

Corporate Medical Policy

General Genetic Testing, Germline Disorders AHS – M2145

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Description of Procedure or Service

Germline variants or mutations are defined as a genetic alteration that occur within the germ cells (egg or sperm), such that the alteration becomes incorporated into the DNA of every cell in the body of the offspring. It may also be called hereditary mutation (Li et al., 2017; NCI, 2017).

Genetic testing refers to the use of technologies that identify genetic variation, which include genomic, transcriptional, proteomic, and epigenetic alterations, for the prevention, diagnosis, and treatment of disease (Li et al., 2017; Raby, 2018b).

Related Policies

General Genetic Testing, Somatic Disorders AHS – M2146

Genetic Cancer Susceptibility Panels Using Next Generation Sequencing AHS – M2066

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for general genetic testing for germline disorders when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When General Genetic Testing for Germline Disorders is covered

1. Reimbursement is allowed for genetic counseling for genetic testing for germline disorders. Genetic counseling is required (IF TESTING IS NOT BEING ORDERED BY A SPECIALIST IN THE DISEASE PROCESS IN QUESTION (e.g. endocrinologist and maturity onset diabetes of youth gene evaluation)) for individuals prior to and after undergoing genetic testing for diagnostic, carrier, and/or risk assessment purposes.
2. Reimbursement is allowed for genetic testing of the individual's genome for inherited diseases once per lifetime, when the following criteria are met:

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- a. The individual for whom the test is requested is either:
- i. Currently symptomatic with suspicion of a known genetic disease where knowledge of mutation will assist in diagnosis, treatment, or procreative management, **OR**
 - ii. Currently asymptomatic but is judged to be at significant risk for an inherited disorder or cancer risk factor based on family history and/or ethnicity, **AND**, if being tested for risk of an adult-onset condition is at or above the age of majority, (e.g., 18 years), unless there is documented evidence that early intervention during childhood may prevent disease severity or time of disease onset, **OR**
 - iii. Asymptomatic but judged to be at risk as a carrier of an inherited disorder or cancer risk factor based on family history and/or ethnicity **AND** would benefit from procreative management
- b. Regarding the test being considered, **ALL** the following are met:
- i. Scientific literature shows association of specific a gene mutation (or mutations) is associated with the disease in question and is clinically actionable (there is clinical utility) with non-investigational treatment; **AND**
 - ii. Other testing for the disease is equivocal or does not exist and confirmation of gene mutation is standard of care for the disease state; **AND**
 - iii. Disease in question is associated with significant morbidity and/or mortality; **AND**
 - iv. Results of testing can impact clinical management via surveillance or treatment strategies and will guide decisions on healthcare management to mitigate symptoms or progression of the disorder.
3. Reimbursement is allowed for germline multi-gene panel testing (See Note 1), defined as multiple gene tests for a medical condition or symptoms/non-specific presentation run on one testing platform, according to the guidelines in the preceding coverage criteria and the reimbursement limitations (see section regarding Reimbursement below).

Note 1: For references regarding the clinical application of genomic sequencing and for appropriate medical coding, please refer to (ACMG, 2012; AMA, 2019).

When General Genetic Testing for Germline Disorders is not covered

Genetic testing of an individual's genome for inherited diseases is not covered in the following situations:

- i. For risk assessment of an individual's genome when the criteria defined above are not met
- ii. For inherited disease diagnosis or carrier assessment using panels of genes that include genes outside of those specifically related to the disease being investigated
- iii. Repeat germline testing of a unique gene using the identical method of gene analysis
- iv. Testing as a screening tool in the general population
- v. Direct-to-consumer genetic testing (e.g. mail order, online ordering, pharmacy, retail)

Policy Guidelines

Background

Gene mutations are referred to as “germline” if they are within gametes (ova and sperm). Therefore, these mutations may be passed on from parent to offspring (Raby & Blank, 2019). There are many different types of germline mutations, such as single nucleotide polymorphisms (SNPs), structural variations such as deletions, inversions, or translocations, smaller chromosomal abnormalities such as short tandem repeats, or gene fusions. Most mutations do not result in disease (Raby, 2018a).

SNPs are the most common type of genetic mutation, such as missense mutations. These mutations are single base-pair changes where one nucleotide is replaced with a different nucleotide. Over 65% of the diseases caused by genetic mutations are due to SNPs (Raby, 2018a). Estimates based on whole genome sequencing have placed the average amount of SNPs in any given individual at 2.8 to 3.9 million (Raby, 2018a). Insertion/deletion (indel) polymorphisms are often a single nucleotide but may be up to four nucleotides. SNPs often lead to frameshift mutations, which can cause premature stop codons and the failure of the allele (Raby, Kohlmann, & Venne, 2018).

Structural variations are usually classified as larger than 1000 base pairs. These include deletions, duplications, inversions, translocations, or ring chromosome formation. Due to the large number of genes affected, these variations commonly lead to severe genetic abnormalities. For example, a major cause of chronic myeloid leukemia is due to the translocation between chromosomes 9 and 22, resulting in a fused gene. The most common structural variation is the copy number variant (CNV), which refers to differing amounts of DNA segments in different individuals. For example, one person may have three copies of a specific segment whereas another may only have two. These variations may lead to dysregulation, gain-of-function, or loss-of-function of the affected genes (Raby, 2018a). The sensitive genes that require or produce precise amounts of a protein product tend to suffer more from these variations (Bacino, 2017).

Germline mutations are unique in that the risk for certain conditions, including many forms of cancer, may be passed from parent to offspring. Testing for these conditions will often involve testing entire families if one member is found to have a germline mutation; for example, the National Comprehensive Cancer Network (NCCN) guidelines for hereditary cancer recommend testing for *BRCA1/2*, *CDH1*, *PALB2*, *PTEN* and *TP53* mutations if any blood relative has a known or likely pathogenic variant in a cancer susceptibility gene (NCCN, 2019). Wilson et al. (2020) estimate that 21,800 adult survivors of childhood cancer in the United States carry a pathogenic or likely pathogenic variant in one of 156 cancer predisposition genes.

Other types of mutations are unique to germline mutations. Errors in chromosome number (aneuploidy) are typically caused by nondisjunctions in meiosis, causing either a monosomic (one chromosome) or a trisomic (three chromosomes) set of chromosomes. Most aneuploidies result in spontaneous abortions, but some aneuploidies, trisomy 21 or Down’s Syndrome being most notable, are compatible with life. Aneuploidies may also result with sex chromosomes, resulting in conditions such as Turner’s Syndrome (one X chromosome) or Klinefelter’s Syndrome (XXY) (Raby, 2018a).

Any size mutation may be pathogenic and must be classified as to how likely they are to cause disease. The American College of Medical Genetics (ACMG) has classified mutations in five categories, which are as follows: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. The “likely pathogenic” and “likely benign” refer to weaker evidence than their respective pathogenic and benign categories, and “uncertain significance” refers to evidence that does not meet criteria for benignity or pathogenicity or has conflicting evidence from both sides (Raby, 2018a). Prediction algorithms have been used to interpret variants and to predict whether a variant will affect the gene function or splicing of the gene. These algorithms are publicly available but have a tendency of predicting harmful impact of a variant. The specificity of these databases has been estimated at 60-80% (Li et al., 2017).

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Due to the enormous number of variants, as well as the rate that variants are discovered, comprehensive databases of genetic variants have been published and are easily available. For example, the Genome-Wide Repository of Associations Between SNPs and Phenotypes (GRASP) database includes information from over 2000 studies and over 1 million variant-related results (Raby, 2018a). Databases focusing on cancer-specific variants, reference sequences, and the general population are all available publicly (Li et al., 2017).

Clinical Validity and Utility

Genetic testing for germline mutations “can be conducted on virtually any tissue type,” although many laboratories prefer blood samples, cheek swabs or saliva samples (Raby, Kohlmann, & Hartzfeld, 2019). Advancements in technology and availability of sequencing, previously constrained by limitations of sequential single-gene testing on limited patient samples, have led to significant strides in the understanding of the genetic basis of inherited and somatic conditions.

Variants detected by genetic testing include inherited germline variants and somatic mutations; next generation sequencing (NGS) has allowed for superior detection for these mutations (Konnick & Pritchard, 2016). The accuracy of NGS varies depending on how many genes are sequenced; fewer genes tends to result in higher accuracy since there will be more “probe-template overlap.” Although Sanger sequencing remains the most accurate at >99.99% accuracy, it cannot sequence a large quantity of genes in a timely fashion and is best used for sequencing of a specific gene (Hulick, 2019). Pogoda et al. (2019) identified rare variants in the *ATM* gene by using single molecule Molecular Inversion Probes (smMIPs), an NGS-based screening method. A total of 373 patients with dystonia and six positive controls with previously identified *ATM* variants participated in this study. Results generated by the smMIPs “produced similar results as routinely used NGS-based approaches” (Pogoda et al., 2019). This suggests that *ATM* screening should be routinely used when genetic testing dystonia patients. Further, smMIPs may be an important technique for the germline screening for all rare neurodegenerative disorders.

The clinical validity of a genetic test depends primarily on the expressivity and penetrance of a given phenotype. Penetrance refers to the likelihood of developing a disease when the pathogenic mutation is present, and expressivity refers to the variations in the way the disease is expressed. For example, virtually any mutation in the *APC* gene will cause symptoms of familial adenomatous polyposis, thereby increasing the clinical validity of an *APC* assessment while other conditions may not clinically manifest at all despite a mutated genotype (Raby et al., 2018).

The clinical utility of a genetic test generally relies on available treatments for a condition. Conditions such as Huntington Disease that do not have many options for treatment will have limited clinical utility compared to another condition even though the actual test is highly valid. Factors, such as severity of the disease and management options, affect the clinical utility of a genetic test (Raby et al., 2018).

Guidelines and Recommendations

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

The ACMG and AMP released criteria on the types and severity of mutations, which are as follows:

- **Very strong evidence of pathogenicity:** Null variants (nonsense, frameshifts, canonical +/- 1-2 splice sites, initiation codon, exon deletions) in a gene where loss of function (LOF) is a known mechanism of disease. The guidelines note to use caution in genes where LOF is not a mechanism, if LOF variants are at the 3' end, if exon skipping occurs, and if multiple transcripts are present.

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- **Strong:** Amino acid change to a pathogenic version, de novo mutations, established studies supporting a damaging gene or gene product, or if the prevalence of the variant is increased in affected individuals compared to healthy controls. The guidelines note to be careful of changes impacting splicing and if only the paternity has been confirmed.
- **Moderate:** Located in a mutational hot spot or well-established functional domain (e.g., active site of an enzyme) without a benign variation, absent from controls in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium, detected in *trans* with pathogenic variants for a recessive disorder, protein length changes, novel missense changes where a different missense change has been pathogenic before, and a possible de novo mutation.
- **Supporting:** Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease, missense variant in a gene with low rate of benign missense variation, if the mutation has evidence that it is deleterious, or if the patient's phenotype is highly specific for disease with a single genetic cause.

The guidelines also list criteria for benign gene variants.

- **Stand-alone evidence of benignity:** Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
- **Strong:** Allele frequency is greater than expected for disorder, observed in healthy adult with full penetrance at early age, lack of segregation in affected family members (although pathogenic variants may masquerade as nonsegregated), or well-established studies that show no damaging effect on protein production.
- **Supporting:** Missense variant of a gene for which truncating mutations are pathogenic, indels in repetitive region of unknown function, silent variants, variants of unknown significance, or a *trans* version of a *cis* mutation (Richards et al., 2015).

National Comprehensive Cancer Network (NCCN) (NCCN, 2018, 2020)

Multiple germline mutations have been incorporated into the diagnostic workups recommended by the NCCN. Furthermore, the NCCN has several guidelines which recommend that gene expression profiling, or multiple gene testing, may be helpful, more efficient and/or cost-effective for selected patients (NCCN, 2018, 2020). Please see the individual policies.

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

The Joint Commission noted that germline variants should focus on the pathogenicity of a given variant rather than their impact on clinical care. The guidelines recommend reporting germline variants with known clinical impact, such as BRCA1 or 2. A genetic counseling recommendation should also be provided if a pathogenic germline mutation is found.

The guidelines note that it is critical to identify a somatic vs a germline mutation as the type of mutation may have significant clinical consequences. (Li et al., 2017).

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

The ASCO published guidelines regarding genetic and genomic testing for cancer susceptibility. These guidelines state that the "ASCO recognizes that concurrent multigene testing (ie, panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of

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cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history... ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history (Robson et al., 2015).”

Applicable Federal Regulations

Numerous FDA-approved tests exist for the assessment of mutations. 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.

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: 81105, 81106, 81107, 81108, 81109, 81110, 81111, 81112, 81161, 81173, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81187, 81188, 81189, 81190, 81204, 81228, 81229, 81233, 81234, 81236, 81237, 81238, 81239, 81247, 81248, 81249, 81252, 81260, 81271, 81274, 81283, 81284, 81285, 81286, 81289, 81305, 81307, 81308, 81312, 81320, 81343, 81344, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81443, 81479, 96040, 0129U, 0130U, 0138U, S0265, S3840

Reimbursement

1. If a procedure code is available for the multi-gene panel test, then this code is to be utilized (i.e. 81442 Noonan spectrum disorders genomic sequence analysis panel).
2. If there is not a specific next generation sequencing procedure code that represents the requested test, the procedure may be represented by a maximum of ONE unit of 81479 [unlisted molecular pathology procedure] (i.e. 81479 X 1 should account for all remaining gene testing) **OR** all genes tested on the panel must be represented by ALL appropriate Molecular Pathology Tier 1 or 2 procedure codes (with exception of 81479 x 1 only being listed once if it appropriately represents more than one gene in the panel)
3. ALL gene tests in the panel must be listed on the request and rationale for the clinical utility for the gene test must come from the ordering provider.
4. If ALL codes that represent the testing of the panel are not submitted, the test will be denied as not medically necessary due to incorrect coding process as neither laboratory or clinical reviewer should assign meaning to incomplete unspecified panel codes.

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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Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Policy Implementation/Update Information

- 1/1/2019 New policy developed. BCBSNC will provide coverage for general genetic testing for germline disorders when it is determined to be medically necessary because the criteria and guidelines are met. Billing/Coding section updated. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
- 7/16/19 Reviewed by Avalon 1st Quarter 2019 CAB. Related Policies added to Description section. Added item 3 and Note 1 to the When Covered sections as follows: “Germline multi-gene panel testing (See Note 1), defined as multiple gene tests for a medical condition or symptoms/non-specific presentation run on one testing platform, is considered medically necessary according to the guidelines in the preceding coverage criteria and the reimbursement limitations (see section regarding Reimbursement below). Note 1: For references regarding the clinical application of genomic sequencing and for appropriate medical coding, please refer to (ACMG, 2012; AMA, 2019).” Policy guidelines extensively revised. The following revisions were made to the Billing/Coding section: codes 81329, 81333, and 81336 were removed, code 81442 was added along with the reimbursement information. Medical Director review 5/2019. Policy noticed 5/14/19, for effective date 7/16/19. (jd)
- 9/10/2019 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)

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- 10/1/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Minor revisions Description section and Policy Guidelines, and references updated. Code table removed from Billing/Coding section. Medical Director review 9/2019. (jd)
- 11/12/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
- 2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. Billing/Coding section: removed the following codes – 81184, 81185, 81186, 81470, 81471. Medical Director review 12/2019. (jd)
- 5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Minor reformatting to When Covered section; policy guidelines and references updated. The following updates were made to the Billing/Coding section: removed G0452 and added 0129U, 0130U, 0138U, 81307, and 81308. Medical Director review 4/2020. (jd)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. The following codes were removed from the Billing/Coding section: 81361, 81362, 81363 81364. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

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