SENTARA HEALTH PLANS, INC.
CLINICAL CARE SERVICES

Medical Policy: **Medical 34D**

Subject: **Genetic Testing 34 D Preconceptional /Prenatal /Preimplantation Genetic Testing**

Also see other Genetic Testing Policies:

See Genetic Testing 34 A Cancer Prevention, Diagnosis, and Treatment

See Genetic Testing 34 B Pre-Treatment or Post Intervention

See Genetic Testing 34 C Cardioneurovascular and Developmental Diagnosis

See Genetic Testing 34 E Pharmacogenetic Testing

See Genetic Testing 34 F Medicare Coverage

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Covered: **See appropriate benefit document for specific coverage determination.**

Exceptions: **Based on current scientific evidence, the requested tests are considered not medically necessary because the result of genetic testing has not been shown to direct clinical management that results in an improvement of clinical outcomes:**

- Ambry's Cystic Fibrosis 508 First and reflex testing if

negative to Cystic Fibrosis Full Gene Sequencing Analysis or Cystic Fibrosis Amplified genetic testing;

- APOE 4 or other Genetic Testing for Alzheimer's Disease (**S3852)**
- CFTR Full Gene Sequencing (**81223**)
- Comparative genomic hybridization microarray testing and single nucleotide polymorphism (SNP) chromosomal microarray analysis are unproven and not medically necessary for preimplantation genetic diagnosis or screening in embryos.
- EPG5 Gene-VICI Syndrome testing
- EpiSign Complete
- FGFR3 mutation Achondroplasia (Dwarfism)
- Genetic testing related to seizure disorders
- GPR56 gene for polymicrogyria
- Hereditary Retinal Disorders Genetic Panel Lab Test
- Holoprosencephaly, schizencephaly & craniosynostosis genetic testing including, but not limited to genes SHH, ZIC2, SIX3, and TGIF1
- Human leukocyte antigen (HLA) typing of an embryo to identify a future suitable stem cell, tissue or organ transplantation donor
- Hyperimmunoglobulin D syndrome (HIDS)
- Genetic disease carrier panel testing for multiple heritable disorders in the general population is considered not medically necessary if the genetic testing includes genes not recommended for routine preconceptional or prenatal screening by the American College of Medical Genetics and the American College of Obstetricians and Gynecologists (e.g. HerediT, Inheritest, NxGen MDx Super Panel/Universal Panels) (see coverage below)
- JAG1 testing for Alagille Syndrome
- KCNC2 or KCNC3
- Mevalonate kinase deficiency (MKD)
- MTHFR
- MYH8 Gene(Trismus-pseudocamptodactyly syndrome)
- NOTCH2 testing for Alagille Syndrome
- Signature Precision Panel™ | Prenatal
- SPRED1 (sprout-related, EVH1 domain containing 1) (eg, Legius syndrome)
- Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) genetic testing
- Uniparental Disomy
- VICI Syndrome (EPG5 Gene)

- Whole Exome Sequencing (WES)
- Exome Sequence Analysis (CPT 81415, 81416, 81417)
- Whole Genome Sequencing (WGS)
- Genome Sequence Analysis (CPT 81425, 81426, 81427)
- Y Chromosome Microdeletion Analysis
- Any other test not listed below as covered is considered among those that are not medically necessary.
- Repeat/Duplicative genetic testing
- Routine requests for cell-free prenatal genetic testing beyond fetal trisomies 21, 18, and 13 are considered not medically necessary (e.g., microdeletion testing, MaterniT21 Plus, InformaSeq with Y analysis, InformaSeq with XY analysis).

Authorization: Pre-certification by the Plan is required.
Medical Director approval is required for Extended Mutation Panels.

Procedure:

Prenatal diagnosis or prenatal screening is testing for diseases or conditions in a fetus or embryo before it is born.
Preconceptual diagnosis for pregnancy planning and care in the form of genetic testing for members of reproductive age may be initiated.
Preimplantation genetic diagnosis (PGD or PIGD) (also known as embryo screening) refers to procedures that are performed on embryos prior to implantation, sometimes even on oocytes prior to fertilization.
Inheritest Carrier Screen: The Inheritest Carrier Screen offers a broad genetic screening option, providing genetic information regarding greater than 90 autosomal recessive inherited diseases found throughout the pan-ethnic US population, all in one simple test.
Cell-free fetal DNA-based prenatal screening for fetal aneuploidies, including but not limited to Trisomy 13 (Patau Syndrome), Trisomy 18 (Edwards Syndrome) and Trisomy 21 (Down syndrome) uses sequence analysis of cell-free fetal DNA in maternal plasma.
Autosomal recessive: A genetic condition that appears only in individuals who have received two copies of an autosomal gene, one copy from each parent. The gene is on an autosome, a nonsex chromosome. The parents are carriers who have only one copy of the gene and do not exhibit the trait because the gene is recessive to its normal counterpart gene
X-linked recessive inheritance - hereditary pattern in which a recessive gene on the X chromosome results in the manifestation of characteristics in male offspring and a carrier state in female offspring

For **Fetal Congenital Abnormalities Risk Score Panel Testing** refer to SHP Medical 165

Clinical Indications:

A. Clinical indications for **Cystic Fibrosis**:

The Plan covers requests for common mutations with included in CPT codes 81221 (single mutation) or 81220 (common variants) endorsed by the American College of Medical Genetics (ACMG) for Cystic Fibrosis testing of members in ONE of the following groups:(see full CF gene sequencing (CPT code 81223) exceptions above)

1. Couples seeking prenatal care;

OR

2. Couples who are planning a pregnancy.

Additional testing (eg. HerediT CF carrier testing):
Extended CFTR mutation panels (**Code 81222 and 81224**) are approved for patients meeting **ANY** of the following 3 criteria (but not full sequencing, see exclusions):

1. Individuals with reproductive partners with cystic fibrosis or congenital absence of the vas deferens and no identified mutation with standard gene sequencing,

OR

2. Individuals with a family history of cystic fibrosis with no identified mutation on basic/standard gene sequencing,

OR

3. Individuals with elevated or indeterminate sweat chloride levels where from zero to up to 2 mutations have been identified by basic/standard gene sequencing.

Full CFTR sequencing (81223) is NOT covered for ANY indication, see in exclusions above)

B. Clinical Indications for the following tests with Specific Criteria:

Preconceptional carrier status genetic testing for pregnancy planning for members of reproductive age OR preimplantation genetic testing, OR prenatal genetic testing to determine carrier status of a fetus, are medically necessary for ANY of the following if criteria are met:

1. **Tay-Sach's** disease (**HEXA gene**) is approved for **1 or more** of the following:

    a. Carrier testing for **1 or more** of the following:

        1) Individual of Ashkenazi Jewish ancestry and of reproductive age

        2) Individual with deficiency of beta-hexosaminidase A enzyme activity on carrier screening assay

        3) Individual with family history of Tay-Sachs disease and of reproductive age, when both disease-causing mutations in HEXA gene have been identified in affected relative

        4) Prior to gamete donation if gamete recipient is carrier

    b. Confirmation of diagnosis of Tay-Sachs disease in symptomatic patient with inconclusive leukocyte or serum activity of beta-hexosaminidase A

    c. Establishment of disease-causing mutation in patient with confirmed diagnosis of Tay-Sachs disease

    d. Preimplantation genetic diagnosis when disease-causing mutation in HEXA gene has been identified in both parents

    e. Prenatal diagnosis when disease-causing mutation in HEXA gene has been identified in both parents

2. **Canavan disease (ASPA Gene)** with the following indication:
    a. Preimplantation genetic diagnosis or Prenatal diagnosis, when disease-causing mutation in ASPA gene has been identified in both parents

    OR

    b. Preconceptional or prenatal carrier testing when reproductive partner is an ASPA gene mutation carrier

    OR

    c. Preconceptional, prenatal, or preimplantation testing if a member is of Ashkenazi Jewish ancestry and of reproductive age

    OR

    d. The member has a family history of Canavan disease in first or second degree relative

    OR

    e. Preconceptional or prenatal testing for a member with levels of urinary N-acetyl aspartic acid that are equivocal or indeterminate

3. **Mucolipidosis Type IV (MCOLN1)** for the following indication:

   a. Preimplantation or Prenatal diagnosis genetic diagnosis, when disease-causing mutation in MCOLN1 gene has been identified in both parents

   OR

   b. Carrier testing for an individual of Ashkenazi Jewish ancestry

   OR

   c. The member has a family history of mucolipidosis IV in first or second degree relative

   OR

   d. Reproductive partner of MCOLN1 gene mutation carrier

   OR

   e. Need to establish disease-causing mutation in patient with confirmed diagnosis.

4. **Nieman Pick Disease** for the following indication

   a. Preimplantation or Prenatal genetic diagnosis, when disease-causing mutations, SMPD1 NPC1 or NPC2 gene have been identified in both parents or in a couple with previously affected child

   OR

   b. Carrier testing for individual of Ashkenazi Jewish ancestry who is of reproductive age

   OR

   c. Carrier testing for individual with family history of Niemann-Pick disease type A or type B

   OR

   d. Establishment of disease-causing mutation in patient with confirmed diagnosis of Niemann-Pick disease type A or type B

5. **Fanconi anemia group (FANC Gene)** for the following indication:

   a Preimplantation or prenatal genetic test when the disease causing mutation has been found in both parents

   OR

   b. Carrier testing for individual of Ashkenazi Jewish ancestry who is of reproductive age

   OR

   c. The member has a family history of Fanconi anemia, and prior identification of disease-causing mutations in a first or second degree relative

OR

d. Reproductive partner of FANC gene mutation carrier

OR

e. Identification of disease-causing mutation in patient with confirmed diagnosis

6. **Bloom syndrome (BKM Gene):**

a. Preimplantation or prenatal genetic diagnosis when disease-causing mutation in BLM gene has been identified in both parents

OR

b. Carrier testing for individual of Ashkenazi Jewish ancestry who is of reproductive age

OR

c. Patient with family history of Bloom syndrome

OR

d. Reproductive partner of BLM gene mutation carrier

OR

e. Need to establish disease-causing mutation in patient with confirmed diagnosis

7. **Gaucher's disease** for the following indication:

a. Preimplantation or prenatal genetic diagnosis for families in which disease-causing mutations have been identified in both parents or in previously affected child,

OR

b. Carrier testing for individual of Ashkenazi Jewish ancestry

OR

c. Carrier testing for preconception testing of partner of known carrier or affected individual

8. **Spinal Muscular Atrophy** (SMA) testing of the SMN1 and SM2 genes is approved for carrier screening in prospective parents who wish to reproduce

9. **Duchene Muscular Dystrophy** for the either of the following indications:

a. Preimplantation genetic diagnosis, when the DMD gene mutation in has been identified in mother

OR

b. Prenatal diagnosis in fetus with 46, XY karyotype, when DMD gene mutation in has been identified in carrier mother or if linkage has been established suggesting mother is carrier

OR

c. Carrier testing for asymptomatic female with family history of Duchenne muscular dystrophy, Becker muscular dystrophy, or DMD-associated dilated cardiomyopathy

OR

d. Member with confirmed diagnosis of muscular dystrophy with need establish disease-causing mutation

10. **Myotonic Dystrophy, DMPK and CNBP gene testing** for **ANY of the following indications:**

a. **DMPK** Testing for ANY of the following

1) Genetic diagnosis when disease-causing mutations have been confirmed in a first degree relative

OR

2) Prenatal diagnosis by amniocentesis if polyhydramnios or decreased fetal activity are detected in third trimester

OR

3) Prenatal diagnosis, when DMPK expansion has been identified in either affected parent

OR

b. **CNBP** gene testing for the following:

1) Prenatal diagnosis when CNBP expansion has been identified in affected parent

OR

2) Preimplantation, prenatal, or preconceptional genetic testing when a CNBP mutation has been identified in an affected first-degree relative

11. **Familial Dysautonomia (Riley-Day syndrome**) for the following indication:

a. Preimplantation or prenatal genetic diagnosis when the IKBKAP gene mutation in has been identified in both parents

OR

b. The member is of Ashkenazi Jewish ancestry and of reproductive age

OR

c. The member has a family history (in a 1st or 2nd degree relative) of familial dysautonomia

OR

d. The member is a reproductive partner of an individual that has been confirmed to be a KBKAP gene mutation carrier

12. **Glycogen storage disease** for the following indication: (**Maple syrup urine disease)**

a. Preimplantation or prenatal genetic diagnosis when the G6PC or SLC37A4 gene mutation in has been identified in both parents.

OR

b. The member is of Ashkenazi Jewish ancestry and of reproductive age

OR

c. The member has a family history of glycogen storage disease type I

OR

d. The member is a reproductive partner of an individual that has been confirmed to be a G6PC or SLC37A4 gene mutation carrier

13. **Retinoblastoma RB1 gene** testing may be indicated for the following indication:

a. Preimplantation or prenatal genetic diagnosis for families RB1 mutation has been identified in either parent.

OR

b. The member has a first degree relative with a known RB1 mutation

OR

c. Prenatal diagnosis for pregnancies at increased risk when disease-causing allele of affected family member has been identified or linkage has been established in family

14. **Huntington's Disease** for the following indication:

a. Preimplantation or prenatal genetic diagnosis when the HTT gene disease-causing has been confirmed in one parent

OR

b. Preimplantation or prenatal diagnostic testing for couples in at-risk family who do not wish to undergo presymptomatic mutation testing themselves

15. **Marfan Syndrome** for the following indications:

a. The use of Marfan syndrome gene testing in patients fulfilling the Ghent diagnostic criteria for the purpose of obtaining information for

reproductive decision making or facilitating the diagnosis of Marfan syndrome in at-risk relatives;

OR

b. The prenatal diagnosis or preimplantation genetic testing for Marfan syndrome in the offspring of patients with known disease-causing variants.

16. **Nonsyndromic Deafness**: Genes GJB2, GJB6, POU3F4, PRPS1, and SMPX. See Milliman guideline A-0596 for criteria.

17. **Paraganglioma-Pheochromocytoma Syndromes**, Hereditary - SDHB, SDHC, SDHD, and TMEM127 Genes: See Milliman guideline A-0535 for criteria.

18. **Polycystic Kidney Disease (Autosomal Recessive)** - PKHD1 Gene: See Milliman guideline A-0852 for criteria.

19. **Wiskott-Aldrich syndrome (WAS)** gene mutation testing 1 or more of the following:
    1. Individual is male with all of the following:
        a) Initial testing points to a WAS related disorder (Wiskott Aldrich Syndrome, X linked thrombytopenia, X-linked congenital neutropenia)
    2. Individual is female with all of the following:
        a) There is a known family history of WAS gene mutation (testing is to identify female carriers)
    3. Testing is prenatal with all of the following indications:
        a) Fetus is male. Testing is being done with chorionic villi sampling or cultured amniocytes
        b) There is known risk of WAS gene mutation (positive family history of WAS gene mutation and/or of known positive carrier females)

C. Clinical indications for Testing with Non-Specific Criteria:

Preconceptional carrier status genetic testing for pregnancy planning for members of reproductive age or prenatal genetic testing to determine **carrier status** of a fetus for **other** inherited disorders when **BOTH** (1 & 2) of the following criteria are met:

1. **Criteria based on family history**

   Genetic testing are considered **medically necessary** when **ONE** of the following criteria is met:

a. An affected child is identified with either an autosomal recessive disorder, an x-linked disorder, or an inherited disorder with variable penetrance;

OR

b. One or both parents or prospective parent(s) have another first or a second degree relative who is affected, or the first degree relative has an affected child, with either an autosomal recessive disorder, an x-linked disorder, or an inherited disorder with variable penetrance;

OR

c. The parent or prospective parent is at high risk for a genetic disorder with a late onset presentation;

OR

d. The parents or prospective parents are members of an ethnic group with a high risk of a specific genetic disorder with an autosomal recessive pattern of inheritance and testing is performed to determine carrier status and to guide subsequent reproductive decisions.

AND

2. **Criteria for Specific Genetic Test**
   For those meeting one of the applicable criteria above, specific genetic testing is considered **medically necessary** when **ALL** of the following criteria are met:

   a. A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with the disease;

   AND

   b. The genetic disorder is associated with a potentially severe disability or has a lethal natural history;

   AND

   c. One of the following:

      1. A biochemical or other test is identified and the results are indeterminate

      OR

      2. The genetic disorder cannot be identified through biochemical or other testing

AND

d. Testing is accompanied by genetic counseling.

AND

3. **Testing is for one or more of the following disorders** approved for targeted testing (**for requests meeting both criteria 1 and 2**):

1. Alpha Thalassemia, Beta Thalassemia and Sickle Cell
2. Congenital muscular dystrophy
3. Deficiency, Familial hyperinsulinism,
4. Dihydrolipoamide dehydrogenase
5. Emery-Dreifuss muscular dystrophy (EDMD1, 2, and 3) (FGFR2, Facioscapulohumeral muscular dystrophy (FSHMD1A)FGFR3)
6. Familial HEMOPHAGOCYTIC,
7. Familial Myotonic Dystrophy, (FMD)
8. Fascioscapulohumeral Muscular Dystrophy (FSHD)
9. Inheritest Universal screening
10. Limb girdle muscular dystrophy (LGMD1, LGMD2) (FKRP (Fukutin related protein))
11. LYMPHOHISTIOCYTOSIS (FHL),
12. Nemaline myopathy,
13. Pontocerebellar Hypoplasia (TSEN54, EXOSC8)
14. type 1C (MDC1C) (FKRP (Fukutin related protein))
15. Ullrich Muscular Dystrophy COL6A2
16. Usher syndrome type 1F or Usher syndrome type 3,
17. Walker-Warburg syndrome (POMGNT1)
18. Hemophilia A or B
19. von Willebrand factor
20. Familial hyperinsulinism
21. 22q11.2 deletion syndromes (Velocardiofacial / DiGeorge syndrome, Catch22, Familial third and fourth pharyngeal pouch syndrome, Hypoplasia of thymus and parathyroid, Pharyngeal pouch syndrome, Sedlackova syndrome, Third and fourth pharyngeal pouch syndrome, Thymic aplasia syndrome, and Velofacial hypoplasia)
22. Mucopolysaccharidosis (MPS)
23. Lissencephaly
24. Hereditary sensory and autonomic neuropathies
25. Leopard syndrome
26. Noonan syndrome
27. Ellis-van Creveld syndrome EVC/EVC2 gene
28. X-linked centronuclear myopathy (MTM1)
29. Autosomal recessive or autosomal dominant centronuclear myopathy (DNM2 and/or BIN1)
30. Primary Ciliary Dyskinesia (PCD) 6/14/16
31. Adrenoleukodystrophy DNA Sequencing (ABCD1 gene) 8/23/16

32. X-linked Lymphoproliferative Syndromes 8/23/16 for transplant patients 8/23/16

D. Testing covered for prenatal diagnosis when **echogenic bowel** is detected on ultrasound examination of fetus during pregnancy;

E. Testing covered for prenatal diagnosis for **VLDLR Associated Cerebellar Hypoplasia**.

F. Cell-free fetal DNA-based prenatal screening for common fetal aneuploidies: Covered without precertification. (i.e., Trisomy 13 (Patau Syndrome), Trisomy 18 (Edwards Syndrome), and Trisomy 21 (Down syndrome)) (e.g., MaterniT21, Informaseq, Verifi)

G. Testing covered for prenatal diagnosis when disease-causing mutation in RYR1 (Malignant Hyperthermia) gene has been identified in one parent.

H. Fanconi anemia Fanconi Testing (FANC)—(FANCC 81242 including DEB Chromosome Assay)

Fanconi anemia is characterized by diverse congenital malformations of multiple body systems including involvement of the skeletal system, eyes, kidneys and urinary tract, ears, heart, gastrointestinal system, and central nervous system. Patients develop progressive pancytopenia, and predisposition to both hematologic malignancies and solid tumors. The condition is associated with a mutation in one of at least 15 genes (collectively called FANC), which are responsible for the 15 known Fanconi anemia complementation groups. Fanconi anemia is diagnosed by performing cytogenetic testing in which increased chromosomal breakage or rearrangement is noted after DNA from peripheral blood is exposed to an interstrand cross-linking agent such as diepoxybutane or mitomycin C

Clinical Indications for genetic Testing for Fanconi Anemia include ANY of the following:

1. Patient of Ashkenazi Jewish ancestry and of reproductive age.

OR

2. Patient with family history of Fanconi anemia, and prior identification of disease-causing mutations in relatives;

OR

3. Prior to gamete donation if gamete recipient is carrier;

OR

4. Reproductive partner of FANC gene mutation carrier;

OR

5. Equivocal or indeterminate cytogenetic testing for chromosomal breakage or rearrangement in presence of DNA interstrand cross-linking agent (eg, diepoxybutane or mitomycin C);

OR

6. Identification of disease-causing mutation in patient with confirmed diagnosis

I. Retinoblastoma (RB1) Testing:

Retinoblastoma (RB1) Retinoblastoma is the most common intraocular cancer in children. It is a malignant tumor of the retina that occurs in young children, usually before the age of 5 years. Approximately 40% to 50% of retinoblastomas are classified as hereditary and are caused by mutations in the RB1 tumor suppressor gene, that's inherited in an autosomal dominant manner. Hereditary retinoblastoma is the result of a germline mutation followed by a somatic mutation in the RB1 gene. (1)(7) (EG 2) Sporadic (nonhereditary) retinoblastoma results from somatic mutations in both alleles of the RB1 gene

RB1 gene testing may be indicated when ALL of the following are present:

1. Diagnosis or screening for hereditary retinoblastoma, as indicated by **1 or more** of the following:

    1. First-degree relative of patient with known RB1 mutation

    OR

    2. Patient with retinoblastoma, with or without family history of retinoblastoma

    OR

    3. Preimplantation genetic diagnosis for families in which disease-causing mutation has been identified;

    OR

    4. Prenatal diagnosis for] pregnancies at increased risk when disease-causing allele of affected family member has been identified or linkage has been established in family;

AND

2. Testing is accompanied by genetic counseling.

J. Familial Hemophagocytic Lymphohistiocytosis:

Covered if requested by name without criteria (there is no specific code)

K. Neurofibromatosis Type1 and 2 (NF1/ NF2)

NF1 or NF2 gene testing may be indicated for the following Indications (1) or (2)

1. Preimplantation genetic diagnosis when NF1 or NF2 gene mutation has been identified in parent

OR

2. Prenatal testing, when parent has NF1 or NF2 gene mutation, or linkage is established in family.

OR

3. Carrier testing, when there is a first-degree relative with either NF1 or NF2.

L. Comparative Genomic Hybridization Microarray testing or Single Nucleotide Polymorphism (SNP) Chromosomal Microarray Analysis for the evaluation of a fetus:

1. Evaluating abnormal fetal anatomic findings detected on fetal ultrasound or fetal magnetic resonance imaging which are characteristic of a genetic abnormality;

OR

2. Women undergoing invasive prenatal diagnostic testing (i.e. amniocentesis, chorionic villus sampling or fetal tissue sampling).

OR

3. Evaluation of recurrent pregnancy loss, after the second consecutive loss

OR

4. Evaluation of intrauterine fetal demise (IUFD) or stillbirth after 20 weeks of gestational age

OR

5. Evaluation of a pregnancy loss with one or more major structural anomalies

M. Familial Mediterranean Fever (FMF):

a) Carrier testing for MEFV gene may be indicated when one of the following are present: Member is from an ethnic group at increased risk (eg, Armenian, Turkish, Arab, North African Jewish) and of reproductive age.

OR

b) Prior to gamete donation if gamete recipient is known carrier

OR

c) Reproductive partner of MEFV gene mutation carrier

N. Ashkenazi Jewish Genetic Panel Testing:

Ashkenazi Jewish genetic panel testing may be indicated when ALL of the following are present:

1. Individual to be tested is of Ashkenazi Jewish ancestry and of reproductive age.

AND

2. Panel testing is being ordered to assess for mutations associated with 3 or more of the following diseases:

    a) Bloom syndrome
    b) Canavan disease
    c) Cystic fibrosis
    d) Dihydrolipoamide dehydrogenase deficiency
    e) Familial dysautonomia (Riley-Day syndrome)
    f) Familial hyperinsulinism
    g) Fanconi anemia group C
    h) Gaucher disease
    i) Glycogen storage disease type 1A
    j) Joubert syndrome 2
    k) Maple syrup urine disease
    l) Mucolipidosis IV
    m) Nemaline myopathy
    n) Niemann-Pick disease type A
    o) Spinal muscle atrophy
    p) Tay-Sachs disease
    q) Usher syndrome type 1F
    r) Usher syndrome type 3

O. Preimplantation Genetic Diagnosis

1. Preimplantation genetic diagnosis, when used as a technique to improve the implantation rate of in vitro fertilization (IVF) procedures in otherwise infertile couples, when **either** below are met:

    a. Three prior failed attempts at IVF;

OR

    b. One of the partners is known to harbor a balanced translocation.

2. Preimplantation genetic diagnosis, when used to deselect embryos with genetic mutations in partners who meet **any** criteria in item #1 **and all** of the item #2 criteria listed below:

   a. Must meet at **LEAST ONE** of the following:

      1. Both partners are known carriers of the same autosomal recessive disorder;

      OR

      2. One partner is a known carrier of an autosomal recessive disorder, and the couple has previously produced offspring affected by that disorder;

      OR

      3. One partner is a known carrier of a single gene autosomal dominant disorder;

      OR

      4. One partner is a known carrier of a single X-linked disorder;

      AND

   b. Must meet **ALL** of the following:

      1. A specific mutation, or set of mutations, has been identified, that specifically identifies the genetic disorder with a high degree of reliability;

      AND

      2. The genetic disorder is associated with severe disability or has a lethal natural history;

      AND

      3. Testing is accompanied by genetic counseling.

3. Preimplantation genetic diagnosis when used to determine the sex of an embryo only when there is a documented history of an X-linked disorder, such that deselection of an affected embryo can be made on the basis of sex alone.

4. Preimplantation genetic diagnosis when used to evaluate human leukocyte antigen (HLA) status alone is in families with a child with a bone marrow disorder requiring a stem cell transplant, and in whom there is no other source of a compatible bone marrow donor other than an HLA matched sibling.

P. Karyotyping codes along with 88230 and 88289 codes are covered without criteria or preauthorization.

HCPCS: When meets medical criteria above:

S3841	Genetic Testing for retinoblastoma
S3842	Genetic Testing for von Hippel-Lindau disease
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic Testing for alpha-thalassemia
S3846	Genetic Testing for hemoglobin E beta-thalassemia
S3849	Genetic Testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic Testing for myotonic muscular dystrophy

CPT Codes

0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
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
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability)

gene analysis, Leiden variant

81242 FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant

81251 GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)

81252 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence

81253 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants

81254 GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])

81255 HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)

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)

81290 MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

81331 SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation 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

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)

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)
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)
81479	Unlisted molecular pathology procedure
83080	b-Hexosaminidase, each assay
84999	Unlisted chemistry procedure
88230	Tissue culture for non-neoplastic disorders; lymphocyte
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos

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REFERENCES

___	Agency for Healthcare Research and Quality (AHRQ)		
___	Diagnostic and Therapeutic Technology Assessment (DATTA) Review		
_X_	Specialty Association Guidelines	___	SHC Guidelines
_X_	Government Regulations	_X_	Literature Review
____	Specialty Advisors	_X_	Winifred S. Hayes, Inc.
_X_	UpToDate	_X_	NCD

X LCD

X Relevant Other Payer Approaches

References used include but are not limited to the following:

(2020). Retrieved May 28, 2020, from Hayes, Inc.: https://evidence.hayesinc.com/search?q=%257B%2522phrase%2522:%2522retinal%2520disorders%2520genetic%2520panel%2522,%2522style%2522:%2522ALL%2522,%2522size%2522:10,%2522page%2522:1,%2522bundle%2522:%257B%2522path%2522:%2522%2522,%2522title%2522:%2522%2522%

(2020). Retrieved May 29, 2020, from Centers for Medicare and Medicaid Services: https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=53&KeyWord=Genetic+testing&KeyWordLookU

(2020). Retrieved May 29, 2020, from National Comprehensive Cancer Network: https://cse.google.com/cse?cx=007894372670309631110:vocdaeamxuy&ie=UTF-8&q=hereditary%20retinal%20disorders&safe=high

(2020, Feb 05). Retrieved May 28, 2020, from MCG: https://careweb.careguidelines.com/ed24/index.html

(2020). Retrieved May 29, 2020, from DynaMed: https://www.dynamed.com/results?q=retinal+disorder+genetic+testing&lang=en

(2020). Retrieved Jun 01, 2020, from Department of Medical Assistance Services: http://www.dmas.virginia.gov/#/index

AAO Quality of Care Secretariat, Hoskins Center for Quality Eye Care. (2016, Jun). Retrieved May 29, 2020, from American Academy of Ophthalmology: https://www.aao.org/clinical-statement/recommendations-on-clinical-assessment-of-patients

Clinical Guidelines: Genetic Testing. (2020). Retrieved May 29, 2020, from AIM Specialty Health: https://aimspecialtyhealth.com/resources/clinical-guidelines/genetic-testing/

Garg, S. (2019, Nov 08). Retinitis pigmentosa: Clinical presentation and diagnosis. Retrieved May 29, 2020, from UpToDate: https://www.uptodate.com/contents/retinitis-pigmentosa-clinical-presentation-and-

diagnosis?search=hereditary%20retinal%20dystrophy&source=search_result&selectedTitle=1~23&usage_type=default&display_rank=1#H420617337

Lenassi, E., Clayton-Smith, J., Douzgou, S., Ramsden, S., Ingram, S., Hall, G., . . . Sergouniotis, P. (2020, Apr). Clinical Utility of Genetic Testing in 201 Preschool Children with Inherited Eye Disorders. Retrieved May 29, 2020, from PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7118019/

Recommendations for Genetic Testing of Inherited Eye Diseases 2014. (2014, Jun). Retrieved May 29, 2020, from American Academy of Ophthalmology: https://www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d

Retinal Dystrophy Xpanded Panel. (2020). Retrieved May 27, 2020, from GeneDx: https://www.genedx.com/test-catalog/available-tests/retinal-dystrophy-xpanded-panel/

Regulations of Genetic Tests. (2019, Nov 20). Retrieved Jun 01, 2020, from National Human Genome Research Institute: https://www.genome.gov/about-genomics/policy-issues/Regulation-of-Genetic-Tests

(2019). Retrieved Dec 30, 2019, from Centers for Medicare and Medicaid Services: https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=53&KeyWord=Uniparental+Disomy&KeyWordLo

(2019, Feb 11). Retrieved Dec 31, 2019, from MCG: https://careweb.careguidelines.com/ed23/index.html

(2019). Retrieved Dec 30, 2019, from National Comprehensive Cancer Network: https://cse.google.com/cse?cx=007894372670309631110:vocdaeamxuy&ie=UTF-8&q=uniparental%20disomy&safe=high

Beygo, J., Buitine, K., Ramsden, S., Ellis, R., Clayton-Smith, J., & Kanber, D. (2019, Jun 24). Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. Retrieved Dec 31, 2019, from European Hournal of Human Genetics: https://www.nature.com/articles/s41431-019-0435-0

Butler, M. G., Miller, J. L., & Forster, J. L. (2019, Jun 24). Pradar-Willi Syndrome - Clinical Genetics, Diagnosis and Treatment Approaches: An Update. Retrieved Dec 31, 2019, from http://www.eurekaselect.com/173540/article. Doi: 10.2174/1573396315666190716120925

Clinical Guidelines Genetic Testing. (2019). Retrieved Dec 30, 2019, from AIM Specialty Health: https://aimspecialtyhealth.com/resources/clinical-guidelines/genetic-testing/

Epidemiology and genetics of Pradar-Willi syndrome. (2019, Dec 03). Retrieved Dec 30, 2019, from UpToDate: https://www.uptodate.com/contents/epidemiology-and-genetics-of-prader-willi-syndrome?search=uniparental%20disomy&source=search_result&selectedTitle=2~40&usage_type=default&display_rank=2

Pradar-Willi Syndrome. (2018, Nov 30). Retrieved Dec 30, 2019, from DynaMed: https://www.dynamed.com/condition/prader-willi-syndrome-27

Uniparental Disomy (UPD) for Chromosomes 6, 7, 11, 14, or 15. (2012, Nov 13). Retrieved Dec 30, 2019, from Hayes, Inc.: https://evidence.hayesinc.com/report/gte.unicompartmental

Carrier Screening for Genetic Conditions, Number 691. (2017, March). Retrieved October 8, 2019, from American College of Obstetricians and Gynecologists: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Genetics/Carrier-Screening-for-Genetic-Conditions

Clinical Appropriateness Guidelines: Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis. (2019, September 9). Retrieved Oct 8, 2019, from AIM Specialty Health: https://aimspecialtyhealth.com/wp-content/uploads/2019/07/ReproductiveCarrierScreeningandPrenatalDiagnosis_Sep_2019.pdf

HEXA Gene Analysis Coding and Billing Guidelines. (2019, Jan 01). Retrieved Oct 8, 2019, from Centers for Medicare and Medicaid Services: https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=53598&ver=14&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=53&KeyWord=HEX

HGNC Data for HEXA. (2019). Retrieved October 8, 2019, from HUGO Gene Nomenclature Committee: https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:4878

Late-onset Tay–Sachs disease, Volume 17, Issue 5. (2017, October 17). doi:10.1136/practneurol-2017-001665

NCCN Guidelines. (2019). Retrieved Oct 8, 2019, from National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/default.aspx

Preconception and Prenatal Carrier Screening for Genetic Disease More Common in the Ashkenazi Jewish Population and Others With A Family History Of These Disorders. (2019, Aug 1). Retrieved Oct 8, 2019, from UpToDate: https://www.uptodate.com/contents/preconception-and-prenatal-carrier-screening-for-genetic-disease-more-common-in-the-ashkenazi-jewish-population-and-others-with-a-family-history-of-these-disorders?search=tay%20sachs&source=search_result&selectedTitle=1~2

Prenatal Diagnosis of Tay-Sachs Disease, MIMB, volume 1885. (2018, December 1). doi:10.1007/978-1-4939-8889-1_16

Tay - Sachs Disease (TSD) Testing in Individuals of Non–Ashkenazi Jewish Origin. (2014, December 12). Retrieved Oct 8, 2019, from Hayes, Inc.: https://evidence.hayesinc.com/report/gte.taysachs2351

Tay-Sachs Disease. (2018, November 30). Retrieved Oct 8, 2019, from DynaMed Plus: https://www.dynamed.com/condition/tay-sachs-disease#GUID-403E22E0-1B95-4631-A687-EFD512585AFD

Tay - Sachs disease and Variants - HEXA Gene, ACG: A-0614 (AC). (2019, Feb 11). Retrieved Oct 8, 2019, from MCG: https://careweb.careguidelines.com/ed23/index.html

ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstetrics and Gynecology 2007; 110(6):1459-67. DOI: 10.1097/01.AOG.0000291570.63450.44.

ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstetrics and Gynecology 2007; 109(1):217-27.
Tabor A, Alfirevic Z. Update on Procedure-Related Risks for Prenatal Diagnosis Techniques. Fetal Diagnosis and Therapy 2009; 27(1):1-7. DOI: 10.1159/000271995.

Odibo AO, Gray DL, Dicke JM, Stamilio DM, Macones GA, Crane JP. Revisiting the fetal loss rate after second-trimester genetic amniocentesis: a single center's 16-year experience. Obstetrics and Gynecology 2008; 111(3):589-95. DOI: 10.1097/AOG.0b013e318162eb53.

Ekoukou D, Khuong-Josses MA, Ghibaudo N, Mechali D, Rotten D. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2008; 140(2):212-7. DOI: 10.1016/j.ejogrb.2008.04.004.

Breathnach FM, et al. First- and second-trimester screening: detection of aneuploidies other than Down syndrome. Obstetrics and Gynecology 2007; 110(3):651-7. DOI: 10.1097/01.AOG.0000278570.76392.a6.

Bornstein E, Lenchner E, Donnenfeld A, Barnhard Y, Seubert D, Divon MY. Advanced maternal age as a sole indication for genetic amniocentesis; risk-benefit analysis based on a large database reflecting the current common practice. Journal of Perinatal Medicine 2008; 37(2):99-102. DOI: 10.1515/JPM.2009.032.

Bornstein E, Lenchner E, Donnenfeld A, Barnhard Y, Seubert D, Divon MY. Advanced maternal age as a sole indication for genetic amniocentesis; risk-benefit analysis based on a large database reflecting the current common practice. Journal of Perinatal Medicine 2008; 37(2):99-102. DOI: 10.1515/JPM.2009.032.

Intracytoplasmic sperm injection (ICSI) in 2006: evidence and evolution. Human Reproduction Update 2007;13(6):515-26. DOI: 10.1093/humupd/dmm024.

Bethune M. Literature review and suggested protocol for managing ultrasound soft markers for Down syndrome: thickened nuchal fold, echogenic bowel, shortened femur, shortened humerus, pyelectasis and absent or hypoplastic nasal bone. Australasian Radiology 2007;51(3):218-25. DOI: 10.1111/j.1440-1673.2007.01713.x.

Breathnach FM, Fleming A, Malone FD. The second trimester genetic sonogram. American Journal of Medical Genetics. Part C. Seminars in medical genetics 2007; 145(1):62-72. DOI: 10.1002/ajmg.c.30116.

Aagaard-Tillery KM, et al. Role of second-trimester genetic sonography after Down syndrome screening. Obstetrics and Gynecology 2009; 114(6):1189-96. DOI: 10.1097/AOG.0b013e3181c15064

Breathnach FM, Malone FD. Screening for aneuploidy in first and second trimesters: is there an optimal paradigm? Current Opinion in Obstetrics and Gynecology 2007;19(2):176-82. DOI: 10.1097/GCO.0b013e3280895e00.

Rosen T, D'Alton ME, Platt LD, Wapner R. First-trimester ultrasound assessment of the nasal bone to screen for aneuploidy. Obstetrics and Gynecology 2007; 110(2 Pt 1):399-404. DOI: 10.1097/01.AOG.0000275281.19344.66.

Bethune M. Management options for echogenic intracardiac focus and choroid plexus cysts: a review including Australian Association of Obstetrical and Gynaecological Ultrasonologists consensus statement. Australasian Radiology 2007; 51(4):324-9. DOI: 10.1111/j.1440-1673.2007.01716.x

Bianco K, Caughey AB, Shaffer BL, Davis R, Norton ME. History of miscarriage and increased incidence of fetal aneuploidy in subsequent pregnancy. Obstetrics and Gynecology 2006; 107(5):1098-102. DOI: 10.1097/01.AOG.0000215560.86673.22.

ACOG Practice Bulletin No. 97: Fetal lung maturity. Obstetrics and Gynecology 2008; 112(3):717-26. DOI: 10.1097/AOG.0b013e318188d1c2.

Premature rupture of membranes. ACOG Practice Bulletin Number 80:. Obstetrics and Gynecology 2007; 109(4):1007-19. DOI: 10.1097/01.AOG.0000263888.69178.1f.

Porreco RP, Heyborne KD, Shapiro H. Amniocentesis in the management of preterm premature rupture of the membranes: a retrospective cohort analysis. Journal of Maternal-Fetal & Neonatal Medicine 2008;21(8):573-9. DOI: 10.1080/14767050802178011

Gelb BD, Tartaglia M. Noonan Syndrome with Multiple Lentigines. 2007 Nov 30 [Updated 2015 May 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1383/

Snape KM, Ruddy D, Zenker M, Wuyts W, Whiteford M, Johnson D, Lam W, Trembath RC (2009). "The spectra of clinical phenotypes in aplasia cutis congenita and terminal transverse limb defects.". Am J Med Genet A 149 (8): 1860–1881. doi:10.1002/ajmg.a.32708