Sentara Health Plans

General Genetic Testing, Germline Disorders

Policy Number: AHS – M2145 – General Genetic Testing Germline Disorders	Prior Policy Name and Number, as applicable: AHS-M2034-General Genetic Testing
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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, 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).

II. 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 Applicable State and Federal Regulations of this policy document.

1) For individuals who have received genetic counseling, 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 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 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 procreative 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 a patient'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 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.

III. Table of Terminology

Term	Definition
ACMG	American College of Medical Genetics and Genomics
AMP	Association For Molecular Pathology
APC	*Adenomatous polyposis coli*

Term	Definition
ASCO	American Society of Clinical Oncology
ATM	*Ataxia telangiectasia mutated*
BRCA1/2	*Breast cancer gene 1/2*
CAP	College Of American Pathologists
CDH1	*Cadherin-1*
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
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	Multigene panel testing
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
PALB2	*Partner and localizer of BRCA2*
PTEN	*Phosphatase and tensin homolog*
PVG	Pathogenic germline variants
smMIPS	Single molecule molecular inversion probes
SNPs	Single nucleotide polymorphisms
TP53	*Tumor protein P53*

IV. 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, 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 Utility and Validity

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).

V. 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).

VI. 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.

VII. 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)

CPT	Code Description
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
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-pallidoluysian 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)

CPT	Code Description
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)
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)

CPT	Code Description
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
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)
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome),

CPT	Code Description
	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
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis 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 adenomatosis 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

CPT	Code Description
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 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

CPT	Code Description
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2

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

VIII. Evidence-based Scientific References

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IX. Review/Revision History

Effective Date	Summary
12/01/2024	Initial Policy Implementation