Department of Origin: Integrated Healthcare Services	**Effective Date:** 09/27/22
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Clinical Policy Document: Genetic Testing, Preimplantation Genetic Diagnosis	**Replaces Effective Clinical Policy Dated**: 06/07/22
Reference #: MC/L026	**Page:** 1 of 6

PURPOSE:
The intent of this clinical policy is to ensure services are medically necessary.

Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.

POLICY:
Benefits must be available for health care services. Health care services must be ordered by a provider. Licensed Genetic Counselors may also order genetic tests if it is within the scope of practice of their state licensure. Health care services must be medically necessary, applicable conservative treatments must have been tried, and the most cost-effective alternative must be requested for coverage consideration.

GUIDELINES:
Medical Necessity Criteria – Must satisfy all of the following: I - II

I. Requests for *preimplantation genetic testing* (PGD) - must satisfy all of the following: A – C

A. Member (includes embryo) displays clinical features (symptomatic), or is at direct risk of inheriting the mutation in question (presymptomatic); and

B. A *health care professional trained in genetics,* independent of the laboratory performing the testing, has reviewed and documented family history, advised the member of the potential harms/benefits of the testing and implications of the test results, and obtained written formal consent; and
[Note: Members who have no knowledge of their genetic family history (such as members who are adopted) will be considered to be at high risk.]

C. After history, physical examination and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain and a valid specific test exists for the suspected condition – as evidenced by all of the following: 1 - 3
1. Each test has been approved for its intended use by the appropriate *regulatory/oversight body* (implies *analytic validity*); and

2. Each test has sufficient sensitivity or specificity (*clinical validity*) for targeting the member's specific clinical condition; and

3. The results of each test will directly impact clinical decision-making and clinical care (*clinical utility)* for the individual, such as but not limited to the following: a – c
a. Guiding surveillance for complications (eg, referral to maternal-fetal-medicine physician, increase in surveillance/frequency of prenatal ultrasounds).
b. Employing direct risk reduction strategies (eg, fetal interventions).
c. Determining avenues of medical therapy (eg, medication, early labor induction).

II. *Preimplantation genetic diagnosis* (PGD) requests for monogenic/single gene defects (PGT-M) or inherited structural chromosomal rearrangements (PGT-SR) using polymerase chain reaction (PCR), next generation sequencing (eg, chromosomal rearrangements), or chromosomal microarray - must satisfy both of the following: A and B
   A. The embryo is increased risk of a recognized inherited disorder due to any of the following: 1 - 3
      1. At least one parent is a known carrier of an *autosomal dominant*, a *sex-linked disord*er, or a *mitochondrial disorder*; or
      2. Both parents are carriers of an *autosomal recessive* condition (eg, cystic fibrosis); or
      3. At least one parent is a carrier of a balanced structural chromosome rearrangement .
   B. The disorder being prevented is caused by a single gene (PGT-M) or structural changes of a parents' chromosome (PGT-SR)

NOT ROUTINELY COVERED:
PGD for sex selection for non-medical purposes, ie, when the embryo is not at risk for a sex-linked disorder

EXCLUSIONS (not limited to):
Refer to member's Certificate of Coverage or Summary Plan Description

Direct-to-consumer testing

The following is considered investigative (see Investigative List):

Preimplantation genetic testing for aneuploidy (PGT-A) (formerly called preimplantation genetic screening (PGS)

DEFINITIONS:
Analytic Validity:
How accurately and reliably the test measures the genotype of interest. A major component in the validation of an analytical technique is the technique's ability to accurately determine the presence of the substance it is seeking. It must measure the target substance without a great range of variation over a number of trials. The technique also must be proven to work reliably at multiple labs to be validated by this testing.

Autosomal:
Pertaining to a chromosome that is not a sex chromosome. People normally have 22 pairs of autosomes (44 autosomes) in each cell, together with 2 sex chromosomes, X and Y in a male and X and X in a female.

Autosomal dominant:
A pattern of inheritance in which an affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal chromosomes. Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant gene and therefore the disorder onto each of their children. Examples of

autosomal dominant diseases include Huntington disease, neurofibromatosis, and polycystic kidney disease.

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. If both parents are carriers, there is a 25% chance of a child inheriting both abnormal genes and, consequently, developing the disease. There is a 50% chance of a child inheriting only one abnormal gene and of being a carrier, like the parents, and there is a 25% chance of the child inheriting both normal genes. Cystic fibrosis (CF) is an example of an autosomal recessive disorder. A CF child has the CF gene on both chromosome 7s and so is said to be homozygous for CF. The parents each have one CF and one normal paired gene and so are said to be heterozygous for CF.

Chromosome:
In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

Clinical Utility:
The evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decision-making compared with current management without the testing.

Clinical Validity:
How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.

Health care professionals trained in genetics:
A genetics professional has experience and an educational background in genetics, counseling, and hereditary syndromes to provide accurate risk assessment and empathetic genetic counseling to patients and their families. Genetics professionals include people certified in any of the following ways:

- American Board of Genetic Counseling (ABGC) or American Board of Medical Genetics (ABMGG) board certified/board eligible or licensed genetic counselor
- American College of Medical Genetics physician board certified in medical genetics
- Advanced Practice Nurse in Genetics (APNG)
- Advanced Genetics Nursing Certification (AGN-BC) credentialed through the American Nurses Credentialing Center (ANCC)
- Genetics Clinical Nurse (GCN)
- Advanced practice nurse or physician assistant who is prepared at the graduate level with specialized education in genetics and hereditary cancer predisposition syndromes
- Board-certified/board eligible physician with experience in cancer genetics
- Board-certified specialty care physician with experience in the diagnosis and treatment of the hereditary condition eg, cardiologist ordering genetic testing for hypertrophic cardiomyopathy
- A registered nurse with specialized education in cancer genetics and hereditary cancer predisposition syndromes (defined as education resulting in a certification and undergoing ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes)

Mitochondrial Disorder:
A group of conditions that affect the mitochondria (the structures in each cell of the body that are responsible for making energy). People with these conditions can present at any age with almost any

affected body system; however, the brain, muscles, heart, liver, nerves, eyes, ears and kidneys are the organs and tissues most commonly affected. Symptom severity can also vary widely. Mitochondrial genetic disorders can be caused by changes (mutations) in either the mitochondrial DNA or nuclear DNA that lead to dysfunction of the mitochondria and inadequate production of energy. Those caused by mutations in mitochondrial DNA are transmitted by maternal inheritance, while those caused by mutations in nuclear DNA may follow an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance. Examples include Leber hereditary optic neuropathy (LHON), neuropathy, ataxia and retinitis pigmentosa (NARP) syndrome, and mitochondrial encephalopathy, and lactic acidosis and stroke-like episodes (MELAS) syndrome.

Preimplantation genetic testing-aneuploidy (PGT-A):
A genetic test used to evaluate embryos for aneuploidy in all chromosomes (including the 22 pairs of autosomes and the sex chromosomes X and Y) before transfer to the uterus.

Preimplantation genetic testing-monogenic PGT-M):
A genetic test that used to evaluate embryos by targeting a single gene disorder, before transfer to the uterus. It uses only a few cells from the early embryo, usually at the blastocyst stage.

Preimplantation genetic testing-structural rearrangements (PGT-SR):
Genetic testing of embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (eg, translocations, inversions, deletions and insertions) before transfer to the uterus.

Regulatory/oversight body:
Such as, but not limited to, Clinical Laboratory Improvement Amendments (CLIA), Food and Drug Administration (FDA) or The Joint Commission

Sex-linked Disorder:
Diseases passed down through families through one of the X or Y chromosomes. X and Y are sex chromosomes. Dominant inheritance occurs when an abnormal gene from one parent causes disease, even though the matching gene from the other parent is normal; the abnormal gene dominates. In recessive inheritance, both matching genes must be abnormal to cause disease. If only one gene in the pair is abnormal, the disease does not occur or it is mild. Someone who has one abnormal gene (but no symptoms) is called a carrier. Carriers can pass abnormal genes to their children. The term "sex-linked recessive" most often refers to X-linked recessive. Examples include Duchenne and Becker muscular dystrophy, Fragile X-syndrome, and hemophilia.

X-linked Disorder:
In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

BACKGROUND:
Preimplantation genetic diagnosis (PGD) is performed on embryos produced after in vitro fertilization (IVF) cycles by using molecular analysis techniques on single cells removed from the embryo. The methods used to retrieve PGD material from embryos are the same, irrespective of the type of genetic analysis required. The biopsy procedure entails micro-manipulation and special techniques are

used to avoid contamination from exogenous DNA (eg, cellular DNA from non-fertilizing sperm) in the IVF laboratory.

Comparative genomic hybridization (CGH) or chromosomal microarray analysis is a laboratory method to aid in the detection of chromosomal imbalances. It allows for the detection of alterations (copy number variants or CNVs) in the genomic content of an individual. The technique works by comparing the DNA content of the individual with a normal control individual to identify pathogenic CNVs that may be responsible for the suspected disorder. Tens of thousands to millions of different DNA fragments (probes) are attached to identifiable locations on a glass slide or gene chip. Array CGH (aCGH) is a variation of CGH that detects chromosomal abnormalities at a higher resolution than conventional CGH, or chromosome-based CGH.

PCR is an established laboratory method used to make numerous copies of a specific DNA sequence, utilizing pairs of oligonucleotide primers to replicate and alternate rounds of DNA. Real-time polymerase chain reaction, also called quantitative real time polymerase chain reaction (Q-PCR/qPCR/qrt-PCR) or kinetic polymerase chain reaction (KPCR), is a PCR technology used to simultaneously amplify and quantify the targeted DNA molecule. In reverse transcriptase PCR (RT-PCR) an RNA strand is reverse transcribed into its DNA complement (cDNA). Methylation-specific PCR (MSP) assesses the methylation status of DNA.

Conventional cytogenetic testing is used to identify balanced rearrangements (eg, translocations or inversions), alterations in chromosome structure, sequence alterations, copy number changes (deletion, duplication and amplification), single-base pair mutation, 20% or lower level of mosaicism, and some types of polyploidy, including triploidy and tetraploidy. Conventional cytogenetic tests identify known genetic abnormalities associated with specific clinical syndromes. These tests may be used when a specific clinical syndrome is suspected.

Prior Authorization: Yes, per network provider agreement

CODING:

CPT®

81228 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis

81229 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis

81349 Cytogenomic (genome-wide) microarray analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss of heterozygosity variants, low-pass sequencing analysis

0209U Cytogenomic constitutional (genome-wide) analysis; interrogation of genomic regions for copy number changes and areas of homozygosity for chromosomal abnormalities

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We will:

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    - Qualified sign language interpreters
    - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provide free language services to people whose primary language is not English, such as:
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    - Information written in other languages

If *you* need these services, contact *us* at the phone number shown on the inside cover of this *COC*, *your* id card, or aspirushealthplan.com.

If *you* believe that *we* have failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a grievance with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1062
Minneapolis, MN 55440
Phone: 1. 866.631.5404 (TTY: 1.866.631.8597)
Fax: 763.847.4010
Email: customerservice@aspirushealthplan.com

You can file a grievance in person or by mail, fax, or email. If *you* need help filing a grievance, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1.866.631.5404 (TTY: 1.866.631.8597).

تنبيه :إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية 1.866.631.5404(رقم هاتف الصم والبك : 1.866.631.8597) متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف **Arabic**

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Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1.866.631.5404 (TTY: 1.866.631.8597).

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Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1.866.631.5404 (телетайп: 1.866.631.8597).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.866.631.5404 (TTY: 1.866.631.8597).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1.866.631.5404 (TTY: 1.866.631.8597).

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Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1.866.631.5404 (TTY: 1.866.631.8597).