2021b, updated 2024) found insufficient evidence for utility of whole-exome sequencing (WES) and whole-genome sequencing (WGS) to guide clinical care in individuals with a primary phenotype of intellectual disability (ID) alone. This evaluation did does not address ID in individuals with other disorders including neurodevelopmental disabilities (NDD) or global developmental disability (GDD), which are discussed in separate Hayes reports. No peer-reviewed studies were found that assessed clinical utility for individuals with a primary phenotype of ID.

AlAbdi et al. (2023) performed an observational utility study of long-read whole genome sequencing (WGS) of 34 families with suspected autosomal recessive diseases previously undiagnosed after exome sequencing. The primary outcome of the study was the diagnostic yield of long-read WGS performed for the index participant using the Pacific Bioscience Sequel IIe platform. Families included in the study were of Middle Eastern ancestry. Both chart review and direct clinical assessment were used to obtain specific phenotypic data and only families whose phenotypes were consistent with autosomal recessive etiologies were included. Results of at least one exome test based on short-read sequencing was available for an index member of each participating family. Likely causal variants were detected in 38% (n = 13) of the overall cohort, however, seven of these participants had causal variants that could have been identified via short-read ES; this underscores the difficulties encountered in the interpretation of these tests. Although their results suggest that there may be a future role for non-coding DNA evaluation in individuals and families with suspected autosomal recessive diseases, larger high-quality studies including sequencing at greater depth are recommended by the authors. Focus on

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interpretation challenges associated with ES is also required along with ongoing efforts to improve existing sequencing methodologies.

Krantz et al. (2021) reported the results of their investigation of the effect of whole-genome sequencing (WGS) on the impact of clinical management of infants admitted to an intensive care unit (ICU) from 5 US children's hospitals. Their multicenter randomized trial incorporated a time-delayed study design and focused on selection of children whose providers suspected genetic disorder. Usual care was continued through the study, capturing variation in management, and helping with the assessment of real-world clinical situations. A total of 354 infants were enrolled from September 2017 to April 2019, with observation through July 2019. Infants between 0 and 120 days old were included (mean age = 15 days). The infants were randomized to receive WGS results either 15 days (early) or 60 days (delayed) after study enrollment. Infants were racially and ethnically diverse with a geographically distributed population in the US. The researchers indicated that twice as many infants in the early group vs the delayed group received a change in management (COM) (34 of 161 vs 17 of 165) and molecular diagnosis (55 of 176 vs 27 of 178) at 60 days. COM and diagnostic efficacy doubled in the delayed group at 90 days (to 45 of 161 and 56/178, respectively). The study, however, showed no measurable difference in length of stay or survival. The authors concluded that comprehensive genomic testing of acute care infants can impact clinical management and that WGS specifically positively impacts patient care and should be considered for critically ill infants with suspected genetic disease as a primary tool. Of note, this study was industry sponsored and conflicts of interest were present which could have impacted choice of methods (in particular, outcomes), or the validity of the interpretation of the findings. In addition, the findings may not be generalizable to ICUs outside of tertiary referral centers, which may have a lower incidence of genetic disease. The relevance of study findings on clinical outcomes is unclear and was not examined in this study.

Smedley et al. (2021) shared results of their pilot study investigating the role of genome sequencing in individuals with undiagnosed rare diseases. The study included 2,183 families with a total of 4,660 participants who were recruited after having been identified by health care providers and researchers as having rare diseases that had not yet been diagnosed after receipt of standard care (including no diagnostic testing or approved diagnostic tests which did not include genome sequencing) in the United Kingdom National Health Service. Among the participants, 161 disorders including a broad array of rare diseases, was present. Data was collected on clinical features, genome sequencing was performed, and new pathogenic variants were identified through the analysis. The disease categories of participants being evaluated for rare genetic conditions included: cardiovascular disorder, ciliopathy, dermatologic disorder, dysmorphic or congenital abnormality, endocrine disorder, gastroenterological disorder, growth disorder, hematologic or immunologic disorder, hearing or ear disorder, metabolic disorder, intellectual disability, neurologic or neurodevelopmental disorder, ophthalmologic disorder, renal and urinary tract disorder, respiratory disorder, rheumatologic disorder, skeletal disorder, or tumor syndrome. The report indicates that diagnostic yields were highest in families with larger pedigrees and were higher for disorders likely to have a monogenic cause (35%) than for disorders with a complex cause (11%). Fourteen percent of diagnoses were made using a combination of automated approaches and research which was especially important for cases with etiologic noncoding, structural, and mitochondrial genome variants as well as variants which were not well covered by exome sequencing (ES). In the course of the study, three new disease genes and 19 new associations were discovered. Ultimately, 25% of diagnoses that were made had immediate implications for clinical decision-making for affected individuals and their families. The researchers concluded that study showed an increase in diagnostic yield for rare diseases when genome sequencing was used and supports the case for using genomic sequencing when diagnosing certain specific rare diseases. However, the study did not include a comparison group and the relevance of the study findings on clinical outcome is only documented in the publication with anecdotal reports.

Malinowski et al. (2020) reported on the outcome of an American College of Medical Genetics and Genomics (ACMG) systematic review performed to assist with creation of an evidence-based guideline addressing the use of exome sequencing (ES) and genome sequencing (GS). This ACMG practice guideline is included in the Clinical Practice Guidelines section of this policy. Primary literature including health, clinical, reproductive, and psychosocial outcomes resulting from ES/GS in individuals with congenital anomalies (CA)/developmental delay (DD)/intellectual disability (ID) was identified. Ultimately, 167 articles were included; these were largely case reports or small case series and of note, all but one study lacked a comparison group. Changes to clinical management or reproductive decision-making were the most frequently reported outcomes and were observed in nearly all included studies. Further, a significant number of the articles reported clinical impact on family members of the affected individual or an impact on reproductive outcomes. The authors concluded that for individuals with CA/DD/ID, ES and GS assists with clinical and reproductive decision-making, potentially improving outcomes for affected individuals and family members. However, there were some noted conflicts of interest and the relevance of these findings on clinical outcomes is not clear.

Hou et al. (2020) conducted a prospective cohort study combining deep phenotyping with whole-genome sequencing (WGS), while following the American College of Medical Genetics and Genomics (ACMG) guidelines to assess variant pathogenicity. Participants were adults (n = 1,190) who consented to WGS and agreed to participate in metabolomics,

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clinical laboratory testing, advanced imaging and provide family/medical history. Phenotypic results were, subsequently, integrated with genomic results. Positive pathogenic findings suggesting a genetic risk predisposition, were found in 17.3% of adults. When genetic results were incorporated with deep phenotyping, 11% had observed genotype/phenotype correlations. Greater than 75% of these correlations included risk for dyslipidemia (n = 24), cardiomyopathy, arrhythmia/other cardiac conditions (n = 42) and endocrine/diabetic conditions (n = 17). Approximately 6% of participants with pathogenic variants did not have a genotype/phenotype correlation. The authors concluded that results of this study and future studies can provide beneficial information to aid in precision medical practice. The authors indicated that this study did not measure health outcomes or benefits. Repeat evaluation of these individuals is required to characterize the clinical significance of the findings.

Clark et al. (2018) conducted a meta-analysis comparing the diagnostic and clinical utility of whole-genome sequencing (WGS), whole-exome sequencing (WES) and chromosome microarray (CMA) in children suspected of having genetic disease. Analysis of the literature from January 2011 to August 2017 was conducted following the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Thirty-seven studies of 20,068 children were included. Overall, the diagnostic utility of WES and WGS was greater than CMA. In studies from only 2017, the diagnostic utility of WGS was greater than CMA. Among studies featuring in cohort comparisons, the diagnostic utility of WES was greater than CMA. The diagnostic utility between WGS and WES was not significantly different. In studies with in-cohort comparisons of WGS and WES, there was a greater chance of achieving a diagnosis when a trio was available than singleton testing, and with in-hospital interpretation vs a reference lab interpretation. In this study, clinical utility was defined as a change in clinical management. Cases where the only change was reproductive planning or a change in genetic counseling were excluded. The clinical utility of WES was greater, but not statistically significant, than CMA. However, WGS was higher for clinical utility than CMA, and met statistical significance ($p < 0.0001$). The authors identified several limitations with the meta-analysis, such as the heterogeneity of the pooled data, taking diagnostic rates at face value, and that only one study met the highest level of evidence criteria for clinical interventions. Overall, they concluded that more randomized, well designed and controlled clinical studies are needed but WES and WGS could be considered over CMA for a first-tier test in a child suspected of having a genetic diagnosis.

Prenatal Genetic Diagnosis or Screening

Shreeve et al. (2023) performed a systematic review and meta-analysis which sought to determine the incremental yield of whole-genome sequencing (WGS), over whole-exome sequencing (WES) and/or chromosome microarray (CMA) in fetuses and infants with an anomaly that either was or could have been detected via ultrasound in the prenatal period. Secondary outcomes included the assessment of turnaround time and quantity of deoxyribonucleic acid (DNA) required for these tests. A total of 18 studies comprising 1,284 individual cases met inclusion criteria for the study. Eight studies (754 cases) were prenatal cohorts and the remaining ten studies included postmortem, neonatal, or infants demonstrating congenital structural abnormalities. The incremental yield of WGS over WES (1%) was not significant [95% confidence interval (CI) 0%-4%, Higgins' I^2 = 4 7%]. Yield of WGS over quantitative fluorescence-polymerase chain reaction (QF-PCR)/CMA was 26% for all (95% CI 18-36%, I2 = 86%), 16% for prenatal (9-24%, I^2 = 85%), and 39% (95%CI 27-51%, I^2 = 53%) for postnatal cases. Pooled median turnaround time for WGS was 18 days; only one study documented turnaround time for CMA/WES, so no comparison could be made. The study found a significant incremental yield with use of WGS compared to CMA for the genetic evaluation of congenital anomalies, but no significant increase in incremental diagnostic yield of WGS over WES. The authors note that there is currently insufficient evidence to promote the use of WGS over CMA and WES, but the use of WGS over standard pathways of testing uses less DNA and has the potential for faster turnaround times. Additional studies are recommended. The authors reported that the primary limitations of their study were the low number of included cases and the high degree of heterogeneity despite adoption of a random-effects model and sub analyses.

Miceikaite et al. (2023) performed a study assessing the diagnostic yield of prenatal genetic testing using trio whole-exome sequencing (WES) and whole-genome sequencing (WGS) compared to standard chromosome microarray (CMA) and found a 25% increase in diagnostic yield when trio WES/WGS was performed in pregnancies where CMA had been negative. Testing took place between the 12th and 21st week of gestation, and all pregnancies included (n = 40) had documented fetal anomalies or increased nuchal translucency (≥ 5 mm). For each pregnancy, trio WES or WGS and standard CMA were performed. Of the 40 total pregnancies, 16 were found to have a genetic sequence variation, copy number variants (CNV) or aneuploidy which corresponded with the fetal phenotype; the overall diagnostic yield of WES/WGS was 40%. A total of six chromosomal abnormalities were detected via CMA and each of these was also identified by WES/WGS. An important finding was that WES testing yielded more consistent identification of mosaic sequence variations than WGS, related to the ability of WES to sequence more deeply. The researchers assert that although this study is limited by small sample size, the results bolster the existing evidence supporting higher diagnostic yield of WES/WGS over CMA and speculate that WES/WGS testing has promise for use as valuable, standalone testing for prenatal diagnostic use.

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A 2020 (updated 2023) Hayes Clinical Utility Evaluation found that the evidence supporting whole-exome sequencing (WES) and whole-genome sequencing (WGS) related to improvement of diagnosis and assistance with pregnancy and post-pregnancy management when abnormalities are detected by ultrasound or other testing is lacking. Large studies including outcome data and impact on clinical management are required to support clinical utility for the use of WES and WGS in the prenatal setting.

HBA1/HBA2 (Alpha Globin 1 and Alpha Globin 2) (e.g., Alpha Thalassemia, Hb Bart Hydrops Fetalis Syndrome, HbH Disease)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing for Alpha-thalassemia is used to diagnose Hb Bart syndrome in a fetus with prenatal onset of generalized edema and pleural and pericardial effusions as a result of congestive heart failure induced by severe anemia. Usually, death occurs in the neonatal period. It is also used to diagnose Hemoglobin H disease, which usually develops in the first year of life. It is also used for carrier testing (Tamary and Dgany, 2024).

In a Hayes Molecular Test Assessment on Alpha-Thalassemia, it is noted that the genetic aspects of alpha-thalassemia are complicated in that it is caused by sequence variants affecting the hemoglobin, alpha 1 (*HBA1*) and hemoglobin, alpha 2 (*HBA2*) genes. For confirmation of diagnosis in an individual showing clinical features of HbH disease, Hayes assigns a rating of C (potential but unproven benefit). For postnatal confirmation of diagnosis in an individual with clinical features of Hb Bart hydrops fetalis syndrome, Hayes assigns a rating of D1 (no proven benefit and/or not safe). For identification of a newborn who is affected with alpha-thalassemia, Hayes assigns a rating of C. For carrier testing in an individual with a positive hematological test, from a family with confirmed alpha-thalassemia, from a high-risk ethnic background, or who is the reproductive partner of a known alpha-thalassemia carrier, Hayes assigns a rating of B (some proven benefit). For prenatal diagnosis or preimplantation genetic diagnosis to identify a fetus or embryo affected with alpha-thalassemia in a couple with known variants, Hayes assigns a rating of B (Hayes, Alpha-Thalassemia, 2015).

HBB (Hemoglobin, Subunit Beta) (e.g., Sickle Cell Anemia, Beta Thalassemia, Hemoglobinopathy)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose Beta-thalassemia which presents between 6-24 months of age with pallor due to severe anemia, poor weight gain, stunted growth, hepatosplenomegaly, and jaundice. The diagnosis of β-thalassemia is established in a proband older than age 12 months by identifying microcytic hypochromic anemia, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, absence of iron deficiency, and reduced or complete absence of hemoglobin A (HbA) and elevated hemoglobin A2 (HbA2) and often hemoglobin F (HbF) on hemoglobin analysis. Identification of biallelic pathogenic variants in *HBB* on molecular genetic testing can diagnosis those younger than 12 months of age who have a positive or suggestive newborn screening result and/or unexplained microcytic hypochromic anemia with anisopoikilocytosis and nucleated red blood cells on peripheral blood smear. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Langer, 2026).

Sickle cell disease is caused by mutations in the *HBB* gene. Signs and symptoms typically start in early childhood (MedlinePlus, 2024c). It is diagnosed with a simple blood test. In the U.S., it is most often found at birth during routine newborn screening tests (CDC, 2025).

Methemoglobinemia, beta-globin type affects red blood cell function and is caused by mutations in the *HBB* gene. It can cause cyanosis which typically initially appears around 6 months of age (MedlinePlus, 2015a). The diagnosis is confirmed by arterial or venous blood gas with co-oximetry, which will speciate hemoglobin to determine the methemoglobin concentration and percentage (Chen et al., 2025).

Hearing Loss Panel (e.g., Nonsyndromic Hearing Loss, Usher Syndrome, Pendred Syndrome)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member.

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Nonsyndromic hearing loss (NSHL) is defined as partial or total hearing loss that does not occur with other medical conditions or symptoms. It is estimated that up to 3/1,000 children are born with hearing loss in one or both ears. The frequency of hearing loss increases with age; by age 85 hearing loss is experienced by more than half of all people (MedlinePlus, 2016b).

Hayes conducted two reports; one that evaluated the clinical utility of genetic testing in those with or suspected of congenital and/or prelingual nonsyndromic hearing loss (Hayes, Clinical Utility Evaluation, Genetic Testing in Patients With or Suspected of Congenital and/or Prelingual Nonsyndromic Hearing Loss, 2019, updated 2022) and a second report that evaluated the clinical utility of genetic testing in individuals with or suspected of postlingual nonsyndromic hearing loss (Hayes, Clinical Utility Evaluation, Genetic Testing in Patients With or Suspected of Postlingual Nonsyndromic Hearing Loss, 2019, updated 2022). Both reports found there was insufficient evidence to support genetic testing in these patient populations. Per Hayes, there were no studies identified that would inform decision making that resulted in improved patient management or influenced outcomes.

Palmer et al. (2013) performed a study to assess the impact of genetic testing on psychological well-being in adults diagnosed with hearing loss at birth to six years of age. The study included 263 eligible patients. A psychological evaluation was performed before and after genetic testing. The authors concluded that there is limited evidence to suggest that knowing genetic test results would impact patient perceived control, depression, and anxiety (this study is included in the Hayes 2019 Genetic Testing in Patients with or Suspected of Postlingual Nonsyndromic Hearing Loss Clinical Utility Evaluation).

Pendred syndrome is usually associated with hearing loss and goiters. Usually, severe to profound hearing loss is apparent at birth. Less often, hearing loss does not develop until later in infancy or early childhood (MedlinePlus, 2016c).

Usher syndrome is an inherited disease that can cause major hearing loss and retinitis pigmentosa. In type 1, deafness is at birth. Type II accompanies moderate to severe hearing loss. Type III are born with normal hearing but develop problems with vision and then hearing loss. There is no cure for Usher syndrome (MedlinePlus, 2025).

Hereditary Peripheral Neuropathies Panel

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition and prenatal diagnostic testing are not a Medicare benefit.

Charcot-Marie-Tooth (CMT) disease is a disorder that damages the peripheral nerves, which can cause loss of sensation and atrophy of the muscles in the feet, legs, and hands (MedlinePlus, 2018c).

There is no cure for Charcot-Marie-Tooth (CMT), and maintaining mobility, flexibility, and muscle strength is important. Starting a treatment program soon after symptoms begin can aid in maintaining quality of life. Medications can be prescribed for severe nerve pain (NIH, 2026).

The diagnosis of Charcot-Marie-Tooth (CMT) disease is based on physical symptoms, family history and clinical tests. These include nerve conduction velocity (NCV) electromyogram (EMG). Treatment is symptomatic and supportive, and there is no cure. With recent advances in molecular genetic testing using both deletion duplication analysis and next generation sequencing (NGS) for patients with a clinical diagnosis of CMT, a genetic cause can be found in about 60% of patients (NORD, 2021).

The large number of Charcot-Marie-Tooth (CMT) causing genes is often challenging for clinicians and patients when trying to determine the underlying genetic diagnosis. There is little information available to guide which gene to test and testing a patient for mutations in all commercially available CMT genes is not realistic. Family planning and prognosis may require an accurate genetic diagnosis and current treatment trials depend on knowing the genetic cause of a patient's CMT even if no cures are presently available (Miller et al., 2011).

Hayes Molecular Test Assessment for Charcot-Marie-Tooth Type 1A (*PMP22*) (2008, updated 2012) describes Charcot-Marie-Tooth disease Type 1A (CMT1A) as a peripheral demyelinating neuropathy caused by a 1.5-megabase (Mb) duplication of chromosome 17 at band p11.2. Product names include complete CMT Evaluation (#400) or *PMP22* Duplication/Deletion deoxyribonucleic acid (DNA) Test (#131) (Athena Diagnostics Inc.); Inherited Peripheral Neuropathies [Charcot-Marie-Tooth Type 1A (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)] FISH analysis (#8467) [Medical Genetics Laboratories (MGL) at Baylor College of Medicine (BCM)]. For confirmation of diagnosis in an individual with suspected CMT based on clinical findings, Hayes assigns a rating of C (potential but unproven benefit). For an asymptomatic individual with a confirmed family history of CMT1A to establish personal risk, Hayes assigns a rating of C. For an oncology patient with unexplained or preexisting familial neuropathy consistent with

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CMT, Hayes assigns a rating of B (some proven benefit. Published evidence indicates that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, there are outstanding questions regarding long-term safety and impact on health outcomes, clinical indications, contraindications, optimal treatment/testing parameters, and/or effects in different patient subpopulations). For prenatal or preimplantation genetic diagnosis of CMT1A, Hayes assigns a rating of B.

Hereditary neuropathy with liability to pressure palsies (HNPP) is a genetic disorder causes recurrent acute sensory and motor neuropathy in a single nerve or multiple nerves. Symptoms usually start at age 20-30s as non-painful focal sensory and motor neuropathy. There is no cure for HNPP and treatment is only to manage symptoms (Chrestian, 2020).

Hereditary sensory neuropathy type I (HSN1) is a genetic disorder that causes abnormalities impacting the nerves, especially of those of the hands and feet. Symptoms appear on average at 37 years old as hearing loss, and cognitive decline (dementia), sensory neuropathy. There is no cure for HSN and treatment is only to manage symptoms (NORD, 2017a).

Hereditary sensory and autonomic neuropathy type 1E (HSAN1E) is a rare genetic disorder that presents symptomatically usually at age 20-30s as hearing loss, cognitive decline, and sensory neuropathy. There is no cure for HSAN and treatment is only to manage symptoms (NORD, 2017b).

Hereditary spastic paraplegia (HSP) is an inherited neurologic disorder that manifests as difficulty walking due to muscle weakness and muscle tightness (spasticity) in the legs. There is no cure for HSP and treatment is only to manage symptoms (NORD, 2017c).

In Hayes Precision Medicine Insights, based on a review of the abstracts, there seems to be minimal support in genetic testing for hereditary spastic paraplegia (HSP). There were no professional guidelines found regarding genetic testing for HSP. Treatment is supportive and addresses the symptoms present in affected individuals. Relevant to genetic testing for HSP are studies that suggest variable expressivity and a lack of genotype-phenotype correlations, therefore making it impossible to predict what features an affected individual will have or how severe the condition will be based on genetic testing results. The abstracts seem to evaluate the role of genetic testing in confirming a diagnosis in individuals with a clinical suspicion of HSP. No studies were found that appear to evaluate further impact of testing on patient management or improved outcomes. (Hayes, Hereditary Spastic Paraplegia, 2021).

Hereditary Retinal Disorders Panel (e.g., Retinitis Pigmentosa, Leber Congenital Amaurosis, Cone-Rod Dystrophy)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose hereditary retinal disorders such as retinal pigmentosa, Leber congenital amaurosis, and cone-rod dystrophy. Retinitis pigmentosa first manifests as loss of night vision in children. Signs and symptoms are usually limited to vision loss (MedlinePlus, 2010). Leber congenital amaurosis presents as severe visual impairment starting at birth or shortly after birth (MedlinePlus, 2022). Cone-rod dystrophy usually first manifest in children as decreased visual acuity and increased sensitivity to light (MedlinePlus, 2018a). It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Kumaran et al., 2025).

In Hayes Precision Medicine Insights, based on a review of the abstracts, there seems to be minimal support in genetic testing for cone-rod dystrophy (CRD). Upon review of professional guidelines, there seems to be weak support for genetic testing for CRD. There is minimal evidence regarding the clinical utility of CRD genetic testing. Genetic testing typically does not have a role in diagnosis, as variants in the same gene can cause multiple conditions. There are currently no treatments to stop vision loss or restore vision (Hayes, Cone-Rod Dystrophy, 2021).

HTT (Huntingtin) (e.g., Huntington Disease)

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

The *HTT* gene provides instruction for making a protein called huntingtin, a protein required for early embryonic development and plays a crucial role in neurogenesis. Huntington disease (HD) is a progressive disorder of cognitive, motor, and psychiatric manifestations. The mean age of onset is around 40-50 years, although childhood onset and late onset do occur. The median survival after onset is 15-18 years. HD diagnosis is made based on family history, clinical

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symptoms, neuroimaging, and the detection of a heterozygous CAG (cytosine, adenine, and guanine) trinucleotide repeat expansion in *HTT* by molecular genetic testing. Of note, pathogenic $(CAG)_n$ repeat expansions in *HTT* can be detected by sequence-based multigene panels, exome sequencing, or whole genome sequencing. However, these approaches are not currently routinely utilized for diagnostic testing. Genetic testing is also performed for carrier screening and prenatal/preimplantation testing (Caldeira Brás et al., 2026).

Pérez-Oliveira et al. (2024) conducted a multicenter study to investigate whether the number of CAG (cytosine, adenine, and guanine) repeats of *HTT* is associated with the risk of developing certain tauopathies and its influence as a modulator of the clinical and neuropathological phenotype, and to evaluate the potential of polyglutamine staining as a neuropathological screening. The study included brain samples of 588 patients with neuropathological diagnoses of tauopathies (34 with corticobasal degeneration (CBD), 98 with progressive supranuclear palsy (PSP) and 456 with Alzheimer's disease (AD)) and a control group of 1,070 patients that included 44 neuropathological controls. The authors reported that they identified significant differences in the number of patients with pathological *HTT* expansions in the CBD group (2.7%) and PSP group (3.2%) compared to control subjects (0.2%) and that there was a significant increase in the size of the *HTT* CAG repeats in the AD group compared to the control group. The authors concluded that the results indicated a link between *HTT* CAG repeat expansion with other non- Huntington Disease (HD) pathology, which suggests that they could share common neurodegenerative pathways and that their findings support that genetic or histological screening for *HTT* repeat expansions should be considered in tauopathies. Limitations of the study reported by the authors included the retrospective design, the small number of cases per disease entity for CBD and PSP, and the lack of controls for possible concomitant pathology seen in neurodegenerative diseases.

Scarabino et al. (2022) conducted a follow-up study to validate their hypothesis that leukocyte telomere length (LTL) was strongly correlated with the estimated time to clinical onset in pre-Huntington Disease (HD) subjects. The study included 90 participants, including 45 controls (mean age 41.9 +/- 10.5 years, 32.4% males) and 45 pre- patients (42.1% males) at baseline (T0) with a mean age of 41.9 +/- 10.4 years and then again after clinical onset at follow-up (T1) at a median of three years (mean age at follow-up was 45.3 +/- 10.2 years). The mean age at clinical HD onset was 44.4 +/- 10.7 years, which was about 2.5 (2.5 +/- 0.99) years before HD clinical onset. The CAG (cytosine, adenine, and guanine) range in the participants was 39-51 repeats. The authors reported that, in pre-HD subjects at T0, LTL was significantly reduced by 22% compared to the controls and by 14% from T0 at T1, and that no relationship was observed between the LTL and CAG numbers in subjects that carried different CAG repeats at T0 and at T1. The authors also reported that the receiver operating characteristic (ROC) curve analysis showed that LTL measurement was extremely accurate in discriminating pre-HD subjects from the controls and pre-HD from manifest HD which yields a robust prognostic value in pre-HD subjects. The authors concluded that their follow-up study showed a marked reduction in telomere length in the pre-HD patients about 2.5 years before HD onset compared to the controls and independent of CAG size, and that the homogeneity allows a common cut-point of less than 0.70 T/S to be identified between pre-HD and manifest HD. The authors recommended longitudinal studies to complete the real timing of telomere shortening. Limitations of the study include the single-center design and the small sample size.

Fang et al. (2022) conducted a study to analyze potential protospacer adjacent motif (PAM) sites immediately following the genomic deoxyribonucleic acid (DNA) single guide ribonucleic acid (sgRNA) complementary region to identify candidate single nucleotide polymorphisms (SNPs) for allele-specific CRISPR-Cas9-mediated targeting. The authors sequenced 1,056 individuals with Huntington Disease (HD), including blood samples from individuals with HD from a French cohort and genomic DNA samples from the CHDI Foundation's Enroll-HD cohort. The authors reported that they developed computational tools (NanoBinner and NanoRepeat) to de-multiplex the data, detect repeats, and phase the reads on the expanded or the wild-type *HTT* allele, and that one SNP that was common to 30% of individuals with HD of European ancestry emerged from the analysis and that this SNP was confirmed as a strong candidate for allele-specific deletion of the expanded *HTT* allele (m*HTT*) in human HD cell lines. The authors also reported that up to 57% HD individuals may be candidates for allele-specific editing through combinatorial SNP targeting. The authors conclude that they developed an experimental and computational workflow to resolve the SNP haplotypes near exon-1 of the *HTT* gene for allele specific editing in individuals affected with HD and that their workflow could be applied to other repeat expansion diseases to facilitate the design of guided RNAs for allele-specific gene editing. Limitations of the study include the single center design and the study's focus on the SNP detection.

A 2008 (updated 2012) Hayes Molecular Test Assessment on Huntington Chorea/Disease (HD) for Diagnostic, Predictive, and Prenatal or Preimplantation Genetic Diagnosis Purposes states that that cause of HD is an expansion of a CAG trinucleotide repeat in exon 1 in the huntingtin (*HTT*) gene. For diagnosis of HD in patients with suspected HD in the absence of a family history of HD, Hayes assigns a rating of C (potential but unproven benefit). For diagnosis of HD in patients with suspected HD from families in which there is a history of HD, Hayes assigns a rating of D1 (no proven benefit and/or not safe). For asymptomatic individuals from families in with a history of HD to define personal risk, Hayes assigns a rating of D2 (insufficient evidence). For asymptomatic individuals from families with a history of HD to define risk

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of transmission, Hayes assigns a rating of B (some proven benefit). For prenatal testing with family history of HD, Hayes assigns a rating of B. For preimplantation testing from parents with penetrant genetic variation for HD, Hayes assigns a rating of C.

IKBKAP (Inhibitor of Kappa Light Polypeptide Gene Enhancer in B-Cells, Kinase Complex-Associated Protein) (e.g., Familial Dysautonomia)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnosis familial dysautonomia, a debilitating disorder present from birth. Symptoms include gastrointestinal dysfunction, recurrent pneumonia, vomiting crises, altered sensitivity to pain and temperature, blood pressure instability, hypotonia, decreased or absent deep tendon reflexes, decreased taste and absence of fungiform papillae of the tongue, alacrima determined either by history in infants older than three months of age or the Schirmer test, progressive vision loss, developmental delay, and intellectual disability. There is decreased life expectancy. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Bar-Aluma, 2021).

There is no cure for familial dysautonomia. Treatment is for symptom management (MedlinePlus, 2024f),

JAK2 (Janus Kinase 2) and MPL (MPL Proto-Oncogene, Thrombopoietin Receptor) (Myeloproliferative Disorders)

Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML). The World Health Organization (WHO) further classifies PV, ET, and PMF as Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The diagnosis of a MPN is suspected based upon clinical, laboratory, and pathological findings (i.e., bone marrow morphology). MPNs are related, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells, while MPN are characterized by an increase in the number of blood cells.

Classification systems for myeloproliferative neoplasms (MPNs) include those established by the World Health Organization (WHO) and the International Consensus Classification (ICC) (Arber et al., 2022a; Khoury et al., 2022). The ICC was established with input from prior WHO editors and senior advisors, leaders from the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) (Arber et al., 2022b). Though there is significant overlap between the two classification systems, there are some differences between them. For example, the WHO 5th edition no longer incorporates increased red cell mass as a diagnostic criterion for the diagnosis of polycythemia vera (Arber et al., 2022a).

Polycythemia Vera (PV)

PV is a chronic myeloproliferative neoplasm (MPN) characterized by increased hemoglobin, hematocrit and red blood cell mass, and with bone marrow biopsy showing panmyelosis (Arber et al., 2022a; Khoury et al., 2022; NCCN Myeloproliferative Neoplasms, v2.2025; Tefferi and Barbui, 2023). Common clinical presentations include pruritus (in nearly half of cases), splenomegaly, and thrombosis; however, patients may also be asymptomatic and the diagnosis may be suspected based on findings from a complete blood count (CBC) performed for other reasons. There is an associated increased risk for thrombosis and transformation to AML or PMF and the most frequent causes of death are leukemic transformation, second malignancies, and thrombotic complications (Tefferi and Barbui, 2023).

The *JAK2* V617F mutation in exon 14 is present in the vast majority of PV, accounting for approximately 95-98% of cases. Functionally similar insertions and deletions in *JAK2* exon 12 account for most remaining cases of *JAK2* V617F mutation-negative PV. Together, they are identified in 98-100% of PV cases and lead to high diagnostic certainty (Tefferi and Barbui, 2023). Absence of a *JAK2* mutation, combined with normal or increased serum erythropoietin level, greatly decreases the likelihood of a PV diagnosis.

Though testing for the *JAK2* mutations can be serially performed given that the exon 14 mutation is by far the most common, some experts favor targeting both exons 14 and 12 at the same time, in order to avoid undue delays in the diagnostic process; additionally, peripheral blood and bone marrow samples are equally informative in detecting and quantifying *JAK2V617F* (Tefferi and Barbui, 2023). Patients with *JAK2* exon 12-mutated PV tend to be younger in age, have increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared

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to those with *JAK2* V617F-mutated PV. However, the different *JAK2* mutations do not confer any differences in prognosis and survival for patients with PV (NCCN Myeloproliferative Neoplasms, v2.2025).

Over 50% of patients with PV harbor deoxyribonucleic acid (DNA) sequence variants/mutations other than *JAK2*, with the most frequent being *TET2* (18%) and *ASXL1* (15%). Prognostically adverse mutations include *SRSF2*, *IDH2*, *RUNX1*, and *U2AF1*, with a combined incidence of 5%–10% (Tefferi and Barbui, 2023). Though these may be prognostically informative, they are not required for a diagnosis when a *JAK2* mutation is identified.

International Consensus Classification (ICC) major criteria for the diagnosis of PV include the presence of *JAK2* V617F or *JAK2* exon 12 mutation. It is recommended that in *JAK2* V617F negative cases to consider searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15. Minor criteria include subnormal serum erythropoietin level (Arber et al., 2022a).

Essential Thrombocythemia (ET)

ET is a disorder of sustained increased platelet count with bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage. Common clinical presentations include hemorrhage and splenomegaly (each occurring in about 30% of patients) though many patients are asymptomatic and, similar to polycythemia vera, the diagnosis may be suspected based on findings from a complete blood count (CBC) performed for other reasons (Kuipers et al., 2023). Hemorrhagic and thrombotic complications occur in < 10% to 84% of patients (Kuipers et al., 2023).

Approximately 50-60% of patients with ET carry a somatic *JAK2* V617F mutation, while a much smaller percentage (3-5%) have activating mutations in *MPL* (particularly MPLW515L/K in exon 10). Frameshift mutations in exon 9 of *CALR* are reported in approximately 20% to 35% of all patients. Another 20% of cases are triple-negative (non-mutated *JAK2*, *MPL*, and *CALR*) (NCCN Myeloproliferative Neoplasms, v2.2025; Tefferi and Barbui, 2023).

International Consensus Classification (ICC) major criteria for the diagnosis of ET include the presence of a *JAK2*, *CALR*, or *MPL* mutation and the exclusion of other myeloproliferative neoplasms (MPNs) and myeloid neoplasms; minor criteria include the presence of another clonal marker or absence of evidence of reactive thrombocytosis (Arber et al., 2022a; NCCN Myeloproliferative Neoplasms, v2.2025).

Primary Myelofibrosis (PMF)

PMF is characterized by a proliferation of abnormal megakaryocytes and granulocytes in the bone marrow, which is replaced with fibrous tissue, leading to bone marrow failure. However, clinical features are similar to essential thrombocythemia (ET) and recognizing the prefibrotic stage of PMF is necessary to separate it from ET, polycythemia vera, and fibrotic PMF (Khoury et al. 2022). The approximate incidence of PMF is 1 in 100,000 individuals. As with the other classic myeloproliferative neoplasms (MPNs), patients can be asymptomatic in the early stages of the disease and progression can include transformation to acute myeloid leukemia (AML). Somatic molecular markers in PMF are similar to those found in ET, and include *JAK2* V617F (60%), *CALR* (~25%), and *MPL* (5-10%), among others like trisomy of chromosome 9 and deletion of chromosome 13q.

International consensus classification (ICC) major criteria for the diagnosis of PMF include presence of a mutation in *JAK2*, *CALR*, *MPL* or presence of another clonal marker (i.e., *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations) or absence of reactive bone marrow reticulin fibrosis in the presence of relevant bone marrow findings (i.e., megakaryocytic proliferation and atypia, and appropriate amount of fibrosis for the pre-fibrotic vs fibrotic stages of disease) (Arber et al, 2022a; NCCN Myeloproliferative Neoplasms, v2.2025). As in essential thrombocythemia (ET), major criteria also include the exclusion of the other myeloproliferative neoplasms (MPNs), myelodysplastic syndromes (MDS) and myeloid neoplasms (Arber et al, 2022a; NCCN Myeloproliferative Neoplasms, v2.2025). Additionally, molecular testing for AML-associated gene alterations (i.e., mutations in *ASXL1*, *EZH2*, *TP53*, *SRSF2*, and *IDH1* or *IDH2*; aberrations in chromosomes 1q and 9p) is recommended as part of the initial workup of patients with accelerated/blast phase PMF (NCCN Myeloproliferative Neoplasms, v2.2025).

Smith et al. (2021) performed a population-based comparative study of outcomes in polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) in the United States from 2001 to 2015. Mutations of Janus Kinase 2 (*JAK2*), myeloproliferative leukemia virus oncogene (*MPL*), and calreticulin (*CALR*) are implicated in these myeloproliferative neoplasms (MPNs), leading to clonal hematopoietic stem cell proliferation. Included in the study were 10,725 patients with PV, 8,768 with ET, and 3,689 with PMF using the Surveillance, Epidemiology, and End Results (SEER) Registry. The median follow-up was 5.8 years for PV, 5.7 years for ET, and 3.1 years for PMF. Five-year relative survival (RS) for PV, ET, and PMF was 88.3%, 88.7%, and 44.9% respectively. The median overall survival (OS) in PV, ET, and PMF was 11.9 years, 12.1 years, and 4.0 years respectively. Incidence and OS noted in the study are predictably

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similar to a recent SEER analysis. During the study period, 105 (1.0%) PV, 134 (1.5%) ET, and 122 (3.3%) patients with PMF progressed to acute myeloid leukemia (AML). The median time to AML transformation was 4.4 years, 5.8 years, and 2.3 years for PV, ET, and PMF respectively. 1,952 patients at Mayo Clinic were diagnosed with the MPNs of interest between 2000 and 2017 (444 with PV, 551 with ET, and 957 with PMF). The median follow-up in this cohort was 5.3 years. Rates of leukemic transformation were as follows: 2.7% in PV, 1.6% in ET, and 9.2% in PMF. The median OS in the Mayo Clinic single institutional series was 12.7 years for PV, 14.9 years for ET, and 4.4 years for PMF. The authors concluded that the incidence and OS of *BCR-ABL-1* negative MPNs were similar to previous reports. Patients with MPN succumbed to a range of conditions, with the largest elevated risk of mortality stemming from subsequent malignancies, namely myeloid cancers. PMF foreshadowed the worst prognosis among MPN phenotypes, with greater observed mortality not only to malignancies but also to cardiovascular disease and infections, showing the morbidity correlated with this MPN. A greater relative burden of cerebrovascular and cardiovascular disease was observed in younger patients with PV and ET, which should encourage clinicians to address and optimize cardiovascular risk factors in the longitudinal care of patients with MPN. Study limitations reported by the authors included the use of the population database which contains limitations including uncertainty about the diagnosis, lack of treatment data and lack of molecular data which are known to be prognostic.

Mejía-Ochoa et al. (2019) performed a systematic review on polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia (ET), and a meta-analysis of the frequency of *JAK2*, *CALR* and *MPL* mutations. Fifty-two studies were evaluated and the frequency of the *JAK2V617F* mutation ranged from 46.7 to 100% in patients with PV, 25.0 to 85.7% in patients with PMF, and 31.3 to 72.1% in those with ET. The frequency of the *MPL* mutation was 0% in PV, from 0 to 17.1% in PMF, and 0.9 to 12.5% in ET. The authors concluded that given the specificity and reported high frequencies of the *MPL* and *JAK2V617F* mutations in this group of neoplasms, diagnosing these diseases should not be made on hematological and clinical characteristics alone but should incorporate genetic screening as well. Study limitations reported by the authors included the impossibility of explaining the sources of heterogeneity in the meta-analyses due to individual studies were not exhaustive in their reporting of results by subgroups.

Clinical Practice Guidelines

British Committee for Standards in Haematology

The thrombopoietin receptor *MPL* is one of several *JAK2* cognate receptors and is considered essential for myelopoiesis. The mutation frequency of *MPL* mutations associated with myeloproliferative disorders is substantially less (< 10%) than *JAK2* mutations. The guideline group for the British Committee for Standards in Haematology (Harrison et al., 2010) recommended a modification to the 2008 World Health Organization (WHO) criteria for essential thrombocythemia (ET) to include the presence of an acquired pathogenetic mutation (e.g., in the *JAK2* or *MPL* genes). Therefore, *MPL* gene testing may be indicated for individuals who would meet WHO's diagnostic criteria for myeloproliferative disorder (MPD) if a clonal marker were identified.

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Myeloproliferative Neoplasms (NCCN Myeloproliferative Neoplasms, v2.2025) state the World Health Organization (WHO) and international consensus classification (ICC) diagnostic major criteria for polycythemia vera includes presence of *JAK2* p.V617F or *JAK2* exon 12 mutation. Molecular testing for the *JAK2* exon 12 mutation should be done for those with suspected polycythemia vera and negative for the *JAK2* V617F mutation. WHO and ICC diagnostic major criteria for primary myelofibrosis includes *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker. WHO and ICC diagnostic major criteria for essential thrombocythemia includes *JAK2*, *CALR*, or *MPL* mutation.

KIT (V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog)

Lam et al. (2024) performed a systematic review and meta-analysis of neoadjuvant imatinib use in locally advanced and metastatic gastrointestinal stromal tumors (GISTs). Thirty-six studies were included and primary outcomes were overall survival (OS) and disease free survival (DFS) rates. Meta-analysis of proportions showed that 1-year, 3-year, and 5-year OS was 100%, 94%, and 88%, respectively. 1-year, 3-year and 5-year DFS was 99%, 89%, and 79%, respectively. An R0 resection rate of 89% and a disease response rate of 67% was accomplished after a mean treatment duration of 8.41 ±0.367 months. Mutation in the *KIT* exon 9 was substantially correlated with poorer 5-year DFS. The authors concluded that patients with locally advanced and metastatic or recurrent GIST stand to benefit from neoadjuvant imatinib with an ideal treatment duration of eight months. The analysis showed potential utility of mutational analysis in guiding treatment with neoadjuvant imatinib. Study limitations reported by the authors included significant heterogeneity in primary outcomes, most of the studies were retrospective observational studies, and the majority of studies used an intention to treat approach when calculating the OS rate.

Steeb et al. (2021) performed a systematic review and one-arm meta-analysis to summarize the safety and efficacy of c-Kit inhibitors for unresectable or metastatic mucosal, chronically sun-damaged or acral melanoma. Nineteen single-arm

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studies with an overall sample size of 601 patients were evaluated. The studies assessed nilotinib (n = 7), imatinib (n = 8), sunitinib (n = 1), and dasatinib (n = 3). The pooled objective response rates (ORR) for all inhibitors was 15% (95% CI: 12–18%). Subgroup analysis showed the highest ORR (20%; 95% CI: 14–26%) for nilotinib. The ORR for acral lentiginous melanoma was 22% (95% CI: 14–30%) and 14% for mucosal melanoma (95% CI: 6–24%). At least one severe adverse event (sAE) was identified in 42% of patients (95% CI: 34–50%). The authors concluded that c-Kit inhibitors are an important treatment option for patients with *KIT*-mutant melanoma, specifically for exons 11 and 13 mutations. High-quality trials are required to explore putative combinations of specific targeted therapies with immunotherapy. Study limitations reported by the authors were statistical heterogeneity, the single-arm design, missing individual data of the survival outcomes, and the lack of participant blinding.

Cattaneo et al. (2021) performed a single-center cohort study to evaluate the bone marrow morphology and the clinical-laboratory parameters of triple-negative [lack of demonstrable mutations affecting *JAK2*, *CALR*, or *MPL,* which is found in about 10% of patients with essential thrombocythemia (ET) and 5–10% of those with primary myelofibrosis (PMF)] ET patients, as well as to determine their molecular profile using next-generation sequencing (NGS) to identify any potential clonal biomarkers. ET, polycythemia vera, and PMF are apart of the classic BCR-ABL1-negative myeloproliferative neoplasm category. Forty patients with triple-negative ET were included in the study. Nucleotide variants were identified in 35 out of 40 patients. Twenty-nine subjects harbored one or two variants and six cases displayed three or more concomitant nucleotide changes. The most frequent sequence variants involved the *TET2* gene (55.0%), followed by *KIT* (27.5%). Histologically, most of the cases showed a classical ET morphology. Prevalent megakaryocytes morphology was more often polymorphic with a mixture of giant megakaryocytes with hyperlobulated nuclei, normal and small sized maturing elements, and naked nuclei. In five cases a mild degree of reticulin fibrosis (MF-1) was evident together with an increase in the micro-vessel density. By means of NGS enabled identification of nucleotide variants in most cases, thus the findings suggest that a significant proportion of patients with triple-negative ET do have a clonal disease. In analogy with driver genes-mutated myeloproliferative neoplasms (MPNs), these findings may prevent issues arising concerning triple-negative ET treatment, especially when a cytoreductive therapy may be warranted. The primary limitations reported by the authors was its retrospective design and small sample size.

Fan et al. (2020) performed a systematic review and meta-analysis to evaluate the impact of *KIT* mutations and prognosing pediatric patients with core-binding factor (CBF) acute myeloid leukemia (AML). The review included 12 studies and 1,123 children with CBF-AML including 256 children with KIT mutations. The effects of *KIT* mutations on the complete remission (CR), relapse, event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) rates were investigated. *KIT* mutations were not correlated with CR [relative risk: 1.01, 95% confidence interval (CI): 0.94–1.09, p = 0.761], but they were correlated with lower OS [hazard ratio (HR): 3.05, 95% CI: 1.23–7.60, p = 0.016], higher relapse risk (HR: 1.69, 95% CI: 1.32–2.16, p = 0.000), lower DFS (HR: 1.65, 95% CI: 1.07–2.54, p = 0.024), and lower EFS (HR: 3.08, 95% CI: 1.02–9.32, p = 0.046). The authors concluded that their findings suggest that *KIT* mutations had an adverse prognostic effect in CBF-AML pediatric patients. For these patients, the initial diagnostic workup should include tests for the identification of KIT mutations. If these mutations are detected, treatment may need to be adjusted. Study limitations reported by the authors included small sample size and that prognostic effects of KIT mutations may differ between inv(16) AML and t(8;21) AML.

Merx et al. (2013) reported on the results of a phase II clinical trial on the effects of imatinib mesylate in patients with polycythemia vera (PV). Imatinib was specifically developed to inhibit the BCR-ABL tyrosine kinase but it also inhibits structurally related tyrosine kinases like *KIT*. Thirty-one patients, median age 64 years old, were included in the trial. Patients started 400 mg of imatinib a day. After the average 8.3 months of treatment, the overall response rate was 55%. Complete remission was not reached in any patient. Thirteen patients (42%) had partial remission, four patients (13%) had minor response, and 14 patients (45%) had no change or progressive disease. Compared to baseline characteristics, imatinib induced the reduction of phlebotomies (p = 0.003), of white blood cell (WBC) count (p = 0.002), and of platelet count (p = 0.04). Three patients became free from phlebotomies. The authors concluded that imatinib has moderate cytoreductive effects in PV, with positive effects mainly restricted to early stages of PV with shorter disease duration and without cytoreductive pretreatment. Of note, some of the authors are consultants or have advisory roles at Novartis Pharmaceuticals.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The standard for gastrointestinal stromal tumors (GISTs) diagnosis is morphologic diagnosis based on microscopic examination of histologic sections. Several ancillary techniques are recommended in support of GIST diagnosis including molecular genetic testing for *PDGFRA* and *KIT* mutations, as well as other potential drivers (e.g., *NF1*, *NTRK*, *BRAF*, and *FGFR* fusions). Testing for *PDGFRA* and *KIT* mutations should be performed if TKIs are considered as part of the treatment plan since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA*

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genes are correlated with response (or lack of a response) to specific TKIs. Imatinib is recommended for *KIT* mutations (NCCN Gastrointestinal Stromal Tumors, v1.2025).

NCCN notes that identification of mutations that carry therapeutic and prognostic impact is rendering molecular profiling for all acute myeloid leukemia (AML) cases a standard for diagnostic workup. On top of basic cytogenetic analysis, new molecular markers can aid in refining prognostics groups, especially in the setting of a normal karyotype. These markers include *KIT* gene mutations. For those with high-risk disease features like *KIT* mutations, NCCN recommends considering allogeneic hematopoietic cell transplant (NCCN Acute Myeloid Leukemia, v3.2026).

KIT mutations are present in 10%–15% of melanomas of mucosal (most frequently vulvovaginal primaries, but also sinonasal and anorectal) and acral (i.e., nailbeds, non-hair-bearing surfaces of palms and soles) origin. They are also present on 2%–3% of chronically sun-exposed skin, but very rarely on intermittently sun-exposed skin. Therefore, clinical features can guide whether or not to perform *KIT* mutation testing. For metastatic or unresectable cutaneous melanoma, second-line or subsequent therapy of *KIT* inhibitor therapy (e.g., imatinib, dasatinib, nilotinib, ripretinib) for activating mutations of *KIT* is useful in certain circumstances. For initial presentation with stage IV disease or clinical recurrence, NCCN recommends obtaining tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy (NCCN Melanoma: Cutaneous, v2.2025).

National Institute for Health and Care Excellence (NICE)

In a technology appraisal guidance for imatinib for the adjuvant treatment of gastrointestinal stromal tumors, NICE recommends imatinib as an option as adjuvant treatment for up to 3 years for adults at high risk of relapse after surgery for *KIT* (CD117)-positive gastrointestinal stromal tumors, as defined by the Miettinen criteria based on tumor location, size and mitotic rate. Those who are currently receiving treatment initiated within the National Health Services (NHS) that is not recommended for them by NICE in this guidance should be able to continue imatinib until they and their NHS clinical consider it appropriate to discontinue (NICE, 2014, last reviewed 2018).

MCOLN1 (Mucolipin 1) (e.g., Mucolipidosis, Type IV)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnosis Mucolipidosis IV, a very rare lysosomal storage disorder characterized by severe psychomotor delay, progressive visual impairment, and achlorhydria. Symptoms manifest usually by the end of the first year of life as delayed developmental milestones and impaired vision. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Misko et al., 2021).

There is no cure for Mucolipidosis IV. Treatment is symptomatic and supportive (NORD, 2015).

MECP2 (Methyl CpG Binding Protein 2) (e.g., Rett Syndrome)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose Rett Syndrome, a progressive neurodevelopmental disorder mostly affecting girls. Rett Syndrome is characterized by apparently normal psychomotor development at 6-18 months of age, followed by a short period of developmental stagnation, then with rapid regression in motor and language skills and then long-term stability. In boys, it is used to diagnose severe neonatal-onset encephalopathy, which is characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, involuntary movements, abnormal tone, severe seizures, and abnormal breathing. Often, death occurs before two years of age. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Kaur and Christodoulou, 2025).

In a Hayes Molecular Test Assessment on *MECP2* Testing for Rett Syndrome and Other Disorders, for testing for *MECP2* sequence variants in patients who meet established clinical diagnostic criteria for classic or variant Rett Syndrome (RS), Hayes assigns a rating of C (potential but unproven benefit). For testing for *MECP2* sequence variants in patients who have some symptoms of RS but do not meet established clinical diagnostic criteria, Hayes assigns a rating of B (some proven benefit. Published evidence indicates that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, there are outstanding questions regarding long-term safety and impact on health outcomes, clinical indications, contraindications, optimal treatment/testing parameters, and/or effects in different patient

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subpopulations). For prenatal testing for *MECP2* sequence variants in the parents of children with RS who meet the established clinical diagnostic criteria and for whom there is evidence that RS was inherited rather than having occurred sporadically, Hayes assigns a rating of B. For testing for *MECP2* sequence variants in disorders other than RS, including autism, Angelman syndrome, X-linked intellectual disability, intellectual disability, *MECP2* duplication syndrome, schizophrenia, and other psychiatric disorders, Hayes assigns a rating of D2 (insufficient evidence) (Hayes, *MECP2* Testing for Rett Syndrome and Other Disorders, 2010, updated 2014).

MTHFR (5,10-Methylenetetrahydrofolate Reductase)

There is insufficient evidence to support *MTHFR* gene testing. Despite many earlier publications suggesting a link between *MTHFR* polymorphisms and a risk for a wide spectrum of obstetric and cardiovascular complications, it is now accepted that *MTHFR* genotype alone is not associated with venous thromboembolism (VTE). There is no clinical indication for *MTHFR* genotyping in any population. There is broad consensus in the medical literature that *MTHFR* genotyping has no clinical utility in any clinical scenario. This testing is considered investigational and is not a Medicare benefit.

In a Hayes Clinical Utility Evaluation, insufficient evidence was found for *MTHFR* genotyping on impacting management and clinical outcomes for patients with hypertension. No evidence was found suggesting genotype-directed treatment has longer-term cardiovascular benefits beyond non-genotype informed standard treatment (Hayes, *MTHFR* Genetic Testing for Hypertension, 2023, updated 2024).

Valeriani et al. (2023) performed a comprehensive systematic review and meta-analysis of Factor V Leiden, prothrombin, *MTHFR*, and *PAI-1* gene polymorphisms in patients with arterial disease. The study included 377 studies for 98,186 patients [32,791 cerebrovascular disease (CVD), 62,266 coronary heart disease (CHD), 3,129 peripheral artery disease (PAD)] and 108,569 controls. Overall, 37,249 patients had *G1691A*, 32,254 *G20210A*, 42,546 *MTHFR C677T*, 8889 *MTHFR A1298C*, and 19,861 *PAI-1 4G/5G* gene polymorphisms. In patients with CVD, pooled prevalences (PPs) were 6.5% for *G1691A*, 3.9% for *G20210A*, 56.4% for *MTHFR C677T*, 51.9% for *MTHFR A1298C*, and 77.6% for *PAI-1*. In CHD, corresponding PPs were 7.2%, 3.8%, 52.3%, 53.9%, and 76.4%. In PAD, PPs were 6.9%, 4.7%, 55.1%, 52.1%, and 75.0%, respectively. Strongest odds ratios (ORs) in CVD were for homozygous *G1691A* [2.76; 95% CI (confidence interval), 1.83-4.18] and for homozygous *G20210A* (3.96; 95% CI, 2.05-7.64). Strongest ORs in CHD were for homozygous *G1691A* (OR 1.68; 95% CI, 1.02-2.77) and *G20210A* (heterozygous 1.49 95% CI, 1.22-1.82; homozygous 1.54 95% CI, 0.79-2.99). The OR for *PAI-1* 4G/4G in PAD was 5.44 (95% CI, 1.80-16.43). Data for *MTHFR C677T* and *A1298C*, and *PAI-1* gene polymorphisms are weaker than for other forms of inherited thrombophilia. No significant differences between cases and controls were found, except for *MTHFR C677T* in cerebrovascular disease and of *PAI-1 4G* in peripheral arterial disease. Specific subgroups with higher PPs and ORs were identified according to age and region. Study limitations reported by the authors included that the studies included patients who were heterogenous in their underlying characteristics, the evaluation of all outcomes on a study-level basis represented an intrinsic design limitation, and patients with multiple gene polymorphisms may have a greater risk of arterial disease than patients with a single gene polymorphism.

Romiti et al. (2020) performed a systematic review and meta-analysis to estimate the prevalence of acquired and inherited thrombophilias in adults with retinal vein occlusion (RVO) or retinal artery occlusion (RAO). Ninety-five studies were included. The analysis calculated pooled prevalences and 95% confidence intervals (CI). FVL and F-II mutations were observed in 6% (95% CI: 5-8) and 3% (95% CI: 2-4) of individuals with RVO, respectively. AT-III, PC, and PS activity deficiencies were observed in < 2%. MTHFR C677T and PAI 4G homozygous polymorphism were found in 13% (95% CI: 10-17) and 23% (95% CI: 16-31) of RVO, respectively; 8% presented APL antibodies. Similar findings were shown in individuals with RAO. The authors concluded that in comparison with healthy subjects, patients with RVO displayed similar prevalences of acquired and inherited thrombophilias. These findings do not support routine thrombophilia screening in individuals with RVO or RAO. Study limitations reported by the authors included that the review protocol did not include screening of gray literature, high heterogeneity between studies, and that most studies were based on small cohorts.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

ACMG (Hickey et al., 2013) published a practice guideline on the lack of evidence for *MTHFR* polymorphism testing. Among a number of recommendations, ACMG experts concluded that *MTHFR* polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss and that *MTHFR* polymorphism genotyping should not be ordered for at-risk family members. However, in an addendum in 2020 (Bashford et al., 2020), it is noted that the document no longer meets the criteria for an evidence-based practice guideline by the College and has been reclassified as a Clinical Practice Resource.

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British Society of Haematology

In an updated guideline for thrombophilia testing by Arachchillage et al. (2022), it is noted that a large number of variants in other genes with a wide range of prevalence have been reported to spark discussions regarding increased risk of thrombosis. Included are variants of *SERPINE1* (encoding plasminogen activator inhibitor type 1) (*PAI-1*), methylenetetrahydrofolate reductase (*MTHFR*), and factor XIII as well as variants linked to the quantitative changes in procoagulant factors. However, either their association with thrombosis is not compellingly consistent or their impact is too minor to change management. Therefore, they should not be included in thrombophilia panels at present.

Nuclear Encoded Mitochondrial Genes Panel (e.g., Neurologic or Myopathic Phenotypes) and Whole Mitochondrial Genome [e.g., Leigh Syndrome, Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS), Myoclonic Epilepsy With Ragged-Red Fibers (MERFF), Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP), Leber Hereditary Optic Neuropathy (LHON), Kearns-Sayre Syndrome, Chronic Progressive External Ophthalmoplegia]

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member.

Genetic testing is used to diagnose mitochondrial diseases such as Kearns-Sayre syndrome (KSS), Leber hereditary optic neuropathy (LHON), Leigh syndrome, and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. Kearns-Sayre syndrome affects many parts of the body but especially the eyes (progressive external ophthalmoplegia) and symptoms usually appear before the age of 20 (MedlinePlus, 2011). Leber hereditary optic neuropathy is an inherited vision loss that usually begins in teens or twenties (MedlinePlus, 2013a). Leigh syndrome manifests as progressive loss of mental and movement abilities and is first seen in the first year of life. Death usually follow 2-3 years later due to respiratory failure (MedlinePlus, 2023b). MELAS symptoms of muscle weakness and pain, loss of appetite, vomiting, recurrent headaches, and seizures usually appear in childhood (MedlinePlus, 2013b).

In a primary mitochondrial disorders overview (Chinnery, 2021), the author notes that comprehensive genomic testing does not require a clinician to determine the likely involved gene. Comprehensive testing includes genome sequencing, exome sequencing, and mitochondrial sequencing which can analyze nuclear deoxyribonucleic acid (DNA) and mitochondrial deoxyribonucleic acid (mtDNA) simultaneously. However, some mtDNA pathogenic variants may not be identified in leukocyte DNA. Genomic testing may not be as accurate as targeted single-gene testing or multigene molecular genetic testing panels due to false negative rates that vary by genomic region. Therefore, most laboratories validate positive results by using a second, well-established method. Some DNA variants, such as large deletions or duplications (> 8-10 bp in length), epigenetic alterations, and triplet repeat expansions, may not be detected through genomic testing.

In a Hayes Precision Medicine Insight on Whole Mitochondrial Genome Sequencing, there appeared to be minimal support in individuals with suspected mitochondrial disorders, based on a review of abstracts. This review included no reported changes in patient management or decision making, one that reported diagnostic yield but changes in clinical management or patient outcomes were not reported, and no comparison of its utility against other testing methods. Review of professional guidelines and position statements appeared to show weak support for individuals with suspected mitochondrial disorders. Four guidelines were identified including American College of Medical Genetics and Genomics (ACMG), National Health Service Rare Mitochondrial Disorders Working Group, Association for Clinical Genomic Science, and Mitochondrial Medicine Society. All four were expert consensus based, and two had overlapping authorship. They generally recommended mitochondrial deoxyribonucleic acid (DNA) testing for patients with suspected mitochondrial disorders. The guidelines varied in respect to whether focused testing vs more comprehensive testing methods should be used as a first step in genetic diagnosis. (Hayes, Whole Mitochondrial Genome Sequencing, 2024).

Plutino et al. (2018) utilized next generation sequencing (NGS) in a cohort of 80 individuals who were clinically diagnosed with mitochondrial disease tests to determine the clinical validity of targeted panel approach to a genetic diagnosis. The participants were diagnosed through clinical, biochemical, and histological analysis. They included 24 children and 56 adults, 38 male participants and 32 female participants. Participants first underwent mtDNA testing, and if negative, a custom nuclear gene panel was run. Single deletions and point mutations in the mtDNA were identified using XL-PCR and NGS and confirmed by Southern blot. The custom panel was comprised of 281 genes known to be involved in mitochondrial disease and were analyzed by NGS and confirmed with Sanger sequencing. Variant filtering and interpretation focused on rare mutations that were predicted to be missense, frame-shift, stop-gain, stop-loss, or splice site variants. Pathogenic variants were found in mtDNA in the first step in one child and 14 adults. The remaining 65 participants had the targeted NGS panel and an additional five children and three adults achieved a genetic diagnosis for

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an overall diagnostic rate of 29%. The authors compared their panel testing results to other studies involving WES and larger panels with reported diagnostic rates of 8-24% and concluded that larger gene panels are not necessary in mitochondrial diseases because of their high heterogeneity, the ongoing discovery of novel genes, and genes that may not appear to be related to mitochondrial function could lead to secondary respiratory chain deficiency. The study was limited by its mix of adult and pediatric patients, which introduces variability in genetic causes and disease presentation.

myPath Melanoma

The myPath Melanoma test quantifies the expression of 23 genes by quantitative reverse transcription-polymerase chain reaction (RT-PCR). Fourteen of the 23 genes are known to be over-expressed by malignant melanomas relative to benign nevi. The remaining 9 are stably expressed reference genes which allow correction for sample-to-sample variations in RT-PCR efficiency and errors in sample quantification (normalization). The signature genes represent three distinct pathways that contribute to melanoma pathogenesis, including aspects of melanocyte differentiation as well as characteristics of the tumor microenvironment such as cell-cell signaling and tumor-induced host immune responses (Warf et al., 2015; Clarke et al. 2015). The test uses five to seven standard-thickness (4-5 μm) sections taken from the routinely processed formalin-fixed paraffin-embedded (FFPE) tissue of the existing biopsy specimen, allowing its integration into routine clinical practice and its use even in small, early-stage lesions. The quantified expression of all 23 genes is combined algorithmically and reported as a single numerical score. That number, (the myPath Melanoma 'score'), is plotted on a scale that depicts the entire range of scores observed in clinical validation studies (Clarke et al., 2015). Physicians receive a report showing this single numerical score and the corresponding classification: 'likely malignant', 'likely benign', or 'indeterminate'.

Witkowski et al. (2024) performed a clinical impact study of dermatologists' use of diagnostic gene expression profile (GEP) testing to guide patient management. The study included six randomized case scenarios with diagnostic/clinical uncertainty were described with/without a benign or malignant diagnostic gene expression profile (GEP) result. Board-certified dermatologists were invited for study participation based on prior use of GEP testing. Clinical impact was evaluated by reporting the mean increase/decrease of management changes normalized to baseline (n = 32 dermatologists). The survey included a brief overview of the accuracy metrics of the 23- and 35-GEP where both reported similar accuracy metrics. However, neither GEP test was specified in the survey scenarios. Only 'GEP result' of benign or malignant (or no GEP result) was provided. Survey data was collected anonymously via a webpage and analyzed using R software (version 4.2.1). Benign GEP results prompted clinicians to decrease surgical margins (84.2%). Malignant GEP results escalated surgical excision recommendations (100%). A majority (72.2%) decreased and nearly all (98.9%) increased follow-up frequency for benign or malignant GEP results, respectively. Overall, there was an increase in management plan confidence with GEP results. The authors concluded that diagnostic GEP tests help guide clinical decision-making in a variety of diagnostically ambiguous or clinicopathologically discordant situations. The authors reported study limitations including that in that non-specific GEP test results were provided and the survey did not poll clinicians with no GEP testing in their current practice. Of note, some of the authors were employees, shareholders, advisors, or speakers for Castle Biosciences, Inc.

Tschen et al. (2021) evaluated prospectively tested patients whose ambiguous melanocytic neoplasms were classified as benign by the gene expression signature and were followed for up to 4.5 years to evaluate the long-term safety of treatment decisions aligned with benign test results. A gene expression signature was developed and validated intended to be used as an adjunct to traditional methods of differentiating malignant melanocytic neoplasms vs benign. This test quantifies the ribonucleic acid (RNA) transcripts produced by 14 genes known to be over-expressed in malignant melanomas by comparison to benign nevi. These values are then algorithmically combined with measurements of nine reference genes to produce an objective numerical score that is classified as malignant, benign or indeterminate. When used by board-certified dermatologists and dermatopathologists coming across ambiguous melanocytic lesions, the test produces significantly more definitive diagnoses and influences changes to treatment recommendations. However, long-term impacts of not undergoing surgical excision of melanocytic neoplasms that are diagnostically ambiguous but classified as benign by this test have not yet been formally evaluated. 25 patients were included in the study. The average follow-up time was 38.5 months and patients attended an average of four post biopsy dermatology appointments [mean duration (SD), 4.6 (3.6)]. Per the participating dermatology care providers, none of the 25 patients showed any signs during follow-up that the benign diagnosis was inaccurate. There was no evidence of locally recurrent or metastatic melanoma and no deaths occurred during the study period. The authors concluded that their findings suggest that many patients with melanocytic neoplasms classified as benign by the test may safely refrain from additional surgical excision. However, the authors emphasize it should not replace histopathologic interpretation nor judgment as all tests can product false-positive and false-negative results. The study was limited by its small sample size and that patients with benign diagnoses may not follow-up.

Clarke et al. (2020) performed a test validation study to assess the accuracy of myPath Melanoma in differentiating benign nevi from melanoma by comparing test results with clinical outcomes. One hundred twenty five cases fulfilled

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criteria for diagnostic un-certainty (69.1%; 95% CI: 61.8–75.7%). Test sensitivity and percent negative agreement in these cases were 90.4% (95% CI: 79.0–96.8%) and 95.5% (95% CI: 87.3–99.1%), respectively. The authors concluded myPath Melanoma has high diagnostic accuracy in diagnostically uncertain cases when evaluated against clinical outcomes. Overall, clinical studies have shown sensitivity and specificity ranges of 90-94% and 91-96%, respectively, for the 23-GEP. The authors concluded that the gene expression signature has high diagnostic accuracy in diagnostically uncertain cases when evaluated against clinical outcomes. Study limitations reported by the authors included the lack of access to complete demographic and clinical data and the reliance on a single diagnostic slide.

Ko et al. (2017) performed a clinical validation study to assess the accuracy of the gene expression signature using a reference standard independent of histopathologic diagnosis and to confirm genuine clinical utility. The test result was compared to the eventual clinical outcomes of tested patients. In a cohort of 182 melanocytic neoplasms collected from patients with documented outcomes (distant metastases for malignant melanomas and median six + year uneventful follow-up for benign nevi), the myPath Melanoma score differentiated malignant melanoma from benign nevi with a sensitivity of 93.8% and a specificity of 96.2%. The authors concluded that the results of gene expression testing closely correlate with long-term clinical outcomes. Study limitations included a high failure rate for samples tested greater than five years after biopsy which may have been due to degraded mRNA quality. This limits applicability to older specimens and introduces selection bias toward newer samples. Of note, some of the authors were employed at Myriad Genetic Laboratories.

Cockerell et al. (2017) performed a clinical utility study which assessed the relationship between test result and change in treatment as measured by pre-test dermatopathologist recommendation and post-test actual treatment delivered to a patient by the dermatologist. A cohort of 77 patients with pre-test diagnoses of “indeterminate” (equivocal, uncertain) were followed throughout their clinical course. The myPath test produced definitive scores for all 77 neoplasms, and after a median 12-month follow-up period, the tested patients’ dermatologists disclosed the actual treatment carried out in each case. The treatment differed from the pre-test recommendation in 55 of 77 (71.4%) cases, 44 of which produced a benign myPath test result. Re-excision was the pre-test treatment recommendation for 41 of these 44 cases, yet re-excision was ultimately performed in just seven, indicating that a benign myPath test result enabled dermatologists to forego further intervention in 33 of the 41 cases, yielding an 80.5% reduction in re-excisions. The authors concluded that their findings show that the use of the test by pathologists in the work-up of difficult melanocytic neoplasms influences patient treatment by dermatologists. Study limitations reported by the authors included the incorporation of an indeterminate reporting range during the course of the clinical experience program.

Cockerell et al. (2016) performed a clinical utility study which quantified the influence of the myPath Melanoma score on both the final diagnoses and the treatment recommendations made by board-certified dermatopathologists for 218 prospectively submitted diagnostically challenging (equivocal or uncertain) melanocytic neoplasms encountered during routine clinical practice. Comparison of pre-test and post-test diagnoses demonstrated a 56% increase in definitive diagnoses with use of the myPath score (a 30% increase in definitive diagnoses of benign nevus and a 12.4% increase in definitive diagnoses of malignant melanoma). In addition, treatment recommendations provided by dermatopathologists changed for 49% of patients after receiving the myPath result, with 76.6% of those changes aligned to the test result. The authors concluded that the gene expression signature can impact diagnostic decision-making and treatment recommendations. Incorporating this test into pathologic diagnosis of melanocytic lesions has the potential to contribute to more definitive diagnoses and optimized clinical care. This study was funded by Myriad Genetic Laboratories.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Melanocytic neoplasms of indeterminate biologic potential are challenging to pathologists and treating clinicians. Ancillary tests to differentiate between benign and malignant melanocytic neoplasms include gene expression profiling (GEP), immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), and single-nucleotide polymorphism (SNP) array. These tests may facilitate a more definitive diagnosis and guide therapy in cases that are controversial or diagnostically uncertain by histopathology. Ancillary tests should be used in adjunct to expert clinical dermatopathologic examination and be interpreted within the context of these findings (NCCN Melanoma: Cutaneous, v2.2025).

Oncotype DX Breast Cancer Assay

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 breast cancer (BC) recurrence within 10 years. The test was initially developed for women with early-stage invasive BC with early-stage cancers that are lymph node-negative (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

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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 distant recurrence (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 recurrence score (RS) with histologic grade, tumor size, and age at surgery for the RSClin tool (a tool that estimates 10-year risk recurrence based on the 21-gene recurrence score result, tumor size, tumor grade, and age at time of surgery)]. Likelihood ratio (LR) tests were used to compare Cox models integrating clinicopathologic factors and the RS. In addition, external 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 reported by the authors 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 et al. (2023) investigated the benefit of chemotherapy based on recurrence score (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 overall survival (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 progesterone receptor (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- breast cancer (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. Study limitations included those inherent with retrospective observational studies. The authors note there was some selection bias by including only patients with reported RS.

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- breast cancer (BC) with one to three positive lymph nodes (N1) disease. To evaluate patterns in practice related to the use of the recurrence score 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 overall survival (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. Recurrence score (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. Study limitations reported by the authors included that the data was from a retrospective database, the authors could not observe clinician influence on treatment decision, the impact of adjuvant chemotherapy on survival outcomes according to different RS categories was unable to be assessed due to outcome data regarding locoregional recurrence and distant metastasis not being available in the SEER database, and average follow-up was only 32 months.

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Davey et al. (2022) performed a systematic review and network meta-analysis to evaluate the Oncotype DX 21-gene recurrence score (RS) for its ability to estimate locoregional recurrence (LRR) in ER +/HER2- breast cancer (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 (3,944/7,935), 33.8% had RS 18–30 (2,680/7,935), and 16.5% had RS > 30 (1,311/7,935). 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 (1,974/12,208), 65.8% had RS 11–25 (8,036/12,208), and 18.0% with RS > 30 (2,198/12,208). LRR rates were comparable for individuals with RS 11–25; however, those with RS > 25 had a considerable risk of LRR vs 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. Study limitations reported by the authors included that patients that were included in the analysis had increased tumor burden in both the axilla and breast, as well as higher tumor grade. Also, all studies were retrospective and over 98% of the patients were taken from the Surveillance, Epidemiology and End Results (SEER) and National Cancer (NCDB) databases limiting the validity of drawn conclusions.

Kalinsky et al. (2021) 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 recurrence score (RS) based on the 21 gene assay (Oncotype Dx) influenced the outcome. A total of 5,018 women with hormone-receptor-positive, HER2- breast cancer (BC), 1 to 3 positive axillary lymph nodes, and an RS of 25 or lower were randomly grouped into an endocrine therapy 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 endocrine treatment. The trial did not show a clinically applicable or statistically significant rise in invasive disease-free survival with the addition of adjuvant chemotherapy to endocrine therapy in the global population with the same characteristics. For this trial, 67% of post-menopausal participants had no chemotherapy advantage. Dissimilarity, adjuvant chemotherapy led to a relative growth of 40% in invasive disease-free survival and a relative rise of 42% in distant relapse-free survival (RFS) among 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 relapse-free survival. The trial showed that between premenopausal women with 1 to 3 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 profit from adjuvant chemotherapy. A limitation of the study is that a notable proportion of the participants did not adhere to their assigned treatment, which may have reduced the statistical power in the intention-to-treat analysis.

Hayes published a Molecular Test Assessment addressing the use of the Oncotype DX Breast Recurrence Score for individuals with ER +, HER2-, lymph node positive breast cancer (BC) to determine the capability of the test to estimate the risk of distant recurrence and the predict the likelihood of chemotherapy benefit in 2020. For individuals with N1 (one to three positive lymph nodes) disease, limited but consistent evidence supports the use of the Oncotype DX test for predicting the risk of 9-year distant recurrence, 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 distant recurrence and the potential benefit of chemotherapy for individuals with N2 disease (4 to 9 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 9-year distant breast cancer (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 distant recurrence 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].

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Poorvu et al. (2020) evaluated women less than 40 years of age with early-stage ER + and HER2- breast cancer (BC) to decide if the 21-gene recurrence score (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 six years. Of the 509 individuals, 300 (59%) had node-negative (N0) BC and 195 of them had a RS of 11-25, of which 86 received chemotherapy. The 6-year distant recurrence free survival (DRFS) varied by the RS with < 11 associated with 94.4% N0 and 92.3% N1 (one to three positive lymph nodes). 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. Study limitations reported by the authors included that risk of later recurrences were not addressed since median follow-up was six years, whether RS is predictive of chemotherapy benefit was unable to be formally evaluated since receipt of chemotherapy was not randomly assigned, and the ability to evaluate the association between chemotherapy-related amenorrhea (CRA) and distant recurrence risk may have been limited by missing information and by resumption of menses after CRA evaluation on the 1-year survey.

Wang et al. (2019) examined the value of Oncotype Dx when determining the prognosis in female individuals with breast cancer (BC) and tumor stage 1-2 (tumor is 20-55 mm), LN + and no evidence of metastasis ($T_{1-2}N_1M_0$). The study reviewed 4,059 cases to categorize them to prognostic stages IA and IIB and used data derived from the National Cancer Institute's limited use Surveillance, Epidemiology, and End Results (SEER) 18 registry databases, released in November 2017. Cases in the SEER database was linked to recurrence score (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, 2,898 (71.4%) had stage T1 cancer, 1,854 (45.7%) had stage N_{1mic} cancer, 743 (18.3%) had grade 3 cancer, and 3746 (92.3%) had positive 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 IIA, and 89 (2.2%) in IIB. The distributions of clinical and pathological characteristics, including breast cancer-specific survival (BCSS) and overall survival (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 ($p < 0.001$) 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. Study limitations reported by the authors included due to the retrospective nature of the study it had an intrinsic bias, median follow-up may have been relatively too short, chemotherapy use is known to be under-reported in SEER, and the database does not collect data on distant recurrence.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines indicate that, "gene expression assays (GEAs) 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, v5.2025).

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

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Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene Oncotype DX for pN1 (1–3 positive nodes)	Yes	Yes	Postmenopausal: Preferred	1
			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 breast cancer (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 estrogen receptor (ER) positive or progesterone receptor (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 judgment should be used to determine is testing is appropriate for men, trans or non-binary or intersex individuals.
- EndoPredict, Oncotype DX, or Prosigna should not be used to guide adjuvant chemotherapy decisions for ER positive 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 positive 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 positive or PR positive, HER2-negative, and LN-negative (including micro metastatic disease) early breast cancer (EBC) while more evidence is generated if:
  - Individual has an intermediate risk of disease recurrence 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 positive or PR positive, HER2-negative, and LN-negative EBC.
- EndoPredict, Oncotype DX or Prosigna may be used to guide adjuvant chemotherapy decisions for ER positive 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 positive and PR positive).
    - Oncotype DX (ER positive or PR positive, or both).
    - Prosigna (ER positive 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.

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Oncotype DX Breast DCIS Score Test (Ductal Carcinoma in Situ)

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.

Muktar et al. (2025) performed a single-center prospective interventional clinical trial to assess if the Oncotype DX Breast DCIS Score Test changed radiotherapy (RT) recommendations, patient anxiety, and decisional conflict. Seventy-one women treated with breast-conserving surgery were included in the trial with a median age of 59.7 years old. Initial RT recommendations and 10-year local recurrence (LR) risk predictions were made before Oncotype testing. After Oncotype testing, final RT recommendations were documented. Patients completed decisional conflict and anxiety questionnaires pre and post Oncotype results. 90% of DCIS was intermediate/high-grade and 12 mm in average size. Oncologists changed RT recommendations in 28% (20/71) of cases post Oncotype result; 21% changed from RT to no RT and 7% from no RT to RT. In 79% of cases, the oncologists' LR estimates were higher than Oncotype predictions. Patient anxiety and decisional conflict decreased after Oncotype testing. The authors concluded that the Oncotype test changed treatment recommendations regarding adjuvant RT in nearly a third of patients. The assay was also associated with decreased treatment-related anxiety and decisional conflict. LR risk predictions by oncologists were higher than the Oncotype predictions showcasing a need for additional tools to aid decision-making. The study's limitations reported by the authors included small sample size and the absence of a control group for the questionnaires.

Ouattara et al. (2023) conducted a systematic review and meta-analysis evaluating 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 3,478 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 vs 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 hazard ratio (HR) of BCS + RT vs BCS was 0.39 [95% confidence interval (CI) 0.20–0.77] for InvBE and 0.34 (95% CI 0.22–0.52) for TotBE. In the low-risk group, pooled hazard ratio of BCS+ RT vs 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 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 authors report that the study was limited by the lack of data on breast-cancer specific mortality and individual data on recurrence-free survival. The authors state further high quality evaluation, including studies focused on impact on mortality are needed.

Leonard et al. (2021) performed a retrospective study on the association of the 12-gene Breast DCIS Score assay with local recurrence in patients with ductal carcinoma in situ (DCIS) treated on accelerated partial breast radiotherapy (APBI) protocols. The study pooled cohorts of women treated with local excision and APBI from prospective phase II (NCT01185145) and phase III (NCT01185132) clinical trials. The study included 104 patients with a median age of 60 years old, in which 79% were postmenopausal. The distribution of DCIS Score results ranged from 0 to 82, with 69% of patients having a DCIS Score result < 39. The median follow-up time was 8.2 years in NCT01185145 vs 3.0 years in NCT01185132. There were six local ipsilateral breast recurrences. DCIS Score result was significantly associated with local recurrence in univariable modeling, hazard ratio = 10.3 (95% confidence interval 1.7, 198.4); p = 0.010. No clinicopathologic characteristics resulted in any significant association with locoregional recurrence. The authors concluded that the Breast DCIS Score assay showed risk stratification but note the study was limited by the small number of local recurrence events and limited follow-up time. They acknowledge that further investigations are needed to validate results.

Manders et al. (2017) performed a prospective multicenter clinical utility study, in which 27 surgeons and 27 radiation oncologists at 13 US centers provided estimates of local recurrence risk and radiotherapy recommendations for 127 patients, before and after DCIS Score results were known. Post-assay, 26.4% of recommendations changed overall , representing 22.0% of recommendations by radiation oncologists and 30.7% of recommendations by surgeons. The DCIS Score result was the most frequently cited reason for post-assay treatment recommendations. The authors concluded that in response to DCIS Score results, surgeons changed treatment recommendations more often than radiation oncologists but further research is needed to grasp a better understanding of how such changes in treatment may impact clinical outcomes. This study was funded by Genomic Health, Inc.

Rakovitch et al. (2015) performed a prospectively designed clinical validation study of the Oncotype DX Breast DCIS Score Assay conducted in a population-based cohort of women diagnosed with DCIS and treated with breast conserving

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therapy alone from 1994-2003 in Ontario, Canada. The final study cohort included 718 patients of whom 571 had negative surgical margins. Median follow-up was 9.6 years. The study found the DCIS Score result to independently predict and quantify local recurrence risk. In the primary analysis, the DCIS Score result was significantly associated with any local recurrence in estrogen receptor positive patients [hazard ratio (HR)/50 units = 2.26, 95% confidence interval (CI) = 1.41-3.59; p < 0.001] as well as all patients regardless of estrogen receptor status (HR = 2.15; 95% CI = 1.43-3.22; p < 0.001). For the same pre-specified risk groups (low < 39, intermediate 39-54, and high = 55), the 10-year risk of a local invasive carcinoma recurrence was 8.0% in the low-risk group compared with 20.9% and 15.5% in the intermediate and high-risk groups, respectively; the risk stratification between the three groups was significant (p = 0.03). The risk of developing a DCIS local recurrence was 5.4% in the low-risk group compared with 14.1% and 13.7% in the intermediate and high-risk groups, respectively (p = 0.002). In multivariable analysis, the DCIS Score result was a significant predictor of local recurrence (HR/50 units = 1.68, 95% CI = 1.08-2.62; p = 0.02) and provided independent recurrence risk information beyond clinical and pathologic measures including age at diagnosis, tumor size, grade, necrosis, multifocality, and subtype. The primary analyses were restricted to patients with clear margins; however, secondary analysis included all patients regardless of surgical margins. The HR in the expanded cohort, adjusting for margin status and other clinical and pathological features, was 2.11 (95% CI = 1.43-3.09; p < 0.001) indicating that the DCIS Score result effectively risk-stratifies patients regardless of margin status. The authors concluded that the DCIS Score can help guide treatment recommendations and decrease over treatment for low-risk women and under treatment in those with significant risk of recurrence. Study limitations reported by the authors included that the patients were not randomized, many pathology reports did not have tumor size and resection margin width, and information on clinical presentation or family history of breast cancer was unavailable.

OVERA and ROMA

There is insufficient evidence to support Overa and ROMA testing. Improving early detection and prevention of ovarian cancer is a priority in women's health. To date, none of the multimarker serum tests addressed in this policy have been shown to reliably screen, improve quality of life, or decrease mortality in women with ovarian cancer. Given that the literature has limitations and in conjunction with the position of the American College of Obstetrics and Gynecology, The Society of Gynecologic Oncology, and the National Cancer Institute, coverage of these tests must await larger, prospective, non-industry funded data on long term outcomes including quality of life, improvement in survival and impact on mortality in women with ovarian cancer.

Hayes Molecular Test Assessment on Overa (ASPiRA Labs) notes the lack of peer-reviewed studies to support the analytical validity. Only one study was found to show clinical validity but one study from a small patient population does not provide adequate evidence. No studies were found to support clinical utility. Therefore, it has not been clearly demonstrated that the test impacts patient management and health outcomes [Hayes, Overa (ASPiRA Labs), 2018, updated 2022].

Shulman et al. (2019) performed a prospective enrollment study to compare the clinical performance of Risk of Ovarian Malignancy Assay (ROMA) and a new second-generation multivariate index assay MIA2G. Among 245 subjects (24.7%) determined to have a malignancy, MIA2G misclassified 22 (including 5 high-grade ovarian malignancies) and ROMA misclassified 51 malignancies (including 10 high-grade ovarian malignancies). Early stage cancers were more often misclassified by ROMA (20 vs 8 cases). The rate of “test-positive” benign cases was substantially higher for MIA2G and the rate of “test-negative” malignancies was substantially higher for ROMA. The authors concluded that MIA2G showed to accurately predict greater cases of ovarian cancer than ROMA. Study limitations reported by the authors included that a good number of participants did not complete the study requirements and lack of a consistent definition of adnexal mass used throughout the study centers.

Minar et al. (2018) performed a retrospective comparative study to compare the Risk of Ovarian Malignancy Algorithm (ROMA) and the Copenhagen Index (CPH-I) to differentially diagnose ovarian tumors. Two hundred sixty seven women who attended University Hospital Brno, Czech Republic were included in study. One hundred ten women had benign tumors, 42 had borderline ovarian tumors, and 115 had malignant tumors. The two indices showed comparable discriminatory performance with no significant variances. In the differentiation of benign tumors from all stages of borderline tumor and ovarian cancer, ROMA had a sensitivity of 71% and a specificity of 88%. CPH-I had a sensitivity of 69% and a specificity of 85%. The authors concluded that CPH-I has the potential to be a tumor index that is independent of menopausal status. It may be an easy alternative to ROMA in basic medical care settings. Study limitations reported by the authors included its retrospective and monocentric design.

Coleman et al. (2016) performed a clinical validity evaluation in a non-concurrent prospective study of 493 preoperatively collected serum specimens from premenopausal and postmenopausal women presenting with an adnexal mass requiring surgical intervention. Overa test scores were determined based on the analysis of archived serum specimens, and the patients were stratified into low or high-risk groups for finding malignancy on surgery. The analysis examined whether

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patient referral to a gynecologic oncologist was supported when dual assessment was determined to be positive (either Overa or clinical assessment was positive, or both were positive). A dual assessment was considered negative when both Overa and clinical assessment were negative. Among the 493 study participants, 92 (19%) had a final pathology diagnosis of malignancy. The clinical performance of the Overa assay, when combined with presurgical physician assessment demonstrated sensitivity of 93.5%, specificity of 64.8%, positive predictive value (PPV) of 37.9%, and negative predictive value (NPV) of 97.7%. Overall, the addition of Overa testing to presurgical physician assessment correctly identified 75% ($p < 0.001$) of the malignancies missed by physician assessment alone. This study had several limitations, including a small patient population and a retrospective study design. Additionally, preoperative physician assessment was not uniform across the patient population and this may have introduced bias into the study. Also the method used for combining clinical assessment and Overa test results was to consider the test positive if either clinical assessment or Overa test was positive. Thus, in practice, Overa testing would not be necessary if clinical assessment alone indicated cancer. Using Overa testing in this manner guarantees that Overa testing will be more sensitive and less specific than clinical assessment alone, even if it has no better than chance capability of detecting ovarian cancer. Sensitivity improved from 74% to 94% and specificity decreased from 93% to 65%. Finally, this study was funded by the manufacturer. This single study provides very-low-quality evidence for the clinical validity of the Overa test. This study is included in the Hayes 2022 Molecular Test Assessment.

Clinical Practice Guidelines

American College of Obstetricians and Gynecologists (ACOG)

ACOG recommend at level C scientific evidence (based primarily on consensus and expert opinion) that physicians can use serum biomarker panels as an alternative to CA125 level alone when evaluating women with adnexal masses to determine the need for referral to or consultation with a gynecologic oncologist when an adnexal mass requires surgery. Consultation with or referral to a gynecologic oncologist is recommended at a level B scientific evidence (based on limited or inconsistent scientific evidence) for patients with an elevated score on a formal risk assessment test (ACOG, 2016, reaffirmed 2025).

In a committee opinion on the role of the obstetrician-gynecologist (OB-GYN) in the early detection of epithelial ovarian cancer in women at average risk (ACOG, 2017, reaffirmed 2024), the ACOG recommend and conclude the following:

- Currently, there is no strategy for early detection of ovarian cancer that decreases ovarian cancer mortality.
- Use of transvaginal ultrasonography and tumor markers (such as CA 125), alone or in combination, for the early detection of ovarian cancer in average-risk women are unproven to reduce mortality, and there are harms from invasive diagnostic testing (e.g., surgery) resulting from false-positive test results.
- Epithelial ovarian cancer is most often detected in an advanced stage (65% of cases are stage III or stage IV) when the cure rate is only 18%.
- Early stage (localized) ovarian cancer is associated with improved survival.
- Taking a detailed personal and family history for gynecologic, breast, and colon cancer facilitates categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer.
- The patient and her OB-GYN should maintain an appropriate level of suspicion when there are potentially relevant signs and symptoms of ovarian cancer.

Society of Gynecologic Oncology (SGO)

The Society of Gynecologic Oncology (SGO) issued a position statement on multiplex serum testing for women with pelvic masses (SGO, 2013) stating that, “Blood levels of five proteins in women with a known ovarian mass have been reported to change when ovarian cancer is present. Tests measuring these proteins may be useful in identifying women who should be referred to a gynecologic oncologist. Recent data have suggested that such tests, along with physician clinical assessment, may improve detection rates of malignancies among women with pelvic masses planning surgery. Results from such tests should not be interpreted independently, nor be used in place of a physician’s clinical assessment. Physicians are strongly encouraged to reference the American College of Obstetricians and Gynecologists’ Committee Opinion “The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer” to determine an appropriate care plan for their patients.” SGO does not formally endorse or promote any specific products or brands.

National Comprehensive Cancer Network (NCCN)

The NCCN ovarian cancer guidelines (NCCN Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, v3.2025) state, “the United States Food and Drug Administration (FDA) has approved the use of ROMA, OVA1, or OVERA for estimating the risk for ovarian cancer in those with an adnexal mass for which surgery is planned, and have not yet been referred to an oncologist. Although the American College of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patients to refer to a gynecologic oncologist, other professional organizations have been non-committal. Not all studies have found that multi-biomarker assays improve all

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metrics (i.e., sensitivity, specificity, positive predictive value, negative predictive value) for prediction of malignancy compared with other methods (e.g., imaging, single-biomarker tests, symptom index/clinical assessment). Currently, the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass."

National Institute for Health and Care Excellence (NICE)

In a diagnostics guidance on tests in secondary care to identify people at high risk of ovarian cancer (NICE, 2017), NICE recommends the following:

- There is currently not enough evidence to recommend the routine adoption of the International Ovarian Tumor Analysis Assessment of Different Neoplasias in the Adnexa (IOTA ADNEX) model, Overa (MIA2G), RMI (risk of malignancy index) I (at thresholds other than 200 or 250), ROMA or IOTA Simple Rules in secondary care in the National Health Service (NHS) to help decide whether to refer people with suspected ovarian cancer to a specialist multidisciplinary team (MDT).
- The NICE guideline on ovarian cancer recommends that people with an RMI I of 250 or more are referred to a specialist MDT. Evidence suggests that there is no substantial change in accuracy if the threshold for RMI I is lowered to 200.
- The IOTA ADNEX model, Overa (MIA2G), RMI I (at thresholds other than 250), ROMA and IOTA Simple Rules show promise. Further research is recommended on test accuracy and the impact of the test results on clinical decision-making.

PDGFRA (Platelet - Derived Growth Factor Receptor, Alpha Polypeptide)

The *PDGFRA* gene provides instructions for making a protein called platelet-derived growth factor receptor alpha (PDGFRA), which is part of a family of proteins called receptor tyrosine kinases (RTKs). Receptor tyrosine kinases transmit signals from the cell surface into the cell through signal transduction. The PDGFRA protein is found in the cell membrane of certain cell types where a specific protein, called platelet-derived growth factor, attaches (binds) to it. This binding turns on (activates) the PDGFRA protein, which then triggers other proteins inside the cell by adding a cluster of oxygen and phosphorus atoms (a phosphate group) at specific positions (a process called phosphorylation). This process leads to activating a series of proteins in multiple signaling pathways. The PDGFRA protein, through the signaling pathways it stimulates, plays a crucial role in controlling vital cellular processes such as cell growth, division (proliferation), and cell survival. This underscores the importance of PDGFRA protein signaling in the development of various cell types throughout the body (MedlinePlus, 2021a).

Joensuu et al. (2023) explored the influence of *KIT* and *PDGFRA* mutations on overall survival (OS) for those with gastrointestinal stromal tumors (GIST) treated with adjuvant imatinib through a randomized trial. The results of this trial showed that during a median follow-up time of 10 years, 164 recurrence free survival (RFS) events and 76 deaths occurred. Most people were re-treated with imatinib when GIST recurred. Those with *KIT* exon 11 deletion or indel mutation treated with three years of adjuvant imatinib survived longer than patients treated for one year [10-year overall survival (OS) 86% vs 64%, respectively; hazard ratio (HR), 0.34; 95% confidence interval (CI), 0.15-0.72; p = 0.007], and also had more prolonged recurrence-free survival (RFS) (10-year RFS 47% vs 29%; HR, 0.48; 95% CI, 0.31-0.74; p < 0.001). People with the *KIT* exon nine mutation had unfavorable OS regardless of the duration of adjuvant imatinib. The authors concluded that compared with one year of imatinib, three years of adjuvant imatinib led to a 66% reduction in the estimated risk of death and a high 10-year OS rate in the subset of those with a *KIT* exon 11 deletion/indel mutation. Study limitations reported by the authors included that the trial was powered for a RFS difference between the two allocation groups with a sample size of 400 patients, which may have resulted in subgroup analyses on RFS and OS likely to have been underpowered.

Qu et al. (2016) performed a single center study analyzing the long-term outcomes of imatinib in *FIP1L1/PDGFRA* (F/P) associated chronic eosinophilic leukemia (CEL). Thirty-three patients in China were included in the study. At median follow up of 64 months, 94% of patients with F/P mutated CEL had complete hematologic remission (CHR). After a median of three (1.5-12) months, 97% had complete molecular remission (CMR). Twenty-four cases were given maintenance therapy, with an average CMR duration of 43 (5-88) months. Imatinib therapy was stopped in eight cases, including four relapse cases, and four patients who maintained CHR or CMR after stopping therapy with an average time of 47 (2-74) months. One case showed primary resistance with a *PDGFRA T674I* mutation. The authors concluded that F/P mutated CEL has a great long-term prognosis after imatinib therapy. Imatinib 100 mg is satisfactory to induce remission, and a single 100 mg weekly dose sustains a durable remission. A subgroup of patients may sustain a durable remission after stopping therapy with a CMR. This study was limited by its single center retrospective design and small sample size.

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Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Chronic eosinophilic leukemia is the most common clinical presentation in myeloid/lymphoid neoplasms with eosinophilia and *FIP1L1::PDGFRA* or other *PDGFRA* rearrangements. Imatinib has resulted in high rates of durable hematologic and molecular responses in the vast majority of patients with myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA* or *PDGFRB* rearrangement. The panel recommends continuing imatinib at the initial disease for achieving a complete response (complete hematologic response, complete cytogenetic response, or complete molecular response). Low doses have been sufficient to maintain molecular remission in the majority of patients with *FIP1L1::PDGFRA* rearrangement. NCCN recommends monitoring hematologic response, cytogenetic response (FISH), and molecular response (if RT-qPCR is available) every three and six months for patients achieving a durable complete response to initial treatment (NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions, v1.2026).

The standard for gastrointestinal stromal tumors (GIST) diagnosis is morphologic diagnosis based on microscopic examination of histologic sections. Several ancillary techniques are recommended in support of GIST diagnosis including molecular genetic testing for *PDGFRA* and *KIT* mutations, as well as other potential drivers (e.g., *NF1*, *NTRK*, *BRAF*, and *FGFR* fusions). Testing for *PDGFRA* and *KIT* mutations should be performed if TKIs are considered as part of the treatment plan since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA* genes are correlated with response (or lack of a response) to specific TKIs. Imatinib is recommended for *PDGFRA* mutations (excluding *PDGFRA* exon 18 mutations that are insensitive to imatinib, including D842V) (NCCN Gastrointestinal Stromal Tumors, v1.2025).

Pigmented Lesion Assay (PLA) (Oncology Melanoma)

The pigmented lesion assay is a non-invasive, adhesive patch gene expression test intended to guide biopsy decisions and rule out melanoma. This adhesive patch collects a tissue sample that is then sent to the DermTech laboratory in California, USA. The patch can be applied to almost the entire body. Results of the samples are analyzed for the presence of two genes: long intergenic non-coding ribonucleic acid (RNA) 518 (*LINC00518*) and preferentially expressed antigen in melanoma (*PRAME*). There are publications describing the gene discovery and analytical validity of the adhesive patch, supporting the genes selected, and method for RNA extraction [Ontario Health (Quality), 2021].

Skelsey et al. (2025) performed a test validation study of the noninvasive genomic rule-out test assessing genes expression of *PRAME* and *LINC00518* across Fitzpatrick skin types (FST). Test performance metrics for patients with FST I-III (n = 4,152) and IV-VI (n = 130) from 73 clinical practice sites in the United States were compared using biopsy results and follow-up information gathered through the DermTech Melanoma Test Registry Protocol. Performance metrics were also calculated for a cohort limited to lesions with at least six months of follow-up or biopsy results. In the full cohort (n = 4,282), specificity was 0.9086 (3,709/4,082), sensitivity was 0.9429 (66/70), positive predictive value (PPV) was 0.1503 (66/439), and NPV was 0.9989 (3,709/3,713) for FST I-III. For FST IV-VI, sensitivity was 1.0 (3/3), specificity was 0.9449 (120/127), PPV was 0.3 (3/10), and NPV was 1.0 (120/120). Three of three melanomas (0.55 mm, 0.40 mm, and melanoma in situ in non-sun-exposed areas on the trunk) in the IV-VI group diagnosed by histopathology were accurately identified as positive with the test. The 95% confidence intervals for the differences in specificity, sensitivity, NPV, and PPV between the 2 groups included 0, indicating no significant difference in any of the performance metrics. The authors concluded that these findings show that the performance of the noninvasive test in patients with FST IV-VI does not differ from that in patients with FST I-III. These findings support the test's utility of guiding biopsy decisions for ambiguous pigmented skin lesions of all skin types without needing to limit access for patients with FST IV-VI. The authors are investigators, consultants, or employees of the manufacturer which proposes a conflict of interest.

Thomsen et al. (2023) performed a systematic review on the detection of cutaneous malignant melanoma by tape stripping of pigmented skin lesions. A meta-analysis wad done to examine the test's accuracy by comparing the existing studies. 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). The authors concluded that the overall quality of the included studies was low therefore the reliability of specificity and sensitivity was questionable. However, tape stripping may supplement well-established diagnostic methods as pooled analysis of five studies indicates a moderate sensitivity.

Heerfordt et al. (2023) performed a diagnostic test validation study on RNA analysis of tape strips to rule out melanoma in lesions clinically assessed as cutaneous malignant melanoma (CMM). The latest test version is called "pigmented lesion assay" (PLA) and uses the detection ability of RNA from the genes *LINC00518* and *PRAME* . PLA has a reported sensitivity of 91%-95% and a specificity of 69%-91%. The sensitivity has raised concerns about the risk of overlooking CMMs, resulting in a need for further validation and improvement of the test. In order to avoid bias, a study of diagnostic

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test accuracy must include a consecutive group of lesions passing through a single set of eligibility criteria, all undergoing both the proposed test and the histopathology reference examination. Previous studies of PLA have not been performed with this design. The study received approval by the Regional Committee on Health Research Ethics (H-15010559). Two hundred lesions were included in the study. Histopathology revealed that 73 CMMs and 127 non-CMMs were included. In CMM lesions *LINC00518* was detected in 67 lesions (92%) and *PRAME* in 56 lesions (77%). The receiver operating characteristic curve with an area under the curve of 0.899 was used to show the potential of the RNA model to differentiate between CMM and non-CMM. The model provided a model score for each lesion with a CMM risk estimate. The model was transformed into a test that provides a positive result (CMM cannot be excluded) or a negative result (CMM excluded) using a cut-off model score of 0.057. The test was used on all 200 lesions. The test was positive for all lesions with a histopathological diagnosis of CMM. The authors concluded that this technique can decrease removal of benign lesions by one-third without overlooking any CMMs. The authors note that the study was limited in that the samples had a very high proportion of CMMs, possibly due to inclusion during COVID-19 shutdown and validation in a separate trial must be performed.

Brouha et al. (2020) evaluated the 2-GEP test [the Pigmented Lesion Assay (PLA) DermTech, La Jolla, CA] from a large U.S. registry. Included in the study were 3,418 lesions tested by 90 clinicians. Biopsied 2-GEP-positive lesions were separated into diagnostic subgroups per corresponding pathology reports. The prevalence of melanoma in biopsies of 2-GEP-positive lesions was 18.7%. Gene expression of both *PRAME* and *LINC* was identified in ever-increasing percentages of melanocytic lesions as pathology reports showed increasing levels of atypia. Of note, 47.5% of the histopathologically-confirmed melanomas displayed this double positive genomic signature while 28.8% were single-positive for *PRAME* and 23.7% were single-positive for *LINC*. The authors concluded that their findings convey that biopsied 2-GEP-positive lesions are enriched almost five-fold for advanced histopathologic features in comparison to those biopsied based solely on visual assessment. The close association between atypical pathology and genomic atypia should be considered when planning treatment of a 2-GEP-positive lesion. Consideration of genomic atypia may be a superior approach to guide biopsy decisions and manage pigmented lesions. Study limitations include single-read pathology reports, limited follow-up, and conflict of interest as several authors were affiliated with the manufacturer.

Ferris et al. (2019) reviewed 12-month management decisions and outcomes for patients tested using the PLA. The study involved retrospective chart reviews of 734 lesions that were PLA(-) and a registry of 175 pigmented lesions tested using the PLA. Among the 734 PLA(-) lesions, 13 were biopsied within one year. Of these 13 biopsied lesions, 11 were nevi with various degrees of atypia, one was a basal cell carcinoma and one was a squamous cell carcinoma. None were melanomas. In the registry cohort, 1,433 of 1,575 total lesions were PLA(-), and in follow-up only two had a surgical evaluation within a year. One of these had a scoop excision and was found to be a melanocytic nevus. The other was a squamous cell carcinoma removed by Mohs surgery. Of the 142 PLA(+) lesions in the registry cohort 96.5% were biopsied. Study limitations reported by the authors included the assumption that lesions of patients not returning for follow-up within 12 months were true negatives and some PLA(-) lesions may have been inadequately re-assessed within the 12 month follow-up period.

Gerami et al. (2017) validated the performance metrics of the PLA against consensus panel histopathologic assessment clearly demonstrating the test's clinical validity in the assessment of early stage pigmented lesions. In this study samples were collected prospectively from multiple dermatology practices and centers, in patients 18 years of age or older, and from pigmented lesions that were suspicious for melanoma, meeting one or more Asymmetry, Border, Color, Diameter, Evolving (ABCDE) criteria. Clinically obvious or frank melanomas were excluded. Lesions were simultaneously sampled using the adhesive patch and surgically biopsied. Biopsy specimens underwent pathologic diagnosis from three independent dermatopathologists, and lesions that received a concordant diagnosis from all three dermatopathologists were enrolled in the study. Overall, 11% of lesions sampled had a discordant pathological read and were excluded, creating a reference set upon which there was diagnostic agreement among pathologists. A blinded evaluation of these concordant biopsy samples was performed against the PLA result. An initial training set of 157 lesions was tested and demonstrated a 91% sensitivity, 53% specificity. An independent validation set was subsequently studied that included 398 pigmented lesion samples (87 melanomas, 253 atypical pigmented lesions, 53 non-melanocytic lesions). All melanomas enrolled in the study were classified as very early stage and were either MIS or Stage 1 with a median Breslow thickness < 0.5 mm. The PLA demonstrated a sensitivity of 91% and a specificity of 69%. This study was sponsored by DermTech Inc.

PIK3CA (Phosphatidylinositol-4, 5-Biphosphate 3-Kinase, Catalytic Subunit Alpha)

Breast Cancer

Rugo et al. (2024) reported on the BYLieve multicenter, open-label, non-comparative, non-randomized clinical trial on Alpelisib plus fulvestrant in *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor. Study locations included 114 centers across 18 countries. Cohort A included 127 patients with at least 18 months of

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follow-up. 119 patients had a centrally confirmed *PIK2CA* mutation. At data cutoff, average follow-up was 21.8 months (interquartile range 10.8–37.6). 64 (53.8%; 95% CI 44.4–63.0) of 119 patients were living without disease progression at 6 months. The greatest grade three or worse adverse events were hyperglycaemia [37 (29%) of 127 patients], rash [13 (10%)], and rash maculopapular [11 (9%)]. Serious adverse events occurred in 37 (29%) of 127 patients. There were no treatment-related deaths reported. The authors concluded that BYLieve demonstrated activity of alpelisib plus fulvestrant with manageable toxicity in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer, after progression on a CDK4/6 inhibitor plus an aromatase inhibitor. The authors note that this study was limited by not having a comparison group. This trial is registered with ClinicalTrials.gov, NCT03056755 funded by Novartis Pharmaceuticals.

Ji et al. (2023) performed a systematic review and network meta-analysis on phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitors, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, and histone deacetylase (HDAC) inhibitors as second-line treatments for hormone receptor-positive, HER2-negative advanced breast cancer. Included in the study were 9,100 participants from 17 randomized trials. For PI3K inhibitors, only studies in patients with *PIK3CA*-mutated cancer were included. Compared with placebo plus fulvestrant, progression-free survival (PFS) was notably improved by CDK4/6 inhibitor plus fulvestrant, mTOR inhibitor plus exemestane, mTOR inhibitor plus fulvestrant, and PI3K inhibitor plus fulvestrant, but not HDAC inhibitor plus exemestane. Although mTOR inhibitor plus exemestane was the best regimen (SUCRA value 89.5%), the mTOR inhibitor plus exemestane regimen caused greater severe adverse events (SAEs) than the HDAC inhibitor plus exemestane regimen [odds ratio (OR) 95%, confidence interval (CI) 2.40 (1.40–4.10)]. The authors concluded that CDK4/6 inhibitor and mTOR inhibitor-based regimens showed superior clinical efficacy and comparable safety profiles as second-line treatment in patients with HR-positive, HER2-negative advanced breast cancer. The authors report that the study was limited in that the meta-analysis was not based on individual patient data, that overall survival could not be analyzed due to lack of data, and that the BELLE-3 study enrolled some patients with mTOR inhibitor resistance.

Turner et al. (2021) reported on the BYLieve non-randomized trial and the effectiveness of Alpelisib + Fulvestrant compared with real-world standard treatment among patients with HR +, HER2–, *PIK3CA*-Mutated Breast Cancer. The BYLieve trial (NCT03056755) confirmed safety and efficacy of alpelisib with fulvestrant for hormone receptor-positive (HR +), human epidermal growth factor receptor-2-negative (HER2-), *PIK3CA*-mutated advanced breast cancer (ABC), after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with an aromatase inhibitor (AI) as immediate prior therapy. 855 patients with *PIK3CA*-mutant disease with prior CDK4/6i plus hormone therapy were included in the study; further matching to 120 patients from BYLieve selected 95 patients with no exposure to HER2-targeting agents, clinical study drug, or alpelisib. In postmatching and unadjusted results, primary and secondary endpoints were in favor of treatment with alpelisib with fulvestrant in BYLieve over standard treatments in the real-world cohort. Postadjustment, median progression-free survival (PFS) for patients treated with alpelisib in BYLieve was 7.3 vs 3.7 months in the real-world cohort, and six-month PFS was 54.6% vs 40.1%, respectively. The authors concluded that weighted/matched analysis comparing BYLieve with the real-world setting further corroborates the clinical benefit of alpelisib with fulvestrant for treatment of HR +, HER2-, *PIK3CA*-mutant ABC after CDK4/6i treatment. The authors note that this study was limited in that the BYLieve trial prospectively collected data whereas this study retrospectively collected data from the clinico-genomics database (CGDB) and not all eligibility criteria of the BYLieve trial could be replicated in this study.

Anderson et al. (2020) performed a systematic review on the prevalence and diagnostic workup of *PIK3CA* mutations in HR+/HER2– metastatic breast cancer (mBC). Thirty-nine studies were identified and the median prevalence of *PIK3CA* mutation was 36% (range: 13.3% to 61.5%). There was stability and concordance between tissues (range: 70.4% to 94%) based on limited data. Identifying *PIK3CA* mutation status is important in the management of patients with HR+/HER2– mBC given the clinical advantages of alpelisib in patients with *PIK3CA* mutant HR+/HER2– mBC. The authors concluded that prevalence of this mutation and utility of test methodologies likely warrants testing of the *PIK3CA* mutation in all patients with HR+/HER2– mBC. Study limitations reported by the authors were that the included studies were published in English, published by 2019, and specifically reported on HR+/HER2- mBC cases. A meta-analysis could not be conducted due to the wide range of study types and designs that were included in the review.

André et al. (2019) performed a randomized controlled trial (SOLAR-1) on Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. Five hundred seventy two patients underwent randomization which included 341 patients with confirmed tumor-tissue *PIK3CA* mutations. In the *PIK3CA*-mutated cancer cohort, progression-free survival at a median follow-up of 20 months was 11.0 months [95% confidence interval (CI), 7.5 to 14.5] in the alpelisib-fulvestrant group, in comparison to 5.7 months (95% CI, 3.7 to 7.4) in the placebo-fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85). In the cohort without *PIK3CA*-mutated cancer, the hazard ratio was 0.85 (95% CI, 0.58 to 1.25; posterior probability of hazard ratio < 1.00, 79.4%). Overall response in all cohort patients with *PIK3CA*-mutated cancer was greater with alpelisib-fulvestrant than with placebo-fulvestrant (26.6% vs 12.8%). Among patients with measurable disease in this cohort, the percentages were 35.7% and 16.2%, respectively. In the overall

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population, the most frequent adverse events of grade 3 or 4 were hyperglycemia (36.6% in the alpelisib-fulvestrant group vs 0.7% in the placebo-fulvestrant group) and rash (9.9% vs 0.3%). Grade 3 diarrhea was seen in 6.7% of patients in the alpelisib-fulvestrant group, in comparison to 0.3% of those in the placebo-fulvestrant group. Grade 4 diarrhea was not reported. The percentages of patients who stopped alpelisib and placebo owing to adverse events were 25.0% and 4.2%, respectively. The authors concluded that treatment with alpelisib-fulvestrant prolonged progression-free survival among patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who previously received endocrine therapy (funded by Novartis Pharmaceuticals; SOLAR-1 ClinicalTrials.gov number, NCT02437318).

Other Indications

Francini et al. (2024) conducted a systematic review and meta-analysis to evaluate the intensification approaches and treatment sequencing in metastatic castration-resistance prostate cancer. Twenty-eight clinical trials and 24 ongoing studies were included in the review. *PIK3CA/AKT1/PTEN* alterations and immunohistochemistry-assessed *PTEN* loss were found in 40–50% of prostate cancer cases, as indicated in the IPATential150 trial. They are promising predictive biomarkers for AKT inhibitors. The authors concluded that AKT inhibitor combination of ipatasertib + abiraterone extends radiographical progression-free survival (rPFS) in individuals with PTEN loss or PIK3CA/AKT1/PTEN alterations. However, the study was limited by immature survival data. While data from prospective trials assessing head-to-head comparisons, combinations, or sequences are useful, these are insufficient to identify the ideal sequence of therapies.

Lau et al. (2024) performed a systematic review to identify genes suggested to have molecular mechanism impacts on the radioresponsiveness of patients with colorectal cancer. Seven studies were included in the review. Twenty-four genes including *PIK3CA* were identified in having roles in pathways including apoptosis, inflammation, deoxyribonucleic acid (DNA) damage response/repair, and cancer metabolism, that may impact cancer radio response. The authors concluded that the gene cohort identified in this review may be used as a foundation for future works. The authors report this review was limited by the fact that there was a lack of retrospective studies to verify findings, the study was solely on rectal cancer and not colon cancer, and that no meta-analysis was performed. Meta-analysis was not conducted due to the primary concern being whether there was any pathological response to therapy and meta-analysis requires low heterogeneity. There were a variety of study designs included in the review which made it challenging to find a suitable number of studies exhibiting low hetereogeneity to perform a meta-analysis.

Lawler et al. (2024) performed a systematic review and meta-analysis regarding prognostic and predictive tumor markers for early (diagnosed before the age of 50) vs late onset colorectal cancer. The study included 149 articles. No significant difference in the prevalence of *PIK3CA* mutations was found for early-onset colorectal cancer. Specifically, a study with over 1,000 distal and rectal tumors displayed no significant age difference in *APC, BRAF*, *KRAS*, *NRAS*, *PIK3CA*, or *TP53*, mutations. The authors concluded that more research is needed to clarify the relationships with novel tumor characteristics including immune markers and to identify molecular subtypes specific to early-onset colorectal cancer that can impact prognosis and treatment. The authors report this review was limited by studies published within the last 10 years, significant estimate heterogeneity, and that residual confounding by differences in tumor location or hereditary conditions may have caused bias in the results.

Roncato et al. (2024) performed a systematic review and meta-analysis to evaluate the impact of the most relevant molecular alterations in cancer-related genes of colorectal cancer (for example, *RAS*, *BRAF*, *SMAD4*, *PIK3CA*) as prognostic markers of survival and disease recurrence in patients with metastatic colorectal cancer who were treated by liver metastases resection. Only three studies for *PIK3CA* were eligible and no significant association with either recurrence free survival or overall survival could be highlighted. The authors concluded that no conclusion could be drawn for *PIK3CA* due to limited availability of literature.

Sadlecki and Walentowicz-Sadlecka (2024) performed a systematic review on molecular changes found in borderline ovarian tumors (BOTs) and their significance on overall therapeutic approach. Twenty-eight publications on proto-oncogenes: *BRAF*, *KRAS*, *NRAS*, *ERBB2*, and *PIK3CA* were included in the review. In one patient, *PIK3CA*, *BRAF*, and *ERBB2* mutations were found solely in lower grade serous ovarian cancer (LGSC) but not in synchronous serous borderline tumor (SBOT). In another patient, *PIK3CA* mutations were found in both LGSC and SBOT. The implication is that *PIK3CA* and *ERBB2* mutations are significant events occurring during the transformation of serous cystadenoma to SBOT and further to LGSC. Of note, the frequency of *PIK3CA* mutations in LGSCs/SBOTs in the Japanese population seems to be considerably higher than in the Western population. *PIK3CA* mutation may play a primary role in developing LGSCs in Japanese patients. Targeting the *PIK3CA*/*AKT* pathway through molecular therapies seems to be a potentially promising treatment for LGSC in the Japanese population. The authors concluded that molecular studies substantially added to the understanding of borderline ovarian tumor pathogenesis. However, substantial research still needs to be performed to clarify the relationship between ovarian neoplasms and extraneous disease, pinpoint accurate prognostic indicators, and form targeted therapeutic approaches. The study was limited in that it included mostly observational and retrospective analyses.

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Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In an updated guideline for Biomarkers to Guide Systemic Therapy for Metastatic Breast Cancer (Henry et al. 2022), ASCO recommends testing for *PIK3CA* mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine eligibility for alpelisib plus fulvestrant in candidates for phosphatidylinositol 3-kinase inhibitor and hormonal therapy. If no mutation is found, testing in tumor tissue, if available, should be used.

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for invasive breast cancer (NCCN Breast Cancer v5.2025) recommend *PIK3CA* biomarker testing for HR-positive, HER2-negative breast cancer. Alpelisib + fulvestrant is the preferred second-or subsequent-line therapy.

National Institute for Health and Care Excellence (NICE)

In a guideline published in 2022, NICE recommends alpelisib plus fulvestrant as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults, only if the patient's cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor and the company provides alpelisib according to the commercial arrangement (NICE, 2022).

PMP22 (Peripheral Myelin Protein 22) (e.g., Charcot-Marie-Tooth, Hereditary Neuropathy With Liability to Pressure Palsies)

Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

The *PMP22* gene provides instructions for making a protein called peripheral myelin protein 22 (PMP22). This protein is found in the peripheral nervous system, which connects the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound. Mutations in gene cause several forms of Charcot-Marie-Tooth (CMT) disease, a disorder that damages the peripheral nerves, which can cause loss of sensation and atrophy of the muscles in the feet, legs, and hands (MedlinePlus, 2018d).

There is no cure for Charcot-Marie-Tooth (CMT), and maintaining mobility, flexibility, and muscle strength is important. Starting a treatment program soon after symptoms begin can aid in maintaining quality of life. Medications can be prescribed for severe nerve pain (NIH, 2026).

The diagnosis of Charcot-Marie-Tooth (CMT) disease is based on physical symptoms, family history and clinical tests. These include nerve conduction velocity (NCV) electromyogram (EMG). Treatment is symptomatic and supportive, and there is no cure. With recent advances in molecular genetic testing using both deletion duplication analysis and next generation sequencing (NGS) for patients with a clinical diagnosis of CMT, a genetic cause can be found in about 60% of patients (NORD, 2021)

More than 80 different genes are associated with Charcot-Marie-Tooth (CMT). *PMP22* duplication accounts for approximately 50% of all CMT and *PMP22* deletion/duplication analysis is recommended as the first test for all probands with CMT. Because the methodology to detect *PMP22* duplication differs from that used in many multigene panels, this test needs to be ordered separately unless a laboratory explicitly states that *PMP22* deletion/duplication analysis is included in its multigene panel. Symptoms usually begins in the first to third decade and results in weakness and atrophy of the muscles in the hands and/or feet. Testing is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Bird, 2025).

The large number of Charcot-Marie-Tooth (CMT) causing genes is often challenging for clinicians and patients when trying to determine the underlying genetic diagnosis. There is little information available to guide which gene to test and testing a patient for mutations in all commercially available CMT genes is not realistic. Family planning and prognosis may require an accurate genetic diagnosis and current treatment trials depend on knowing the genetic cause of a patient's CMT even if no cures are presently available (Miller et al., 2011).

Hayes Molecular Test Assessment for Charcot-Marie-Tooth Type 1A (*PMP22*) describes Charcot-Marie-Tooth disease Type 1A (CMT1A) as a peripheral demyelinating neuropathy caused by a 1.5-megabase (Mb) duplication of chromosome 17 at band p11.2, which includes the peripheral myelin protein 22 (*PMP22*) gene. Product names include complete CMT Evaluation (#400) or *PMP22* Duplication/Deletion deoxyribonucleic acid (DNA) Test (#131) (Athena Diagnostics Inc.); Inherited Peripheral Neuropathies [Charcot-Marie-Tooth Type 1A (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)] FISH analysis (#8467) [Medical Genetics Laboratories (MGL) at Baylor College of Medicine

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(BCM)]. For confirmation of diagnosis in an individual with suspected CMT based on clinical findings, Hayes assigns a rating of C (potential but unproven benefit). For an asymptomatic individual with a confirmed family history of CMT1A to establish personal risk, Hayes assigns a rating of C. For an oncology patient with unexplained or preexisting familial neuropathy consistent with CMT, Hayes assigns a rating of B (some proven benefit). For prenatal or preimplantation genetic diagnosis of CMT1A, Hayes assigns a rating of B [Hayes, Charcot-Marie-Tooth Type 1A (*PMP22)*, 2018, updated 2012].

RiskReveal (Formerly DetermaRx) (Oncology Lung)

Approximately 87% of lung cancers are non-small cell lung cancer (NSCLC) and 13% are small cell lung cancer (SCLC). In 2025, the American Cancer Society estimates 229,410 new cases of lung cancer and 124,990 deaths from lung cancer. The average age of diagnosis is 70 years old (ACS, 2026a). The 5 year relative survival rate for NSCLC according to the Surveillance, Epidemiology, and End Results (SEER) database is 67% for localized, 40% for regional, 12% for distance and 32% for all SEER stages combined (ACS, 2026b). The staging system most often used for lung carcinoid tumors is the American Joint Committee on Cancer (AJCC) TNM system, which is based on three key pieces of information: t = the size and extent of the main tumor, n = the spread to nearby lymph nodes, and m = the spread (metastasis) to distant sites. Stage I tumors are not larger than 4 cm across and the cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0). Stage IIa tumors are larger than 4 cm but not larger than 5 cm across and the cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0). (ACS, 2026c).

The frequent recurrence of non-small cell lung cancer (NSCLC) following resection in patients classified as low risk based on clinical and pathologic data motivated the development of a molecular classifier that might be able to more accurately identify which patients are likely to have disease recurrence or metastatic disease.

The Razor 14-Gene Lung Cancer Assay is quantitative polymerase chain reaction (PCR) analysis designed to be used on formalin-fixed, paraffin embedded lung cancer tissue. The test relies on an algorithmic interpretation of the quantitative PCR data on ribonucleic acid (RNA) from 11 cancer-related target genes (*BAG1*, *BRCA1*, *CDC6*, *CDK2AP1*, *ERBB3*, *FUT3*, *IL11*, *LCK*, *RND3*, *SH3BGR*, *WNT3A*) and 3 reference genes (*ESD*, *TBP*, *YAP1*).

Of note, Oncocyte acquired the rights to develop and market Razor's treatment stratification test in September 2019. Therefore, the Razor 14-Gene Lung Cancer Assay changed its name to DetermaRx (Oncocyte, 2021). DetermaRX is now known as RiskReveal (Ho et al., 2025).

Spigel et al. (2025) reported on an international, randomized, phase 3 clinical trial on adjuvant chemotherapy for stage IA-IIA non-squamous, non-small-cell lung cancer identified as molecular high-risk by a 14-gene expression profile (AIM-HIGH). The clinical trial included 45 centers in the USA, France, and Germany and 449 patients with stage IA-IIA non-squamous non-small cell lung cancer (NSCLC). Randomization was stratified according to sex, age, and tumour size of 4 cm or more. The primary outcomes were 48-month and 24-month disease-free survival, respectively, in the modified intention-to-treat (mITT) population. 236 patients with molecular high risk were randomly assigned to chemotherapy (n = 124) or observation (n = 112). At the time of the prespecified interim analysis, 87 patients were evaluable in the mITT population [47 (54%) males and 40 (46%) females; median age 63 years (IQR 52-74)] in the chemotherapy group and 107 [58 (54%) males and 49 (46%) females; 66 years (56-76)] in the observation group. Fourty-eight (55%) patients in the chemotherapy group and 58 (54%) patients in the observation group had stage IA disease; 34 (39%) and 44 (41%), respectively, had stage IB disease, and five (6%) and five (5%), respectively, had stage IIA disease. Six (3%) of 200 patients in the mITT population had passed away at the time of the interim analysis. Twenty-four-month disease-free survival was 96% (95% CI 92-100) with adjuvant chemotherapy vs 79% (70-90) with observation [hazard ratio 0.22 (0.06-0.76); p = 0.0087]. The authors concluded that the 14-gene assay identified patients with molecular high risk who benefited from adjuvant chemotherapy. Use of the assay to determine eligibility for adjuvant therapy in stage IA–IIA non-squamous NSCLC has the potential to significantly improve otherwise persistently poor outcomes. Study limitations reported by the authors included the non-compliance of a significant proportion of patients with random assignment to chemotherapy, the positive result from this interim analysis depended on a large reduction in disease recurrence, and the study not powered to support subgroup analyses or other secondary analyses that will await longer-term follow-up. This study was funded by Razor Genomics.

Lan et al. (2025) performed a retrospective study to evaluate the predictive accuracy of the 14-gene molecular assay in determining treatment response among patients with non-small cell lung cancer (NSCLC) undergoing neoadjuvant immunochemotherapy (nICT). The percentage of residual viable tumor cells (%RVT), tumor-infiltrating lymphocyte (TIL), and tertiary lymphoid structures (TLS) within the primary lesion were evaluated through hematoxylin and eosin staining of surgical specimens. Correlations between the 14-gene molecular risk stratification and pathological response, as well as between the 14-gene molecular risk stratification and patient prognosis were evaluated. One hundred fourteen patients were included in the study. The pathological complete response (pCR) rate was substantially higher in the 14-gene low-

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risk group, while the RVT was notably lower (both $p < 0.05$). The low-risk group displayed substantial elevated levels of TIL and positivity for TLS (both $p < 0.05$). Survival analysis showed that patients in the low-risk group had markedly longer disease-free survival (DFS) compared to those in the intermediate-risk and high-risk groups (both $p < 0.05$). Univariate Cox regression analysis identified pathological TNM stage, vascular invasion, pathological response, and 14-gene molecular risk stratification as significant factors influencing DFS (all $p < 0.05$). Multivariate analysis confirmed that the 14-gene risk stratification was an independent prognostic factor for DFS (HR = 2.496, 95% CI: 1.264–4.931, $p = 0.008$). The authors concluded that DetermaRx showed that low-risk status correlates with improved pathological response and prognosis, potentially attributable to higher TLS positivity rates and increased TIL infiltration. This assay offers critical insights for refining neoadjuvant treatment strategies in patients with NSCLC. The authors reported that the study was limited by its single-center retrospective design and a relatively small sample size.

Jiang et al. (2025) performed a retrospective cohort study to compare the predictive performance of clinicopathological factors and the 14-gene assay to assess postoperative prognosis and predict the potential benefit of adjuvant *EGFR*-TKIs in stage I non-small cell lung cancer (NSCLC). The primary endpoint was the five-year disease-free survival (DFS) rate. One hundred eighty patients with Stage I NSCLC were included in the study. The 14-gene assay displayed superior performance compared to clinicopathological factors in predicting recurrence events. Patients with molecular high-risk, rather than clinicopathological high-risk factors, showed a greater favorable response to adjuvant *EGFR*-TKIs. Adjuvant *EGFR*-TKIs benefited molecular high-risk patients, regardless of clinicopathological high-risk (DFS rate rose from 65.9% to 95.0%, $p = 0.02$) or low-risk subgroups (80.0% to 100%, $p = 0.04$). Those with molecular low risk did not show any benefit from *EGFR*-TKIs, regardless of clinicopathological high-risk (DFS rate rose from 93.3% to 100%, $p = 0.37$) or low-risk subgroups (97.0% to 100%, $p = 0.73$). The authors concluded that DetermaRx is proven superior over clinicopathological factors, offering valuable guidance for adjuvant *EGFR*-TKIs decisions in stage I NSCLC. Study limitations reported by the authors included the relatively small sample size of eligible patients and its retrospective design. There are ongoing larger prospective studies to address these limitations.

Huang et al. (2024) performed a retrospective cross-sectional study to evaluate a 14-gene ribonucleic acid (RNA)-level quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis of formalin-fixed paraffin-embedded (FFPE) tissue samples assay of lung cancer and its relationship with risk stratification. Included in the study were 102 patients with resectable non-squamous non-small cell lung cancer (NSCLC). Mean age was 55.19 years old, 65.7% were female, and 17.6% had a history of smoking. The majority of patients (n = 76, 74.4%) had stage IA adenocarcinoma, six had adenocarcinoma in situ (AIS), one had atypical adenomatous hyperplasia (AAH), one had stage IIB disease, and two had stage IIIA disease. The test classified patients into three categories: low-risk (n = 63), intermediate-risk (n = 25), and high-risk (n = 14). Genomic profiling of 89 patients showed specific mutations that were significantly correlated with the higher-risk groups. Tumor mutational burden (TMB) was greater in higher-risk groups ($p = 0.007$). In clinically low-risk patients (n = 85) as recognized by NCCN guidelines, the 14-gene risk stratification model re-grouped 30 out of the 85 clinically low-risk patients. Nineteen were placed in the medium-risk group and 11 in the high-risk group, and the remaining samples remained in the low-risk group. Also, three patients who were not recommended for adjuvant therapy by the Multiple-gene Index to Evaluate the Relative benefit of Various Adjuvant therapies (MINERVA) model were categorized as high-risk and 13 were classified as intermediate-risk. The Kaiser Permanente Division of Research assessed the prognostic impact of this risk stratification on patients with stage I NSCLC, displaying significant variances in five-year overall survival (OS) among the low-, medium-, and high-risk groups based on the 14-gene risk stratification. The high-risk group was linked to a worse prognosis. Also, some studies showed that the 14-gene RNA-level assay can predict recurrence in early-stage NSCLC, with a substantial difference in five-year disease-free survival (DFS) between the low- and high-risk groups. In stage I–IIA patients, those at high-risk may benefit from adjuvant therapy (chemotherapy vs targeted therapy). Therefore, the 14-gene RNA-level assay showed capability to improve upon the existing National Comprehensive Cancer Network (NCCN) risk categories. The authors concluded that the assay is associated with specific genetic mutations which provide a better foundation for incorporating molecular risk assessment with clinical and imaging data, which offers a additional comprehensive information to guide more targeted and effective treatment options. Study limitations reported by the authors included a short follow-up period which hindered accurate assessment of recurrence statistics.

Jiang et al. (2023) performed a retrospective cohort study to assess the impact of adjuvant *EGFR*-TKIs and 14-gene molecular assay on stage I non-small cell lung cancer with sensitive *EGFR* mutations. Included in the study were 227 patients with stage I non-small cell lung cancer (NSCLC). Fifty-five of them were in the *EGFR*-TKI group and 172 were in the observation group. The median duration of follow-up was 78.4 months. After inverse probability of treatment weighting (IPTW), the five-year disease-free survival (DFS) [hazard ratio (HR) = 0.30, 95% confidence interval (CI), 0.14-0.67; $p = 0.003$ and overall survival (OS) HR = 0.26, 95% CI, 0.07-0.96; $p = 0.044$] of the *EGFR*-TKI group were substantially better than the observation group. For subgroup analyses, adjuvant *EGFR*-TKIs were associated with favorable 5-year DFS rates in both IA (100.0% vs 84.5%; $p = 0.007$), and IB group (98.8% vs 75.3%; $p = 0.008$). DetermaRx was performed in 180 patients. Among intermediate-high-risk patients, *EGFR*-TKIs were correlated with a considerable improvement in five-

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year DFS rates compared to observation (96.0% vs 70.5%; p = 0.012). No difference was noted in low-risk patients (100.0% vs 94.9%; p = 0.360). The authors concluded that the results suggested that adjuvant *EGFR*-TKI might improve DFS and OS of stage IA and IB *EGFR*-mutated NSCLC, and DetermaRx could help patients that would benefit the most from treatment. Study limitations reported by the authors included limited statistical power for survival analysis and recurrence events since patients with stage I NSCLC receiving adjuvant *EGFR*-TKI therapy as an off-label treatment is a relatively small population. This also resulted in the inability to provide comprehensive results on tolerability and toxicity of adjuvant *EGFR*-TKI.

In a Hayes Precision Medicine Research Brief, reviewing abstracts suggests there is adequate published peer-reviewed literature to analyze the evidence for DetermaRx for patients with early stage non-squamous non-small cell lung cancer (NSCLC). However, conclusions about the safety and analytical validity, clinical validity, or clinical utility cannot be made as a full-text review of the evidence is needed. A full appraisal report may be warranted [Hayes, DetermaRx (Oncocyte Corporation) 2022].

Woodard et al. (2021) performed a prospective study to assess the 14-gene prognostic assay and its risk stratification. Platinum doublet adjuvant chemotherapy (AC) was recommended for molecular high-risk (MHR). Differences in freedom from recurrence (FFR) and disease-free survival (DFS) were evaluated. Two hundred fifty patients with stage I-IIA non-squamous NSCLC were included in the study. At 29 months, prospective molecular testing yielded an estimated FFR of 94.6% and 72.4% in low-risk and untreated MHR patients, respectively, and 97.0% among MHR patients receiving AC (p < 0.001). No association was found between *EGFR* status and recurrence, while molecular risk predicted survival and response to AC within both the *EGFR* mutation(+) and mutation(-) populations. Sixty-seven percent of EGFR(+) and 49% of EGFR(-) patients were molecular low-risk. The authors concluded that their study showed the utility of the 14-gene assay independent of *EGFR* mutation. Basing adjuvant intervention in early-stage NSCLC on *EGFR* status alone may undertreat up to 51% of EGFR(-) patients likely to benefit from adjuvant intervention, and overtreat up to 67% of EGFR(+) patients more likely to be free of residual disease. The authors reported that this study was limited in the non-randomized distribution of MHR patients between adjuvant therapy and observation, and difficulty fully converting seventh to eighth edition staging.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for non-small cell lung cancer (NSCLC) (NCCN NSCLC, v1.2026) acknowledge that there are many gene alterations that impact therapy selection in NSCLC. It is important to test lung cancer specimens for these alterations to identify potentially efficacious targeted therapies and to avoid those unlikely to provide clinical benefit. Several methodologies are generally considerations for use such as next generation sequencing (NGS), RNA-based NGS if no identifiable driver oncogenes with DNA-based broad molecular profiling are identified, and real-time polymerase chain reaction (PCR) can be utilized in a highly targeted fashion.

Resolution ctDX Lung

There is insufficient evidence to support Resolution ctDX Lung for non-small cell lung cancer. Well-designed, randomized controlled trials with large sample sizes and long-term follow-up are needed to establish the impact on health outcomes.

Liu et al. (2024) conducted a retrospective study analyzing patients with metastatic *HER2*-mutant NSCLC who underwent prospective clinical circulating tumor deoxyribonucleic acid (ctDNA) sequencing and received systemic therapy. *HER2* mutations were identified by next-generation sequencing through MSK-IMPACT, MSK-ACCESS, or Resolution ctDx Lung assay. Primary endpoints were time to the next treatment (TTNT) and overall survival (OS). Sixty-three patients were included in the study. Chemoimmunotherapy was the primary first-line treatment with a median TTNT of 5.1 months, whereas 55.0% of patients who received second-line T-DXd had a median TTNT of 9.2 months. Plasma ctDNA was tested before first-line therapy in 40 patients with a median OS of 28.0 months. Thirty-one of those patients (78.0 %) had identifiable ctDNA. *HER2* mutations were found on ctDNA with an average turnaround time of 13 days, occasionally occurred simultaneously with *MET* and *EGFR* alterations and were monitored longitudinally correlating with treatment response. Those who had detectable baseline ctDNA had substantially shorter OS. Thirty-one patients had at least one detectable ctDNA alteration by ctDx Lung or MSK-ACCESS. The authors concluded that chemoimmunotherapy continues to be main treatment option for metastatic *HER2*-mutant NSCLC. ctDNA can rapidly detect *HER2* and co-mutations. It can potentially guide and monitor ideal first-line therapy. As a negative prognostic biomarker, detectable ctDNA at baseline should be taken into account for patient selection in future studies. Study limitations reported by the authors included the retrospective nature of the study and small sample size. This prevented further multivariable analysis investigating the independent prognostic value of ctDNA. These include the trend that *HER2* mutations occurred more often in younger patients and subgroup analyses comparing the clinical outcomes associated with the different *HER2*-targeted agents.

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Also, radiologic tumor measurements were not available. Although TTNT reflects duration of clinical benefit as determined by the clinician, it can be impacted by toxicity and treatment interruptions.

Supplee et al. (2019) tested the sensitivity of Guardant360™ (G360, Guardant Health) and ctDx-Lung (Resolution Bioscience) in detecting oncogenic fusions in plasma cell-free deoxyribonucleic acid (DNA). Out of 16 patients assayed known to harbor an *ALK*, *ROS1*, or *RET* in tumor, G360 identified fusions in seven cases, ctDx-Lung identified fusions in 13 cases, and 3 cases were not identified by G360 or ctDx-Lung. Out of the seven fusions identified by both assays, G360 reported lower mutant allelic fractions (AF). In cases missed by G360, tumor derived *TP53* mutations were frequently identified confirming the presence of tumor DNA. Raw sequencing data displayed that inverted or out-of-frame variants were overrepresented in cases identified using ctDx-Lung but not by G360. The authors concluded that focusing on complex, clinically actionable mutations using tumor as a reference standard enables evaluation of technical differences in plasma next-generation sequencing (NGS) assays that may impact clinical performance. Noting the heterogeneity of fusion sequences observed in non-small cell lung cancer (NSCLC), the authors hypothesize that differences in hybrid capture techniques and bioinformatic calling may be sources of variations in sensitivity among these assays. There needs to be continued efforts to better existing assays to fully leverage their potential to impact patient care. The authors report that this study was limited by its retrospective design and small sample size. While a good model for evaluating complex variants, actionable fusions are uncommon in NSCLC. Routine clinical plasma NGS is fairly new, thus precluding a larger sample size. Also, although samples were batched together for sequencing with ctDx-Lung, G360 testing has been in use variably for two years. At this time, the G360 assay has evolved through four commercial versions (v14.0- v17.0). Future comparative studies should strive to use latest version of all assays. Another limitation reported included that the two plasma specimens were not regularly obtained at the same time.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for non-small cell lung cancer (NSCLC) (NCCN NSCLC, v1.2026) states that the panel feels that tissue should be used to diagnose NSCLC, not plasma circulating tumor deoxyribonucleic acid (ctDNA). Guidelines and standards for plasma ctDNA testing for somatic variants/mutations have not been published, variants can be detected that are not related to the tumor, and there is up to a 30% false-negative rate.

However, the guideline states that plasma circulating tumor deoxyribonucleic acid (ctDNA) can be used in specific circumstances including:

- Patient is not medically fit for invasive tissue sampling
- There is insufficient tissue for molecular analysis and follow-up tissue-based analysis is planned if an oncogenic driver is not identified

Plasma circulating tumor deoxyribonucleic acid (ctDNA) molecular testing should be performed using tests that are clinically validated referencing the International Association for the Study of Lung Cancer (IASLC), but notes that plasma-based ctDNA is less sensitive than tissue assays. In an updated consensus statement from the International Association for the Study of Lung Cancer (IASLC) (Rolfo et al., 2021), two commercially available Food an Drug Administration approved plasma-based next generation sequencing (NGS) assays for NSCLC FoundationOne Liquid CDx and Guardant360 were identified. IASLC recommends plasma ctDNA testing be done using a clinically validated NGS platform.

SMN1 (Survival of Motor Neuron 1, Telomeric) (e.g., Spinal Muscular Atrophy)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnosis spinal muscular atrophy, which is characterized by muscle weakness and atrophy. The onset of weakness ranges from before birth to adulthood. It is also used for prenatal testing and carrier testing (Prior et al. 2026).

The *SMN1* gene provides instructions for making the survival motor neuron (SMN) protein. SMN is found throughout the body, especially in the spinal cord. This protein is in the group of proteins called the SMN complex, which is essential for the maintenance of motor neurons. These cells are located in the brainstem which connects the spinal cord to the brain. Motor neurons tell skeletal muscles to contract which allows the body to move. Several known mutations in the *SMN1* gene have been found to cause spinal muscular atrophy (SMA). This condition leads to weakness and wasting in the skeletal muscles and progresses with age. *SMN1* has also been associated with amyotrophic lateral sclerosis (ALS) in a small number of cases (MedlinePlus, 2018b). SMA has been the leading genetic cause of infant mortality. At this time,

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there is no cure for SMA although there are new disease modifying therapies that are available that are shown to extend life expectancy and allow for further motor milestones more so than without the modifying treatment. Ongoing studies are needed for these replacement therapies for SMA therapy management and preservation of quality of life. (Chaytow et al., 2021).

SMPD1 (Sphingomyelin Phosphodiesterase 1, Acid Lysosomal) (e.g., Niemann-Pick Disease, Type A)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose acid sphingomyelinase deficiency (ASMD)/Niemann-Pick disease, which most commonly presents as hepatosplenomegaly detectable by three months of age. Usually, failure to grow is apparent by the second year of life. Psychomotor development progresses no further than the 12-month level, followed by relentless neurologic deterioration. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Wasserstein and Schuchman, 2023).

There is no effective treatment for the neurologic symptoms of Niemann-Pick disease type A at this time (MedlinePlus, 2024g).

SNRPN/UBE3A (Small Nuclear Ribonucleoprotein Polypeptide n and Ubiquitin Protein Ligase E3A) (e.g., Prader-Willi Syndrome and/or Angelman Syndrome)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Prenatal diagnostic testing and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose Angelman syndrome and Prader-Willi syndrome. Angelman syndrome is characterized by severe developmental delay or intellectual disability, severe speech impairment, unique behavior including frequent smiling, laughing, and excitability, gait ataxia and/or limb tremors, seizures, and microcephaly. Delays are first detected at six months of age but the unique clinical symptoms do not become apparent until after age one (Dagli et al., 2025). Prader-Willi syndrome is characterized by poor appetite, severe hypotonia, and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity and developmental delays. It is also used for prenatal testing, preimplantation genetic testing, and carrier testing (Driscoll et al., 2026).

There is no cure for Angelman syndrome. Treatment is to manage symptoms (MedlinePlus, 2025b). There is no cure for Prader-Willi syndrome. Treatment is to manage symptoms (NORD, 2023b).

In a Hayes Molecular Test Assessment on Angelman Syndrome (AS), it is noted that genetic testing for AS involves the *SNRPN/UBE3A* genes. For symptomatic children for diagnosis of Angelman Syndrome (AS), Hayes assigns a rating of B (some proven benefit). For symptomatic adults for diagnosis of AS, Hayes assigns a rating of C (potential but unproven benefit). For prenatal testing for *UBE3A* variants in familial cases of AS, Hayes assigns a rating of D2 (insufficient evidence) [Hayes, Angelman Syndrome (AS), 2008, updated 2012].

In a Hayes Molecular Test Assessment on Prader-Willi Syndrome (PWS), it is noted that genetic testing for PWS is usually focused on the *SNRPN* gene. For the diagnosis of PWS in symptomatic neonates, infants, children, or adults, Hayes assigns a rating of B (some proven benefit. Published evidence indicates that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, there are outstanding questions regarding long-term safety and impact on health outcomes, clinical indications, contraindications, optimal treatment/testing parameters, and/or effects in different patient subpopulations). For prenatal diagnosis of PWS in the presence of risk factors, Hayes assigns a rating of D2 (insufficient evidence) [Hayes, Prader-Willi Syndrome (PWS), 2008, updated 2012].

TERT (Telomerase Reverse Transcriptase)

The *TERT* gene provides instructions for making one component of an enzyme called telomerase. Telomerase maintains structures called telomeres, which are composed of repeated segments of deoxyribonucleic acid (DNA) found at the ends of chromosomes. Telomeres protect chromosomes from abnormally sticking together or breaking down. Telomerase is highly active in cells that divide rapidly, such as cells that line the lungs and gastrointestinal tract, bone marrow, and cells of the developing fetus, and most cancer cells (MedlinePlus, 2020b).

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Hua et al. (2023) performed a systematic review and meta-analysis on the association of human telomerase reverse transcriptase promoter mutation with unfavorable prognosis in glioma. Twenty-eight articles were included in the review. Hazard ratios (HRs) were calculated by the random effect model and the pooled result suggested that *TERT* promoter mutation predicted lower overall survival [HR: 1.53, 95% confidence interval (CI): 1.34-1.75, $p < 0.001$, I^2: 49.9%, $p_{heterogeneity}$: 0.002] and progression-free survival (HR: 1.55, 95% CI: 1.27-1.88, $p < 0.001$, I^2: 0.0%, $p_{heterogeneity}$: 0.473). For subgroup analysis, multiple factors were analyzed including iso-citrate dehydrogenase (*IDH*) genotype, diagnosis, age, pTERT region, to identify the sources of heterogeneity. In *IDH* mutant subgroup, *pTERT* mutation was a beneficial prognostic factor (HR: 0.73, 95% CI: 0.57-0.93, I^2: 22.3%, $p_{heterogeneity}$: 0.277), which contradicts the findings in the pooled analysis. The authors concluded that generally *pTERT* mutations may may result in lower survival time in patients with glioma, but greater survival time when patients with glioma are combined with IDH mutation. Study limitations reported by the authors included its retrospective nature, all articles were in English, and insufficient data on possible interaction among *TERT* and *MGMT*, 1p/19q co-deletion, etc.

Olympios et al. (2021) performed a systematic review providing an overview of the recent advances related to physiopathological mechanisms, diagnosis, and clinical implications of alterations in the promoter region of the telomerase reverse transcriptase (*TERTp*) gene which occurs in 70% to 80% of all glioblastomas. Ninety-two studies were included. The results showed that *TERTp* mutations are the most represented alterations in glioblastoma, suggesting a pivotal role in oncogenesis. The identification of *TERTp* mutations is essential and is currently integrated into glioblastoma diagnostic procedures. However, the prognostic impact remains controversial and a better understanding of the molecular mechanisms are needed for the development of *TERT* targeted therapies, and to date, there are no efficient *TERT* mutation related glioblastoma treatments. The authors note variability in diagnostic sensitivity across methods.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

In the NCCN Clinical Practice Guidelines for Central Nervous System Cancers (NCCN v2.2025), *TERT* (Promoter Mutations) recommendations are as follows:

- Recommendation: *TERT* promoter mutation testing is recommended for the workup of gliomas.
- Description: *TERT* encodes telomerase, which is the enzyme responsible for maintaining telomere length in dividing cells. *TERT* mutations found in gliomas are located in its noncoding promoter region, and cause increased expression of the TERT protein.
- Detection: *TERT* mutation can be detected by sequencing the promoter region.
- Diagnostic value: *TERT* promoter mutations are almost always present in 1p/19q codeleted oligodendroglioma, and are found in most glioblastomas. *TERT* promoter mutation, in combination with IDH mutation and 1p/19q codeletion, is characteristic of oligodendroglioma. Absence of *TERT* promoter mutation, coupled with the presence of mutant IDH, strongly suggests astrocytoma.
- Prognostic value: In the absence of an *IDH* mutation, *TERT* promoter mutation in diffusely infiltrative gliomas is associated with decreased overall survival compared to similar gliomas lacking *TERT* promoter mutation. Combined *TERT* promoter mutation and *IDH* mutations in the absence of 1p/19q codeletion is an uncommon event. However, such tumors have a prognosis as favorable as gliomas with all three molecular alterations.

Thyroid Cancer/Indeterminate Thyroid Nodules

Chowdhury et al. (2025) performed a systematic review and meta-analysis on the impact of molecular testing on surgical decision-making in indeterminate thyroid nodules. Studies on Afirma Gene Expression Classifier (GEC), Afirma Genomic Sequencing Classifier (GSC), ThyroSeq V2, ThyroSeq V3, and ThyGenX/ThyraMIR were included with 31 studies consisting of 4,464 indeterminate thyroid nodules meeting inclusion criteria. The pooled surgical avoidance rates differed across platforms: ThyroSeq V2 [50.3%, 95% confidence interval (CI): 20.8-79.6%], ThyroSeq V3 (62.5%, 95% CI: 54.8-70.0%), Afirma GEC (58.8%, 95% CI: 43.6-73.1%), Afirma GSC (50.6%, 95% CI: 34.3-66.8%), and ThyGenX/ThyraMIR (68.6%, 95% CI: 63.1-73.9%). ThyGenX/ThyraMIR had the highest surgical avoidance rate and lowest heterogeneity (I2 = 51.2%), and ThyroSeq showed improvement from V2 to V3. The authors concluded that molecular testing decreases unnecessary thyroid surgeries, with avoidance rates ranging from 50.3% to 68.6%. The authors report that the study was limited due to the majority of studies being observational and while ThyGenX/ThyraMIR showed the highest avoidance rate, its limited representation warrants cautious interpretation. To optimize clinical application, standardized protocols are needed. Further prospective studies should compare platforms and assess cost-effectiveness and long-term outcomes.

Saleem et al. (2025) conducted a systematic review of the diagnostic role of *BRAF V600E* testing in thyroid nodules with atypia of undetermined significance (AUS). The primary outcomes were improvements in diagnostic accuracy, malignancy risk stratification, and cost effectiveness. Thirteen articles were included in the review. The *BRAF V600E* mutation in thyroid nodules with AUS has significant diagnostic implications for papillary thyroid carcinoma (PTC). This mutation is highly specific for PTC, with some studies showing a specificity of 100% and a positive predictive value of 100% for

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malignancy in such nodules. The presence of the *BRAF V600E* mutation in AUS nodules significantly increases the likelihood of PTC, with malignancy rates as high as 97.5% in mutation-positive nodules. The authors concluded that the incorporation of the *BRAF* V600E mutation into multigene classifiers, such as ThyroSeq v3, further supports cost-effective and personalized management strategies for indeterminate thyroid nodules. By combining molecular and imaging data, *BRAF V600E* testing plays a pivotal role in advancing thyroid cancer diagnosis and treatment. It enhances malignancy risk stratification and facilitates precise clinical decision-making, leading to improved patient outcomes. The authors reported that the study was limited by a small sample size, some of the studies had limited participant numbers, and there were differences in patient populations, institutional practices, and diagnostic protocols.

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 6,490 fine needle aspirations (FNAs) and showed pooled estimates of sensitivity at 0.95 and specificity at 0.35. TSv3 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 reported by the authors 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.

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 reported by the authors included 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.

Lee et al. (2022) 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%), Positive predictive value (PPV) of 63% (51–74%), and negative predictive value (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, reported by the authors, 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. Publication by Livhits et al. (2021) previously discussed in this policy, was included in this systematic review.

DiGennaro et al. (2022) performed a systematic review and meta-analysis to assess the accuracy of commercially available molecular tests for malignancy in indeterminate thyroid nodules and quantify biases and limitations in studies that validate those tests. Forty-nine studies were included. Meta-analysis of Afirma Gene expression classifiers (GEC; n = 38 studies) revealed a sensitivity of 0.92 (confidence interval: 0.90-0.94), specificity of 0.26 (0.20-0.32), negative likelihood ratio (LR-) of 0.32 (0.23-0.44), positive LR+ of 1.24 (1.15-1.35), and area under the curve (AUC) of 0.83 (0.74-

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0.89). Afirma Genomic Sequencing Classifier (GSC; n = 10) had a sensitivity of 0.94 (0.89-0.96), specificity of 0.38 (0.27-0.50), LR- of 0.18 (0.10-0.30), LR+ of 1.52 (1.28-1.87), and AUC of 0.91 (0.62-0.92). ThyroSeq v1 and v2 (n = 10) had a sensitivity of 0.86 (0.82-0.90), specificity of 0.74 (0.59-0.85), LR- of 0.19 (0.13-0.26), LR+ of 3.52 (2.08-5.92), and AUC of 0.86 (0.81-0.90). ThyroSeq v3 (n = 6) had a sensitivity of 0.92 (0.86-0.95), specificity of 0.41 (0.18-0.69), LR- of 0.24 (0.09-0.62), LR+ of 1.67 (1.09-2.98), and AUC of 0.90 (0.63-0.92). Fourteen percent of studies conducted a blinded histopathologic review of excised thyroid nodules, and 8% decided to go to surgery blind to molecular test results. The authors concluded that their findings show a high diagnostic accuracy of molecular tests for thyroid nodule assessment of malignancy risk. Study limitations reported by the authors included that they found high between-study variation, there were limited studies assessing ThyraMIR, only one study had head-to-head comparisons of molecular tests, and only studies that reported diagnostic results were included. Of note, two studies received industry sponsorship but they report a blinded study design and their results do not seem to be different from non-sponsored studies.

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 in the study. The authors report that there was no central blinded histopathologic review and there is potential selection bias, especially among Bethesda V and VI samples.

Labourier and Fahey (2021) performed a systematic review to better understand the potential value of molecular testing to risk-stratify thyroid nodules with malignant cytology (Bethesda VI). Twenty-one studies totaling 2,036 preoperative specimens were included in the review. Pooled rates and I2 heterogeneity tests were calculated using fixed or random effect models and the Cochran Q statistic. Proportions were compared using Pearson chi-square tests. The *BRAF* p.V600E substitution was found in 46% to 90% of cases with a pooled positivity rate of 70% (95% confidence intervals: 64%-76%). None of the studies utilized comprehensive oncogene panels. Retrospective analysis of 531 clinical specimens evaluated with ThyGeNEXT Thyroid Oncogene Panel detected 436 gene alterations. *BRAF* mutation rate was 64% in specimens tested as part of standard clinical care and 75% in specimens from cross-sectional research studies (p = 0.022). Testing for additional actionable gene alterations such as *TERT* promoter mutations or *NTRK* and *RET* gene rearrangements further increased the diagnostic yield to 78%-85% and up to 95% when including the ThyraMIR Thyroid miRNA Classifier. The authors concluded that their findings support the role of molecular cytopathology in surgical and therapeutic decision-making and warrant additional studies. Of note, one of the authors is a consultant for Interspace Biosciences Inc. The study was limited by heterogeneity across studies due to different molecular methods used and regional prevalence differences.

Silaghi et al. (2021) performed a systematic review and meta-analysis to assess the ThyroSeq v3, Afirma GSC, and microRNA panels vs previous molecular tests in the preoperative diagnosis of indeterminate thyroid nodules (ITNs). Using a random-effects bivariate model the authors estimated the summary sensitivity, specificity, positive (PLR) and negative likelihood ratios (NLR), and area under the curve (AUC) for each panel. Forty studies consisting of 7,831 ITNs from 7,565 patients were included in the review. ThyroSeq v3 displayed the best overall performance [AUC 0.95; 95% confidence interval (CI): 0.93-0.97], followed by Afirma GSC (AUC 0.90; 0.87-0.92) and ThyroSeq v2 (AUC 0.88; 0.85-0.90). Regarding "rule-out" abilities, ThyroSeq v3 (NLR 0.02; 95% CI: 0.0-2.69) surpassed Afirma GEC (NLR 0.18; 95% CI: 0.10-0.33). ThyroSeq v2 (PLR 3.5; 95% CI: 2.2-5.5) and ThyroSeq v3 (PLR 2.8; 95% CI: 1.2-6.3) had superior "rule-in" properties compared to Afirma GSC (PLR 1.9; 95% CI: 1.3-2.8). There appeared to be higher quality of evidence for ThyroSeq v3. Both ThyroSeq v2 and Afirma GEC performance have been affected by noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) reclassification. ThyGeNEXT/ThyraMIR and RosettaGX show prominent preliminary results. The authors concluded that the newer tests Afirma GSC and ThyroSeq v3 have been proved to outperform in abilities to rule out malignancy, thus surpassing previous tests no longer available, Afirma GEC and ThyroSeq 2. However, ThyroSeq v2 still ranks as the best rule-in molecular test. Study limitations reported by the authors included that the analyzed diagnostic tests could not be compared and ranked due to the limited number of studies with direct head-to-head comparisons, only considered patients with surgical pathology, final pathology was unavailable, and overall unclear methodological quality of the included studies could have led to inaccurate assumptions.

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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 2025].

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:

- Nondiagnostic cytology: Some studies suggest 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, 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

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molecular profiling involving multiple mutations or other genetic alterations on clinical management of individuals with primary thyroid medullary cancer.
- Postoperative radioiodine (RAI) therapy: Molecular testing to guide postoperative RAI use is not recommended at this time.
- A complete history and physical focusing on the thyroid gland and adjacent cervical lymph nodes be performed when a thyroid nodule is discovered. Malignancy risk factors include a history of radiation therapy, exposure to ionizing radiation, family history of thyroid cancer, rapid nodule growth, hoarseness, cervical lymphadenopathy, vocal cord paralysis, progressive dysphagia, respiratory symptoms, and fixation of the nodule to surrounding tissue.

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 2025 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 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, v1.2025).

X-linked Intellectual Disability (XLID) Panel (e.g., Syndromic and Non-Syndromic XLID)

Molecular pathology tests for diseases or conditions that manifest severe signs or symptoms in newborns and in early childhood or that result in early death are generally not relevant to a Medicare member. Screening services such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition, prenatal diagnostic testing, and carrier screening are not a Medicare benefit.

Genetic testing is used to diagnose X-linked intellectual disabilities such as alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome, fragile X syndrome, and X-linked intellectual disability Siderius type. ATR-X is characterized by distinctive craniofacial features, hypotonia, genital anomalies, growth impairment including microcephaly and short

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statue (usually present at birth) and mild-to-profound developmental delay/intellectual disability. Treatment is for manifestations (Stevenson, 2020). Genetic testing for Fragile X Syndrome (FXS) is used to diagnosis individuals with intellectual disability and/or autism spectrum disorder of unknown cause, and/or other features of FXS. It is also used for carrier screening in women to aid in the decision of having a pregnancy/child with FXS, prenatal diagnosis, and newborn screening. There is no cure for FXS (Hayes, Clinical Utility Evaluation Genetic Testing For Fragile X Syndrome, 2017, updated 2021). The average age of FXS diagnosis is 42 months for girls and 35-37 months for boys (CDC, 2024). X-linked intellectual disability, Siderius type is characterized by mild to moderate intellectual disability in males. Affected boys usually have developmental delays (MedlinePlus, 2015b).

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.

PIK3CA (Phosphatidylinositol-4, 5-Biphosphate 3-Kinase, Catalytic Subunit Alpha)

The U.S. FDA approved Piqray (alpelisib) tablets, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression on or after an endocrine-based regimen.

The FDA also approved the companion diagnostic test, therascreen PIK3CA RGQ PCR Kit, to detect the *PIK3CA* mutation in a tissue and/or a liquid biopsy. Patients who are negative by the therascreen test using the liquid biopsy should undergo tumor biopsy for *PIK3CA* mutation testing.

The FDA granted this application Priority Review designation. The FDA granted approval of Piqray to Novartis. The FDA granted approval of the therascreen PIK3CA RGQ PCR Kit to QIAGEN Manchester, Ltd. Refer to the following website for more information: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer. (Accessed April 22, 2026)

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Policy History/Revision Information

Date	Summary of Changes
06/01/2026	**Coverage Rationale** • Removed content/language addressing Genomic Prostate Score® (GPS) test (previously Oncotype DX® Genomic Prostate Score) **Applicable Codes** ***Diagnosis Codes*** For CPT Code 0047U • Added notation to indicate C71 was "deleted May 13, 2026" **Centers for Medicare and Medicaid Services (CMS) Related Documents** • Updated list of documents available in the *Medicare Coverage Database* to reflect the most current information **Supporting Information** • Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version MMP210.34

Instructions for Use

The Medicare Advantage Policy documents are generally used to support UnitedHealthcare coverage decisions. It is expected providers retain or have access to appropriate documentation when requested to support coverage. This document may be used as a guide to help determine applicable:

- Medical necessity coverage guidelines; including documentation requirements, and/or
- Medicare coding or billing requirements.

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Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The member specific benefit plan document identifies which services are covered, which are excluded, and which are subject to limitations. In the event of a conflict, the member specific benefit plan document supersedes this policy. For more information on a specific member's benefit coverage, call the customer service number on the back of the member ID card or refer to the Administrative Guide.

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been fully established in applicable Medicare guidelines because there is an absence of any applicable Medicare statutes, regulations, NCDs, or LCDs setting forth coverage criteria and/or the applicable NCDs or LCDs include flexibility that explicitly allows for coverage in circumstances beyond the specific indications that are listed in an NCD or LCD. As a result, in these circumstances, UnitedHealthcare applies internal coverage criteria as referenced in this Medical Policy. The internal coverage criteria in this Medical Policy was developed through an evaluation of the current relevant clinical evidence in acceptable clinical literature and/or widely used treatment guidelines. UnitedHealthcare evaluated the evidence to determine whether it was of sufficient quality to support a finding that the items or services discussed in the policy might, under certain circumstances, be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

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For members in UnitedHealthcare Medicare Advantage plans where a delegate manages utilization management and prior authorization requirements, the delegate's requirements need to be followed.

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