MEDICAL POLICY	Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business Except Medicare)
Effective Date: 1/1/2023  1/1/2023 Medical Officer Date	Medical Policy Number: 213 Medical Policy Committee Approved Date: 4/18; 8/18; 12/18; 4/19, 5/19; 9/19; 11/19; 07/2020; 9/2020; 1/2021; 3/2021; 5/2021; 6/2021; 9/2021; 11/2021; 3/2022; 6/2022; 8/2022; 9/2022; 11/2022

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business except Medicare (*unless otherwise directed by a Medicare medical policy. Note that investigational services are considered "**not medically necessary**" for Medicare members.)*

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request:

- Name of the panel test or the name of the gene(s) and/or components of the test
- Name of laboratory that performed or is performing the test
- Clinical notes should include the following:
  - Reason for performing test, including the suspected condition
  - Signs/symptoms/test results related to rationale for genetic testing
  - Family history, if applicable
  - How test results will impact clinical decision making
- CPT codes billed

POLICY CRITERIA

Notes:

- This policy does not address the following:
  - Whole exome or genome sequencing.
  - Pharmacogenetic panel tests (gene testing to determine the appropriate course of therapy).
  - Genetic tests related to reproductive planning or prenatal testing.
- The list of investigational panels addressed in this policy is not all-inclusive.
- Due to the rapidly changing field of genetic testing; panel names, genes included within the panel, and coding may change subsequent to the last update of this policy.
- Other Medical Policies may apply:
  - Please see Cross References section below for medical policies which may apply to specific hereditary or oncologic conditions.
  - If available, condition- or test-specific policies should be used to review singe gene or genetic panel tests. For example, genetic panel testing for hereditary colorectal cancer is addressed in the *Genetic Testing: Inherited Susceptibility to Colorectal Cancer* medical policies.
  - Please refer to the PHP *Genetic and Molecular Testing (All Lines of Business Except Medicare)* medical policy for genetic panel testing medical necessity criteria not addressed in more specific medical policies.

Non-Coverage Criteria

I. Genetic panel testing is considered **investigational and is not covered** when there is insufficient evidence that the panel has proven clinical utility. (Please see Policy Guidelines below for definition of panel testing.) To establish clinical utility, **both** of the following criteria (A. and B) must be met for each gene and/or component of the panel test:

   A. Testing allows for a definitive diagnosis or risk classification and **either** of the following are met:
      1. Other clinical and/or laboratory tests were inconclusive; **or**
      2. Testing avoids a more invasive diagnostic testing (i.e., muscle biopsy); **and**
   B. Test results will guide decisions in clinical management (predictive, diagnostic, prognostic, or therapeutic).

Genetic panel tests for which clinical utility has not been established are considered **investigational and not covered**, including but not limited to the following tests:

Proprietary Test Name	Laboratory	Policy Cross-Reference
AlloSure Kidney	CareDx	None
Augusta Optical Genome Mapping	Bionano Genomics	None
BreastNext®	Ambry Genetics/Sema4	Genetic Testing: Hereditary Breast and Ovarian Cancer (All Lines of Business Except Medicare)
Bridge Urinary Tract Infection Detection and Resistance Test	Bridge Diagnostics	None
CancerTYPE ID®	Biotheranostics	None
Cardiomyopathy Panel	GeneDx	None
Clarava	Verici Dx	None
CNT (CEP72I, NUDT15, and TPMT) panel	RPRD Diagnostics	Inflammatory Bowel Disease: Serologic Testing and Therapeutic Monitoring (All Lines of Business Except Medicare)
Colvera	Clinical Genomics	None
Comprehensive Hearing Loss Panel	OHSU	None
Comprehensive Personalized Medicine Panel	Alpha Genomix	• Genetic Testing: MTHFR (All Lines of Business Except Medicare) • Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Copper Metabolism Disorders Panel	Invitae	None
CxBladder Detect	Pacific Edge, Ltd.	None
CxBladder Monitor	Pacific Edge, Ltd.	None
CxBladder Triage	Pacific Edge, Ltd.	None
DecisionDx DiffDx- Melanoma	Castle Biosciences	Genetic Testing: Gene Expression Profile Testing for Melanoma (All Lines of Business Except Medicare)
DecisionDx-SCC	Castel Biosciences	None
DCISionRcT	PreludeDx	Genetic Testing: Gene Expression Profile Testing for Breast Cancer (All Lines of Business Except Medicare)
DCMNext	Ambry Genetics	None
DetermaRx	Oncocyte Corporation	None
Developmental Eye Disease Panel	Molecular Vision Laboratory	None

EpiSign Complete	Greenwood Genetic Center	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
EpiSwitch® CiRT (Checkpoint-inhibitor Response Test)	Next Bio-Research Services, LLC, Oxford BioDynamics, PLC	
GenoMind Professional PGx Express (includes CORE Anxiety & Depression Report [15 Genes] and/or FULL Mental Health Report [24 Genes])	Genomind	None
GeneSight® Psychotropic	Assurex Health, Inc.	Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
GeneTrails® Hematologic Malignancies 76 Gene Panel	OHSU Knight Diagnostic Laboratories	None
GPS Cancer®	NantHealth	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Hemiplegic Migraine Panels	GeneDx	None
Hearing Loss Panel	GeneDx	None
Hereditary Hearing Loss and Deafness Panel	Prevention Genetics	None
Infantile Epilepsy Panel	GeneDx	None
Invitae Comprehensive Neuromuscular Disorders Panel	Invitae	None
Invitae Comprehensive Neuropathies Panel	Invitae	None
Invitae Dystonia Comprehensive Panel	Invitae	None
Invitae Ehlers-Danlos Syndrome Panel	Invitae	None
Invitae Epilepsy Panel	Invitae	None
Invitae Monogenic Inflammatory Bowel Disease Panel	Invitae	Inflammatory Bowel Disease: Serologic Testing and Therapeutic Monitoring (All Lines of Business Except Medicare)
Invitae PCM Tissue Profiling and MRD Baseline Assay	Invitae	Next Generation Sequencing for Minimal Residual Disease Detection (All Lines of Business Except Medicare)
Maternal Fetal Screen T1	Eurofins	None

Megalencephaly Panel	Seattle Children's Hospital	None
Mental Health DNA Insight™	Pathway Genomics®	Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
MindX Blood Test- Longevity	MindX Sciences	None
MindX Blood Test- Memory/Alzheimer's	MindX Sciences	None
MindX Blood Test- Mood	MindX Sciences	None
MindX Blood Test- Pain	MindX Sciences	None
MindX Blood Test- Stress	MindX Sciences	None
MindX Blood Test- Suicidality	MindX Sciences	None
Mind.Px	Mindera	None
mRNA Cancer Detect	Viome Life Sciences	None
Neuro IDGenetix	AltheaDx, Inc.	• Genetic Testing: MTHFR (All Lines of Business Except Medicare) • Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Oncotype DX Colon Cancer	Genomic Health	None
Optic Atrophy Panel	Blueprint Genetics	None
PancraGen test	Interpace Diagnostics	None
Pain Panel	Alpha Genomix	• Genetic Testing: MTHFR (All Lines of Business Except Medicare) • Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Percepta Genomic Sequencing Classifier	Veracyte Inc	None
Peripheral Neuropathy Genetics Panel	Mayo Clinic Laboratories	None
PGxOne™ Plus Pharmacogenomics Test	Admera Health	Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Polypharmacy Panel	Genelex Corporation	Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)

Polypharmacy Comprehensive Panel	Genelex Corporation	• Genetic Testing: MTHFR (All Lines of Business Except Medicare) • Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Praxis Somatic Optical Genome Mapping	Praxis Genomics	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Praxis Optical Genome Mapping	Praxis Genomics	None
Praxis Somatic Whole Genome Sequencing	Praxis Genomics	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Praxis Whole Genome Sequencing	Praxis Genomics	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Praxis Somatic Transcriptome	Praxis Genomics	None
Praxis Transcriptome	Praxis Genomics	None
Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping	Praxis Genomics	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Praxis Combined Whole Genome Sequencing and Optical Genome Mapping	Praxis Genomics	Genetic Testing: Whole Exome, Whole Genome, and Proteogenomic Testing (All Lines of Business Except Medicare)
Psychiatry/ADHD Panel	Alpha Genomix	Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Reverse Phase Protein Array	Theralink	Genetic Testing: Gene Expression Profile Testing for Breast Cancer (All Lines of Business Except Medicare)
RightMed Comprehensive Test	OneOme	• Genetic Testing: MTHFR (All Lines of Business Except Medicare) • Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
Tempus xT Gene Panel	Tempus	None

Tissue of Origin® (TOO®)	Cancer Genetics Inc.	None
Tuteva	Verici Dx	None
VistaSeq Breast	LabCorp / Integrated Genetics / Integrated Oncology	Genetic Testing: Hereditary Breast and Ovarian Cancer (All Lines of Business Except Medicare)
VistaSeq Breast and Gyn	LabCorp / Integrated Genetics / Integrated Oncology	Genetic Testing: Hereditary Breast and Ovarian Cancer (All Lines of Business Except Medicare)
Vita Risk®	Arctic Medical Laboratories	None

Link to Policy Summary

POLICY GUIDELINES

Genetic panel tests may be used for a number of indications. This policy only addresses genetic panel tests that may be used for diagnosis or risk assessment of hereditary conditions and/or oncologic indications.

Genetic panel tests may be either be proprietary, “off-the-shelf”, tests with a set number of genes (subject to change without notice), or they may be customized, “a la cart”, tests with genes selected by the ordering provider or genetic counselor based on a patient’s symptoms.

BILLING GUIDELINES

Some, but not all, panel tests may have a specific CPT or HCPCS code assigned (81410-81471). When no specific CPT or HCPCS code exists for the panel, the provider is required to bill using an unlisted code. It is not appropriate for the provider to bill any of the tests/genes in a panel separately as if they were performed individually. See Coding Policy 30.0, Laboratory Panel Billing, for more information.

CPT/HCPCS CODES

Note: Codes addressed by this policy, may include, but are not limited to, the following:

All Lines of Business Except Medicare	
Prior Authorization Required	
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, level 3 (e.g.,>10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon)
81403	Molecular pathology procedure, level 4 (e.g. analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons
81404	Molecular pathology procedure, level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder /triplet repeat by southern blot analysis
81405	Molecular pathology procedure, level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81407	Molecular pathology procedure, level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology, level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
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
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81430	Hearing loss (eg, nonsyndromic 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 (eg, nonsyndromic 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 (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
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
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)

81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
S3870	Comparative genomic hybridization (cgh) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability
No Prior Authorization Required	
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism variants, comparative genomic hybridization [CGH] microarray analysis
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
Not Covered	
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])

0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
0131U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
0132U	Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report
0258U	Autoimmune (psoriasis), mRNA, next-generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes
0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing
0271U	Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid

0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
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
0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0294U	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalinfixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
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 (ie, Class 1, Class 2A, Class 2B)

0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection
0321U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 20 bacterial and fungal organisms and identification of 16 associated antibiotic-resistance genes, multiplex amplified probe technique
0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations
0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint–inhibitor therapy
0363U	Oncology (urothelial), mRNA, geneexpression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination
81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype

Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **denied as not covered.**	
81479	Unlisted Molecular Pathology
81599	Unlisted multianalyte assay with algorithmic analysis
84999	Unlisted chemistry procedure

DESCRIPTION

Genetic panel tests are genetic tests that may be comprised of as few as three genes to as many as thousands of genes. The advantage of genetic panel tests is that they allow for simultaneous testing of test of multiple genes and/or mutations, potentially improving the scope and efficiency of a patient's genetic evaluation. One major disadvantage of genetic panel tests is that the results may provide information on genetic mutations 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.

Numerous commercially available genetic panel tests are available for diagnostic, prognostic and management purposes for individuals harboring symptoms of hereditary conditions or oncologic indications. In addition, panel tests have also been marketed for risk assessment and screening purposes in asymptomatic individuals. However, high-quality studies published in peer-reviewed literature have only shown that certain genetic panel tests are valuable when diagnosing conditions, conferring risk or guiding treatment. To date, the majority of genetic panel tests have not been well studied.
This policy lists a number of genetic panel tests where there is insufficient evidence in published peer-reviewed literature to indicate that they consistently lead to improved diagnostic rates and/or health outcomes. These tests are considered investigational.

REVIEW OF EVIDENCE

The panels addressed in this policy underwent a focused review using the GeneReviews, ECRI, Hayes, and NIH Genetic and Rare Diseases (GARD) databases as well as information extracted from the testing laboratory's website as of July of 2022.

The main criterion for inclusion in this policy was the limited evidence of clinical utility for every gene or test component of a specific genetic panel test. (Please see Policy Guidelines section above for definition of clinical utility.)

CLINICAL PRACTICE GUIDELINES

American Society of Clinical Oncology (ASCO)

The 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addressed multigene panel testing and stated the following:[1]

> "ASCO recognizes that concurrent multigene testing (ie, 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 (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. 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…"

In addition, ASCO stated:

> "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.
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> … [A] substantial proportion of tests identify [variants of uncertain significance] VUS in one or more genes. VUSs are alterations in the genetic code that may or may not affect the function of the protein. 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. It is usually inappropriate to change the clinical management of a patient based on the finding of a VUS. Unfortunately, there is some evidence that clinicians may overinterpret VUSs and make recommendations that should be reserved for individuals with clearly deleterious mutations."

POLICY SUMMARY

There is insufficient evidence that the genetic panels listed in this policy have proven clinical utility. Specifically, there is insufficient evidence that all genes and/or components in a given genetic panel test have proven to provide actionable risk, diagnostic or prognostic information, or information impacting medical management, that has led to improved health outcomes.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

General Principles of Genetic Testing

Due to the high complexity of genetic panel tests and their interpretation, tests must be Food and Drug Administration (FDA)-approved and/or performed in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. Furthermore, the laboratory offering a panel test must have scientifically validated the panel test for the indication for which the panel has been developed and is being requested.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Genetic and Molecular Testing (All Lines of Business Except Medicare)

- Genetic Counseling (All Lines of Business Except Medicare)
- Genetic Testing: CADASIL Disease
- Genetic Testing: Cytochrome P450 and VKORC1 Polymorphisms (All Lines of Business Except Medicare)
- Genetic Testing: Gene Expression Profile Testing for Breast Cancer (All Lines of Business Except Medicare)
- Genetic Testing: Hereditary Breast and Ovarian Cancer: Genetic Counseling and Testing (All Lines of Business Except Medicare)
- Genetic Testing: Inherited Susceptibility to Colorectal Cancer (All Lines of Business Except Medicare)
- Genetic Testing: Inherited Thrombophilias (All Lines of Business except Medicare)
- Genetic Testing: MTHFR (All Lines of Business Except Medicare)
- Genetic Testing: Myeloproliferative Diseases (All Lines of Business Except Medicare)
- Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare)
- Genetic Testing: Whole Exome, Whole Genome and Proteogenomic Testing (All Lines of Business Except Medicare)

REFERENCES

1. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(31):3660-3667.