

## 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:** NA  
**Next CAP Review:** 4/2020  
**Last Review:** 9/2019

#### Description of Procedure or Service

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Next generation sequencing (NGS) is a term used to describe a DNA sequencing technology to decode DNA. Sequencing is performed on millions of small fragments of DNA in parallel. “The speed of sequencing and amounts of DNA sequence data generated with NGS are exponentially greater and are produced at significantly reduced costs” (Hulick, 2017).

***\*\*\*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

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**BCBSNC will provide coverage for genetic cancer susceptibility panels using next generation sequencing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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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

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Genetic cancer susceptibility panels using next generation sequencing is considered medically necessary for the following:

1. Pre-test genetic counseling is required and is considered medically necessary; and counselor intends to engage in post-test follow-up counseling.
2. Genetic cancer susceptibility panels\* (see Appendix 1) 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

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- c. Specific mutation(s) in the genes on the panel contain(s) AMA CPT coding guideline required genes at a minimum\* (see Appendix 1).
- 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

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The genetic panels that do not meet all of the above-mentioned criteria 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.

## Policy Guidelines

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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

Hulick (2017) provided an overview of clinical applications of next generation sequencing that stated that consideration of NGS as a diagnostic tool is appropriate in individuals for whom sequencing of a single gene is unlikely to provide a diagnosis. Examples include suspected genetic disorders in the following settings:

- “One of many potential genes may be responsible, and/or the clinician does not know which gene(s) to test because many different genes cause the same phenotype (eg, due to genetic heterogeneity).”
- “Obvious candidate genes have been tested and were found to be normal. This is especially applicable when the percentage of disease attributed to these candidate genes is low, and other potentially causative genes for the disorder are thought to exist but have not yet been identified. Such analyses are often aided by comparison of NGS

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results from affected and unaffected family members.”

- “It would be less costly and more efficient to sequence the entire genome, exome, or gene panel than to sequence individual candidate genes sequentially.”

The author noted that evaluation of severe intellectual disability or developmental delay believed to have a genetic etiology in a patient with a negative initial evaluation is a very common indication for using whole genome and whole exome sequencing. Another indication for NGS is the evaluation of an affected child and both parents ("trio sequencing") especially when the inheritance pattern is dominant, and a de novo mutation is suspected.

## Practice Guidelines and Position Statements

### National Comprehensive Cancer Network (NCCN)

The 2017 NCCN guidelines for hereditary forms of cancers stated that “the recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.” Multi-gene testing should be offered to patients and families in the context of professional genetic expertise for pre- and post-test counseling. NCCN recommended that “patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.” The guidelines stated that “there may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.” NCCN further recommended that “multi-gene testing can include intermediate penetrant (moderate-risk) genes” but cautions that “not all genes included on available multi-gene tests are necessarily clinically actionable”.

### American Society of Clinical Oncology (ASCO)

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 (Robson et al, 2015).

“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. Multigene panel testing will also identify variants of uncertain significance (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. 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. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history.”

ASCO stated that “so far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing (although common variants are rarely included). This heterogeneity presents a number of challenges.” ASCO further stated that “Clinical utility remains the fundamental issue with respect to testing for mutations in moderate-penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers.”

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ASCO recommended that “Until these questions are resolved, it remains appropriate to conduct limited testing for mutations in genes of established clinical utility suggested by the patient's history. Because of the complexities attendant on the interpretation of broad panel–based testing, it is particularly important that providers with particular experience in the assessment of inherited cancer risk be involved in the ordering and interpretation of these tests.”

## **American College of Medical Genetics (ACMG)**

In 2012, the ACMG released a policy statement outlining points to consider in the clinical application of genomic sequencing to the detection of germ-line mutations (ACMG, 2012). The ACMG stated that “although this is an area that will continue to evolve with further research and technological development, there are already instances in which genomic sequencing approaches can and should contribute to clinical care.” The ACMG recommended that WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

- “The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.”
- “A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.”
- “A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.”
- “A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.”

## **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

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the target genes by other methods, AND

- The laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing.

## Billing/Coding/Physician Documentation Information

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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](http://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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ACMG Board of Directors (2012). Points to consider in the clinical application of genomic sequencing. *Genetics in Medicine, 14*: 759-761  
Center for Medical Technology Policy: Green Park Collaborative (2015). Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology. Retrieved online in August 2017 from [http://www.cmtpnet.org/docs/resources/Full\\_Release\\_Version\\_August\\_13\\_2015.pdf](http://www.cmtpnet.org/docs/resources/Full_Release_Version_August_13_2015.pdf)

Hulick, P.J. (2017). Principles and clinical applications of next-generation DNA sequencing. Retrieved online in August 2017 from <https://www.uptodate.com/contents/principles-and-clinical-applications-of-next-generation-dna-sequencing#H16116036>

National Comprehensive Cancer Network (2017). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Retrieved online in August 2017 from [https://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_screening.pdf](https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf)

Robson, M.E., Bradbury, A.R., Arun, B., et al (2015). American Society of Clinical Oncology Policy Statement Update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol., 33*(31):3660-3667.

Medical Director review 4/2019

Medical Director review 8/2019

## 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<sup>th</sup> Quarter 2018 CAB. Under “When Covered” revised bullet d. Medical Director review 4/2019. (lpr)

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- 7/1/19 Added PLA codes 0101U, 0102U, 0103U, 0104U to Billing/Coding section for effective date 7/1/19. (lpr)
- 10/15/19 Reviewed by Avalon 2<sup>nd</sup> Quarter 2019 CAB. Deleted coding table from Billing/Coding section and deleted PLA code 0104U per October 1, 2019 code update. Medical Director review 8/2019. (lpr)

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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.

**\*Appendix 1: Approved hereditary cancer panel testing**

Lab	Test	Genes	81432	81433	81435	81436	81437
Myriad	myRisk Hereditary Cancer Update	28	Yes	Yes	Yes	Yes	No
Quest	myVantage	34	Yes	Yes	Yes	Yes	No
LabCorp	a. VistaSeq Hereditary Cancer Panel	27	Yes	Yes	Yes	Yes	No
	b. VistaSeq Breast and GYN panel	23	Yes	Yes	No	No	No
	c. VistaSeq Colorectal Cancer panel	20	No	No	Yes	Yes	No
	d. VistaSeq Endocrine Panel	13	No	No	No	No	Yes
	d. VistaSeq Hereditary Cancer Panel without BRCA	25	No	No	Yes	Yes	No
Ambry	a. CancerNext	34	Yes	Yes	Yes	Yes	No
	b. ColoNext	17	No	No	Yes	Yes	No
	c. OvaNext	25	Yes	Yes	No	No	No
Counsyl (Myriad)	Reliant Cancer Screen Comprehensive	29	Yes	Yes	Yes	Yes	No
GeneDx/Genepath (Bioreference)	a. Comprehensive Common Cancer Management Panel	46	Yes	Yes	Yes	Yes	No
	b. Common Cancer Management Panel	37	No	No	Yes	Yes	No
	c. Colorectal Cancer Panel	19	No	No	Yes	Yes	No
	d. PGL/PCC (Paraganglioma/Pheochromocytoma) Panel	12	No	No	No	No	Yes
Invitae	a. Common Hereditary Cancers Panel	46	Yes	Yes	Yes	Yes	No
	b. Multi- Cancer Panel	83	Yes	Yes	Yes	Yes	No
	c. Breast and Gyn Cancers Panel	23	Yes	Yes	No	No	No
	d. Colorectal Cancer Guidelines-Based Panel	19	No	No	Yes	Yes	No
	e. Invitae Cancer Screen	61	Yes	Yes	Yes	Yes	No
	f. Invitae Colorectal Cancer Panel	29	No	No	Yes	Yes	No
	g. Invitae Breast and Gyn Cancers Guidelines-Based Panel	19	Yes	Yes	No	No	No