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Corporate Medical Policy

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing AHS-M2066

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Description of Procedure or Service

Next generation sequencing (NGS) is a type of DNA sequencing technology that sequences many small fragments of DNA in parallel. This has been used for conditions such as cancer that may be caused by many different gene variants (Hulick, 2020).

Related Policies:
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146
Whole Genome Whole Exome Sequencing AHS-2032

******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 genetic cancer susceptibility panels using next generation sequencing 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 Genetic Cancer Susceptibility Panels are covered

Reimbursement is allowed for genetic counseling for testing for genetic cancer susceptibility using next generation sequencing. Pre-test genetic counseling is required and counselor intends to engage in post-test follow-up counseling.

Genetic cancer susceptibility panels* (see Notes 1 and 2) using next generation sequencing is considered medically necessary when all the following criteria are met:

a. Individual displays clinical features and/or has a family history consistent with a hereditary cancer syndrome as listed in the policies for BRCA (AHS-M2003), Lynch syndrome (AHS-M2004), and Familial Adenomatous Polyposis (AHS-M2024)

b. All genes in the panel are relevant based on the personal and family history for the individual

being tested

c. Specific mutation(s) in the genes on the panel contain(s) AMA CPT coding guideline required genes at a minimum.

d. The results of the genetic test will impact the management of the individual and likely improve health outcomes.

When Genetic Cancer Susceptibility Panels are not covered

All other genetic panels are considered investigational because the current scientific evidence is not yet sufficient to establish how test results from panels which include a broad number of genes may be used to direct treatment decisions and improve health outcomes associated with all components of the panels.

*Note 1: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

*Note 2: Concurrent ordering of multi-gene panel tests for a specific condition **is strictly prohibited**; only one multi-gene panel test may be ordered at a time for a specific condition.

Policy Guidelines

NGS allows for the rapid sequencing of multiple strands of DNA. It is not limited to one specific type of test; rather it encompasses numerous technologies that produce swift and high-volume sequencing. NGS can be used to sequence multiple genes, the exome, or even the entire genome. This is opposed to the traditional Sanger sequencing, which is more useful for sequencing a specific gene (ACMG, 2012; Hulick, 2020).

The NGS procedure typically includes the following steps: first the patient's DNA is prepared to serve as a template, then DNA fragments are isolated (on solid surfaces such as small beads) where sequence data is generated, then these results are compared against a reference genome. Any DNA sample may be used if the quality and quantity of that sample are sufficient, but the methods of library generation and data analysis often vary from panel to panel. Evaluating the results of a gene panel typically requires some expertise in bioinformatics. Since NGS reports data on any variants found, great care must be taken to evaluate these gene variants, especially variants of unknown significance (VUS) and secondary findings (Hulick, 2020; Rehm et al., 2013).

Panels that sequence multiple, specified genes are referred to as "targeted panels" and may range from 5 to over 1000 genes. Targeted panels are generally more cost-effective than whole exome or whole genome sequencing and are useful for conditions where many different genes may cause a disease phenotype. For example, nonsyndromic hearing loss may be caused by variants in over 60 genes and sequencing each gene individually would not be cost effective. Many companies have developed a wide variety of gene panels. From the FDA-approved MSK-IMPACT to well-validated proprietary panels, many different options of panel testing are available (Hulick, 2020).

Exome and genome sequencing may be necessary. The exome represents all the protein-encoding genes, and at least 85% of pathogenic mutations are found in the exome. The exome only represents approximately 1.5%-2% of the genome, thereby making it more cost effective than genome sequencing. The entire exome includes about 30 megabases compared to the genome's 3.3 gigabases. However, sequencing an entire genome may be useful as a pathogenic mutation may be in a non-coding region of the genome, such as gene regulation dysfunction. Most clinical NGS testing uses targeted panels or whole exome sequencing, and whole genome sequencing is only used in select cases (Hulick, 2020).

Clinical genomics play a significant part in treatment, diagnosis, and understanding of cancer. Assessment of multiple pathogenic genes has become a widely used technique with the rise of NGS technologies, and the NCCN often recommends genetic panels in certain clinical situations. Some panels may also test for other genetic

defects, such as microsatellite instabilities or expression levels of specific proteins. Evaluation of genomic information (somatic changes, inherited germline changes, and so on) is widely prevalent in treatment and diagnosis of numerous types of cancer (Hulick, 2020).

Clinical Validity and Utility

Findings such as pathogenic variants are traditionally confirmed by Sanger sequencing, which is considered the gold standard of gene sequencing (>99.99% accuracy). NGS has been shown to compare favorably to Sanger sequencing. In a study performed by Strom et al., 110 single-nucleotide variants (SNVs) were found by NGS, with 103 of those SNVs meeting the minimum quality score threshold of 500 set by the lab and 7 falling below this threshold. However, 109 of the 110 total SNVs were validated by Sanger sequencing (Strom et al., 2014). Another study focusing on the agreement between Sanger sequencing and NGS results found only 2 variants out of 5800 that did not have cross-method agreement. Overall, the agreement rate was 99.965%. The authors concluded that a single round of Sanger sequencing was "more likely to incorrectly refute a true-positive variant from NGS than to correctly identify a false-positive variant from NGS" (Beck, Mullikin, & Biesecker, 2016).

D'Haene et al. designed and validated a custom NGS panel for routine diagnosis of gliomas. 14 genes were included, which are as follows: *H3F3A, ACVR1, IDH1, PDGFRA, TERT, HIST1H3B, HIST1H3C, EGFR, BRAF, CDKN2A, PTEN, IDH2, TP54,* and *ATRX*. The 1p/19q codeletion was also included. The panel was first validated to 52 known glioma samples and then applied to 91 unknown brain lesions. For these brain lesions, a sensitivity of 99.4% and specificity of 100% was achieved. "Orthogonal" methods (such as in situ hybridization and immunohistochemistry) demonstrated high concordance with the panel (D'Haene et al., 2019).

NGS has utility in numerous clinical scenarios. For example, NGS may be useful in situations where:

- multiple genes cause the same phenotype
- other candidate genes were found to be normal
- sequencing individual genes would not be timely or cost effective (Hulick, 2020).

Discussions of utility may also revolve around what is done with the findings of a gene panel. For instance, a study by Zehir et al. focused on the MSK-IMPACT gene panel. This panel of 410 cancer-related genes was used to sequence 10945 tumors from 10336 patients. 36.7% (3792/10336) of these patients were found to have a "clinically actionable" gene variant, such as *TP53* and *KRAS*. Of these, 527 patients were enrolled in clinical trials (Zehir et al., 2017). NGS has also helped provide diagnostic information to patients. A study focusing on 382 patients with a previously undiagnosed condition used NGS technology to diagnose 98 patients with exome or genome sequencing, allowing for changes in diagnostic testing, treatment, and genetic counseling. A total of 31 new syndromes were defined as well (Splinter et al., 2018).

Surrey et al. evaluated the clinical utility of a custom NGS panel for pediatric tumors. Sequencing was performed on 367 pediatric cancer samples. The authors found that results from the panel testing were "incorporated successfully into clinical care" for 88.7% of leukemias and lymphomas, 90.6% of central nervous system (CNS) cancers, and 62.6% of non-CNS solid tumors. A diagnosis change occurred in 3.3% of cases, and 19.4% of patients had variants requiring further germline testing (Surrey et al., 2019).

Tayshetye et al. (2020) analyzed the clinical utility of NGS in tumor testing using FoundationOne, a validated NGS genomic profiling test. 157 NGS results were collected of many different tumor types, with 63% being stage IV cancer at the time of testing. With NGS analysis, 185 genes with mutations were found in the RTK/RAS pathway, PI3K pathway, p53 pathway and cell cycle pathway. Overall, 82% of the patients had a mutation that could be treated with an FDA-approved treatment. NGS results were used in treatment decisions for 18% of these patients and only 7% of the patients initiated therapy based on NGS results. The most common reason for not initiating NGS-based therapy was the lack of an FDA-approved medication used for that specific tumor type, as a major challenge is insurance approval for an off-label indication. The authors state that "while there are numerous potential benefits from the use of NGS, further studies are still needed to determine its full clinical utility (Tayshetye 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)."

State and Federal Regulations, as applicable

A search of the FDA Device database on 01/29/2021 for "gene panel" yielded 12 results, last updated 01/25/2021. 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 November 6, 2020, 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 311 genes, rearrangements in 3 genes, and copy number alterations in 3 genes. FoundationOne CDx also utilizes circulating cell-free DNA collected in FoundationOne® Liquid CDx Blood Sample Collection Kit to identify patients with non-small cell lung cancer, prostate cancer, ovarian cancer, or breast cancer who may benefit from treatment with the targeted therapies (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, 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, 2017a).

On June 29, 2017, the FDA approved Praxis Extended RAS Panel, by Illumina, Inc. The Praxis™ Extended RAS Panel is a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples (FDA, 2017b).

On June 22, 2017, the FDA approved Oncomine Dx Target Test, by Life Technologies Corporation. The Oncomine Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM Dx System (FDA, 2017c).

On December 19, 2016, the FDA approved FoundationFocus CDxBRCA, by Foundation Medicine, Inc. The FoundationFocus CDxBRCA is a next generation sequencing based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. The FoundationFocus CDxBRCA assay detects sequence alterations in BRCA1 and BRCA2 (BRCA1/2) gene (FDA, 2016).

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

Numerous gene panels have been recommended by the NCCN. Cancers, such as breast, ovarian, and leukemia, may be caused by many different gene variants, and the NCCN recommends panels in genetic testing for these conditions. These conditions are as follows:

Acute Lymphoblastic Leukemia (ALL):

The NCCN notes that NGS assays used to detect leukemia-specific fusion genes are in development, but are not recommended for MRD quantification outside a clinical trial (NCCN, 2020a).

Acute Myeloid Leukemia (AML):

The NCCN states that NGS analysis may be used for the ongoing management of AML and various phases of treatment" of gene mutations involved with AML such as *TP53* (NCCN, 2020b).

Breast Cancer:

NCCN notes that *NTRK* mutations may be detected with NGS (NCCN, 2021b).

Central Nervous Cancers:

Evaluation of *IDH1* and *IDH2* mutations is highly recommended. The most common mutation of *IDH1* of R132H is reliably screened by immunohistochemistry, but sequencing (through Sanger or NGS-based assays) of *IDH1* and *IDH2* may also be highly recommended in the appropriate contexts. NGS is included as a "standard sequencing method" (NCCN, 2020e).

Colon and Rectal Cancer:

NCCN recommends that sequencing for *RAS* and *BRAF* genes be performed if a patient is suspected or proven to have a metastatic synchronous adenocarcinoma. The NCCN does not recommend any sequencing method over another, but lists NGS and Sanger sequencing as possible methods (NCCN, 2020o, 2021d).

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia:

NCCN recommends assessing Minimal Residual Disease (MRD) using an assay with a sensitivity of 10^{-4} according to the standardized NGS method (NCCN, 2021c).

Esophageal and Esophagogastric Junction Cancers and Gastric Cancers:

NCCN recommends the use of NGS for assessing esophageal cancer and gastric cancer when there is limited diagnostic tissue available for testing and the patient is unable to undergo additional procedures. NGS can be considered instead of sequential testing for single biomarkers. NCCN notes that NGS has certain limitations; therefore, gold-standard assays (immunohistochemistry/in-situ hybridization) should be used whenever possible (NCCN, 2020f, 2020g).

Gastrointestinal Stromal Tumors:

NCCM recommends the use of NGS testing to identify alternative driver mutations such as *BRAF, NF1, NTRK,* and *FGFR* that could provide insight for a targeted therapy (NCCN, 2021e).

Multiple Myeloma:

NCCN notes NGS as a valid method for informing treatment decisions. For instance, NGS is listed as a way to assess minimum residual disease (MRD) and categorize responses to treatment. However, this criterion is based on recommendations from the International Myeloma Working Group.

In Version 4.2021 of the Multiple Myeloma guidelines, the NCCN commented that NGS panels may be "useful in certain circumstances" for bone marrow samples in the initial diagnostic workup stage (NCCN, 2021f).

Myelodysplastic Syndromes:

NCCN recommends that evaluation of mutations should include panels incorporate the 21 most frequently mutated genes, which are as follows: *TET2, DNMT3A, ASXL1, EZH2, SF3B1, SRSF2, U2AF1, ZRSR2, RUNX1, TP53, STAG2, NRAS, CBL, NF1, JAK2, CALR, MPL, ETV6, GATA2, DDX41, IDH1, IDH2, SETBP1, PHF6, BCOR, FLT3, WT1, NPM1, STAT3,* and *PPM1D.*

NCCN added in version 3.2021 that NGS has low sensitivity for the *KIT D816V* mutation. In this case, allele-specific PCR is more sensitive and recommended in patients with high clinical suspicion of mast cell disease (NCCN, 2021g).

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes

NCCN recommends that "NGS may be used to identify novel fusion gene or cryptic rearrangements when clinical suspicion is high and fluorescence in situ hybridization (FISH) for *PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, or FLT3* are negative. The impact on outcomes of additional mutations detected by NGS is unclear and further studies are needed to determine the impact of mutations on disease course (NCCN, 2020j)."

Myeloproliferative Neoplasms:

NCCN states that NGS may be useful in establishing clonality in selected circumstances, such as the "triple negative" of non-mutated *JAK2, CALR,* and *MPL.* The NCCN also notes that workup may include a multi-gene NGS panel that includes all three of *JAK2, CALR,* and *MPL* (NCCN, 2020k).

Ovarian Cancer:

The NCCN recommends NGS for *BRCA1/2* somatic mutations, as clinically indicated (NCCN, 2021h).

Pancreatic Adenocarcinoma:

The NCCN states that NGS may be used to detect "actionable somatic findings", such as *ALK, NRG1, NTRK, ROS1, BRAF, BRCA1/2, HER2, KRAS, PALB2,* and MMR deficiency-related genes (NCCN, 2020m).

B-Cell Lymphomas:

NCCN states that NGS may be used if a high suspicion of clonal process remains but other techniques have not clearly identified a clonal process. The NCCN states that an NGS panel including TNFRSF14 and STAT6 may be useful "under certain circumstances" for Follicular Lymphoma. NGS may also be useful for "treatment selection" (NCCN, 2021a).

T-Cell Lymphomas:

NCCN states that "NGS will usually identify clonal rearrangement of T-cell receptor genes". The NCCN also states that "genetic testing, including…NGS that detect[s] somatic gene abnormalities are often informative and in some cases essential for an accurate and precise diagnostic and prognostic assessment of T-cell lymphomas". The NCCN further notes *TET2*, *IDH1*, *IDH2*, *RHOA*, *DNMT3A*, *STAT3*, and *STAT5B* as mutations that may be detected with sequencing methods (NCCN, 2020s).

Non-Small Cell Lung Cancer (NSCLC):

The NCCN recommends that testing be performed in a "panel-based approach, most typically performed by next-generation sequencing (NGS)", if feasible. RNA-based NGS should be considered in patients without identifiable driver oncogene mutations, "especially in never smokers". The NCCN mentions NGS as a commonly used method for mutations such as EGFR and BRAF. However, the NCCN notes that NGS may be considered in biomarker analysis but cautions that not all types of alterations will be detected and to be aware of the nuances of NGS (NCCN, 2020l).

Prostate Cancer:

The NCCN recommends NGS cancer predisposition screening for *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2 (NCCN, 2020n).*

Small Bowel Adenocarcinoma:
Universal microsatellite instability (MSI) testing is recommended in all patients with a history of small bowel adenocarcinoma. NCCN recommends using NGS panels to test for MSI (NCCN, 2020p).

Soft Tissue Sarcoma:

NGS is mentioned among the techniques used to identify genetic aberrations in soft tissue sarcoma (NCCN, 2020q).

Systemic Mastocytosis:

NCCN recommends against NGS panels for detection of KIT D816V, citing their low sensitivity (approximately 5%). However, a myeloid mutation panel should be performed on bone marrow (although testing can be done on peripheral blood). Prognostically relevant mutations include *TET2*, *SRSF2*, *CBL*, *ASXL1*, *RUNX1*, *JAK2*, and *RAS* (NCCN, 2020r).

Genetic/Familial High-Risk Assessment for Colorectal Cancer:

NCCN states that there are numerous scenarios in which multi-gene testing may be more effective. For example, it may be useful for an NGS panel to be used if a condition may be caused by more than one gene, or if a patient has tested negative for a single syndrome but is suspicious but for another inherited condition.

The NCCN notes certain cons associated with panel testing, such as higher chance of identifying variants of unknown significance, unactionable variants, or variants that do not have a clear course of treatment. The NCCN also identifies two examples of clinical scenarios in which multi-gene testing should not be considered: "an individual from a family with a known pathogenic variant and no other reason for multi-gene testing, and as first-line testing when the family history is strongly suggestive of a known hereditary syndrome."

The NCCN does state that NGS can be used to assess microsatellite instability (MSI) in hereditary non-polyposis colorectal cancer (HNPCC). Analysis of whole exome sequencing data, whole genome sequencing data, or targeted genome sequencing data may be performed to evaluate MSI. If the laboratory has validated the NGS assay being used for HNPCC, confirmation by more traditional methods such as immunohistochemistry or PCR is not needed. Any patient with a tumor that demonstrates micro instability-high status by NGS should be referred to a cancer geneticist for germline mismatch repair (MMR) testing.

Overall, the NCCN acknowledges the significant benefits of panel testing, such as value compared to single gene sequencing, as well as providing more information for causes of illnesses, but states that choice of panel and testing is critical.

As a final aside, the NCCN is in agreement with the 2015 ASCO recommendations (NCCN, 2020i).

Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic Cancer:

The NCCN notes the following genes as "could potentially be included in a multi-gene test" for breast cancer: *BRCA1/2, ATM, BARD1, CHEK2, PALB2, TP53, PTEN, STK11,* and *CDH1*. For ovarian cancer, the following genes are mentioned: *BARD1, BRIP1, MRE11A, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D,* and *TP53* (NCCN, 2020h).

American Society of Clinical Oncology (ASCO)

ASCO released guidelines discussing tumor testing for epithelial ovarian cancer. In it, they recommend germline sequencing of *BRCA1/2* "in the context of a multigene panel" that includes "at minimum" the following genes: *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2,* and *PALB2* (Konstantinopoulos et al., 2020).

ASCO published guidelines regarding evaluating susceptibility to pancreatic cancer. In it, they recommend that germline genetic testing be performed using a multigene panel that includes the following genes: *APC, ATM, BRCA1/2, CDKN2A, MLH1, MSH2, MSH6, PMS2, EPCAM, PALB2, STK11, TP53.* An exception is if a genetic diagnosis has been previously confirmed in a family member; a panel should not be used in this case. Further, ASCO recommends that every patient diagnosed with pancreatic adenocarcinoma should undergo a risk assessment for hereditary syndromes associated with increased risk of pancreatic adenocarcinoma (Stoffel et al., 2018).

In 2015, ASCO published a policy statement update on genetic and genomic testing for cancer susceptibility that included recommendations for multi-gene panel testing for cancer susceptibility. ASCO recognizes that 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". ASCO notes that panel testing will identify variants of uncertain significance (VUSs) often, but that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility (Robson et al., 2015).

ASCO states that there is little consensus as to which genes should be on gene panels and that clinical utility is "the fundamental issue with respect to testing for mutations in moderate-penetrance genes". At this time (2015) there is insufficient evidence to "conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations" and that until these questions are answered, testing should be limited to mutations of established clinical utility (Robson et al., 2015).

American College of Medical Genetics (ACMG)

The ACMG published guidelines on inclusion criteria for genes with "various gene–disease evidence levels". For confirming a clinical diagnosis, the ACMG stated to include any gene associated (with a "moderate", "strong" or "definitive" association) with the disease, as long as the primary method of diagnosis was a "Disease-focused multigene panel or other non–sequencing-based ancillary assays". Genes with no emerging evidence or without evidence at all were to be excluded. Genes with emerging evidence should "typically" be excluded, although the

ACMG notes some inclusions that may be "meaningful". The ACMG also states that genes with this level of evidence should be reported with a statement that disease association and inheritance has not been established.

For panels intended to "Establish genetic diagnosis for clinically complex cases" and that are used for conditions primarily diagnosed through exome/genome sequencing, genes that have evidence levels of "definitive", "strong" and "moderate" should be included. Genes of unknown significance should be qualified with a statement that disease association and inheritance have not been completely established (Bean et al., 2019).

The ACMG recommends that the selection of genes and transcripts in any given panel be limited to genes with "sufficient scientific evidence for a causative role in the disease". Genes without clear evidence of association with the disease should not be included.

ACMG recommends validating diagnostic testing through another method such as Sanger sequencing.

ACMG cannot recommend a minimum threshold for "coverage" as many factors of the platform and assay may influence minimum coverage. However, the ACMG recommends that each laboratory independently validate their panel tests (Rehm et al., 2013).

ACMG released a statement regarding some points to consider for germline findings using NGS in patients undergoing tumor testing. ACMG states that NGS has some limitations that make it harder to identify some types of germline variants, such as genomic rearrangements, large insertions/deletions, or expansion/contraction of repetitive sequences. In addition, the assay and analytical performance varies between laboratories. Therefore, confirmation with an orthogonal method such as PCR, microarray, or multiplex ligation-dependent probe amplification (MLPA) is recommended (Marilyn M. Li et al., 2020).

Center for Medical Technology Policy (CMTP): Green Park Collaborative

In 2015, the Green Park Collaborative recommended that panels containing from 5 to 50 genes should be covered when the following criteria are met:

A subset of at least 5 constituent genes or variants is cited in the label of an FDA-approved companion diagnostic indicated for the treatment, designated as standard of care for the underlying condition by molecular testing committees of at least 3 National Cancer Comprehensive Network (NCCN) member institutions, or recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the NCCN or other guidelines that meet the IOM criteria for clinical guidelines.

OR

The provider has submitted two peer-reviewed journal articles of studies designed to demonstrate the safety and effectiveness of using the genomic information in question for clinical management of the patient's diagnosis and support the conclusion that use of the information is reasonably likely to provide a health benefit for the patient.

AND, in all cases:

The cost of analysis by NGS does not exceed the cost of individual sequencing of the target genes by other methods, AND the laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing. (CMTP, 2015)

The Collaborative proposed panels over 50 genes that "should be considered" for coverage if providers have sought prior authorization demonstrating the following diagnoses:

- Stage IV adenocarcinoma of the lung
- Carcinoma of unknown primary site

- Stage IV rare or uncommon solid tumors for whom no systemic treatment exists in clinical care guidelines and/or pathways;
- Stage IV solid tumors where the median overall survival is less than two years (such as pancreatic cancer)
- Stage IV solid tumors and has exhausted established guideline-driven systemic therapy options and requisite molecular testing and maintains functional status (ECOG score 0-2) OR
  newly diagnosed hematologic malignancies with limited treatment options in defined clinical care guidelines (CMTP, 2015).

Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists (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."

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 haven't 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).

European Society for Medical Oncology (ESMO) Precision Medicine Working Group (2020)

ESMO released clinical practice guidelines on the use of NGS to diagnose tumors. 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. Tumor mutational burden (TMB) should be tested in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumors, and vulvar cancer. 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 payers taking into account the overall cost of the strategy (drug included) and if they report accurate ranking of alterations. 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 p 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 sp agreements with payers taking into account the overall cost of the strategy (drug included) and if they report accurate rankir 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 p can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug inclu 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 differenti neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 anti is not available otherwise) (Mosele et al., 2020)."

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: 0101U, 0102U, 0103U, 0129U, 81432, 81433, 81434, 81435, 81436, 81437, 81438, 81442, 81455, 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.

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Medical Director review 4/2019

Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

Medical Director review 4/2021

Policy Implementation/Update Information

1/1/2019	New policy developed. BCBSNC will provide coverage for genetic cancer susceptibility panels using next generation sequencing when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
4/16/19	Reviewed by Avalon 4th Quarter 2018 CAB. Under "When Covered" revised bullet d. Medical Director review 4/2019. (lpr)
7/1/19	Added PLA codes 0101U, 0102U, 0103U, 0104U to Billing/Coding section for effective date 7/1/19. (lpr)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
5/12/20	Specialty Matched Consultant Advisory Panel review 4/15/2020. Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Updated When Covered Section. Added Notes 1 and 2. Deleted Appendix 1. Updated Description, Policy Guidelines, References. (lpr)
7/1/21	Reviewed by Avalon 1st Quarter 2021 CAB. Medical Director review 4/2021. Updated Policy Guidelines and References. Under Billing/Coding section: added PLA code 0129U. (lpr)