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Medical Policy Manual Genetic Testing, Policy No. 64

Evaluating the Utility of Genetic Panels

Effective: January 1, 2019

Next Review: July 2019
Last Review: December 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic panel tests evaluate many genes simultaneously, and have been developed for numerous indications, including hereditary cancer risk assessment, pharmacogenetics, and diagnosis of congenital disorders. Many panel tests include genes that do not have demonstrated clinical utility for their testing.

MEDICAL POLICY CRITERIA

Note: Where applicable, specific policies that have criteria and evidence used to review genetic panel tests are noted (see *Policy Cross-References* in the table below).

When there is not enough research to show that a gene and/or gene variant in a genetic panel test may be used to manage treatment decisions and improve net health outcomes, then the entire genetic panel test is considered **investigational**, including but not limited to the following:

Test Name	Laboratory	Policy Cross-Reference
23-Gene NGS Pyruvate Metabolism and Related Disorders Panel	Case Western Reserve University	None

50 Gene Cancer Panel	Nebraska Medicine Clinical Laboratory	None
Abbreviated Comprehensive Phenotype Panel	X-Gene Diagnostics	GT10
Advanced Pain Care Pharmacogenetic Panel	Advanced Pain Care Laboratory	GT10
Aeon Pain Management PGX Profile	Aeon Clinical Laboratories	GT10
aHUS Panel	Machaon Diagnostics	None
Albinism Panel	Baylor Genetics	None
AmHPR Helicobacter Pylori Antibiotic Resistance NGS Panel	American Molecular Laboratories	None
Amyotrophic Lateral Sclerosis Advanced Evaluation Gene Panel	Athena Diagnostics	None
Anophthalmia/Microphthalmia/Anterior Segment Dysgenesis/ Anomaly: Sequencing Panel	EGL Genetics	None
Arrhythmia and Cardiomyopathy Comprehensive Panel	Invitae	None
Ataxia, Comprehensive Evaluation	Athena Diagnostics	None
Atlas Expanded Carrier Screen	Atlas Genomics	GT81
Audiome Tier 2	Children's Hospital of Philadelphia	GT76
AutismNext	Ambry Genetics™	None
Autism/ID and Autism/ID Xpanded Panel	GeneDx	None
Autoimmune Lymphoproliferative Syndrome Panel	Cincinnati Children's Cytogenetics and Molecular Genetics Laboratories	None
Autosomal Dominant and Recessive Polycystic Kidney Disease Nextgen Sequencing (NGS) Panel	Prevention Genetics	None
Bacterial Typing by Whole Genome Sequencing	Mayo Clinic	None
BRCA Full Risk Panel	GeneID	GT02
BRCAPlus Expanded Panel	Ambry Genetics™	GT02
Breast and Gyn Cancer Panel	Invitae	GT02
BreastNext™	Ambry Genetics™	GT02
BreastTrue™ High Risk Panel	Pathway Genomics	GT02
Breast/Ovarian Cancer Panel	GeneDx	GT02

BROCA Cancer Risk Panel	University of Washington	GT02
Cancer Somatic Mutation Panel	Stanford Hospital and Clinics	None
CancerNext™	Ambry Genetics™	GT02
CancerTYPE ID®	bioTheranostics	GT15
Carbohydrate Metabolism Deficiency NextGen DNA Screening Panel	MNG Laboratories	None
Cardiac Arrhythmia Panel	Center for Precision Diagnostics, University of Washington	None
Cardiac DNA Insight	Pathway Genomics®	None
Cardiac Healthy Weight DNA Insight	Pathway Genomics®	None
CardioIDgenetix	AltheaDx	GT10
Cardiomyopathy Panel	Center for Precision Diagnostics, University of Washington	None
Cardiomyopathy Panel	GeneDx	None
CarrierMap	Cooper Genomics	GT81
Cardiovascular Health Panel	X-Gene Diagnostics	GT10
CGD Universal Test Panel	NxGEN MDx	None
Cholestasis Sequencing Panel	Prevention Genetics	None
Ciliopathies: Sequencing Panel	EGL Genetics	None
Ciliopathy NextGen Sequencing (NGS) Panel	Prevention Genetics	None
ColoNext™	Ambry Genetics™	GT06
Colorectal Cancer Panel	GeneDx	GT06
Colorectal Cancer Panel	Invitae	GT06
ColoSeq™	University of Washington	GT06
Combined Cardiac Panel	GeneDx	None
Common Hereditary Cancer Panel	Invitae	GT02
Complete Hereditary Spastic Paraplegia Evaluation Panel	Athena Diagnostics	None
Complete Lung	Cancer Genetics Inc.	GT56
Comprehensive Arrhythmia/Cardiomyopathy Panel	Center for Precision Diagnostics, University of Washington	None
Comprehensive Cancer Panel	GeneDx	GT02
Comprehensive Cardiomyopathy Multi-Gene Panel	Mayo Clinic / Mayo Medical Laboratories	None
Comprehensive Dystonia NextGen DNA Screening Panel	MNG Laboratories	None

Comprehensive Inherited Retinal Dystrophies Sequencing Panel	Prevention Genetics	None
Comprehensive Molecular Genetic Panel	Molecular Testing Lab	GT10
Comprehensive Muscular Dystrophy/Myopathy Next Generation DNA Sequencing Panel	MNG Laboratories	None
Comprehensive Myopathy Panel	Invitae	None
Comprehensive Neuromuscular Disorders Panel	Invitae	None
Comprehensive Neuromuscular Sequencing Panel	Prevention Genetics	None
Comprehensive Panel	Lab Genomics	GT10
Comprehensive Personalized Medicine Panel	Alpha Genomix Laboratories	GT10
Comprehensive PGX Panel	CQuenta	GT10
Comprehensive Pharmacogenetic Panel	Advanced Genomics	GT10
Comprehensive Pharmacogenetic Panel	Medical DNA Labs	GT10
Comprehensive Pharmacogenetics Panel	Southern Premier Lab	GT10
Comprehensive Phenotype Panel	X-Gene Diagnostics	GT10
Comprehensive PinPointDNA Panel	PinPoint Clinical, GeneAlign	GT10
Comprehensive Spinocerebellar Ataxia Repeat Expansion Panel	MNG Laboratories	None
Congenital Ichthyosis XomeDxSlice Panel	GeneDx	None
Congenital Myopathy and Congenital Muscular Dystrophy Panel	GeneDx	None
Congenital Myopathy NextGen Sequencing (NGS) Panel	Prevention Genetics	None
Congenital Stationary Night Blindness panel	Oregon Health & Science Univ, CEI Molecular Diagnostics Laboratory	None
Cortical Brain Malformation Panel	GeneDx	None
Craniofacial Panel	Children’s Hospital of Philadelphia	None
Cystic Lung Disease Panel	Partners Healthcare	None

DarwinOncoTarget™ and DarwinOncoTreat™	Columbia University Medical Center	None
DBANext	Ambry	None
DetoxiGenomic® Profile Test	Genova®	GT10
Developmental Eye Disease	Molecular Vision Lab (MVL)	None
Dilated Cardiomyopathy (DCM) Left Ventricular Non-Compaction (LVNC)	GeneDx	None
Disorders of Sex Development (DSD) Panel	UCLA Lab	GT76
Distal Arthrogryposis Sequencing Panel	University of Chicago Genetics Services Laboratories	None
Distal Arthrogryposis Sequencing Panel	Prevention Genetics	None
Distal Hereditary Motor Neuropathy NextGen Sequencing (NGS) Panel	Prevention Genetics	None
Early Onset IBD Sequencing and Del/Dup Panels	EGL Genetics	None
Ehlers-Danlos Syndromes Sequencing Panel with CNV Detection	Prevention Genetics	None
EndCLL Assay	MD Anderson	None
Endometrial Cancer Panel	GeneDx	GT02
Epidermolysis Bullosa (EB) XomeDxSlice	GeneDx	None
Episodic Pain Syndrome Sequencing Panel	Prevention Genetics	None
EpiXpanded Panel	GeneDX	GT76
Expanded Neuromuscular Disorders: Sequencing and Deletion/Duplication Panel #MM360	EGL Genetics	None
Expanded Pan-Ethnic Panel	Sema4	GT81
Expanded RASopathy Panel	Partners Healthcare Personalized Medicine	None
Familial Hemiplegic Migraine NextGen Sequencing (NGS) Panel	Prevention Genetics	None
Fetal Akinesia Deformation Sequence/Lethal Multiple Pterygium Syndrome NextGen Sequencing (NGS) Panel	Prevention Genetics	None
Foresight™ Carrier Screen	Counsyl	GT81

FoundationAct™	Foundation Medicine, Inc.	None
FoundationOne™	Foundation Medicine, Inc.	None
FoundationOne CDx™	Foundation Medicine, Inc.	None
FoundationOne Heme™	Foundation Medicine, Inc.	None
Frontier PGx Comprehensive Pharmacogenomics Testing	Frontier Toxicology	GT10
Full Hereditary Cancer Panel	myTest Diagnostics	None
GEM Cancer Panel	Ashion Analytics	None
GenArray™	GenPath Diagnostics	None
GeneAware	Miraca, Baylor Genetics	GT81
Genecept™ Assay for Psychotropic Treatment	Genomind LLC	GT53
GeneDose™	Coriell Life Sciences	GT10
GeneSight ADHD	Assurex Health	GT53
GeneSight Analgesic	Assurex Health	GT10
GeneSight Psychotropic Genetic Testing	Assurex Health	GT53
GeneTrails® AML/MDS Genotyping Panel (Ion Torrent panel)	Oregon Health & Science Univ	None
GeneTrails® NSCLC Genotyping Panel (Ion Torrent panel)	Oregon Health & Science Univ	GT56
GeneTrails® Comprehensive Solid Tumor Panel	Oregon Health & Science Univ	None
GeneTrails® Hematologic Malignancies 76 Gene Panel	Oregon Health & Science Univ	None
GeneVu	GoodStart Genetics	GT81
genTrue	True Health Diagnostics	None
GPS Cancer	NantHealth	GT76
Guardant360 Biopsy-Free Tumor Sequencing	Guardant Health	None
GynPlus	Ambry Genetics™	GT02
HCMNext	Ambry Genetics™	GT72
Healthy Weight DNA Insight	Pathway Genomics®	None
Healthy Woman DNA Insight	Pathway Genomics®	None
Hematologic Malignancy Mutation Panel	Baylor Genetics	None
Hematologic Malignancy Sequencing Panel	Penn Medicine	None

Heme Amplicon Panel	University of Washington Molecular Hematopathology Laboratory	None
Hemiplegic Migraine Profile	Athena Diagnostics	None
Hemophagocytic Lymphohistiocytosis Panel by next generation sequencing (NGS)	Cincinnati Children's Human Genetics- Cytogenetics and Molecular Genetics Laboratories	None
Hereditary Colon Cancer Multi-Gene Panel	Mayo Clinic	GT06
Hereditary Hemolytic Anemia Sequencing, 28 Genes	ARUP	None
Hereditary Renal Tubular Disorder Panel	Athena Diagnostics	None
Hereditary Sensory/Autonomic Neuropathy Panel	Mayo Clinic	None
Hereditary Sensory and Autonomic Neuropathy Panel	Invitae	None
Hereditary Spherocytosis/Elliptocytosis NextGen Sequencing Panel	Prevention Genetics	None
Heterotaxy, Situs Inversus, and Kartagener’s Syndrome Sequencing Panel	Prevention Genetics	None
High-Moderate Risk Panel	GeneDx	GT02
High Risk Hereditary Breast Cancer Panel	Miraca, Baylor Genetics	GT02
Horizon™	Natera, Inc.	GT81
Horizon™ 27	Natera, Inc.	GT81
Horizon™ 106	Natera, Inc.	GT81
Horizon™ 274	Natera, Inc.	GT81
Hyper-IgE Syndromes Panel	GeneDx	None
Hypertrophic Cardiomyopathy (HCM) Panel	GeneDx	GT72
Hypertrophic Cardiomyopathy panel	OHSU, Knight Diagnostic Lab	GT72
Hypokalemic and Hyperkalemic Periodic Paralysis Disorders NGS Sequencing Panel	MNG Laboratories	None
ICG100	Intermountain Cancer Genomics	GT02
iGene Cancer Panel	ApolloGen	GT06

Immunoplex Panel	University of Washington Medical Center, Seattle Children's Hospital	None
Inherigen Panel	GenPath Diagnostics	GT81
Inheritest Carrier Screen	LabCorp	GT81
Inheritest Society-guided Screening Panel	LabCorp	GT81
Intellectual Disability (IDNEXT) Panel	Ambry Genetics™	None
Invitae Breast Cancer Panel	Invitae	GT02
Leukodystrophy Xpanded Panel	GeneDx	None
Leukoencephalopathy NGS Panel	Fulgent	None
Lipodystrophy NGS Panel	Fulgent	None
Lung Cancer Mutation Panel	Quest Diagnostics	GT56
LUNGSEQ® Panel	med fusion	GT56
Lymphoid Molecular Profile	Genoptix	None
MarrowSeq Panel	University of Washington	None
Medical Management Panel	Vantari	GT10
Megalencephaly Panel	Seattle Children's Hospital	None
Mental Health DNA Insight™	Pathway Genomics®	GT53
Metabolic Myopathy Panel	GeneDx	None
Metabolic Myopathy/Rhabdomyolysis Panel	Fairview Diagnostic Laboratories	None
Microcephaly Sequencing Panel	University of Chicago Genetics Services Laboratory	None
Microphthalmia, Anophthalmia and Anterior Segment Dysgenesis Panel	Blueprint Genetics	None
MitoMED-Autism™	MEDomics™	None
Molecular Intelligence (MI) Profile™	Caris Life Sciences™	None
Molecular Intelligence (MI) Profile X™	Caris Life Sciences™	None
Movement Disorder Panel	Center for Precision Diagnostics, University of Washington	None
MSK-Impact	Memorial Sloan Kettering	None
Multi-Cancer Panel	Invitae	GT02
Multianalyte Assays with Algorithmic Analyses (MAAA) for HeproDX™	GoPath Laboratories	None
Multiple Epiphyseal Dysplasia Panel	Connective Tissue Gene Tests (CTGT)	None
MyAML	Invivoscribe	None

myChoice® HRD	Myriad	None
Myeloid Malignancies Mutation Panel	ARUP Laboratories	None
Myeloid Molecular Profile	Genoptix®	None
Myeloid MPN/MDS/CMML Comprehensive Panel	Providence Regional Molecular Diagnostics Laboratory	None
Myopathy, Rhabdomyolysis Panel by Massively Parallel Sequencing (BCM-MitomeNGS)	Baylor Genetics	None
Myotonic Syndrome Advanced Evaluation Panel	Athena Diagnostics	None
myRisk™ Hereditary Cancer Panel (Update myRisk™)	Myriad	GT02
MyVantage Hereditary Comprehensive Cancer Panel	Quest Diagnostics	GT02
NeoTYPE™ CLL Prognostic Profile	NeoGenomics Laboratories	None
NeoTYPE™ Lung Tumor Profile Panel	NeoGenomics Laboratories	GT56
NeoTYPE™ Myeloid Disorders Profile	NeoGenomics Laboratories	N/A
Nephronophthisis Panel	Invitae	None
Nervous System/Brain Cancer Panel	Invitae	None
Neurodevelopment Expanded Panel	Ambry Genetics™	None
NeuroIDgenetix	AltheaDX	GT53
Neuromuscular Disorder Panel	Center for Precision Diagnostics, University of Washington	None
Neuro-ophthalmology Panel	Blueprint Genetics	None
Neurotransmitter Metabolism Deficiency NextGen DNA Screening Panel	MNG Laboratories	GT65
Newborn Gene ID	GeneID	GT81
Newborn Panel	Baby Genes™	None
NexCourse® NSCLC	Genoptix	GT56
NexCourse® Solid Tumor Assay Panel	Genoptix	None
Next Generation Sequencing Panel for ASXL1, RECQL4, RNU4ATAC, SOX2	Sistemas Genomicos	None
Next Generation Sequencing Panel for Hereditary Myeloid Malignancy and Inherited Bone Marrow Failure	University of Chicago	None

Next Gen RASopathy Panel	University of Alabama	None
NextStepDx PLUS®	Lineagen	None
NF2, SMARCB1, and LZTR1, Neurofibromatosis Type 2, Schwannomatosis Panel	University of Alabama	None
NGS RASopathy Panel	Greenwood Genetic Center	None
NGS Retinal Dystrophy SmartPanel	Molecular Vision Laboratory	None
Noonan and RASopathies NGS Panel	Fulgent	None
Noonan RASopathies Panel	GeneDx	None
Noonan Spectrum Chip	Seattle Children's Hospital	None
Noonan Spectrum Disorders Panel	ARUP	None
Noonan Spectrum Disorders/RASopathies NextGen Sequencing Panel	Prevention Genetics	None
Noonan Syndrome Panel	GeneDx	None
Noonan Syndrome Panel	Oregon Health & Science Univ, Knight Diagnostic Laboratories	None
NxGen Super Panel	NxGen MDx	GT81
OI and Genetic Bone Disorders Panel	Center for Precision Diagnostics, University of Washington	None
OmniSeq® Immune Report Card	OmniSeq®	None
Osteogenesis Imperfecta NGS Panel-Recessive	Connective Tissue Gene Tests (CTGT)	None
Osteogenesis Imperfecta Panel	University of Nebraska Medical Center	None
OvaNext™	Ambry Genetics™	GT02
Pain Management Panel	X-Gene Diagnostics	GT10
Pan Cardiomyopathy Panel	Seattle Children's Hospital	None
PancNext™	Ambry Genetics™	GT02, GT06
Pancreatic Cancer Panel	GeneDx	GT02, GT06
Pediatric Solid Tumors Panel	Invitae	None
Periodic Fever Syndrome Chip / Panel	Seattle Children's Hospital / GeneDx	None
Periodic Fever Syndromes Panel	ARUP Laboratories	None
Periodic Paralysis Advanced Sequencing Evaluation Panel	Athena Diagnostics	None
Personalized Cancer Mutation Panel	University of Pittsburgh Medical Center	None

Personalized Medicine Panel Comprehensive Panel	ISPM Labs/Capstone Genetics	GT10
Personalized Medication Panel	UpFront Laboratories	GT10
PGxl Multi-Drug Sensitivity Panel	PGXL Laboratories	GT10
PGxOne Plus	Admera Health	GT10
Pharmacogenetic Panel	X-Gene Diagnostics	GT10
Pharmacogenetic Panel	Vantari Genetics	GT10
Pharmacogenetic Testing (PGT)	Millennium Laboratories	GT10
Pharmacogenetics Panel	Gulfstream Diagnostics	GT10
Pharmacogenetics Panel	Predictive Medical Solutions	GT10
Pharmacogenetics PGx	Lineagen	GT10
Pigmentation Panel	Molecular Vision Lab (MVL)	None
Polycystic Kidney Disease Panel	Blueprint Genetics	None
Prelude™ and Informed Pregnancy Screen	Counsyl	GT44
Prenatal Skeletal Dysplasia Panel	GeneDx	None
Preparent™ Carrier Screening Global Panel	Progenity®	GT81
Preparent™ Carrier Screening Standard Panel	Progenity®	GT81
Preventest	GeneID	None
Primary Antibody Deficiency Panel	Primary Children's Health Laboratory, Intermountain Laboratory Services, ARUP	None
Primary Ciliary Dyskinesia Panel	Invitae	None
Primary Immunodeficiency Panel	Invitae	None
Proportionate Short Stature/Small for Gestational Age Sequencing Panel	EGL Genetics	None
ProstateNext	Ambry Genetics™	GT17
Psychiatric Dosing Panel	X-Gene Diagnostics	GT10
Pulmonary Arterial Hypertension Panel	GeneDx	None
Qherit Expanded Carrier Screen	Quest Diagnostics	GT81
Rapid Heme Panel	Dana-Farber Cancer Institute	None
Reliant™ Comprehensive and Expanded Cancer Screening Panels	Counsyl	GT02
RenalNext™	Ambry Genetics™	None
Retinal Dystrophy Panel	Blueprint Genetics	None

Retinal Dystrophy Panel	Center for Precision Diagnostics, University of Washington	None
Retinal Dystrophy Panel	Oregon Health & Science Univ, CEI Molecular Diagnostics Laboratory	None
Retinal Dystrophy Panel	UCLA Laboratories	None
Rett/Angelman Syndrome 2nd Tier Sequencing Panel	Greenwood Genetic Center	None
Rett/Angelman Syndrome Panel	GeneDx	None
Riscover Comprehensive Panel	Progenity	GT02
Rubinstein-Taybi Syndrome Panel	Oregon Health & Science Univ, CEI Molecular Diagnostics Laboratory	None
RxMatch Antidepressant Panel	Intermountain Healthcare	GT53
Severe Congenital Neutropenia Panel	Prevention Genetics	None
Severe Congenital Neutropenia Panel	Washington University	None
Skeletal Dysplasias NGS Panel	Fulgent	None
Solid SNAPSHOT Assay, SNaPshot-NGS-V1 Assay	Massachusetts General Hospital (MGH)	None
Solid Tumor Actionable Mutation Panel (STAMP)	Stanford Hospital and Clinics	None
Solid Tumor Mutation Genomic Assay	MD Anderson	None
Solid Tumor Mutation Panel Next Generation Sequencing	ARUP Laboratories	None
Solid Tumor Targeted Mutation and Fusion NGS Panel	Providence Regional Molecular Diagnostics Laboratory	None
Somatic Overgrowth Panel	Washington University	None
Spastic Paraplegia Next Generation Sequencing Panel	MNG Laboratories	None
Spinocerebellar Ataxia Panel	University of Washington	None
Spinocerebellar Ataxia Repeat Expansion Panel	MNG Laboratories	None
Spondylo-Epi-Metaphyseal Dysplasias	Connective Tissue Gene Tests (CTGT)	None
Stargardt Disease and Macular Dystrophies Sequencing Panel with CNV Detection	Prevention Genetics	None
Stargardt/Macular Dystrophy Panel	Oregon Health & Science Univ, CEI Molecular Diagnostics Laboratory	None

Stickler Syndrome NGS Panel	Connective Tissue Gene Tests (CTGT)	None
Stickler Syndrome Sequencing Panel	Prevention Genetics	None
SureGene Test for Antipsychotic and Antidepressant Response® Gene Panel (STAR2)	PGXL Laboratories	GT53
SymGene68™ Next Generation Sequencing Cancer Panel	CellNetix®	None
Syndromic Autism Panel	Greenwood Genetic Center	None
Syndromic Macrocephaly Overgrowth Panel	GeneDx	None
Targeted Cancer Gene Panel, Blood and Bone Marrow	Tricore Reference Laboratories	None
Tempus xO	Tempus	None
Thrombocytopenia NextGen Sequencing (NGS) Panel	Prevention Genetics Laboratory	None
Thyroid Cancer Panel	Invitae	None
TumorNext-HRD	Ambry Genetics	GT02
Universal Carrier Panel	Insight Medical Genetics	GT81
UW-OncoPlex-Cancer Gene Panel	University of Washington	GT10
VistaSeq Hereditary Cancer Panel	LabCorp	GT02
Vitreoretinopathy NGS Panel	Connective Tissue Gene Tests (CTGT)	None
Vitreoretinopathy Panel	Molecular Vision Laboratory	None
Waardenburg Sequencing Panel Test	Prevention Genetics	None
Women's Hereditary Cancer Assessment Panel	Origen Laboratories	GT02
X-linked Intellectual Disability	EGL Genetics	None
X-linked Intellectual Disability	Greenwood Genetic Center	None
XomeDx and XomeDxPlus (Whole Exome Sequencing [WES] + mtDNA Sequencing and Deletion Testing)	GeneDx	GT76
YouScript® Personalized Prescribing System	Genelex Corporation	GT10

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test, if available:
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided

CROSS REFERENCES

1. Medical Policy Manual: Genetic Testing Section Table of Contents

BACKGROUND

New genetic technology, such as next generation sequencing and chromosomal microarray, has led to the ability to examine many genes simultaneously.[1] This in turn has resulted in a proliferation of genetic panels. The intended use for these panels is variable. For example, for the diagnosis of hereditary disorders, a clinical diagnosis may already be established, and genetic testing is performed to determine whether there is a hereditary condition, and/or to determine the specific variant that is present. In other cases, there is a clinical syndrome (phenotype) with a broad number of potential diagnoses and genetic testing is used to make a specific diagnosis. For cancer panels, there are also different intended uses. Some panels may be intended to determine whether a known cancer is part of a hereditary cancer syndrome. Other panels may include somatic variants in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select best treatment.

Panels using next generation technology are currently available in the areas of cancer, cardiovascular disease, neurologic disease, psychiatric conditions, and for reproductive testing.[2-4] These panels are intuitively attractive to use in clinical care because they can screen for numerous variants within a single or multiple genes quickly, and may lead to greater efficiency in the work-up of genetic disorders. It is also possible that these “bundled” gene tests can be performed more cost effectively than direct sequencing, although this may not be true in all cases. However, panel testing also provides information on genetic variants that are of unclear clinical significance or which would not lead to changes in patient management.

One potential challenge of genetic panel testing is the availability of a large amount of ancillary genetic information, much of which has uncertain clinical consequences and management strategies. Identification of variants for which the clinical management is uncertain may lead to unnecessary follow-up testing and procedures, all of which have their own inherent risks.

Additionally, the design and composition of genetic panel tests have not been standardized. Composition of the panels is variable, and different commercial products for the same condition may test different sets of genes. The make-up of the panel is determined by the specific lab that has developed the test. In addition, the composition of any individual panel is likely to change over time, as new variants are discovered and added to the existing panels.

GENETIC COUNSELING

Due to the complexity of interpreting genetic test results, patients should receive pre- and post-test genetic counseling from a qualified professional when testing is performed to diagnose or predict susceptibility for inherited diseases. The benefits and risks of genetic testing should be fully disclosed to individuals prior to testing, and counseling concerning the test results should be provided.

REGULATORY STATUS

The majority of genetic panel tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Note: Separate Medical Policies may apply to some specific genetic tests and panels not addressed in the criteria below. See the Genetic Testing Section of the Medical Policy Manual Table of Contents for additional genetic testing policies.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[5] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Genetic cancer susceptibility panels utilizing next generation sequencing are best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. The clinical utility of genetic panel testing refers to the likelihood that the panel will result in improved health outcomes.
For positive test results, the health benefits are related to interventions that reduce the risk of developing the disease, earlier or more intensive screening to detect and treat early disease symptoms, or interventions to improve quality of life.

- Alternatively, negative test results may prevent unnecessary intensive monitoring, invasive tests or procedures, or ineffective therapies.

For genetic panels that test for a broad number of variants, some components of the panel may be indicated based on the patient's clinical presentation and/or family history, while other components may not be indicated. The impact of test results related to non-indicated variants must be well-defined and take into account the possibility that the information may cause harm by leading to additional unnecessary interventions that would not otherwise be considered based on the patient's clinical presentation and/or family history.

Therefore, the focus of the following review is on evidence from well-designed controlled trials or large cohort studies that demonstrate the clinical utility of each panel test, i.e., the ability of results from the comprehensive genetic panels to:

1. Guide decisions in the clinical setting related to either treatment, management, or prevention; and

2. Improve health outcomes as a result of those decisions.

A limited body of literature exists on the potential clinical utility of available next generation sequencing (NGS) panels.

NONRANDOMIZED STUDIES

Desmond (2015) reported on an observational study assessing whether testing of hereditary cancer gene variants other than BRCA1/2 altered clinical management in a prospectively collected cohort of 1046 patients from three institutions who were negative for BRCA1/2.[6] Patients were tested with the 29-gene Hereditary Cancer Syndromes test (Invitae) or the 25-gene MyRisk test (Myriad Genetics). The investigators evaluated the likelihood of a post-test change in management considering gene-specific consensus management guidelines, gene-associated cancer risks, and personal and family history. Of this cohort, 40 patients (3.8%; 95% CI, 2.8%-5.2%) harbored deleterious variants, most commonly in moderate-risk breast and ovarian cancer genes and Lynch syndrome genes. Among 63 variant-positive patients, 20 were found to harbor variants in high-risk genes associated with detailed NCCN management guidelines which would change the pretest recommendations for screening and/or preventive surgery. However, the most common variants found were those in genes associated with low or moderately increased breast cancer risk (40 of 63 patients), where a change in management would be recommended for these patients in a minority of cases (10 of 40), involving either increased screening or preventive surgery. Since this study only reported anticipated changes in management, these variant-positive patients were not provided with these post-test recommendations. The investigators conceded that the potential clinical effect reported in this cohort is likely to apply only to an appropriately ascertained cohort, thereby limiting the generalizability of the results.

Kurian (2014) evaluated the information from a NGS panel of 42 cancer associated genes in women who had been previously referred for clinical BRCA1/2 testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012.[7] The authors aimed to assess concordance of the results of the panel with prior clinical sequencing, the prevalence of potentially clinically actionable results, and the downstream effects on cancer screening and risk reduction. Potentially actionable results were defined as pathogenic variants that cause recognized hereditary caner syndromes or have a published association with a two-fold or greater relative risk of breast cancer compared to average risk women. In total, 198 women participated in the study. Of these, 174 had breast cancer and 57 carried 59 germline BRCA variants. Testing with the panel confirmed 57 of 59 of the pathogenic BRCA variants; of the two others, one was detected but reclassified as a VUS and the other was a large insertion that would not be picked up by NGS panel testing. Of the women who tested negative for *BRCA* variants (n=141), 16 had pathogenic variants in other genes (11.4%). The affected genes were *ATM* (n=2), *BLM* (n=1), *CDH1* (n=1), *CDKN2A* (n=1), *MLH1* (n=1), *MUTYH* (n=5), *NBN* (n=2), *PRSS1* (n=1), and *SLX4* (n=2). Eleven of these variants had been previously reported in the literature and five were novel. 80% of the women with pathogenic variants in the non BRCA1/2 genes had a personal history of breast cancer. Overall, a total of 428 VUS were identified in 39 genes, among 175 patients.

Six women with variants in *ATM*, *BLM*, *CDH1*, *NBN* and *SLX4* were advised to consider annual breast MRIs because of an estimated doubling of breast cancer risk, and six with variants in CDH1, MLH1 and MUTYH were advised to consider frequent colonoscopy and/or endoscopic gastroduodenoscopy (once every 1-2 years) due to estimated increases in

gastrointestinal cancer risk. One patient with a MLH1 variant consistent with Lynch syndrome underwent risk-reducing salpingo-oophorectomy and early colonoscopy which identified a tubular adenoma that was excised (she had previously undergone hysterectomy for endometrial carcinoma).

Mauer (2014) reported a single academic center's genetics program's experience with NGS panels for cancer susceptibility.[8] The authors conducted a retrospective review of the outcomes and clinical indications for the ordering of Ambry's next generation sequencing panels (BreastNext, OvaNext, ColoNext, and CancerNext) for patients seen for cancer genetics counseling from April 2012 to January 2013. Of 1,521 new patients seen for cancer genetics counseling, 1,233 (81.1%) had genetic testing. Sixty of these patients (4.9% of the total) had a next generation sequencing panel ordered, 54 of which were ordered as a second-tier test after single-gene testing was performed. Ten tests were cancelled due to out-of-pocket costs or previously identified variants. Of the 50 tests obtained, five were found to have a deleterious result (10%; compared with 131 [10.6%] of the 1,233 single-gene tests ordered at the same center during the study time frame). The authors report that of the 50 completed tests, 30 (60%) did not affect management decisions, 15 (30%) introduced uncertainty regarding the patients' cancer risks, and five (10%) directly influenced management decisions.

A number of other studies have evaluated the impact of panel testing on clinical management of a variety of conditions, including prostate cancer,[9] breast and/or ovarian cancer,[10-13] and non-specific hereditary cancers,[14] as well as genetic profiling of tumor tissue to guide cancer treatment.[15,16] While some of these studies noted specific changes in medical management resulting from the testing, none of them evaluated whether these changes led to improvements in patient outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

A 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addresses the application of next-generation sequencing.[17] According to this statement:

> ASCO recognizes that concurrent multigene testing (i.e., panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUS) in a substantial proportion of patient cases. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history.
>
> This type of testing may be particularly useful in situations where there are multiple high-penetrance genes associated with a specific cancer, the prevalence of actionable

mutations in one of several genes is high, and it is difficult to predict which gene may be mutated on the basis of phenotype or family history.

So far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing- this heterogeneity presents a number of challenges. All panels include high-penetrance genes that are known to cause autosomal-dominant predisposition syndromes, but often include genes that are not necessarily linked to the disease for which the testing is being offered. There is uncertainty regarding the appropriate risk estimates and management strategies for families with unexpected mutations in high-penetrance genes when there is no evidence of the associated syndrome. Clinical utility remains the fundamental issue with respect to testing for mutations in moderate penetrance genes. It is not yet clear whether clinical management should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers. Early experience with panel-based testing indicates that a substantial proportion of tests identify a VUS in 1 or more genes, and VUSs are more common in broad-panel testing both because of the number of genes tested and because of the limited understanding of the range of normal variation in some of these genes.

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v1.2019)[18] state the following regarding multi-gene testing:

- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene test are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. Therefore, it may be difficult to use a known pathogenic/likely pathogenic variant alone to assign risk for relatives.
- In many cases, the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
- Pathogenic/likely pathogenic variants in many breast cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions.

- There is an increased likelihood of finding variants of unknown significance when testing for pathogenic/likely pathogenic variants in multiple genes.
- It is for these and other reasons that multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

SUMMARY

Genetic test panels are available for many clinical conditions. Genetic test panels may be focused to a few genes or include a large number of genes. The advantage of genetic test panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of the genetic workup. A disadvantage of genetic test panels is that the results may provide information on genetic variants that are of unclear clinical significance or which would not lead to changes in patient management. These results may potentially cause harm by leading to additional unnecessary interventions and anxiety that would not otherwise be considered based on the patient's clinical presentation and/or family history. There is not enough research to show that the genetic panels listed in the policy criteria can lead to better health outcomes for patients. When there is not enough research to show that all genes and/or gene variants in a genetic test panel may be useful for guiding patient management to improve health outcomes, the entire genetic test panel is considered investigational.

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CODES

NOTE: There are few specific codes for molecular pathology testing by panels. If the specific analyte is listed with a CPT code, the specific CPT code should be reported. If the specific analyte is not listed with a specific CPT code, unlisted code 81479 should be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

Codes	Number	Description
CPT	0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier
	0007M	Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index

Codes	Number	Description
	0008U	Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, pbp1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue or fecal sample, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin
	0010U	Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate
	0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents
	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
	0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
	0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
	0057U	Oncology (solid organ neoplasia), mRNA, gene expression profiling by massively parallel sequencing for analysis of 51 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a normalized percentile rank
	81105	Human platelet antigen 1 genotyping (HPA-1), ITGB3 (integrin, BETA 3 [platelet glycoprotein iiia], antigen CD61 [gpiiia]) (eg, neonatal alloimmune thrombocytopenia [nait], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)
	81106	Human platelet antigen 2 genotyping (hpa-2), GP1BA (glycoprotein ib [platelet], alpha polypeptide [GPIBA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, hpa-2a/b (T145M)
	81107	Human platelet antigen 3 genotyping (HPA-3), ITGA2B (integrin, ALPHA 2b [platelet glycoprotein iib of iib/iiia complex], antigen CD41 [GPIIB]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S)
	81108	Human platelet antigen 4 genotyping (HPA-4), ITGB3 (integrin, BETA 3 [platelet glycoprotein IIIA], antigen CD61 [GPIIIA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)
	81109	Human platelet antigen 5 genotyping (HPA-5), ITGA2 (integrin, ALPHA 2 [CD49B, ALPHA 2 subunit of VLA-2 receptor] [GPIA]) (eg, neonatal alloimmune

Codes	Number	Description
		thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E))
	81110	Human platelet antigen 6 genotyping (HPA-6W), ITGB3 (integrin, BETA 3 [platelet glycoprotein IIIA, antigen CD61] [GPIIIA]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)
	81111	Human platelet antigen 9 genotyping (HPA-9W), ITGA2B (integrin, ALPHA 2B [platelet glycoprotein IIB of IIB/IIIA complex, antigen CD41] [GPIIB]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M)
	81112	Human platelet antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [Nait], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	;full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81165	;full sequence analysis
	81166	;full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81167	;full duplication/deletion analysis (ie, detection of large gene rearrangements)
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
	81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
	81176	;targeted sequence analysis (eg, EXON 12)
	81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants
	81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	;known familial variants
	81203	;duplication/deletion variants
	81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
	81206	*BCR/ABL1 (t(9;22))* (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
	81207	;minor breakpoint, qualitative or quantitative
	81208	;other breakpoint, qualitative or quantitative
	81209	*BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
	~~81211~~	~~BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion~~

Codes	Number	Description
		~~variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)~~ (Deleted 1/1/2019)
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	~~81213~~	~~;uncommon duplication/deletion variants~~ (Deleted 1/1/2019)
	~~81214~~	~~*BRCA1 (breast cancer 1)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)~~ (Deleted 1/1/2019)
	81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	*BRCA2* (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	;known familial variant
	81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
	81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
	81220	*CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81221	;known familial variant
	81222	;duplication/deletion variants
	81223	;full gene sequence
	81224	;intron 8 poly-T analysis (eg, male infertility)
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
	81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants
	81229	Interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
	81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81240	*F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	*F5 (coagulation factor V)* (eg, hereditary hypercoagulability) gene analysis, Leiden variant
	81242	*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
	81243	*FMR1 (Fragile X mental retardation 1)* (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	;characterization of alleles (eg, expanded size and promoter methylation status)
	81245	*FLT3 (fms-related tyrosine kinase 3)* (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
	81246	;tyrosine kinase domain (TKD) variants (eg, D835, I836)

Codes	Number	Description
	81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, a, a-)
	81248	;known familial variant(s)
	81249	;full gene sequence
	81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
	81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
	81252	*GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)* (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	;known familial variant
	81254	*GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)* (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
	81256	*HFE (hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
	81257	*HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
	81261	*IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
	81262	;direct probe methodology (eg, Southern blot)
	81263	*IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
	81264	*IGK@ (Immunoglobulin kappa light chain locus)* (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
	81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
	81266	;each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
	81267	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
	81268	;with cell selection (eg, CD3, CD33), each cell type
	81270	*JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

Codes	Number	Description
	81272	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)*
	81273	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)*
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81287	*MGMT (O-6-methylguanine-DNA methyltransferase)* (eg, glioblastoma multiforme), promoter methylation analysis
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
	81291	*MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	;known familial variants
	81294	;duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	;known familial variants
	81297	;duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	;known familial variants
	81300	;duplication/deletion variants
	81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
	81303	;known familial variants
	81304	;duplication/deletion variants
	81310	*NPM1 (nucleophosmin)* (eg, acute myeloid leukemia) gene analysis, exon 12 variants
	81311	*NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)*
	81314	*PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)*
	81315	*PML/RARalpha, (t(15;17))*, *(promyelocytic leukemia/retinoic acid receptor alpha)* (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
	81316	;single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

Codes	Number	Description
	81318	;known familial variants
	81319	;duplication/deletion variants
	81321	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, *PTEN* hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	;known familial variants
	81323	;duplication/deletion variants
	81324	*PMP22 (peripheral myelin protein 22)* (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	;full sequence analysis
	81326	;known familial variants
	81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
	81331	*SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
	81332	*SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1)* (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
	81340	*TRB@ (T cell antigen receptor, beta)* (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
	81341	;using direct probe methodology (eg, Southern blot)
	81342	*TRG@ (T cell antigen receptor, gamma)* (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
	81350	*UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1)* (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
	81355	*VKORC1 (vitamin K epoxide reductase complex, subunit 1)* (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
	81400	Molecular pathology procedure, Level 1
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81408	Molecular pathology procedure, Level 9
	81412	Ashkenazi Jewish associated disorders (eg, 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
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A

Codes	Number	Description
	81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
	81434	Hereditary retinal disorders (eg, 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
	81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
	81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
	81440	Nuclear encoded mitochondrial genes (eg, 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
	81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
	81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, 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 (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater

Codes	Number	Description
		genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81460	Whole mitochondrial genome (eg, 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
	81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromicXLID); genomic sequence analysis panel, must include sequencing of at least60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1,IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3,and SLC16A2
	81471	;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
	81479	Unlisted molecular pathology procedure
	81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score
	81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
	81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score
	81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
	81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score
	81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
	81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
	81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score
	81599	Unlisted multianalyte assay with algorithmic analysis
	84311	Spectrophotometry, analyte not elsewhere specified
	88299	Unlisted cytogenetic study
	88380	Microdissection (ie, sample preparation of microscopically identified target); laser capture
HCPCS	S3854	Gene expression profiling panel for use in the management of breast cancer treatment

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