BlueCross BlueShield of North Carolina

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Corporate Medical Policy

General Genetic Testing, Germline Disorders AHS – M2145

File Name: general_genetic_testing_germline_disorders
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Description of Procedure or Service

Germline variants or mutations are defined as genetic alterations 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 a 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 (Kohlmann & Slavotinek, 2022, Li et al., 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

BCBSNC will provide coverage for general genetic testing for germline disorders when it is determined the medical criteria 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. For individuals who have received genetic counseling, single gene or multi-gene panel testing (see Note 1 and Note 2) for inherited diseases is considered medically necessary (once per patient lifetime) when **one** of the following criteria are met:

    a. The individual is currently symptomatic with the suspicion of a known genetic disease in which knowledge of the mutation will assist in the diagnosis, treatment, or procreative management.

    b. For asymptomatic individuals who are judged to be at significant risk (based on family history and/or ethnicity) for an inherited disorder or an inherited cancer risk factor, **and** meet one of the following conditions:

        i. The individual being tested for their risk of an adult-onset condition and is at or above the age of majority, (e.g., 18 years).
        ii. An individual not at or above the age of majority is being tested for their risk of an adult-onset condition for which there is documented evidence

that early intervention during childhood may prevent disease severity or time of disease onset.

c. For asymptomatic individuals who are both:

i. judged to be at risk as a carrier of an inherited disorder or cancer risk factor based on family history and/or ethnicity;
ii. would benefit from procreative management.

NOTES:
Note 1: Genetic tests being considered must meet all of the following conditions:

a. Scientific literature shows that a specific a gene mutation (or mutations) is associated with the disease in question and that identification of the mutation is clinically actionable (there is clinical utility) with a non-investigational treatment;
b. When confirmation of a gene mutation is standard of care for the disease state and other testing for the disease is either equivocal or does not exist;
c. The disease in question is associated with significant morbidity and/or mortality;
d. The 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.

Note 2: For 5 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

When General Genetic Testing for Germline Disorders is not covered

The following genetic tests for inherited diseases are not covered in the situations below:

a. Tests for genes that do not meet the above criteria.
b. Inherited disease diagnosis or carrier assessment using panels of genes that include genes outside of those specifically related to the disease being investigated.
c. Repeat germline testing of a unique gene using the identical method of gene analysis.
d. Testing as a screening tool for the general population
e. 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, 2022). There are many different types of germline mutations, such as single nucleotide polymorphisms (SNPs), structural variations such as deletions, inversions, or translocations, as well as smaller chromosomal abnormalities such as short tandem repeats, or gene fusions. Mutations may not necessarily result in disease (Christensen & Hulick, 2022).

Single nucleotide polymorphisms (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. Millions of SNPs have been identified through genome-wide association studies, approximately 4000 SNPs have a potential association with disease (Attia, 2022). 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 (Kohlmann & Slavotinek, 2022).

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 bases affected, these variations may lead to severe genetic abnormalities. For example, a major cause of Duchenne muscular dystrophy is the deletion of large portions of exons (coding portions of genes). 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. The sensitive genes that require or produce precise amounts of a protein product tend to suffer more from these variations (Bacino, 2022).

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, 2023a). 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.

Some 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. Some aneuploidies, trisomy 21, or Down 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) (Bacino, 2021; Schrijver, 2021).

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 and Genomics (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 (Christensen & Hulick, 2022). 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).

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 Haplotype Reference Consortium contains over 40 million identified SNPs (Christensen & Hulick, 2022). Databases focusing on cancer-specific variants, reference sequences, and the general population are all available publicly (Li et al., 2017).

For many years, single-gene testing was the standard approach for germline mutation testing. In recent years, multigene panel testing (MGPT) has been introduced and widely accepted as the first-tier test. MGPT increases the probability of identifying pathogenic mutations and represents an affordable application of next-generation sequencing (NGS) into clinical practice. However, the clinical utility of MGPT is not well established, especially in cases where more than one pathogenic variant is identified. The risk for a specific malignancy is complex and if a gene panel discovers a mutation incidentally,

management can be difficult. Many guidelines call for radical procedures for these disease states and it may cause unnecessary harm for the patient concerned about predisposition to the disease. Additionally, a combination of mutations may interact to alter the profile of the disease. For instance, certain combinations of mutations may be detrimental and increase the overall risk of cancer malignancy, while other combinations may reduce overall risk of malignancy. In this regard, identifying clinically actionable mutations may be unclear with MGPT (Slaught et al., 2021).

Clinical Validity and Utility

Genetic testing for germline mutations "can be conducted on virtually any tissue type," although many laboratories prefer blood samples, check swabs or saliva samples (Kohlmann & Slavotinek, 2022). 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 tend 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, 2022). Pogoda et al. (2019) identified rare variants in the *ATM* gene by using single molecule Molecular Inversion Probes (smMIPSs), 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 (Kohlmann & Slavotinek, 2022).

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 (Kohlmann & Slavotinek, 2022).

Lincoln et al. (2020) performed a retrospective study to investigate the yield and utility of germline testing on cancer patients following tumor DNA sequencing. The authors calculated the prevalence of pathogenic germline variants (PVG) and the potential actionability of the PVGs in 2023 cancer patients. 30.5% (n=617) of participants had PVGs. Participants with PVGs spanned all ages and cancer types. Tumor DNA sequencing missed 8.1% of PGVs. 11.2% of missed PVGs were only detected after developing a second primary cancer. The results suggest that missed PVGs could have been detected earlier and the second cancer could have been treated earlier or prevented. The authors concluded that germline testing following tumor DNA sequencing can result in important findings that can impact patient care (Lincoln et al., 2020).

There is an ethical concern associated with genetic testing for germline disorders, and patients can have mixed preferences about receiving their results. Although the information can be clinically useful, it can also be burdensome knowledge on patients and their families. Best et al. (2022) studied the preferences on receiving results in patients who have undergone germline genome sequencing. The study included 335 cancer patients and 199 of their relatives, all of whom were undergoing germline genome sequencing. "A significantly higher percentage of probands thought people would like to be informed about genetic conditions for which there is prevention or treatment that can change cancer risk compared to conditions for which there is no prevention or treatment (93% [311] versus 65% [216]; $p < 0.001$). Similar results were obtained for relatives (91% [180] versus 61% [121]; $p < 0.001$)." The authors also conducted interviews with 40 participants and identified four themes: "1) Recognised benefits of GS, (2) Balancing benefits with risks, (3) Uncertain results are perceived as unhelpful and (4) Competing obligations." The authors conclude by noting the importance in ensuring patient understanding of the relevant test validity and consent options (Best et al., 2022).

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)

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.
- **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)

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,2023b)) . Please see the individual policies.

Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP)

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 (Li et al, 2017).

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)

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 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)."

The ASCO released guidelines regarding germline testing for epithelial ovarian cancer. ASCO recommends that "all women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1, BRCA2,* and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history." In addition, "first- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene mutation or variant should be offered individualized genetic risk evaluation, counseling, and genetic testing." Lastly, "clinical decisions should not be based on a variant of uncertain significance (VUS)." In this case, the patient's clinical features and family history should be taken into consideration and should inform clinical decision making (Konstantinopoulos et al., 2020).

European Society for Medical Oncology (EMSO)

The EMSO published recommendations on the use of circular tumor DNA (ctDNA) assays in patients with cancer. Regarding germline disorders, the authors report that "Pathogenic germline variants in cancer susceptibility genes may be detected in ctDNA (such as BRCA1, BRCA2, PALB2), and detection of such variants requires reflex germline testing with a validated assay to confirm somatic versus germline nature." They also note that "Caution should be carried out in interpretation of pathogenic variants in high penetrance cancer susceptibility genes (such as BRCA1, BRCA2, PALB2); validated germline testing should be carried out to confirm germline or somatic nature" (Pascual et al., 2022).

The ESMO reports that ctDNA assays are validated and sensitive enough to "genotype advanced cancers and select patients for targeted therapies." They note that ctDNA assay results are limited by false-negative results and lower sensitivity for fusion and copy number changes, and ctDNA should not be used to detect molecular residual disease (Pascual et al., 2022).

The ESMO released recommendations for germline-focused analysis of tumor-only sequencing:

> "1. Germline-focussed tumour analysis should be carried out in all laboratories as part of routine analysis of a large tumour panel.
> 2. Germline-focussed tumour analysis can be delivered via an automated pipeline so as not to add substantial additional manual work, cost or delay to tumour analysis.
> 3. Variants in should be flagged which are (i) predicted to result in protein truncation in genes acting through loss-of-function and/or (ii) classified as Pathogenic/Likely Pathogenic via a well-maintained, comprehensive and curated clinical resource (ClinVar is recommended).
> 4. Germline-focussed tumour analysis can be restricted to variants of VAF >30% (SNVs) or >20% (small insertions/deletions). Local validation will be required to confirm the accuracy of tumour VAF estimates, especially for PCR-based NGS methodologies.
> 5. Samples known or suspected to be hypermutated should be included for germline-focussed tumour analysis.
> 6. Germline-focussed tumour analysis in the off-tumour context should be restricted to 'High Actionability- [cancer susceptibility genes] CSGs'.
> 7. Recessively acting 'High Actionability-CSGs' (currently MUTYH alone) should be included for germline-focussed tumour analysis but reporting and germ-line follow-up testing should be undertaken only on detection of two pathogenic variants.
> 8. Germline-focussed tumour analysis of 'standard actionability'-CSGs should be restricted to the on-tumour setting.
> 9. 'Standard actionability'-CSGs included for germline-focussed tumour analysis can be restricted to genes of high penetrance.
> 10. Germline-focussed tumour analysis can be restricted to gene-scenarios for which the germline conversion rate is >10%. For selected genes, it may therefore be appropriate to restrict germline-focussed tumour analysis to just those tumours arising age <30 years.
> 11. Formal variant review and classification should be undertaken by an experienced clinical scientist before initiation of patient re-contact and/or germline testing.
> 12. Before analysis of their germline sample for the pathogenic variant, adequate information should be provided to the patient regarding the implications of germline testing, along with documentation of their consent.
> 13. The tumour-observed pathogenic variant should be analysed in an appropriate germline sample (lymphocytes, saliva/buccal swab, normal tissue) in a laboratory accredited for germline analysis.
> 14. A patient in whom a germline pathogenic variant is detected should be referred to a specialist genetics service for long term follow-up and management of the family.
> 15. A normal/negative tumour sequencing result should not be taken as equivalent to a normal/negative germline result unless robust analysis of dosage has been carried out. This distinction is particularly important for genes such as BRCA1 and MSH2, for which whole exon deletion/duplications constitute a substantial proportion of pathogenic variants.
> 16. Re-evaluation of this workflow, revised analyses and update of these recommendations should be undertaken at least 2-yearly. Reanalysis should include updated data regarding pathogenicity of variants and penetrance of CSGs, along with review of thresholds for 'germline conversion rates' and VAF cut-offs" (Mandelker et al., 2019)

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; 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, 81329, 81333, 81336, 81337, 81343, 81344, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81441, 81442, 81443, 81470, 81471, 81479, 96040, 0130U, 0138U, 0230U, 0232U, 0236U, 0269U, 0270U, 0271U, 0272U, 0273U, 0274U, 0276U, 0277U, 0318U, 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

Attia, J. (2022, 05/20/2022). *Genetic association and GWAS studies: Principles and applications*. https://www.uptodate.com/contents/genetic-association-and-gwas-studies-principles-and-applications

Bacino, C. (2021, 03/16/2022). *Sex chromosome abnormalities*. https://www.uptodate.com/contents/sex-chromosome-abnormalities

Bacino, C. (2022, 06/22/2022). *Genomic disorders: An overview*. https://www.uptodate.com/contents/genomic-disorders-an-overview

Best, M. C., Butow, P., Savard, J., Jacobs, C., Bartley, N., Davies, G., Napier, C. E., Ballinger, M. L., Thomas, D. M., & Biesecker, B. (2022). Preferences for return of germline genome sequencing results for cancer patients and their genetic relatives in a research setting. *European Journal of Human Genetics*, 1-8. https://pubmed.ncbi.nlm.nih.gov/35277654/

Christensen, K., & Hulick, P. (2022, 08/23/2022). *Basic genetics concepts: DNA regulation and gene expression*. https://www.uptodate.com/contents/basic-genetics-concepts-dna-regulation-and-gene-expression

Hulick, P. (2022, 08/10/2022). *Next-generation DNA sequencing (NGS): Principles and clinical applications*. https://www.uptodate.com/contents/next-generation-dna-sequencing-ngs-principles-and-clinical-applications

Kohlmann, W., & Slavotinek, A. (2022, 10/07/2022). *Genetic testing*. https://www.uptodate.com/contents/genetic-testing

Konnick, E. Q., & Pritchard, C. C. (2016). Germline, hematopoietic, mosaic, and somatic variation: interplay between inherited and acquired genetic alterations in disease assessment. *Genome Med*, *8*(1), 100. https://doi.org/10.1186/s13073-016-0350-8

Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., Kohn, E. C., Levine, D. A., Liu, J. F., Lu, K. H., Sparacio, D., & Annunziata, C. M. (2020). Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *Journal of Clinical Oncology*, *38*(11), 1222-1245. https://doi.org/10.1200/jco.19.02960

Li, M. M., Datto, M., Duncavage, E. J., Kulkarni, S., Lindeman, N. I., Roy, S., Tsimberidou, A. M., Vnencak-Jones, C. L., Wolff, D. J., Younes, A., & Nikiforova, M. N. (2017). Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*, *19*(1), 4-23. https://doi.org/10.1016/j.jmoldx.2016.10.002

Lincoln, S. E., Nussbaum, R. L., Kurian, A. W., Nielsen, S. M., Das, K., Michalski, S., Yang, S., Ngo, N., Blanco, A., & Esplin, E. D. (2020). Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer. *JAMA Netw Open*, *3*(10), e2019452. https://doi.org/10.1001/jamanetworkopen.2020.19452

Mandelker, D., Donoghue, M., Talukdar, S., Bandlamudi, C., Srinivasan, P., Vivek, M., Jezdic, S., Hanson, H., Snape, K., Kulkarni, A., Hawkes, L., Douillard, J. Y., Wallace, S. E., Rial-Sebbag, E., Meric-Bersntam, F., George, A., Chubb, D., Loveday, C., Ladanyi, M., . . . Turnbull, C. (2019). Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group. *Ann Oncol*, *30*(8), 1221-1231. https://doi.org/10.1093/annonc/mdz136

NCCN. (2023a). *Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic - Version 2.2023*. Retrieved 2/15/21 from https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

NCCN. (2023b). *NCCN Guidelines® & Clinical Resources*. https://www.nccn.org/guidelines/category_1

NCI. (2017). *Definition of germline mutation* https://www.cancer.gov/publications/dictionaries/cancer-terms/def/germline-mutation

Pascual, J., Attard, G., Bidard, F. C., Curigliano, G., De Mattos-Arruda, L., Diehn, M., Italiano, A., Lindberg, J., Merker, J. D., Montagut, C., Normanno, N., Pantel, K., Pentheroudakis, G., Popat, S., Reis-Filho, J. S., Tie, J., Seoane, J., Tarazona, N., Yoshino, T., & Turner, N. C. (2022). ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from

the ESMO Precision Medicine Working Group. *Ann Oncol*, *33*(8), 750-768. https://doi.org/10.1016/j.annonc.2022.05.520

Pogoda, M., Hilke, F. J., Lohmann, E., Sturm, M., Lenz, F., Matthes, J., Muyas, F., Ossowski, S., Hoischen, A., Faust, U., Sepahi, I., Casadei, N., Poths, S., Riess, O., Schroeder, C., & Grundmann, K. (2019). Single Molecule Molecular Inversion Probes for High Throughput Germline Screenings in Dystonia. *Front Neurol*, *10*, 1332. https://doi.org/10.3389/fneur.2019.01332

Raby, B., & Blank, R. (2022). *Genetics: Glossary of terms*. Retrieved 2/15/21 from https://www.uptodate.com/contents/genetics-glossary-of-terms?topicRef=2895&source=see_link

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*, *17*(5), 405-424. https://doi.org/10.1038/gim.2015.30

Robson, M. E., Bradbury, A. R., Arun, B., Domchek, S. M., Ford, J. M., Hampel, H. L., Lipkin, S. M., Syngal, S., Wollins, D. S., & Lindor, N. M. (2015). American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*, *33*(31), 3660-3667. https://doi.org/10.1200/jco.2015.63.0996

Schrijver, I., Zehnder, James. (2021, 05/21/2021). *Chromosomal translocations, deletions, and inversions*. https://www.uptodate.com/contents/chromosomal-translocations-deletions-and-inversions

Slaught, C., Berry, E. G., Bacik, L., Skalet, A. H., Anadiotis, G., Tuohy, T., & Leachman, S. A. (2021). Clinical challenges in interpreting multiple pathogenic mutations in single patients. *Hereditary Cancer in Clinical Practice*, *19*(1), 15. https://doi.org/10.1186/s13053-021-00172-3

Wilson, C. L., Wang, Z., Liu, Q., Ehrhardt, M. J., Mostafavi, R., Easton, J., Mulder, H., Hedges, D. J., Wang, S., Rusch, M., Edmonson, M., Levy, S., Lanctot, J. Q., Currie, K., Lear, M., Patel, A., Sapkota, Y., Brooke, R. J., Moon, W., . . . Yasui, Y. (2020). Estimated number of adult survivors of childhood cancer in United States with cancer-predisposing germline variants. *Pediatr Blood Cancer*, *67*(2), e28047. https://doi.org/10.1002/pbc.28047

Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Medical Director review 4/2023

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)

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)

7/1/21 Reviewed by Avalon 1st Quarter 2021 CAB. The following codes were added to the Billing/Coding section for PPA effective 7/1/21: 0230U, 0232U, 0236U; code 0129U was removed from this section. Medical Director review. (jd)

9/7/21 Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)

7/1/22 Reviewed by Avalon 1st Quarter 2022 CAB. Policy guidelines updated; added Table of Terminology. The following codes were added to Billing/Coding section: 0269U, 0270U, 0271U, 0272U, 0273U, 0274U, 0276U, 0277U, 0318U. Medical Director review 4/2022. (jd)

12/30/22 Updated Billing/Coding section to add 81441 effective 1/2023. (tm)

2/7/23 Updated Billing/Coding section to include codes 81329, 81333, 81336, 81337, 81442, 81470, 81471, 0232U, 0230U. Related Policies section removed. (tm)

5/16/23 Reviewed by Avalon 1st Quarter 2023 CAB. Description, Policy Guidelines and References updated. When Covered and Not Covered sections edited for clarity, notes 1 and 2 added. No change to policy intent. Billing/Coding section updated. Medical Director review 4/2023. (tm)

10/24/23 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Reimbursement to Medical Necessity. Table of Terminology removed. (tm)