

Corporate Medical Policy

General Approach to Evaluating the Utility of Genetic Panels

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Description of Procedure or Service

This policy applies only if there is not a separate corporate medical policy (CMP) that outlines specific criteria for testing. If a separate CMP does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy.

Purpose. The purpose of this policy is to provide a framework for evaluating the utility of genetic panels that use newer genetic testing methodologies. In providing a framework for evaluating genetic panels, this policy will not attempt to determine the clinical utility of genetic testing for specific disorders per se. For most situations, this will mean that at least one variant in the panel has been already determined to have clinical utility and that clinical indications for testing have been established. Once the clinical utility for at least one of the included variants in the panel is established, then the focus is on whether the use of a panel is a reasonable alternative to individual tests.

Definition of a genetic panel. A genetic panel will be defined as a test that simultaneously evaluates multiple genes, as opposed to sequential testing of individual genes. This includes panels performed by next generation sequencing (NGS), massively parallel sequencing, and chromosomal microarray analysis (CMA) testing. The definition of a panel will not include panels that report on gene expression profiling, which generally do not directly evaluate genetic variants.

Background. New genetic technology, such as next generation sequencing and chromosomal microarray analysis, has led to the ability to examine many genes simultaneously. This in turn has resulted in a proliferation of genetic panels. Panels using next generation technology are currently available in the areas of cancer, cardiovascular disease, neurologic disease, mitochondrial disorders and for reproductive testing. These panels are intuitively attractive to use in clinical care because they can analyze multiple genes quickly, and may lead to greater efficiency in the work-up of genetic disorders. It is also possible that newer technology can be performed more cheaply than direct sequencing, although this may not be true in all cases.

Newer sequencing techniques were initially associated with a higher error rate than direct sequencing. While there is limited published data directly comparing the accuracy of NGS with direct sequencing, several publications in 2015 report that the concordance between NGS and Sanger sequencing was greater than 99% for cancer susceptibility testing, inherited disorders, and hereditary hearing loss. Another potential pitfall is the easy availability of a multitude of genetic information, much of which has uncertain clinical consequences. Variants of unknown significance are found commonly and in greater numbers with NGS compared with direct sequencing.

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The intended use for these panels is variable. For example, for the diagnosis of hereditary disorders, a clinical diagnosis may be already established, and genetic testing is performed to determine whether this is a hereditary condition, and/or to determine the specific variant that is present. In other cases, there is a clinical syndrome (phenotype) with a broad number of potential diagnoses, and genetic testing is used to make a specific diagnosis. For cancer panels, there are also different intended uses. Some panels may be intended to determine whether a known cancer is part of a hereditary cancer syndrome. Other panels may include somatic variants in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select best treatment.

There is no standardization to the makeup of genetic panels. Composition of the panels is variable, and different commercial products for the same condition may test a different set of genes. The make-up of the panels is determined by the specific lab that has developed the test. In addition, the composition of any individual panel is likely to change over time, as new variants are discovered and added to the existing panels.

Despite the variability in the intended use and composition of panels, there are a finite number of broad panel types that can be identified and categorized. Once categorization is done, specific criteria regarding the utility of the panel can then be developed for each category. One difficulty with this approach is that the distinction between the different categories, and the distinction between the intended uses of the panels, may not be clear. Some panels will have features or intended uses that overlap among the different categories.

Related Policies:

General Genetic Testing, Germline Disorders AHS-M2145

General Genetic Testing, Somatic Disorders AHS-M2146

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing-M2066

Chromosomal Microarray-M2033

******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 Panels when it is determined to be medically necessary because the medical criteria and guidelines noted 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 Panels are covered

Genetic panels that use next-generation sequencing or chromosomal microarray analysis, and are classified in one of the categories below, may be considered medically necessary when all criteria are met for each category, as outlined in the Policy Guidelines Section:

Panels for hereditary or genetic conditions

- Diagnostic testing of an individual's germline to benefit the individual
- Testing of an asymptomatic individual to determine future risk of disease

Cancer panels

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- Testing of an asymptomatic individual to determine future risk of cancer
- Testing cancer cells from an individual to benefit the individual by identifying targeted treatment
- Serial testing in cancer cells to identify targeted treatment

Reproductive panels

- Carrier testing of the parent(s) - Preconception
- Carrier testing of the parent(s) – Prenatal (during pregnancy)
- In utero testing of a fetus

****Note:** Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (e.g., previous testing methodology is inaccurate or a new discovery has added significant relevant variants for a disease).

When Genetic Panels are not covered

Genetic panels that use next generation sequencing or chromosomal microarray that do not meet the criteria for a specific category are considered investigational.

Policy Guidelines

Genetic panels using next-generation technology or chromosomal microarray analysis are available for many clinical conditions. The major advantage of these genetic panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of genetic work-up. Limited published evidence reports that the analytic validity of these panels approaches that of direct sequencing. The clinical validity and clinical utility of panels are condition-specific. The clinical validity of panels will reflect the clinical validity of the underlying individual variants. The clinical utility of panels will depend on the context in which they are used, for example whether the advantages of panel testing outweigh the disadvantages for the specific condition under consideration. Disadvantages of the panels are that their accuracy may be lower compared with direct sequencing and that the impact of a large amount of ancillary information may be uncertain.

Panels can be classified into categories based on the intended use and composition of the panel. For each category of panels, specific criteria can be used to evaluate medical necessity. When all of the criteria for a given category of panels are met, that panel may be considered medically necessary.

Types of panels

Genetic panels are classified into three major categories: panels for genetic and hereditary conditions, cancer panels, and reproductive panels. Within these categories, sub-categories are created according to the intended use of the panels.

Panels for Genetic or Hereditary Conditions

These are generally single-gene disorders, which are inherited in Mendelian fashion. They are defined by a characteristic phenotype, which may be characteristic of a specific disease, or which may represent a syndrome that encompasses multiple underlying diseases.

The intended use of these panels may be for:

- Diagnostic testing of an individual's germline to benefit the individual. To confirm a suspected diagnosis in patients with signs and/or symptoms of the condition; or to

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identify a causative etiology for a clinical syndrome, for which there are multiple possible underlying conditions.

- Testing an asymptomatic individual to determine future risk of disease.

There are several variations of panels for use in diagnosis or risk assessment of genetic or hereditary conditions. For the purposes of this policy, panels will be divided into the following types:

Panels containing variants associated with a single condition. They generally include all of the known pathogenic variants for a defined disease, and do not include variants associated with other diseases. An example of such a panel would be one that includes pathogenic variants for hypertrophic cardiomyopathy but doesn't include variants associated with other cardiovascular disorders. These panels can be used for diagnostic or risk assessment purposes.

Panels containing variants associated with multiple related conditions. They include all of the known pathogenic variants for a defined disease, and variants associated with other related disorders. An example of such a panel would be a pan cardiomyopathy panel that includes pathogenic variants for hypertrophic cardiomyopathy and other types of cardiomyopathy, such as dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. These panels can be used for diagnostic or risk assessment purposes.

Panels containing variants for clinical syndromes that are associated with multiple distinct conditions. These panels include variants that are associated with multiple potential disease states that define a particular clinical syndrome. In general, a specific diagnosis cannot be made without genetic testing, and genetic testing can identify one among a number of underlying disease states that manifests as a clinical syndrome. An example of this type of panel is a panel for intellectual disability that includes variants associated with many potential underlying disease states. These panels are used for diagnostic purposes.

Cancer panels

- Genetic panels for cancer can be of several types, and may test for either germline or somatic variants. The intended purpose of these panels can be for:
 - Testing an asymptomatic patient to determine future risk of cancer
 - Therapeutic and serial testing of cancer cells from an affected individual to benefit the individual by directing targeted treatment based on specific somatic variants.

There are variations of panels for use in risk assessment or for directing targeted treatment. For the purposes of this policy, panels will be divided into the following types:

Panels containing multiple variants indicating risk for a specific type of cancer or cancer syndrome (germline variants). These panels contain multiple related variants that indicate susceptibility to one or more cancers. They include germline variants and will generally be used for risk assessment in asymptomatic individuals who are at risk for variants based on family history or other clinical data. An example of this type of panel would be a panel testing for multiple BRCA1 and BRCA2 variants associated with hereditary breast and ovarian cancer syndrome.

Panels containing multiple variants that are associated with a wide variety of cancer types (somatic variants). These panels are generally used to direct treatment with drugs that target specific variants. They test for somatic variants from tissue samples of existing cancers. Many of these somatic variants are found across a wide variety of solid tumors. An example of this type of panel is the CancerNext panel (Ambry genetics) that tests for a broad number of somatic variants that can direct treatment.

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Reproductive panels test for variants that are associated with heritable conditions and are intended either for:

- Carrier testing of parent(s) preconception
- Carrier testing of parent(s) postconception (during pregnancy)
- preimplantation testing
- prenatal (in utero) testing

Preconception testing usually tests for variants that are autosomal recessive or X-linked, or in some cases, for autosomal dominant variants with late clinical onset. Preconception tests can be performed on parents who are at risk for a variants based on family history, or can be done as screening tests in parents without a family history suggestive of a variant. Prenatal testing refers to tests that are performed during a pregnancy. At the present time, prenatal testing for genetic variants is performed on the fetus, using amniocentesis or chorionic villous sampling. Testing of maternal blood for chromosomal aneuploidy is currently available, and in the future it may be possible to test for fetal variants using maternal blood.

There are variations of panels for use in preconception or prenatal testing. For the purposes of this policy, panels will be divided into the following types:

Panels containing variants associated with a single disorder. These panels are generally performed in at-risk individuals who have a family history of a heritable disorder. An example of this type of panel would be a cystic fibrosis gene panel that is intended for use in individuals with a family history of cystic fibrosis.

Panels containing variants associated with multiple disorders. These panels are generally performed as screening tests for parents who do not have a family history of a heritable disorder. They can also be used to evaluate individuals without a family history of a heritable disorder. An example of this type of panel is the Signature Prenatal Microarray Panel.

Criteria to be used in evaluating genetic panels

The following is a list of all the criteria that can be applied to evaluating genetic panels, with an explanation of the way the criteria are to be defined and applied. Not all criteria will apply to all panels.

Test is performed in a Clinical Laboratory Improvement Amendment (CLIA)-licensed lab

- Testing is performed in a laboratory licensed under CLIA for high-complexity testing. This requires delivery of a reproducible set of called, quality filtered variants from the sequencing platform.
- These calculations should occur prior to variant annotation, filtering, and manual interpretation for patient diagnosis.

Analytic validity of panels approaches that of direct sequencing

- The analytic validity for detecting individual variants, compared to the gold standard of conventional direct Sanger sequencing or other conventional method of testing, is reported. (The testing methods are clearly described, and the overall analytic validity for that type of testing is defined.)
- Any decrease in analytic sensitivity and specificity is not large enough to result in a clinically meaningful difference in diagnostic accuracy (clinical validity)

Clinical utility has been established for at least one component of the panel

- For each panel, there is a least one variant included for which clinical utility has been established.
- The patient meets the clinical indications for testing of that variant.

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Panel testing offers substantial advantages in efficiency compared to sequential analysis of individual genes

The composition of the panel is sufficiently complex such that next generation sequencing, or chromosomal microarray analysis, is expected to offer considerable advantages. Complexity of testing can be judged by:

- The number of genes tested
- The size of the genes tested
- The heterogeneity of the genes tested

The impact of ancillary information is well-defined

If a panel contains both indicated variants and non-indicated variants, the probability that the results of non-indicated variants impacts the patients is considered, taking into account the following possibilities:

- The information may be ignored (no further impact).
- The information may result in further testing or changes in management.
- Positive impact
- Negative impact
- The probability is that the results of non-indicated tests cause a negative impact on the patient.

Decision making based on genetic results is well-defined

- Results of the genetic test will lead to changes in diagnosis and/or treatment.
- The potential changes in treatment are defined prior to testing, and are in accordance with current standard or care.
- Changes in diagnosis or management are associated with improvements in health outcomes.
- For prenatal and preconception testing, alterations in reproductive decision making are expected, depending on the results of testing

Yield of testing is acceptable for the target population

The number of individuals who are found to have a pathogenic variant, in relation to the total number of individuals tested, is reasonable given the underlying prevalence and severity of the disorder, and the specific population that is being tested.

- It is not possible to set an absolute threshold for acceptable yield across different clinical situations. Some guidance can be given from clinical precedence as follows:
 - For preconception and prenatal (testing), testing for trisomy 21 is well established in clinical care. In general, testing for trisomy 21 is recommended when the likelihood of a positive result is in the 1 in 200 to 1 in 300 range, such as for individuals 35 years or older.
 - For diagnosis of hereditary disorders, genetic testing is generally performed when signs and symptoms of disease are present, including family history. The likelihood of a positive genetic test depends on the accuracy of the signs and symptoms (pre-test probability of disorder), and the clinical sensitivity of genetic testing. For disorders such as testing for congenital long QT syndrome and Duchenne's muscular dystrophy, the likelihood of a positive result in patients with signs and symptoms of disease is greater than 10%.
 - For cancer susceptibility, testing is recommended for genetic abnormalities such as BRCA and Lynch syndrome when the likelihood of a positive result is in the range of 2-10%.
 - For a clinical syndrome that has multiple underlying etiologies, such as developmental delay in children, chromosomal microarray analysis is recommended when the likelihood of a positive result is in the 5-20% range.
- There is increase in yield over alternate methods of diagnosis, and this increase is clinically significant.

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Other issues to consider

- Most tests will not, and possibly should not, be ordered by generalists.
 - Guidance for providers is appropriate on the expertise necessary to ensure that test ordering is done in optimal fashion.
- Many tests, particularly those for inherited disorders, should be accompanied by patient counseling, preferably by certified genetic counselors.
 - Counseling may be needed both before and after testing, depending on the specific condition being tested.

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.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: Effective in 2013, if a specific analyte is listed in codes 81200-81355 or 81400-81408, that CPT code would be reported along with the unlisted code 81479 (1 unit) for any analytes on the panel that are not listed in the CPT codes. If none of the analytes on the panel are listed in the more specific CPT codes, unlisted code 81479 would be reported for the whole test.

If the panel utilizes an algorithmic analysis of the results of the component tests to produce a numeric score or probability, it would be a multianalyte assay with algorithm analysis (MAAA) and reported with one of the specific codes in the 815XX section or appendix O in CPT. If there is no specific code listed, the unlisted MAAA code 81599 would be used.

Applicable Codes : 81434, 81437, 81438, 81442

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

Choi M, Scholl UI, Ji W et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A* 2009; 106(45):19096-101.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768590/>

National Center for Biotechnology Information (NCBI). Genetics and Medicine. Retrieved from <http://www.ncbi.nlm.nih.gov/guide/genetics-medicine/>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92, 6/13/13

Specialty Matched Consultant Advisory Panel review 1/2014

Medical Director review 1/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92, 5/22/14

Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nat Rev Genet* 2012; 13(12):878-90.

Chinnery PF. Mitochondrial Disorders Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*(R). Seattle (WA)2014.

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DaRe JT, Vasta V, Penn J et al. Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity. *BMC Med Genet* 2013; 14:118.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.117, 6/12/14

Medical Director review 8/2014

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92, 4/23/15

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.117, 5/21/15

Specialty Matched Consultant Advisory Panel review 3/2016

Medical Director review 3/2016

Kohda M, Tokuzawa Y, Kishita Y, et al. A comprehensive genomic analysis reveals the genetic landscape of mitochondrial respiratory chain complex deficiencies. *PLoS Genet.* Jan 2016;12(1):e1005679. PMID 26741492

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.117, 6/2016

Medical Director review 6/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92 1/2016

Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92 6/2017

Medical Director review 6/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.92 12/2017

Specialty Matched Consultant Advisory Panel review 3/2018

Medical Director review 3/2018

Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Policy Implementation/Update Information

8/27/13 New policy developed. Genetic panels that use next-generation sequencing or chromosomal microarray, and are classified in one of the test categories, may be considered medically necessary when all criteria are met for each category, as outlined in the Policy Guidelines Section. Medical Director review 7/2013. (mco)

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- 2/25/14 Specialty Matched Consultant Advisory Panel review 1/2014. Medical Director review 1/2014. (mco)
- 8/12/14 Added the following statement to the “When not Covered” section: “Genetic testing for mitochondrial disorders using expanded panel testing is considered investigational.” Added panel names and laboratories to the Description section. References updated. Policy Guidelines updated. Medical Director review 8/2014. (mco)
- 12/30/14 Added CPT codes 81440, 81460 and 81465 to the Billing/Coding section for effective date 1/1/2015. (td)
- 5/26/15 Added the following statement under “When Covered” section: Note: “Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (e.g., previous testing methodology is inaccurate or a new discovery has added significant relevant mutations for a disease).” References updated. Specialty Matched Consultant Advisory Panel review 4/2015. Medical Director review 4/2015. No change to policy intent. (td)
- 7/28/15 Description section updated. When Covered section updated. Policy Guidelines section updated. References updated. Policy Statements unchanged. (td)
- 12/30/15 Billing/Coding section updated to add codes: 81434, 81437, 81438, 81442 effective 1/1/16. (td)
- 4/29/16 Added the following under “When Covered” section: “Serial testing in cancers cells to identify targeted treatment”. Specialty Matched Consultant Advisory Panel review 3/2016. Medical Director review 3/2016.
- 7/26/16 References updated. Medical Director review 6/2016. (jd)
- 12/30/16 Minor revisions to policy guidelines section. No change to policy statement/intent. (jd)
- 4/28/17 Specialty Matched Consultant Advisory Panel review 3/2017. Medical Director review 3/2017. (jd)
- 7/28/17 Under Description section, the table for Genetic Panel Testing for Mitochondrial Disorders was updated with current laboratories that offer panel testing. No change to policy intent. Medical Director review 6/2017. (jd)
- 4/13/18 Genetic nomenclature updated throughout policy, replacing “mutation” with “variant”. References updated. Specialty Matched Consultant Advisory Panel review 3/2018. Medical Director review 3/2018. (jd)
- 4/1/19 Policy revised: removed “Genetic Testing Panels for Mitochondrial Disorders” and corresponding table from the Description section and “Panels for Mitochondrial Disorders” along with corresponding language from Policy Guidelines. See Genetic Testing of Mitochondrial Disorders AHS-M2085. Removed General Approach to Genetic Testing from the Related Policies and added General Genetic Testing AHS-M2145, General Genetic Testing, Somatic Disorders AHS-M2146, Genetic Cancer Susceptibility Panels Using Next Generation Sequencing-M2066, Chromosomal Microarray-M2033 The following statement removed from the When Not Covered section: “Genetic testing for mitochondrial disorders using expanded panel testing is considered investigational.” Removed the following codes from the Billing/Coding section: 81440, 81460, (jd)

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8/13/19 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)

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