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General Genetic Testing, Somatic Disorders

Policy Number: AHS – M2146	**Prior Policy Name and Number:** Not applicable
Initial Effective Date: June 01, 2023	**Current Effective Date:** August 1, 2026
Line(s) of Business: HMO; PPO; QUEST; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

I. Policy Description

Genetic testing refers to the use of technologies that identify genetic variation, which include genomic, transcriptional, proteomic, and epigenetic alterations, for the prevention, diagnosis, and treatment of disease.[1,2]

Somatic variations or mutations are defined as a genetic alteration that occurs after conception in any of the cells of the body, except the germ cells, and therefore are not passed on to offspring.[1]

For guidance concerning Tumor Mutational Burden Testing (TMB) and/or Microsatellite instability analysis please refer to the AHS-M2178-Microsatellite Instability and Tumor Mutational Burden Testing policy.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

This policy addresses the general use of somatic (tumor) genetic testing and applies to all tests for which a policy addressing a specific clinical condition is not available.

1) For diagnosis, selection of therapy, or prognostication (when there is a documented benefit based on the presence of such mutations in the tumor or neoplastic cells), genetic testing for a specific genetic mutation or mutations that have documented clinical utility **MEETS COVERAGE CRITERIA**.

2) Repeat testing **MEETS COVERAGE CRITERIA** in **either** of the following situations:
   a) For recurrence monitoring.
   b) When there is the possibility of further genetic alterations in the hematologic malignancy, primary tumor, or metastasis **and** knowledge of these changes would result in the addition, elimination, or alteration of non-investigational therapies.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3) For all situations not described above, genetic testing (single gene or multi-gene panel testing) for somatic disorders **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note: For two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

III. Table of Terminology

Term	Definition
ACMG	American College of Medical Genetics and Genomics
ACTC1	*Actin alpha cardiac muscle 1*
AMP	Association For Molecular Pathology
APC	*Adenomatous polyposis coli*
APOB	*Apolipoprotein B*
ASCO	American Society of Clinical Oncology
ATP7B	*ATPase copper transporting beta*
BAG3	*BAG cochaperone 3*
BMPR1A	*Bone morphogenetic protein receptor type 1A*
BRCA	*Breast cancer gene*
BRCA1	*Breast cancer gene 1*
BRCA2	*Breast cancer gene 2*
BSG	British Sarcoma Group
CACNA1S	*Calcium voltage-gated channel subunit alpha1 S*
CALM1	*Calmodulin I*
CALM2	*Calmodulin 2*
CALM3	*Calmodulin 3*
CAP	College Of American Pathologists
CD	*Cluster of differentiation*
CD34	*Cluster of differentiation 34*
CGP	Comprehensive genomic profiling
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers For Medicare and Medicaid Services
CNA	Copy number alteration
CNV	Copy number variant
COL3A1	*Collagen type III alpha 1*
CTLA-4	*Cytotoxic T-lymphocyte-associated protein 4*
D842V	*Platelet-derived growth factor receptor alpha*
DES	*Desmin*
dMMR	Mismatch repair deficiency
DNA	Deoxyribonucleic acid

DOG1	**Delay of germination**
DSC2	*Desmocollin-2*
DSG2	*Desmoglein 2*
DSP	*Desmoplakin*
EGIST	Extragastrointestinal stromal tumor
EP	Expected pathogenic
ESCAT	European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets
ESMO	European Society for Medical Oncology
EZH2	*Enhancer of zeste 2 polycomb repressive complex 2 subunit*
FBN1	***Fibrillin-1***
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescence in situ hybridization
GIS	Genomic instability score
GIST	Gastrointestinal stromal tumor
GLA	*Alpha-galactosidase A*
GRASP	Genome-Wide Repository of Associations Between SNPs And Phenotypes
HGSC	High-grade serous ovarian, fallopian tube, and peritoneal carcinoma
HOXC6	*Homeobox C6*
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
Indel	Insertion/deletion
KCNH2	*Potassium voltage-gated channel subfamily H member 2*
KCNQ1	*Potassium voltage-gated channel subfamily Q member 1*
KIT	*KIT proto-oncogene receptor tyrosine kinase*
LP	Likely pathogenic
LDLR	Low density lipoprotein receptor
LDT	Laboratory-developed test
LMNA	Lamin A/C
LOF	Loss of function
LOH	Loss of heterozygosity
LST	Large scale state transitions
MBR	Major breakpoint region
MCR	Minor cluster region
MLH1	*MutL homolog 1*
MSH2	*MutS homolog 2*
MSH6	*MutS homolog 6*
MSI	Microsatellite instability
MSK-IMPACT	Memorial Sloan Kettering- integrated mutation profiling of actionable cancer targets
MUTYH	*MutY DNA glycosylase*
MYBPC3	*Myosin binding protein C*
MYH7	*Myosin heavy chain 7*

MYH11	*Myosin heavy chain 11*
MYL2	***Myosin light chain 2***
MYL3	***Myosin light chain 3***
NCCN	National Comprehensive Cancer Network
NF2	*Neurofibromin 2*
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
OCEANs	Oncogene Concatenated Enriched Amplicon Nanopore Sequencing
ORR	Overall response rate
OTC	*Ornithine transcarbamylase*
PARPi	Poly-ADP ribose inhibitors
PCR	Polymerase chain reaction
PCSK9	*Proprotein convertase subtilisin/kexin type 9*
PD-1/PD-L1	*Programmed death-1/ programmed death ligand-1*
PDGFRA	*Platelet-derived growth factor receptor alpha*
PKP2	*Plakophilin 2*
PMS2	*PMS1 homolog 2, mismatch repair system component*
poly-ADP	Polymeric adenosine diphosphate
PRKAG2	*Protein kinase AMP-activated non-catalytic subunit gamma 2*
PTEN	*Phosphatase and tensin homolog*
RB1	*RB transcriptional corepressor 1*
RBM20	*RNA binding motif 20*
RNA	Ribonucleic acid
RYR1	*Ryanodine receptor 1*
RYR2	*Ryanodine receptor 2*
SCL	Small cell lung cancer
SCN5A	*Sodium voltage-gated channel alpha subunit 5*
SCNEC	Small cell neuroendocrine carcinoma
SDHAF2	*Succinate dehydrogenase complex assembly factor 2*
SDHB	*Succinate dehydrogenase complex subunit B*
SDHC	*Succinate dehydrogenase complex subunit C*
SDHD	*Succinate dehydrogenase cytochrome b*
SMAD4	*Mothers against decapentaplegic homolog 4*
SNP	Single nucleotide polymorphism
SNV	single nucleotide variant
STK11	***Serine/threonine kinase 11***
STR	Short tandem repeat
TAI	Telomeric allelic imbalance
TF	Tumor fraction
TGFBR1	*Transforming growth factor, beta receptor I*
TGFBR2	*Transforming growth factor, beta receptor II*
TMB	Tumor mutational burden
TMEM43	*Transmembrane protein 43*

TNNC1	*Troponin C1, slow skeletal and cardiac type*
TP53	*Tumor protein P53*
TSC1	*Tuberous sclerosis complex 1*
TSC2	*Tuberous sclerosis complex 2*
UPD	Uniparental disomy
VUS	Variants of unknown significance
WES	Whole-exome sequencing
WT1	*Wilms' tumor 1*

IV. Scientific Background

Gene mutations are referred to as "somatic" if they are not within the germline (i.e., within gametes); therefore, these mutations are not passed on from parent to offspring. Somatic mutations may arise *de novo* or later in life and are very common in neoplasms.[3] There are many different types of somatic mutations, including single nucleotide polymorphisms (SNPs); structural variations such as deletions, inversions, or translocations, and smaller chromosomal abnormalities such as short tandem repeats or gene fusions. Most mutations do not result in disease.[2]

Single nucleotide polymorphisms are the most common type of genetic mutation, including missense mutations. These mutations are single base-pair changes where one nucleotide replaces a different nucleotide. More than 65% of the diseases caused by genetic mutations are due to SNPs.[2] Estimates based on whole genome sequencing have placed the average amount of SNPs in any given individual at 2.8 to 3.9 million.[2] Insertion/deletion (indel) polymorphisms are often a single nucleotide but may be up to four nucleotides. SNPs often lead to frameshift mutations that can cause premature stop codons and the failure of the allele.[2]

Structural variations are usually classified as larger than 1000 base pairs. These include deletions, duplications, inversions, translocations, or ring chromosome formations. Due to the large number of genes affected, these variations commonly lead to severe genetic abnormalities; for example, a major cause of chronic myeloid leukemia is due to the translocation between chromosomes nine and 22, resulting in a fused gene. The most common structural variation is the copy number variant (CNV), referring to a differing number of DNA segment copies in different individuals. For example, one person may have three copies of a particular segment whereas another may only have two. These variations may lead to dysregulation, gain-of-function, or loss of function of the affected genes.[2] The sensitive genes that require or produce precise quantities of a protein product tend to suffer more from these variations.[4]

Any size mutation may be pathogenic and must be categorized as to how likely the mutation is to cause disease. The American College of Medical Genetics and Genomics (ACMG) has classified mutations in five categories, which are as follows: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. The "likely pathogenic" and "likely benign" refer to weaker evidence than their respective pathogenic and benign categories, and "uncertain significance" refers to evidence that does not meet criteria for benignity or pathogenicity or has conflicting evidence from both sides.[2] Prediction algorithms

have been used to interpret variants and to predict whether a variant will affect the gene function or splicing of the gene. These algorithms are publicly available but have a tendency of predicting the harmful impact of a variant. The specificity of these databases has been estimated at 60-80%.[1]

Due to the enormous number of variants, as well as the rate that variants are discovered, comprehensive databases of genetic variants have been published and are easily available. For example, the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) database includes information from over 2000 studies and over one million variant-related results.[2] Databases focusing on cancer-specific variants, reference sequences, and the general population are all available publicly.[1]

Spontaneous mutations accumulate in somatic cells over a lifetime. Early somatic mutations can cause developmental disorders while the accumulation of mutations throughout life can lead to cancer and contribute to aging.[5] Molecular profiles of tumors have clinical utility in guiding the clinical management of cancer patients, providing diagnostic or prognostic information, or identifying a potential treatment regimen.[1] Increasingly, somatic mutations are being identified in diseases other than cancer, such as neurodevelopmental diseases.[6]

A malignant neoplasm is another term for cancer, which may encompass many types including breast, prostate, skin, lung, rectum, colon, and brain. Gastrointestinal stromal tumors (GISTs) are considered rare neoplasms with approximately 95% of these cancers non-hereditary; GISTs are mainly identified by KIT protein expression with typical mutations in the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes.[7] These GISTs are the most common mesenchymal tumor of the gastrointestinal tract that originate from the cell of Cajal.[8] Primary prostate and lung tumors have been associated with different types of GISTs such as gastric and small bowel; genetic analysis of one patient found "that the gastric GIST and abdominal tumors were characterized by two different c-KIT mutations."[8] Extragastrointestinal stromal tumors (EGISTs) are another type of rare neoplasm which also arise in the gastrointestinal tract. Liu, et al. (2014) report that an EGIST was identified in the prostate of a patient. "The results of immunohistochemical staining showed positive immunoreactivity for cluster of differentiation (CD)117 (c-kit), CD34 and DOG1 in the tumor. On mutation analysis, loss of heterozygosity of the c-kit gene was observed in the prostatic EGIST; however, the platelet-derived growth factor receptor-α (*PDGFRA*) gene was normal."[9] Due to the rarity of EGIST of the prostate, immunohistochemistry analysis is important to confirm a diagnosis.

Mutations of the *KIT* and *PDGFRA* genes in small cell neuroendocrine carcinoma (SCNEC) of the prostate have been researched by Terada (2012). A total of 706 malignant prostate tumors were identified, and four of these tumors were classified as SCNEC. Of these four tumors, three tumors were positive for *KIT*, and *PDGFRA,* among other genes. Molecular genotyping via PCR showed no *KIT* or *PDGFRA* mutations.[10] Another study completed by McCabe, et al. (2008) noted that homeobox C6 (HOXC6) is overexpressed in prostate cancers and completed an analysis of prostate cancer cells to identify which promoters are bound by HOXC6. "We show that HOXC6 directly regulates expression of bone morphogenic protein 7, fibroblast growth factor receptor 2, insulin-like growth factor binding protein 3, and platelet-derived growth factor receptor alpha (*PDGFRA*) in prostate cells."[11] The researchers also note that *PDGFRA* is able

to reduce the proliferation of prostate cancer cells, and that if HOXC6 is overexpressed, the effects of *PDGFRA* inhibition may be overcome. The fusion gene *FIP1L1-PDGFRA* has also been associated with chronic eosinophilic leukemia.[12]

Proprietary Testing

Clinical biomarkers are widely used for making personalized and actionable decisions for cancer treatment. TMB, the number of somatic mutations per mega base of the DNA in cancer cells, is an emerging biomarker associated with predicting the response to immunotherapy treatment.[13] A high TMB value indicates better treatment outcomes, which is observed in patients with melanoma on CTLA-4 inhibitors and patients with melanoma, non-small cell lung carcinoma, bladder cancer, microsatellite instability cancers, and pan-tumors on PD-1/PD-L1 inhibitors. High TMB has also been associated with improved outcomes in patients on a combination of PD-1/PD-L1 and CTLA-4 inhibitors.[14] TMB was originally measured with whole-exome sequencing (WES), but this method has limited clinical utility due to a six to eight week sequencing period and expensive costs. Alternatively, targeted NGS panels can reliably estimate TMB from a subset of the exome with reduced sequencing time and increased clinical application. Two FDA-approved products for calculating TMB include the FoundationOne CDx assay (Foundation Medicine Inc.) and MSK-IMPACT (Memorial Sloan Kettering Cancer Center). Both of these tests, referred to as comprehensive genomic profiling (CGP), can identify all types of "molecular alterations (i.e., single nucleotide variants, small and large insertion-deletion alterations, copy number alterations, and structural variants) in cancer-related genes, as well as genomic signatures such as microsatellite instability (MSI), loss of heterozygosity, and TMB.[15] Studies show that TMB calculation from CGP has high concordance with TMB" measured from WES. On June 16, 2020, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with a TMB value of greater than 10 mutations per mega base as determined by the FoundationOne CDx assay.[16]

Analysis of somatic mutations in solid tumors and hematologic malignancies using next generation sequencing has become common practice in oncology clinics as well as clinical trials. There are several known approved NGS tests for detection of somatic mutations. MyChoice HRD CDx, by Myriad Genetic Laboratories, was FDA-approved on October 23, 2019, and ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) by Pillar Biosciences was FDA-approved on July 30, 2021. Myriad MyChoice® CDx is a next generation sequencing based in vitro diagnostic test that detects single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes.[17] The ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) by Pillar Biosciences, is a next generation sequencing test for detection of somatic mutations for non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumor tissue. The test simultaneously detects clinically relevant mutations in *KRAS* for CRC and epidermal growth factor receptor (EGFR) for NSCLC in a single assay. In the accuracy study, positive percent agreement (PPA) and negative percent agreement (NPA) between O/RDx-LCCA and externally validated comparator method (CompO) was >99%. The authors conclude that O/RDx-LCCA "is a highly accurate assay for the detection of clinically relevant *KRAS* variants in CRC and EGFR variants in NSCLC."[18,19]

In 2020, the FDA approved Guardant360® CDx for tumor mutation profiling in patients with any solid malignant neoplasm. The Guardant360 CDx is also approved as a companion diagnostic to identify NSCLC patients with *EGFR* alterations who may benefit from treatment with Tagrisso® (osimertinib).[20] In an analytical study, the positive and NPA for Guardant360 CDx relative to Therascreen® KRAS RGQ PCR was 0.71 and 1.00 respectively; overall percent agreement was 0.82.[21] In 2020, the FDA also approved Therascreen BRAF V600E RGQ PCR Kit by QIAGEN. This is a real-time PCR test for the qualitative detection of V600E mutations in the *BRAF* gene in human colorectal cancer (CRC) tumor tissue. Therascreen can help select patients with metastatic colorectal cancer (mCRC) whose tumors carry the *BRAF* V600E mutation for treatment with BRAFTOVI (encorafenib) in combination with cetuximab.[22]

Analytical Validity

Woodhouse, et al. (2020) evaluated the analytical performance of FoundationOne Liquid CDx assay to detect genomic alterations in cancer patients. The assay was evaluated across more than 30 different cancer types in over 300 genes and greater than 30,000 gene variants. "Results demonstrated a 95% limit of detection of 0.40% variant allele fraction for select substitutions and insertions/deletions, 0.37% variant allele fraction for select rearrangements, 21.7% tumor fraction (TF) for copy number amplifications, and 30.4% TF for copy number losses. The false positive variant rate was 0.013% (approximately one in 8,000). Reproducibility of variant calling was 99.59%."[23] In comparison to in situ hybridization and immunohistochemistry, FoundationOne had an overall 96.3% positive percent agreement and > 99.9% negative percent agreement. "These study results demonstrate that FoundationOne Liquid CDx accurately and reproducibly detects the major types of genomic alterations in addition to complex biomarkers such as microsatellite instability, blood tumor mutational burden, and tumor fraction."[23]

Thirunavukarasu, et al. (2021) developed the Oncogene Concatenated Enriched Amplicon Nanopore Sequencing (OCEANS) method for rapid, accurate, and affordable somatic mutation detection. The OCEANS method involves amplified variants with low variant allele frequency and subsequently concatenating with Nanopore Sequencing. In this study, the 15-plex OCEANS melanoma panel was compared to NGS. OCEANS had a 100% sensitivity relative to NGS. Of the 9584 NGS-negative loci, OCEANS was able to detect an additional 97 variants; thus, relative to NGS, OCEANS had a 99.0% specificity and very low false positive rate. These 97 NGS-negative and OCEANS-positive results were believed to be true mutations, and droplet digital PCR (ddPCR) confirmation experiments supported this hypothesis. The authors conclude that "Integrating OCEANS with long-read and base modification detection capabilities of Nanopore Sequencing can enable development of comprehensive oncology panels."[24]

Clinical Utility and Validity

Advancements in technology and availability of sequencing, previously constrained by limitations of sequential single-gene testing on limited patient samples, have led to significant strides in our understanding of the genetic basis of inherited and somatic conditions. Variants detected by genetic testing include inherited germline variants and somatic mutations; next generation sequencing (NGS) has allowed for superior detection of these mutations.[25] The accuracy of NGS varies depending on how many

genes are sequenced; fewer genes tend to result in higher accuracy since there will be more "probe-template overlap." Although Sanger sequencing remains the most accurate at >99.99% accuracy, it cannot sequence a large amount of genes in a timely fashion and is best used for sequencing of a specific gene.[26] NGS also can be used clinically to guide screening, preventive options, and cancer treatment such as the "analysis of tumor tissue or non-tumor tissue to identify genetic abnormalities that may be present in the germline and/or the tumor that could potentially match molecularly targeted therapies. As an example, a poly(ADP ribose) polymerase (PARP) inhibitor could be considered in a patient with an identified BRCA1 or BRCA2 mutation."[26]

Next generation sequencing has been used to identify several types of somatic mutations associated with cancer and may help to single out therapeutic targets. Genetic mutations in *BRCA*1 & 2 are associated with breast and ovarian cancer. Kowalik, et al. (2019) have identified somatic genetic mutations in *BRCA*1 & 2 for ovarian cancer prognostic purposes using NGS. Ovarian cancer tissue samples were used for the analysis. A total of three percent of mutations (6/201) were identified as somatic; with only 24% (49/201) of samples identified with a pathogenic mutation overall.[27] The other 35 mutations were of germline origin. This corroborated the report by Nagahashi, et al. (2019) which states that approximately 2.5% of *BRCA*1 & 2 mutations are somatic. Detection of a BRCA1/2 germline mutation is essential for planning individual therapy, where indicated, testing should be arranged as early as possible. It is the only way of identifying patients suitable for PARPi therapy and ensuring they receive the best possible treatment.[29]

The clinical validity of a genetic test depends primarily on the expressivity and penetrance of a given phenotype. Penetrance refers to the likelihood of developing a disease when the pathogenic mutation is present, and expressivity refers to the variations in the way the disease is expressed. For example, virtually any mutation in the *APC* gene will cause symptoms of familial adenomatous polyposis, thereby increasing the clinical validity of an *APC* assessment. Some conditions may not clinically manifest at all despite a mutated genotype.[2]

The clinical utility of a genetic test generally relies on available treatments for a condition. Conditions such as Huntington's Disease that do not have many options for treatment will have limited clinical utility compared to another condition even though the actual test is highly valid. Factors such as severity of the disease and management options affect the clinical utility of a genetic test.[2]

McCabe, et al. (2008),Hayano, et al. (2016) noted that homeobox C6 (HOXC6) is overexpressed in prostate cancers and completed an analysis of prostate cancer cells to identify which promoters are bound by HOXC6.

In a prospective study, Takeda evaluated the clinical application of the FoundationOne CDx Assay in decision-making for patients with advanced solid tumors. A total of 175 samples were analyzed using the FoundationOne assay and 153 of these patients were assessed for TMB. "The most common known or likely pathogenic variants were *TP53* mutations (n = 113), *PIK3CA* mutations (n = 33), *APC* mutations (n = 32), and *KRAS* mutations (n = 29). The median TMB was four mutations/Mb, and tumors with a high TMB (≥10 mutations/Mb) were more prevalent for lung cancer (11/32) than for other solid tumor types."

From the 175 samples found to have known or likely pathogenic variants, 24 subjects (14%) received the optimal targeted therapy. The authors conclude that "such testing may inform the matching of patients with cancer with investigational or approved targeted drugs."[31]

V. Guidelines and Recommendations

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

The Joint Commission recommended that somatic variants be categorized by and reported based on their impact on clinical care. The Joint Commission notes that somatic variants include indels, single nucleotide variants (SNVs), fusion genes from genomic rearrangements, and CNVs and should focus on their impact on clinical care. Any variant may be considered a biomarker if it predicts response to therapy, influences prognosis, diagnosis, treatment decisions, or the gene function itself. The Joint Commission proposes four levels for these biomarkers which are as follows:

> "1. Level A, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors;
> 2. Level B, biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on well-powered studies with expert consensus;
> 3. Level C, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (i.e., off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies;
> 4. Level D, biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus."[1]

The Joint Commission also includes variants in different tiers based on the amount of evidence there is to support its significance. For example, tier 1 variants include significance of levels A and B, while tier 2 includes significance of levels C and D. Tier 3 is variants of unknown significance (VUS), such as variants in cancer genes that have not been reported in any other cancers. These variants are not typically seen in significant frequencies in the general population. When evaluating these variants, the type of mutation and gene function should be considered. Tier 4 is benign variants or likely benign variants. These alleles are often observed in significant amounts in general populations. Tier 3 variants should be reported while ensuring that the most important information is communicated to the patient.[1]

National Comprehensive Cancer Network (NCCN)

Multiple somatic mutations have been incorporated into the diagnostic workups recommended by the NCCN. Furthermore, the NCCN has several guidelines which recommend that gene expression profiling, or multiple gene testing, may be helpful, more efficient and/or cost-effective for selected patients.[32]

Please see the individual policies.

American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)

The ACMG and AMP released criteria on the types and severity of mutations, which are as follows:

- **Very strong evidence of pathogenicity**: Null variants (nonsense, frameshifts, canonical +/- 1-2 splice sites, initiation codon, exon deletions) in a gene where loss of function (LOF) is a known mechanism of disease. The guidelines note to use caution in genes where LOF is not a mechanism, if LOF variants are at the 3' end, if exon skipping occurs, and if multiple transcripts are present.
- **Strong:** Amino acid change to a pathogenic version, de novo mutations, established studies supporting a damaging gene or gene product, or if the prevalence of the variant is increased in affected individuals compared to healthy controls. The guidelines note to be careful of changes impacting splicing and if only the paternity has been confirmed.
- **Moderate:** Located in a mutational hot spot or well-established functional domain (e.g., active site of an enzyme) without a benign variation, absent from controls in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium, detected in *trans* with pathogenic variants for a recessive disorder, protein length changes, novel missense changes where a different missense change has been pathogenic before, and a possible de novo mutation.
- **Supporting:** Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease, missense variant in a gene with low rate of benign missense variation, if the mutation has evidence that it is deleterious, if the patient's phenotype is highly specific for disease with a single genetic cause.

The guidelines also list criteria for benign gene variants.

- **Stand-alone evidence of benignity:** Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
- **Strong:** Allele frequency is greater than expected for disorder, observed in healthy adult with full penetrance at early age, lack of segregation in affected family members (although pathogenic variants may masquerade as nonsegregated), or well-established studies that show no damaging effect on protein production.
- **Supporting:** Missense variant of a gene for which truncating mutations are pathogenic, indels in repetitive region of unknown function, silent variants, VUS, or a *trans* version of a *cis* mutation.[33]

American College of Medical Genetics and Genomics (ACMG)

The ACMG has released a list of genes for which secondary findings should be disclosed. Secondary findings refer to incidental findings unrelated to why a genetic test was originally ordered but are of significant clinical value to the patient. The portion of the table, from version 3.3, containing the conditions, the associated genes, and which variants should be report is listed below:[34]

Genes Related to Cancer Predisposition		
Condition	Gene(s)	Variants to Report
Hereditary breast and/or ovarian cancer	*BRCA1, BRCA2, PALB2*	LP (likely pathogenic), P (pathogenic)
Li-Fraumeni syndrome	*TP53*	LP, P
Peutz-Jeghers syndrome	*STK11*	LP, P
Juvenile polyposis syndrome	*BMPR1A*	LP, P
Juvenile polyposis syndrome/ hereditary hemorrhagic telangiectasia syndrome	*SMAD4*	LP, P
PTEN hamartoma syndrome	*PTEN*	LP, P
Lynch syndrome/hereditary nonpolyposis colorectal cancer	*MLH1, MSH2, MSH6, PMS2*	LP, P
Familial adenomatous polyposis	*APC*	LP, P
MUTYH-associated polyposis	*MUTYH*	LP, P (2 variants)
Von Hippel Lindau syndrome	*VHL*	LP, P
Retinoblastoma	*RB1*	LP, P
Tuberous sclerosis complex	*TSC1, TSC2*	LP, P
***WT1*-related Wilms tumor**	*WT1*	LP, P
Multiple endocrine neoplasia 1	*MEN1*	LP, P
Familial medullary thyroid cancer	*RET*	LP, P
Hereditary paraganglionoma-pheochromocytoma syndrome	*SDHD, SDHAF2, SDHC, SDHB, MAX*	LP, P
Neurofibromatosis type 2	*NF2*	LP, P

Genes Related to Cardiovascular Disease Predisposition		
Condition	Gene(s)	Variants to Report

Aortopathies	*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11*	LP, P
Arrhythmogenic right ventricular cardiomyopathy	*PKP2, DSP, DSC2, TMEM43, DSG2*	LP, P
Catecholaminergic polymorphic ventricular tachycardia	*RYR2, CASQ2, TRDN*	LP, P
Dilated cardiomyopathy	*TNNT2, LMNA, FLNC, TTN, BAG3, DES, RBM20, TNNC1, PLN*	LP, P
Ehlers–Danlos syndrome, vascular type	*COL3A1*	LP, P
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*	LP, P
Hypertrophic cardiomyopathy	*MYH7, MYBPC3, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, MYL2*	LP, P
Long QT syndrome types 1 and 2	*KCNQ1, KCNH2*	LP, P
Long QT syndrome 3; Brugada syndrome	*SCN5A*	LP, P
Long QT syndrome types 14-16	*CALM1, CALM2, CALM3*	LP, P
Genes Related to Inborn Errors of Metabolism		
Condition	Gene(s)	Variants to Report
Biotinidase deficiency	*BTD*	LP, P (2 variants)
Cerebrotendinous xanthomatosis	*CYP27A1*	LP, P (2 variants)
Fabry disease	*GLA*	All hemi, het, homozygous P and LP
Hereditary hemochromatosis	*HFE*	*HFE* p.C282Y homozygotes only
Ornithine transcarbamylase deficiency	*OTC*	All hemi, het, homozygous P and LP
Pompe disease	*GAA*	P and LP (2 variants)

X-linked adrenoleukodystrophy	*ABCD1*	All hemi, homozygous or 2 het. P and/or LP
Genes Related to Other Disease Phenotypes		
Condition	Gene(s)	Variants to Report
Hereditary hemorrhagic telangiectasia	*ACVRL1, ENG*	LP, P
Hereditary TTR amyloidosis	*TTR*	LP, P
Malignant hyperthermia	*RYR1, CACNA1S*	LP, P
Maturity-onset of diabetes of the young	*HNF1A*	LP, P
RPE65-related retinopathy	*RPE65*	LP, P (2 variants)
Wilson disease	*ATP7B*	LP, P (2 variants)

American Society of Clinical Oncology (ASCO)

The ASCO published guidelines regarding genetic and genomic testing for cancer susceptibility. These guidelines state that the "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… 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."[35]

The ASCO released guidelines regarding somatic tumor testing for ovarian cancer. ASCO recommends that, for individuals with ovaries "diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for time of recurrence for [those] who have completed upfront therapy and are currently in observation, as presence of these mutations qualifies the patient for FDA-approved treatments."[36] In a 2021 update of these guidelines, ASCO adds "Implementation of techniques and pipelines enabling both SNV and CNV detection should be preferred, optimally by next-generation sequencing,"[37] The 2025 ASCO guidelines on advanced ovarian cancer recommend "all patients with [epithelial ovarian cancer] should be offered germline genetic and somatic testing for *BRCA1* and *BRCA2*." "Somatic tumor testing should include measure(s) of homologous recombination. Testing should occur at the time of diagnosis or as soon as feasibly possible."[38]

In 2022, a provisional opinion was released by ASCO. It addressed the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors. A lack of clarity in clinical practice "as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection," was the impetus. In the opinion of ASCO, patients with metastatic or advanced cancer "should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease."

Additionally:

- "Multigene panel-based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease."
- "Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) provide a rationale for genomic testing for all solid tumors."
- "Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker-linked options relative to other approved or investigational treatments."[39]

The ASCP published guidelines for germline and somatic genomic testing for metastatic prostate cancer. The guidelines recommend "patients with metastatic prostate cancer should undergo both germline and somatic DNA sequencing using panel-based assays." Specifically, "those patients with metastatic prostate cancer (both CSPC and CRPC) who are being considered for biomarker-directed systemic treatment should undergo somatic testing with next-generation sequencing technologies." Additionally, "the panel recommends that sequential somatic testing may be offered when there has been a meaningful change in the patient's status or treatment plan, especially in cases where prior tests were negative or uninformative (eg, insufficient or low tumor content)."[40] The ASCO also published guidelines for systemic therapy in patients with metastatic castration-resistant prostate cancer. The guidelines recommend "both germline and somatic testing for patients with metastatic prostate cancer at the earliest available opportunity."[41]

European Society for Medical Oncology (ESMO)

The ESMO recommends that "Mutational analysis inclusion in the diagnostic work-up of all GISTs should be considered standard practice [II, A] (with the possible exclusion of < 2 cm non-rectal GISTs)."[42] The article also states that "Mutational analysis for known mutations involving *KIT* and *PDGFRA* can confirm the diagnosis of GIST, if doubtful (particularly in rare CD117/DOG1-negative suspect GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and to prognostic value. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice."[42,43]

The ESMO Translational Research and Precision Medicine Working Group released clinical practice guidelines to define best practice for homologous recombination deficiency (HRD) testing in high-grade serous ovarian, fallopian tube and peritoneal carcinoma (HGSC). ESMO recommends that "pathological evaluation of the tumour tissue specimens used for assessment of somatic molecular alterations is essential."[44] Regarding homologous recombination repair (HRR) tests, *BRCA* germline and somatic mutation tests are recommended as they consistently identify the subgroup of ovarian cancer patients who benefit the most from poly-ADP ribose inhibitors (PARPi) therapy. There is insufficient evidence to determine the clinical validity of a panel of non-*BRCA* HRR genes and *BRCA1* or *RAD51C* promoter methylation to predict PARPi benefit. "In the first-line maintenance setting, germline and somatic *BRCA* mutation testing is routinely recommended to identify HGSC patients who should receive a PARPi."[44]

British Sarcoma Group (BSG)

The BSG has published guidelines on the management of GIST and state that most GIST cases are associated with a *KIT* or *PDGFRA* mutation. The guidelines recommend the following:

- "The diagnosis should be made by a pathologist experienced in the disease and include the use of immunohistochemistry and mutational analysis, which should be performed by an accredited laboratory.
- If neoadjuvant treatment with imatinib is planned, it is vital to confirm the diagnosis, since there is a wide differential. It may be necessary to perform a percutaneous core needle biopsy if the tumour is inaccessible to endoscopic ultrasound-guided biopsy. Mutational analysis is obligatory, since some GISTs are insensitive to imatinib (e.g. those with *D842V* mutation in exon 18 of *PDGFRA*)."[45]

These guidelines were updated in 2024 and recommended with the following minor changes:

- "The diagnosis of GIST should be established by a pathologist experienced in the disease and should include the use of IHC and, if necessary, molecular analysis (which should be performed by an accredited laboratory).
- If initial treatment with imatinib is planned, it is essential to confirm the diagnosis of GIST, since there is a wide differential. It may be necessary to perform a percutaneous core needle biopsy if the tumour is inaccessible to EUS biopsy. Molecular analysis is particularly critical, since some GISTs are insensitive to tyrosine kinase inhibitors (e.g. the PDGFRA exon 18 D842V mutation)."[46]

European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG)

The EAU/EANM/ESTRO/ESUR/SIOG released guidelines on prostate cancer in 2021. These guidelines strongly recommend offering patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) "somatic molecular testing to identify patients suitable for treatment with PARP inhibitors."[47] The

guidelines were updated in 2024, but somatic testing is not mentioned.[48]

The American Urological Association / American Society for Radiation Oncology / Society of Urologic Oncology (AUA/ASTRO/SUO)

The AUA/ASTRO/SUO released guidelines on prostate cancer in 2021. These guidelines recommend that "clinicians should offer germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status that may inform prognosis in patients with mCRPC and counseling regarding family risk as well as potential targeted therapies."[49]

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

On July 30, 2021, the FDA approved ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) by Pillar Biosciences. "The device is a qualitative next generation sequencing based in vitro diagnostic test that uses amplicon-based target enrichment technology for detection of single nucleotide variants (SNVs) and deletions in 2 genes from DNA isolated from formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) tumor tissue specimens."[50]

On July 18, 2020, the FDA approved Cobas® EZH2 Mutation Test, a somatic gene mutation detection system by Roche Molecular System, Inc. "The device is a real-time allele-specific PCR test for qualitative detection of single nucleotide mutations for *Y646N, Y646F or Y646X (Y646H, Y646S,* or *Y646C), A682G*, and *A692V* of the *EZH2* gene in DNA extracted from formalin-fixed paraffin embedded (FFPE) human follicular lymphoma tumor tissue specimens."[51]

On August 7, 2020, the FDA approved Guardant360 CDx, by Guardant Health, Inc. This device is a next generation sequencing based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology to detect SNVs, insertions, and deletions in 55 genes, copy number amplifications in two genes, and fusions in four genes. Guardant360 CDx also utilizes circulating cell-free DNA collected in Streck Cell-Free DNA Blood Collection Tubes to identify NSCLC patients who may benefit from treatment with the targeted therapy.[52]

On April 15, 2020, the FDA approved Therascreen *BRAF* V600E RGQ PCR Kit by QIAGEN. The Therascreen *BRAF* V600E RGQ PCR Kit is a real-time PCR test for the qualitative detection of V600E mutations in the *BRAF* gene using genomic DNA extracted from FFPE human colorectal cancer (CRC) tumor tissue. The Therascreen *BRAF* V600E RGQ PCR Kit is an in vitro diagnostic device intended to be used as an aid in selecting patients with metastatic colorectal cancer (mCRC) whose tumors carry the *BRAF* V600E mutation for treatment with BRAFTOVI (encorafenib) in combination with cetuximab."[53]

On October 23, 2019, the FDA approved MyChoice HRD CDx, by Myriad Genetic Laboratories, Inc. This device is a next generation sequencing based in vitro diagnostic device for detection of SNVs, insertions, deletions, and large rearrangement variants of the BRCA1 and BRCA2 genes. This test also determines the Genomic Instability Score (GIS), a measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large Scale State Transitions (LST), which is used to identify ovarian cancer patients with positive HRD status.[54]

On November 30, 2017, the FDA approved FoundationOne CDx, by Foundation Medicine, Inc. This device is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and TMB using DNA isolated from FFPE tumor tissue specimens.[55]

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
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	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); 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	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or

CPT	Code Description
	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	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
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	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
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	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); 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)
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
81370	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1

CPT	Code Description
81371	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)
81372	HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
81373	HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each
81374	HLA Class I typing, low resolution (eg, antigen equivalents); one antigen equivalent (eg, B*27), each
81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377	HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81382	HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81383	HLA Class II typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, HLA-DQB1*06:02P), each
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 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 (eg, >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 of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, 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)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or

CPT	Code Description
	rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure
81524	Oncology (central nervous system tumor), DNA methylation analysis of at least 10,000 methylation sites, utilizing DNA extracted from formalin-fixed tumor tissue, algorithm(s) reported as probability of matching a reference tumor family and class, and MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation status, if performed
81599	Unlisted multianalyte assay with algorithmic analysis
88237	Tissue culture for neoplastic disorders; bone marrow, blood cells
88239	Tissue culture for neoplastic disorders; solid tumor
88240	Cryopreservation, freezing and storage of cells, each cell line
88241	Thawing and expansion of frozen cells, each aliquot
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
88289	Chromosome analysis; additional high resolution study
88291	Cytogenetics and molecular cytogenetics, interpretation and report
88299	Unlisted cytogenetic study
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score Proprietary test: myChoice® CDx Lab/Manufacturer: Myriad Genetics Laboratories, Inc
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ aHUS Genetic Evaluation Lab/Manufacturer: Versiti™ Diagnostic Laboratories
0444U	Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s) Proprietary test: Aventa FusionPlus ™ Lab/Manufacturer: Aventa Genomics, LLC

CPT	Code Description
0523U	Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of singlenucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffinembedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change Proprietary test: oncoRevealTMCDx Lab/Manufacturer: Pillar Biosciences Inc, Pillar Biosciences Inc

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Policy History

Action Date	Action
June 01, 2023	Policy created
March 17, 2026	Policy approved by Medical Directors
March 27, 2026	Policy approved at UMC
August 1, 2026	Policy effective date following notification period