

Corporate Medical Policy

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing AHS-M2066

File Name:	genetic_cancer_susceptibility_panels_using_next_generation_sequencing
Origination:	1/2019
Last CAP Review:	4/2020
Next CAP Review:	4/2021
Last Review:	4/2020

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

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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

Numerous genetic mutations are associated with certain types of hereditary cancer. Genetic testing using next generation sequencing technology allows for the analysis of multiple genes at one time (panel testing), and these panels are commercially available. The utility of these genetic panels will be reviewed, in comparison with testing for individual mutations.

Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for well-characterized mutations based on a clinical suspicion of which gene(s) may be the cause of the familial cancer. Panel testing involves testing for multiple mutations in multiple genes at one time.

Several companies, including Ambry Genetics and GeneDx, offer genetic testing panels that use next generation sequencing methods for hereditary cancers. Next generation sequencing refers to 1 of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic mutations that are of unclear clinical significance or which would not lead to changes in patient management. Currently available panels do not include all genes associated with hereditary cancer syndromes. In addition, these panels do not test for variants (ie, single nucleotide polymorphisms [SNPs]), which may be associated with a low, but increased cancer risk.

State and Federal Regulations, as applicable

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing. Ambry Genetics is CLIA licensed.

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):

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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 to obtain “a more comprehensive prognostic assessment” of gene mutations involved with AML such as *TP53* (NCCN, 2019a).

Breast Cancer:

NCCN notes that *NTRK* mutations may be detected with NGS (NCCN, 2020c).

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, 2019b).

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, 2019c, 2019l).

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 2.2020 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, 2019f).

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, 2019g).

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, 2019h).

Ovarian Cancer:

The NCCN recommends NGS for *BRCA1/2* somatic mutations, as clinically indicated (NCCN, 2019j).

Pancreatic Adenocarcinoma:

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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, 2019k).

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, 2020b).

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, 2020e).

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, 2019i).

Soft Tissue Sarcoma:

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

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, 2018).

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.”

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.

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As a final aside, the NCCN is in agreement with the 2015 ASCO recommendations (NCCN, 2019e).

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, 2019d).

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.

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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).

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 of the patient; OR
- A subset of at least 5 constituent genes or variants is recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the National Cancer Comprehensive Network (NCCN), or the American Society of Clinical Oncology (ASCO) or other guidelines that meet the IOM criteria for clinical guidelines; 10 OR
- A subset of at least 5 constituent genes are designated as standard of care for the underlying condition by the molecular testing committees of at least 3 NCCN member institutions; 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.

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)

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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).

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, 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.

Scientific Background and Reference Sources

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Medical Director review 4/2019

Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

Policy Implementation/Update Information

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| 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 4 th 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 1 st 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) |

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.