Corporate Medical Policy

General Genetic Testing, Somatic Disorders AHS-M2146

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Description of Procedure or Service

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 (Kohlmann & Slavotinek, 2022; Li et al., 2017).

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 (Li et al., 2017).

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.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for general genetic testing for somatic disorders when it is determined the medical criteria guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When General Genetic Testing, Somatic Disorders is covered

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 is considered medically necessary.

2. Repeat testing is considered medically necessary 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.

Note: For 5 or more gene tests being run on the same platform, please refer to policy AHS-R2162 Laboratory Procedures Medical Policy.

When General Genetic Testing, Somatic Disorders is not covered

For all situations not described above, genetic testing (single gene or multi-gene panel testing) for somatic disorders is considered not medically necessary.

Policy Guidelines

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 (Raby & Blank, 2022). 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 (Kohlmann & Slavotinek, 2022).

SNPs 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 (Kohlmann & Slavotinek, 2022). Estimates based on whole genome sequencing have placed the average amount of SNPs in any given individual at 2.8 to 3.9 million (Kohlmann & Slavotinek, 2022). Insertion/deletion (Garrett et al.) 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 (Kohlmann & Slavotinek, 2022).

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 9 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 (Kohlmann & Slavotinek, 2022). The sensitive genes that require or produce precise quantities of a protein product tend to suffer more from these variations (Bacino, 2022).

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 (Kohlmann & Slavotinek, 2022). 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% (Li et al., 2017).

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 (Kohlmann & Slavotinek, 2022). Databases focusing on cancer-specific variants, reference sequences, and the general population are all available publicly (Li et al., 2017).

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 (Martincorena & Campbell, 2015). 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 (Li et al., 2017). Increasingly, somatic mutations are being identified in diseases other than cancer, such as neurodevelopmental diseases (Poduri et al., 2013).

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 (Morgan et al., 2022). These GISTs are the most common mesenchymal tumor of the gastrointestinal tract that originate from the cell of Cajal (Comandini et al., 2017). 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 (Comandini et al., 2017)." 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 male 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" (Liu et al., 2014). 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 (Terada, 2012). 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 (McCabe et al., 2008)." 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 (Legrand et al., 2013).

Proprietary Testing

Clinical biomarkers are widely used for making personalized and actionable decisions for cancer treatment. Tumor mutational burden (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 (NCI, 2021). 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 (Merino et al., 2020). TMB was originally measured with whole-exome sequencing (WES), but this method has limited clinical utility due to a 6–8-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 (Bauml et al.), loss of heterozygosity, and TMB (Klempner et al., 2020)." 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 (FDA, 2020b).

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 2 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 (Myriad_Genetics, 2020). 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 EGFR for NSCLC in a single assay. In the accuracy study, positive percent agreement (Pappas et al.) 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" (Pillar_Biosciences, 2020, 2021).

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 non-small cell lung cancer patients with epidermal growth factor receptor (EGFR) alterations who may benefit from treatment with Tagrisso® (osimertinib) (Guardant, 2020). In an analytical study, the positive and negative percent agreement for Guardant360 CDx relative to Therascreen® KRAS RGQ PCR was 0.71 and 1.00 respectively; overall percent agreement was 0.82 (Bauml et al., 2021). 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 (QIAGEN, 2020).

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 (USPSTF) for copy number amplifications, and 30.4% TF for copy number losses. The false positive variant rate was 0.013% (approximately 1 in 8,000). Reproducibility of variant calling was 99.59% (Woodhouse et al., 2020)." 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 (Woodhouse et al., 2020)."

Thirunavukarasu 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 (VAFs) 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" (Thirunavukarasu et al., 2021).

Clinical Validity and Utility

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 (Lamont et al.) has allowed for superior detection of these mutations (Konnick & Pritchard, 2016). 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 (Hulick, 2022).

NGS has been used to identify several types of somatic mutations associated with cancer and may help to single out therapeutic targets. Genetic mutations in BRCA1 & 2 are associated with breast and ovarian cancer. Kowalik et al. (2019) have identified somatic genetic mutations in BRCA1 & 2 for ovarian cancer prognostic purposes using NGS. Ovarian cancer tissue samples were used for the analysis. A total of 3% of mutations (6/201) were identified as somatic; with only 24% (49/201) of samples identified with a pathogenic mutation overall (Kowalik et al., 2019). The other 35 mutations were of germline origin. This corroborated the report by Nagahashi et al. (2019) which states that approximately 2.5% of BRCA1 & 2 mutations are somatic.

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 (Kohlmann & Slavotinek, 2022).

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 (Kohlmann & Slavotinek, 2022).

Hayano et al. (2016); 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.

In a multi-cohort, open-label, non-randomized study to establish the relationship between TMB and pembrolizumab treatment response, 790 patients were tested for TMB with the FoundationOne CDx assay. 102/790 patients had high TMB (≥10 mutations per mega base) in solid tumors of anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small cell lung, thyroid, and vulvar cancers. The overall response rate (ORR) in patients with a high TMB was 29%, with a 4% complete response rate and 25% partial response rate compared to an ORR of 6% in patients with a low TMB. The overall response rate was nearly 5-fold in patients with a high TMB. The authors conclude "TMB could be a novel and useful predictive biomarker for response to pembrolizumab monotherapy in patients with previously treated recurrent or metastatic advanced solid tumours" (Marabelle et al., 2020).

In a prospective study, Takeda evaluated the clinical application of the FoundationOne CDx Assay in decision-making for patients with advanced solid tumors. 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 4 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" (Takeda et al., 2021).

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, 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 (Li et al., 2017)."

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 (Li et al., 2017).

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 (NCCN, 2023). 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, variants of unknown significance, or a *trans* version of a *cis* mutation (Richards et al., 2015).

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 containing the conditions, the associated genes, and which variants should be report is listed below (Kalia et al., 2016; Miller et al., 2021):

Condition	Gene(s)	Variants to Report
Breast/ovarian cancer	*BRCA1, BRCA2*	LP (likely pathogenic), P (pathogenic)
Li-Fraumeni syndrome	*TP53*	LP, P
Peutz-Jeghers syndrome	*STK11*	LP, P
Juvenile polyposis syndrome	*BMPR1A, SMAD4*	LP, P
PTEN hamartoma syndrome	*PTEN*	LP, P
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	LP, P
Familial adenomatous polyposis	*APC*	LP, P
MYH-associated polyposis	*MUTYH*	LP, P
Von Hippel Lindau syndrome	*VHL*	LP, P
Retinoblastoma	*RB1*	LP, P
Tuberous sclerosis complex	*TSC1, TSC2*	LP, P
Wilms tumor	*WT1*	LP, P
Multiple endocrine neoplasia 1 or 2	*MEN1 (1), RET (2)*	LP, P
Familial medullary thyroid cancer	*RET*	LP, P
Hereditary paraganglionoma-pheochromocytoma syndrome	*SDHD, SDHAF2, SDHC, SDHB*	LP, P
Neurofibromatosis type 2	*NF2*	LP, P
Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysms and dissections	*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11*	LP, P
Malignant hyperthermia	*RYR1, CACNA1S*	LP, P
Wilson disease (copper metabolism)	*ATP7B*	LP, P

Ornithine transcarbamylase deficiency (urea cycle)	*OTC*	All hemi, het, homozygous P and LP
Hereditary hemochromatosis	*HFE*	HFE p.Cys282Tyr homozygotes only
Hereditary hemorrhagic telangiectasia	*ACVRL1, ENG*	LP, P
Maturity-onset diabetes of the young	*HNF1A*	LP, P
RPE65-related retinopathy	*RPE65*	LP, P

Cardiac and/or blood vessel related		
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*	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
Genes related to inborn errors of metabolism phenotypes		
Condition	Gene(s)	LP, P
Biotinidase deficiency	*BTD*	LP, P (2 variants)

Fabry disease	*GLA*	All hemi, het, homozygous P and LP
Ornithine transcarbamylase deficiency	*OTC*	All hemi, het, homozygous P and LP
Pompe disease	*GAA*	P and LP (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 (Robson et al., 2015)."

ASCO released guidelines regarding somatic tumor testing for ovarian cancer. ASCO recommends that "Women 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 women who have completed upfront therapy and are currently in observation, as presence of these mutations qualifies the patient for FDA-approved treatments" (Konstantinopoulos et al., 2020). 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" (Pujol et al., 2021).

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) (Casali et al., 2018)." 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" (Casali et al., 2018; Casali et al., 2022).

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" (Miller et al., 2020). 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" (Miller et al., 2020).

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)" (Judson et al., 2017).

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)

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" (Mottet et al., 2021).

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

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" (Lowrance et al., 2021).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

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" (FDA, 2021).

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" (FDA, 2020a).

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 2 genes, and fusions in 4 genes. Guardant360 CDx also utilizes circulating cell-free DNA collected in Streck Cell-Free DNA Blood Collection Tubes to identify non-small cell

lung cancer (NSCLC) patients who may benefit from treatment with the targeted therapy (FDA, 2020c).

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 formalin-fixed paraffin-embedded (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" (FDA, 2020d).

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 single nucleotide variants, 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 homologous recombination deficiency (HRD) status (FDA, 2019).

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 (Bauml et al.) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens (FDA, 2017).

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81168, 81191, 81192, 81193, 81194, 81233, 81261, 81262, 81263, 81264, 81265, 81266, 81267, 81268, 81277, 81278, 81305, 81314, 81315, 81316, 81340, 81341, 81342, 81347, 81348, 81357, 81360, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 81400, 81401, 81402, 81403, 81405, 81479, 81599, 88237, 88239, 88240, 88241, 88269, 88271, 88272, 88273, 88274, 88275, 88280, 88283, 88285, 88289, 88291, 88299, 0268U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020
Specialty Matched Consultant Advisory Panel review 3/2021

Medical Director review 3/2021

Medical Director review 1/2022

Medical Director review 7/2022

Medical Director review 4/2023

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for general genetic testing for somatic disorders when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. Added "Related Policies" to Description section. Added item 4 under the When Covered section: "MSI testing for all solid tumors is considered medically necessary for individuals being considered for pembrolizumab (Keytruda) therapy", along with statement regarding 5 gene tests to refer to policy AHS-M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy. Policy guidelines extensively revised. Billing/Coding section updated and added the following codes: 81267, 81268, and 81301. Referenced updated. Medical Director review 5/2019. (jd)

10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Minor revisions only: Changed item #5 under the When Covered section to a "Note" and minor update to the Related Policies section. No change to policy statement intent. Medical Director review 9/2019. (jd)

11/12/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Policy guidelines and references updated. The following updates were made to the Billing/Coding section: added 81314, 81233, 81236, 81305, and removed G0452. Medical Director review 4/2020. (jd)

4/20/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)

5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Added item 5 as follows to When Covered section: "TMB testing is covered for all solid tumors for individuals being considered for pembrolizumab (Keytruda) therapy." Description, policy guidelines, and references updated. Medical Director reviewed 4/2021. (jd)

1/25/22 Reviewed by Avalon 4th Quarter 2021 CAB. Removed items #4 and 5 from the When Covered section, as follows: "MSI testing for all solid tumors is considered medically necessary for individuals being considered for pembrolizumab (Keytruda) therapy, and TMB testing is covered for all solid tumors for individuals being considered for pembrolizumab (Keytruda) therapy." Description, policy guidelines, and references updated with minor revisions. Added code 0268U and removed 81301 under the Billing/Coding section. Policy noticed 1/25/22 for effective date of 3/31/22. Medical Director review 1/2022. (jd)

5/17/22 Reviewed by Avalon 1st Quarter 2022 CAB. Policy guidelines revised; added Table of Terminology. Reference updated. Medical Director review 4/2022. (jd)

9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB, coding updates only. Removed Related Policy "Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS – M2109" due to archival. Updated Billing/Coding section. No change to policy statement. Medical Director review 7/2022. (tm)

5/16/23 Reviewed by Avalon 1st Quarter 2023 CAB. Description, Policy Guidelines and References updated. Related Policies section removed. Coverage criteria edited for clarity, no change in policy statement. Medical Director review 4/2023. (tm)

10/24/23 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Reimbursement to Medical Necessity. Table of Terminology removed. (tm)