

General Genetic Testing, Germline Disorders

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I. Policy Description

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, 2024).

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, 2024; Li et al., 2017).

II. Related Policies

| Policy Number | Policy Title |
|---------------|--|
| AHS-M2146 | General Genetic Testing, Somatic Disorders |

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) Single gene or multi-gene panel testing (see Note 1 and Note 2) for inherited diseases **MEETS COVERAGE CRITERIA** (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 likely pathogenic or pathogenic variant 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 is 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 proactive management.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 2) The following genetic tests for inherited diseases **DO NOT MEET COVERAGE CRITERIA:**
- 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).

NOTES:

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

- a) Scientific literature shows that a specific a gene likely pathogenic or pathogenic variant (or variants) is associated with the disease in question and that identification of the variant is clinically actionable (there is clinical utility) with a non-investigational treatment;
- b) When confirmation of a gene likely pathogenic or pathogenic variant 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 two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

IV. Table of Terminology

| Term | Definition |
|----------|--|
| ACMG | American College of Medical Genetics and Genomics |
| AMP | Association For Molecular Pathology |
| APC | <i>Adenomatous polyposis coli</i> |
| ASCO | American Society of Clinical Oncology |
| ATM | <i>Ataxia telangiectasia mutated</i> |
| BRCA1/2 | <i>Breast cancer gene 1/2</i> |
| CAP | College of American Pathologists |
| CDH1 | <i>Cadherin-1</i> |
| CLIA '88 | Clinical Laboratory Improvement Amendments of 1988 |

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|--------------|--|
| CMS | Centers for Medicare and Medicaid Services |
| CNV | Copy number variant |
| CSG | Cancer susceptibility gene |
| ctDNA | Circular tumor deoxyribonucleic acid |
| FDA | Food and Drug Administration |
| EMSO | European Society for Medical Oncology |
| LDTs | Laboratory-developed tests |
| LOF | Loss-of-function |
| MGPT | Multi-gene panel testing |
| NCCN | National Comprehensive Cancer Network |
| NGS | Next-generation sequencing |
| <i>PALB2</i> | <i>Partner and localizer of BRCA2</i> |
| PCR | Polymerase chain reaction |
| <i>PTEN</i> | <i>Phosphatase and tensin homolog</i> |
| PVG | Pathogenic germline variants |
| smMIPS | Single molecule molecular inversion probes |
| SNPs | Single nucleotide polymorphisms |
| <i>TP53</i> | <i>Tumor protein P53</i> |
| VUS | Variant of uncertain significance |

V. Scientific 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, 2024). 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, 2024).

Single nucleotide polymorphisms 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, 2024). 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, 2024).

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, 2023).

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 breast cancer recommend testing for high-penetrance breast cancer susceptibility genes such as *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, *STK*, and *TP53* mutations if any blood relative has a known or likely pathogenic variant in a cancer susceptibility gene (NCCN, 2024a). 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, 2024; Schrijver & Zehnder, 2024).

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, 2024). 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, 2024). 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, multi-gene 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 Utility and Validity

Genetic testing for germline mutations “can be conducted on virtually any tissue type,” although many laboratories prefer blood samples, cheek swabs or saliva samples (Kohlmann & Slavotinek, 2024). 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; 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, 2024). 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 (Kohlmann & Slavotinek, 2024).

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, 2024).

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. A total of 30.5% (n=617) of participants had PVGs. Participants with PVGs spanned all ages and cancer types. Tumor DNA sequencing missed 8.1% of PVGs. A total of 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).

VI. 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 +/- one to two 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 > five percent 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, 2024b).

The NCCN includes some general testing criteria. They believe that testing is indicated in the following scenarios:

- “Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene”
- “Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing”
- “A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline”
- “To aid in systemic therapy and surgical decision-making” (NCCN, 2024a).

It is also notes that testing may be considered in the following scenario with appropriate pre-test education and access to post-test management: an individual of Ashkenazi Jewish ancestry without additional risk factors and with a personal history of serous endometrial cancer (NCCN, 2024a).

Regarding the choice of multi-gene testing, the NCCN states that:

- “The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to hereditary cancer testing of patients at increased risk of inherited susceptibility to cancer and their families. Based on next-generation sequencing (NGS) technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.”
- “An individual’s personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost effective and increases the yield of detecting a P/LP variant in a gene that will impact medical management for the individual or their family members with increased risk.”

- The NCCN explains here that ‘tailored’ is “defined as a disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance.”
- “There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.”
- “Some individuals may carry P/LP germline variants in more than one cancer susceptibility gene; thus, consideration of a multi-gene panel for individuals already known to carry a single P/ LP germline variant from phenotype-directed testing may be considered on a case-by-case basis, based on the degree of suspicion for there being additional variants.”
- “Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg, methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel.”
- “Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes.” This is because “For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of P/LP variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history.”
- “It may be possible to refine risks associated with both moderate and high penetrance genes, taking into account the influence of gene/gene or gene/ environment interactions. In addition, certain P/LP variants in a gene may pose higher or lower risk than other P/LP variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their relatives who also have increased risk.”
- “P/LP variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring if the partner is also a carrier.”
- “As more genes are tested, there is an increased likelihood of finding VUS, mosaicism, and clonal hematopoiesis of indeterminate potential.”
- “When a P/LP variant with clinical implications for the patient and/or their family members is found on tumor genomic testing, germline confirmatory testing should be recommended.”
- “There are significant limitations in interpretation of polygenic risk scores (PRS). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations” (NCCN, 2024a).

For more information, 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 (i.e., 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 [individuals] 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).

The ASCO released guidelines for the selection of germline genetic testing panels in patients with cancer. ASCO recommends “all patients should have a family history taken and recorded that includes details of cancers in first- and second-degree relatives and the patient's ethnicity.” The guidelines went on to add that “when germline genetic testing is indicated for a patient with cancer, multi-gene panel testing should be offered if more than one gene is relevant” (Tung et al., 2024).

European Society for Medical Oncology (ESMO)

The ESMO 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-focussed 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 LOF 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 germline 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 analyzed 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).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

| CPT | Code Description |
|-------|--|
| 81105 | Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P) |
| 81106 | Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M) |
| 81107 | Human Platelet Antigen 3 genotyping (HPA-3), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex], antigen CD41 [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S) |
| 81108 | Human Platelet Antigen 4 genotyping (HPA-4), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q) |
| 81109 | Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b [K505E]) |
| 81110 | Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q) |
| 81111 | Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M) |
| 81112 | Human Platelet Antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y) |
| 81161 | DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed |

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| 81173 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence |
| 81174 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant |
| 81177 | ATN1 (atrophin 1) (eg, dentatorubral-pallidoluyisian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81178 | ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81179 | ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81180 | ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81181 | ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81182 | ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81183 | ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81187 | CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81188 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |
| 81189 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence |
| 81190 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s) |
| 81204 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status) |
| 81228 | Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis) |
| 81229 | Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities |
| 81233 | BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F) |
| 81234 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles |
| 81236 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence |
| 81237 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646) |
| 81238 | F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence |
| 81239 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size) |

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| 81247 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) |
| 81248 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) |
| 81249 | G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence |
| 81252 | GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence |
| 81260 | IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P) |
| 81271 | HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles |
| 81274 | HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size) |
| 81283 | IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant |
| 81284 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles |
| 81285 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size) |
| 81286 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence |
| 81289 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s) |
| 81305 | MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant |
| 81307 | PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence |
| 81308 | PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant |
| 81312 | PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) |
| 81329 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed |
| 81333 | TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q) |
| 81336 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence |
| 81337 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s) |
| 81343 | PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |
| 81344 | TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles |

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| 81400 | Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 81402 | Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) |
| 81403 | Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) |
| 81404 | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) |
| 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 81406 | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) |
| 81407 | Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) |
| 81408 | Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) |
| 81437 | Hereditary neuroendocrine tumor-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants |
| 81438 | Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL |
| 81441 | Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2 |
| 81442 | Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1 |

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| 81443 | Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolysaccharidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH) |
| 81470 | X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2 |
| 81471 | X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2 |
| 81479 | Unlisted molecular pathology procedure |
| 0130U | Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure - 81435, 0101U) Proprietary test: RNAinsight™ for ColoNext® Lab/Manufacturer: Ambry Genetics |
| 0138U | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) Proprietary test: RNAinsight™ for BRCA1/2 Lab/Manufacturer: Ambry Genetics |
| 0230U | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation), full sequence analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions Proprietary test: Genomic Unity® AR Analysis Lab/Manufacturer: Variantyx Inc |
| 0232U | CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions Proprietary test: Genomic Unity® CSTB Analysis Lab/Manufacturer: Variantyx Inc |
| 0236U | SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions Proprietary test: Genomic Unity® SMN1/2 Analysis Lab/Manufacturer: Variantyx Inc |
| 0269U | Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid |

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| | Proprietary test: Versiti™ Autosomal Dominant Thrombocytopenia Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0270U | Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Coagulation Disorder Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0271U | Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Congenital Neutropenia Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0272U | Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive Proprietary test: Versiti™ Comprehensive Bleeding Disorder Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0273U | Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Fibrinolytic Disorder Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0274U | Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Comprehensive Platelet Disorder Panel Lab/Manufacturer: Versiti™ Diagnostic Laboratories/Versiti™ |
| 0276U | Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Inherited Thrombocytopenia Panel Lab/Manufacturer: Versiti™ Comprehensive Bleeding Disorder Panel |
| 0277U | Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid Proprietary test: Versiti™ Platelet Function Disorder Panel Lab/Manufacturer: Versiti™ Comprehensive Bleeding Disorder Panel |
| 0318U | Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood Proprietary test: EpiSign Complete Lab/Manufacturer: Greenwood Genetic Center |
| S3840 | DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2 |

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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X. Review/Revision History

| Effective Date | Summary |
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| 04/01/2025 | <p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency:</p> <p>Removed “For individuals who have received genetic counseling,” from CC1, policy deals with rare disorders that do not have explicit guideline requirements for genetic counseling.</p> <p>Changed “mutation” to “likely pathogenic or pathogenic variant” in CC1a and Note 1 to align with nomenclature for germline vs somatic genetic changes.</p> |

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| | <p>Note 2 was updated to reflect changes to Avalon’s definition of a genetic panel within R2162. Now reads: “Note 2: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.”</p> <p>Added CPT code 81437, 81438; 81441 (missing from last published policy document)</p> <p>Removed CPT code 96040, S0265 as genetic counseling is not managed by Avalon</p> |
| 12/01/2024 | Initial Policy Implementation |