BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

General Genetic Testing, Somatic Disorders AHS-M2146

File Name:	general_genetic_testing_somatic_disorders
Origination:	01/2019
Last CAP Review:	03/2021
Next CAP Review:	03/2022
Last Review:	04/2021

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 (Li et al., 2017; Raby, Kohlmann, & Venne, 2020).

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).

Related Policies
General Genetic Testing, Germline Disorders AHS – M2145
Whole Genome and Whole Exome Sequencing AHS – M2032
Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS – M2109

******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 or reimbursement 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. Genetic testing is covered for a specific genetic mutation or mutations that have documented clinical utility 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 hematologic cells.

2. Repeat testing is covered for recurrence monitoring, OR

3. Repeat testing is covered 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.

4. MSI testing for all solid tumors is considered medically necessary for individuals being considered for pembrolizumab (Keytruda) therapy.

5. TMB testing is covered for all solid tumors for individuals being considered for pembrolizumab (Keytruda) therapy.

Note: For more than 5 gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to policy AHS-R2162 Laboratory Procedures Medical Policy.

When General Genetic Testing, Somatic Disorders is not covered

Testing with a gene panel containing genes that do not meet the criteria in item 1 above is not covered.

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 (B. Raby, Blank, Robert, 2020). 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 (Raby et al., 2020).

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 (B. Raby, 2020). Estimates based on whole genome sequencing have placed the average amount of SNPs in any given individual at 2.8 to 3.9 million (B. Raby, 2020). 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 (B. Raby, 2020).

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 (B. Raby, 2020).

The sensitive genes that require or produce precise quantities of a protein product tend to suffer more from these variations (Bacino, 2019).

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 (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 (B. Raby, 2020). 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 (B. Raby, 2020). 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, Evrony, Cai, & Walsh, 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, Raut, Duensing, & Keedy, 2020). These GISTs are the most common mesenchymal tumor of the gastrointestinal tract that originate from the cell of Cajal (Comandini, Damiani, & Pastorino, 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 considered to be 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, Spyropoulos, Martin, and Moreno (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).

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 (MSI), 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, 2020a).

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 (NGS) 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 tends 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, 2020).

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 *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 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 is similar to the report by Nagahashi et al. (2019) which states that approximately 2.5% of *BRCA*1 & 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 (B. Raby, Kohlmann, Wendy, Venne, Vickie, 2020).

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 (B. Raby, Kohlmann, Wendy, Venne, Vickie, 2020).

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)."

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 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)."

Guidelines and Recommendations

Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) (Li et al., 2017)

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 (ie, 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 and 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) (NCCN, 2018, 2021)

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, 2018, 2021). Please see the individual policies

American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (Richards et al., 2015)

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 (ACMG) (Kalia et al., 2016)

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):

Condition	Gene(s)	Variants to Report
Breast/ovarian cancer	BRCA1, BRCA2	KP, EP
Li-Fraumeni syndrome	TP53	KP, EP
Peutz-Jeghers syndrome	STK11	KP, EP
Juvenile polyposis	BMPR1A, SMAD4	KP, EP
PTEN hamartoma syndrome	PTEN	KP, EP
Lynch syndrome	MLH1, MSH2, MSH6, PMS2,	KP, EP
Familial adenomatous polyposis	APC	KP, EP
MYH-associated polyposis	MUTYH	KP, EP
Von Hippel Lindau syndrome	VHL	KP, EP
Retinoblastoma	RB1	KP, EP
Tuberous sclerosis complex	TSC1, TSC2	KP, EP
Wilms tumor	WT1	KP, EP
Multiple endocrine neoplasia 1 or 2	MEN1 (1), RET (2)	KP
Familial medullary thyroid cancer	RET	KP
Hereditary paraganglionoma-pheochromocytoma syndrome	SDHD, SDHAF2, SDHC, SDHB	KP, EP for all but SDHAF2 (KP only)
Neurofibromatosis type 2	NF2	KP, EP
Hypertrophic or dilated cardiomyopathy	MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA	KP, EP for LMNA, GLA, MYBPC3, TNNT2, KP only for MYH7, TNNI3, MYL2
Catacholamenergic polymorphic ventricular tachycardia	RYR2	KP
Arrhythmogenic right ventricular cardiomyopathy	PKP2, DSP, DSC2, TMEM43, DSG2	KP, EP for all but DSP (KP only)

Romano-Ward Long QT syndromes, Brugada syndrome	KCNQ1, KCNH2, SCN5A	KP, EP for all
Familial hypercholesterolemia	LDLR, APOB, PCSK9	KP, EP for LDLR, KP only for APOB and PCSK9
Ehlers Danlos syndrome	COL3A1	KP, EP
Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysms and dissections	FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11	KP, EP for all
Malignant hyperthermia sensitivity	RYR1, CACNA1S	KP only
Wilson disease (copper metabolism)	ATP7B	KP, EP
Ornithine transcarbamylase deficiency (urea cycle)	OTC	KP, EP

American Society of Clinical Oncology (ASCO) (Konstantinopoulos et al., 2020; Robson et al., 2015)

The ASCO published guidelines regarding genetic and genomic testing for cancer susceptibility. These guidelines state that the "ASCO recognizes that concurrent multigene testing (ie, panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history… 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)."

European Society for Medical Oncology (ESMO) (Casali et al., 2018; Miller et al., 2020)

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)."

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).”

European Society for Medical Oncology (ESMO) Precision Medicine Working Group (2020) (Mosele et al., 2020)

ESMO released clinical practice guidelines on the use of NGS to evaluate patients with metastatic cancers. Overall, ESMO suggests that NGS should be used routinely in patients with metastatic cancers including advanced lung adenocarcinoma, prostate cancer, ovarian cancer, and cholangiocarcinoma. For colon cancer, NGS can be an alternative option to PCR if it does not incur additional costs.

ESMO also recommends that “based on the KN158 trial”, tumor mutational burden (TMB) should be tested in cervical cancers, salivary cancers, thyroid cancers, well- or moderately- differentiated neuroendocrine tumors, and vulvar cancers. ESMO notes that this trial found that pembrolizumab was effective for TMB-high cases of these cancer types.

Patients with other cancers may decide with their physician to order NGS on a large gene panel, if "pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit (Mosele et al., 2020)." ESMO states that more evidence is still needed to improve understanding on how to use NGS to treat patients based on precision biomarkers.

Recommendations according to cancer type are summarized below. Recommendations were provided based on the ESCAT scale ranking that calculates the number of patients that would need to be tested with NGS to identify one patient who could be matched to an effective drug. Level I means that the match between drug and genomic alterations has been validated in clinical trials and should drive treatment decision in daily practice. Level II means that alteration has been associated with phase I/phase II trials. Level III means that genome alteration has been validated in another cancer, but not for that specific one. Level IV are hypothetically targetable alterations based on preclinical data (Mosele et al., 2020).

Cancer Type	Recommendation
Lung Adenocarcinoma	“Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.
Squamous cell lung cancer	No current indication for tumour multigene NGS
Breast cancer	No current indication for tumour multigene NGS
Colon cancer	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost
Prostate cancer	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.
Gastric cancer	No current indication for tumour multigene NGS
Pancreatic cancer	No current indication for tumour multigene NGS
Hepatocellular carcinoma	No current indication for tumour multigene NGS

Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included) and if they report accurate ranking of alterations. RNA-based NGS can be used.
Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic *BRCA1/2* mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included) and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary. It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL [small-cell lung cancer] cancers if anti-PD1 antibody is not available otherwise) (Mosele et al., 2020)."

British Sarcoma Group (BSG) (Judson et al., 2017)

The BSG has published guidelines on the management of GIST and state that the majority of 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)."

Applicable Federal Regulations

A search for the phrase "somatic mutation" yielded 24 results on 2/11/2021. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

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, 2020b).

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

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: 81175, 81176, 81233, 81236, 81261, 81262, 81263, 81264, 81265, 81266, 81267, 81268, 81301, 81305, 81314, 81315, 81316, 81340, 81341, 81342, 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, 96040, S0265

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.

Scientific Background and Reference Sources

Bacino, C. (2019). Genomic disorders: An overview. Retrieved from https://www.uptodate.com/contents/genomic-disorders-an-overview?sectionName=COPY%20NUMBER%20VARIATIONS&topicRef=2895&anchor=H16722199&source=see_link#H16722199

Casali, P. G., Abecassis, N., Aro, H. T., Bauer, S., Biagini, R., Bielack, S., . . . Blay, J. Y. (2018). Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 29*(Suppl 4), iv267. doi:10.1093/annonc/mdy320

Comandini, D., Damiani, A., & Pastorino, A. (2017). Synchronous GISTs associated with multiple sporadic tumors: a case report. *Drugs Context, 6*, 212307. doi:10.7573/dic.212307

FDA. (2017). FoundationOne CDx. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=407172

FDA. (2019). MyChoice HRD CDx. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=440605

FDA. (2020a). FDA approves pembrolizumab for adults and children with TMB-H solid tumors. Retrieved from https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors

FDA. (2020b). Guardant360 CDx. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=454228

Hayano, T., Matsui, H., Nakaoka, H., Ohtake, N., Hosomichi, K., Suzuki, K., & Inoue, I. (2016). Germline Variants of Prostate Cancer in Japanese Families. *PLoS One, 11*(10), e0164233. doi:10.1371/journal.pone.0164233

Hulick, P. (2020). Next-generation DNA sequencing (NGS): Principles and clinical applications. Retrieved from https://www.uptodate.com/contents/next-generation-dna-sequencing-ngs-principles-and-clinical-applications?search=variant%20of%20unknown%20significance&source=search_result&selectedTitle=4~25&usage_type=default&display_rank=4

Judson, I., Bulusu, R., Seddon, B., Dangoor, A., Wong, N., & Mudan, S. (2017). UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). *Clin Sarcoma Res, 7*, 6. doi:10.1186/s13569-017-0072-8
Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., . . . Miller, D. T. (2016). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genetics In Medicine, 19*, 249. doi:10.1038/gim.2016.190
https://www.nature.com/articles/gim2016190#supplementary-information
Klempner, S. J., Fabrizio, D., Bane, S., Reinhart, M., Peoples, T., Ali, S. M., . . . Reddy, P. (2020). Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors: A Review of Current Evidence. *Oncologist, 25*(1), e147-e159. doi:10.1634/theoncologist.2019-0244
Konnick, E. Q., & Pritchard, C. C. (2016). Germline, hematopoietic, mosaic, and somatic variation: interplay between inherited and acquired genetic alterations in disease assessment. *Genome Med, 8*(1), 100. doi:10.1186/s13073-016-0350-8
Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., . . . Annunziata, C. M. (2020). Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *Journal of Clinical Oncology, 38*(11), 1222-1245. doi:10.1200/jco.19.02960
Kowalik, A., Zalewski, K., Kopczynski, J., Siolek, M., Lech, M., Hincza, K., . . . Gozdz, S. (2019). Somatic mutations in BRCA1&2 in 201 unselected ovarian carcinoma samples - single institution study. *Pol J Pathol, 70*(2), 115-126. doi:10.5114/pjp.2019.82905
Legrand, F., Renneville, A., MacIntyre, E., Mastrilli, S., Ackermann, F., Cayuela, J. M., . . . Kahn, J. E. (2013). The Spectrum of FIP1L1-PDGFRA-Associated Chronic Eosinophilic Leukemia: New Insights Based on a Survey of 44 Cases. *Medicine (Baltimore), 92*(5), e1-e9. doi:10.1097/MD.0b013e3182a71eba
Li, M. M., Datto, M., Duncavage, E. J., Kulkarni, S., Lindeman, N. I., Roy, S., . . . Nikiforova, M. N. (2017). Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn, 19*(1), 4-23. doi:10.1016/j.jmoldx.2016.10.002
Liu, S., Yu, Q., Han, W., Qi, L., Zu, X., Zeng, F., . . . Liu, J. (2014). Primary gastrointestinal stromal tumor of the prostate: A case report and literature review. *Oncol Lett, 7*(6), 1925-1929. doi:10.3892/ol.2014.1968
Marabelle, A., Fakih, M., Lopez, J., Shah, M., Shapira-Frommer, R., Nakagawa, K., . . . Bang, Y.-J. (2020). Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *The Lancet Oncology, 21*(10), 1353-1365. doi:10.1016/S1470-2045(20)30445-9
Martincorena, I., & Campbell, P. J. (2015). Somatic mutation in cancer and normal cells. *Science, 349*(6255), 1483-1489. doi:10.1126/science.aab4082
McCabe, C. D., Spyropoulos, D. D., Martin, D., & Moreno, C. S. (2008). Genome-wide analysis of the homeobox C6 transcriptional network in prostate cancer. *Cancer Res, 68*(6), 1988-1996. doi:10.1158/0008-5472.Can-07-5843
Merino, D. M., McShane, L. M., Fabrizio, D., Funari, V., Chen, S. J., White, J. R., . . . Allen, J. (2020). Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer, 8*(1). doi:10.1136/jitc-2019-000147
Miller, R. E., Leary, A., Scott, C. L., Serra, V., Lord, C. J., Bowtell, D., . . . Yates, L. R. (2020). ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Annals of Oncology, 31*(12), 1606-1622. doi:10.1016/j.annonc.2020.08.2102
Morgan, J., Raut, C., Duensing, A., & Keedy, V. (2020). Epidemiology, classification, clinical presentation, prognostic features, and diagnostic work-up of gastrointestinal stromal tumors (GIST) - UptoDate. Retrieved from https://www.uptodate.com/contents/epidemiology-classification-clinical-presentation-prognostic-features-and-diagnostic-work-up-of-gastrointestinal-stromal-

tumors-gist?search=PDGFRA&source=search_result&selectedTitle=1~40&usage_type=default&display_rank=1
Mosele, F., Remon, J., Mateo, J., Westphalen, C. B., Barlesi, F., Lolkema, M. P., . . . André, F. (2020). Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Annals of Oncology, 31*(11), 1491-1505. doi:10.1016/j.annonc.2020.07.014
Nagahashi, M., Shimada, Y., Ichikawa, H., Kameyama, H., Takabe, K., Okuda, S., & Wakai, T. (2019). Next generation sequencing-based gene panel tests for the management of solid tumors. *Cancer Sci, 110*(1), 6-15. doi:10.1111/cas.13837
NCCN. (2018). NCCN Clinical Practice Guidelines in Oncology. *NCCN Clinical Practice Guidelines in Oncology.* Retrieved from https://www.nccn.org/professionals/physician_gls/
NCCN. (2021). NCCN Guidelines® & Clinical Resources. Retrieved from https://www.nccn.org/professionals/physician_gls/
NCI. (2021). tumor mutational burden. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tumor-mutational-burden
Poduri, A., Evrony, G. D., Cai, X., & Walsh, C. A. (2013). Somatic Mutation, Genomic Variation, and Neurological Disease. *Science, 341*(6141), 1237758. doi:10.1126/science.1237758
Raby, B. (2020). Overview of genetic variation. Retrieved from https://www.uptodate.com/contents/genetic-testing
Raby, B., Blank, Robert. (2020). Genetics: Glossary of terms. Retrieved from https://www.uptodate.com/contents/genetics-glossary-of-terms?topicRef=2895&source=see_link
Raby, B., Kohlmann, W., & Venne, V. (2020). Genetic testing. Retrieved from https://www.uptodate.com/contents/genetic-testing?sectionName=Assessing%20the%20validity%20of%20a%20genetic%20test&topicRef=96539&anchor=H20&source=see_link#H20
Raby, B., Kohlmann, Wendy, Venne, Vickie. (2020). Genetic testing. Retrieved from https://www.uptodate.com/contents/genetic-testing?sectionName=Assessing%20the%20validity%20of%20a%20genetic%20test&topicRef=96539&anchor=H20&source=see_link#H20
Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., . . . Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med, 17*(5), 405-424. doi:10.1038/gim.2015.30
Robson, M. E., Bradbury, A. R., Arun, B., Domchek, S. M., Ford, J. M., Hampel, H. L., . . . Lindor, N. M. (2015). American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol, 33*(31), 3660-3667. doi:10.1200/jco.2015.63.0996
Terada, T. (2012). Small cell neuroendocrine carcinoma of the prostate: incidence and a report of four cases with an examination of KIT and PDGFRA. *Prostate, 72*(10), 1150-1156. doi:10.1002/pros.22464
Woodhouse, R., Li, M., Hughes, J., Delfosse, D., Skoletsky, J., Ma, P., . . . Dennis, L. (2020). Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. *PLOS ONE, 15*(9), e0237802. doi:10.1371/journal.pone.0237802

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

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)