


MEDICAL POLICY	Genetic Testing: Reproductive Planning and Prenatal Testing (All Lines of Business Except Medicare)
Effective Date: 9/1/2022	Medical Policy Number: 78
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Medical Officer	Date

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
 - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making

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- Reason (indication) for performing test, including the suspected condition
- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed
- Please refer to the medical policy “Genetic Counseling (All Lines of Business Except Medicare)” for additional information.

POLICY CRITERIA

Notes:

- This policy does not address the following, which may be considered medically necessary:
 - *GJB2* and *GJB6* genes for hereditary hearing loss
 - Invasive prenatal diagnosis, including but not limited to *SMN1* and *SMN2* testing
- The tests addressed in this policy only apply to biological parents.
- This policy addresses the following types of genetic testing and associated services:
 - [Carrier Screening](#)
 - Genetic testing of asymptomatic prospective biologic parents before or during pregnancy to determine the risk of having a child with a single gene disorder. Conditions addressed in this section include:
 - Cystic Fibrosis (CF)
 - Spinal Muscular Atrophy (SMA)
 - Fragile X Syndrome
 - Hemoglobinopathies and Thalassemias
 - Genetic Conditions in Individuals of Ashkenazi Jewish (Eastern and Central European) Descent
 - Other Single-Gene Genetic Conditions
 - Expanded Genetic Panel Testing for Carrier Screening
 - [Preimplantation Genetic Testing](#)
Genetic testing of an embryo for a specific genetic disorder prior to implantation as a part of in vitro fertilization.
 - [Noninvasive Prenatal Screening](#)
Noninvasive prenatal screening (NIPS), also known as noninvasive prenatal testing (NIPT), is genetic testing of cell-free fetal DNA from maternal blood to screen for an increased risk of chromosomal abnormalities in the fetus.
 - [Pregnancy Loss](#)
Genetic testing of parental DNA and/or fetal tissue after stillbirth or recurrent pregnancy loss to determine causative abnormalities.
 - [Genetic Panel Testing](#)
All components of a panel test must be medically necessary in order for the test to be covered.

Carrier Screening for Genetic Conditions

Note: Carrier screening testing has limits. See [Billing Guidelines](#) below.

Cystic Fibrosis (CF)

- I. Carrier screening for CF using the American College of Obstetricians and Gynecologists/ American College of Medical Genetics and Genomics (ACOG/ACMG) recommended standard mutation panel* (panels may include 23-25 mutations listed below in the [Policy Guidelines](#) section) may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:
 - A. A woman is considering pregnancy or is currently pregnant; **or**
 - B. A woman's reproductive partner meets **any one** of the following criteria (1.-3.):
 1. The partner has a family history of CF; **or**
 2. The partner is either affected with CF or is a known carrier of a common CF-causing mutation; **or**
 3. The partner is affected with congenital absence of the vas deferens.
- II. Carrier screening for CF using an expanded CF mutation panel (>25 mutations) may be considered **medically necessary** when the individual meets criterion I. above and the standard mutation panel for CF is negative.
- III. Carrier screening for CF by complete *CFTR* gene sequencing may be considered **medically necessary** when the individual meets criterion I. above, and the standard or expanded mutation panel (criterion II.) for CF is negative.
- IV. Carrier screening for CF by targeted sequencing of a single mutation may be considered **medically necessary** when the individual meets criterion I. above and when **either** of the following criteria (A. or B.) are met:
 - A. The known familial mutation is not included in the standard or expanded CF mutation panels; **or**
 - B. Their partner is a known carrier of a CF-causing mutation not in the standard or expanded CF mutation panels.
- V. Carrier screening for CF is considered **not medically necessary and not covered** in all other situations, including but not limited to:
 - A. When any of the criteria (I.-IV.) above are not met.
 - B. For standard population-based screening.
 - C. When a family member has been tested for mutations and received a result of variant of uncertain significance (VUS).

Fragile X Syndrome

- VI. Carrier screening for Fragile X syndrome (*FMR1* gene) for a woman who is considering pregnancy or is currently pregnant may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:
 - A. There is a family history of fragile X-related disorders (including fragile X syndrome, fragile X-associated tremor/ataxia syndrome, and/or *FMR1*-related primary ovarian insufficiency) or intellectual disability suggestive of fragile X syndrome; **or**
 - B. Documentation of unexplained ovarian insufficiency or failure **or** an elevated follicle-stimulating hormone level before 40 years of age.

- VII. Carrier screening for Fragile X syndrome (*FMR1*) is considered **not medically necessary and not covered** when criterion VI., above is not met, including, but not limited to testing for standard population-based screening.

Hemoglobinopathies and Thalassemias

- VIII. Carrier screening for hemoglobinopathies and thalassemias (including but not limited to: Sickle Cell Anemia [*HBB* gene], Alpha Thalassemia [*HBA1/HBA2* genes] and Beta Thalassemia [*HBB* gene]) in individuals considering pregnancy (a woman and/or her reproductive partner) or a woman who is currently pregnant, may be considered **medically necessary** when Genetic Counseling general criteria have been met and any **one** of the following criteria are met:
 - A. Family history of a hemoglobinopathy; **or**
 - B. Affected or carrier first- or second-degree family member with a known pathogenic mutation. (First-degree relatives are parents, siblings, and children; and second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings); **or**
 - C. Suspicion of hemoglobinopathy based on results of a complete blood count (CBC) and hemoglobin analysis (by electrophoresis, high performance liquid chromatography [HPLC] or isoelectric focusing).

- IX. Carrier screening for hemoglobinopathies and thalassemias is considered **not medically necessary and not covered** when criterion VIII., above is not met, including, but not limited to testing for standard population-based screening.

Spinal Muscular Atrophy (SMA)

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- X. Carrier screening for SMA by genetic testing of the *SMN1* and *SMN2* genes may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:
- A. A woman is considering pregnancy or is currently pregnant; **or**
 - B. A woman's reproductive partner meets either of the following criteria (1. or 2.):
 - 1. The partner has a family history of SMA; **or**
 - 2. The partner is affected with SMA or is a known carrier of a SMA-causing mutation.
- XI. Carrier screening for SMA is considered **not medically necessary and not covered** in all other situations, including, but not limited to:
- A. When criterion X. above is not met.
 - B. For standard population-based screening.
 - C. When a family member has been tested for mutations and received a result of VUS (variant of uncertain significance).

Genetic Conditions Associated with Ashkenazi Jewish (Eastern and Central European) Descent

- XII. Carrier screening for individuals (a woman and/or her reproductive partner) of Ashkenazi Jewish descent who are considering pregnancy, or for a woman of Ashkenazi Jewish descent who is currently pregnant may be **medically necessary** when Genetic Counseling general criteria have been met and for **any one or more** of the following conditions:

Note: Testing may be ordered as a single gene test or a multi-gene panel test. All genes included in the panel test must be specific to the condition being tested and must have established clinical utility. (See [Policy Guidelines](#) below)

- A. Bloom syndrome (*BLM* gene)
- B. Canavan disease (*ASPA* gene)
- C. Cystic Fibrosis (*CFTR* gene)
- D. Familial dysautonomia (*IKBKAP* gene)
- E. Familial hyperinsulinism (*ABCC8* gene)
- F. Fanconi anemia group C (*FANCC* gene)
- G. Gaucher disease type 1 (*GBA* gene)
- H. Glycogen storage disease type Ia (also known as von Gierke disease)(*G6PC* gene)
- I. Joubert syndrome (*TMEM216* gene)
- J. Maple syrup urine disease (*BCKDHA*, *BCKDHB*, and/or *DBT* genes)
- K. Mucopolidosis type IV (*MCOLN1* gene)
- L. Niemann–Pick disease type A (*SMPD1* gene)
- M. Spinal Muscular Atrophy (*SMN1* and *SMN2* genes)
- N. Tay-Sacks Disease (*HEXA* gene)

O. Usher syndrome type 1 (*PCDH15* gene)

XIII. Carrier screening for an individual (**either** a woman or her reproductive partner) whose reproductive partner is of Ashkenazi Jewish descent **and** is a confirmed carrier for any of the above listed conditions in criterion XII. may be considered **medically necessary** for that condition when Genetic Counseling general criteria have also been met.

XIV. Carrier screening for the conditions listed above for those who are not of Ashkenazi Jewish (Eastern and Central European) descent is considered **not medically necessary and not covered**.

Other Genetic Conditions Not Listed Above

XV. Carrier screening for single-gene conditions not listed above for couples who are considering pregnancy (a woman and/or her reproductive partner), or for a woman who is currently pregnant may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:

A. Testing is for a known pathogenic mutation confirmed in an affected first- or second-degree blood relative. (First-degree relatives are parents, siblings, and children; and second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings); **or**

B. Targeted mutation analysis or gene sequencing when **either** of the following criteria (1. **or** 2.) are met:

1. An individual's reproductive partner is a known carrier of a disease-causing mutation in a recessively inherited condition; **or**
2. A genetic condition has been confirmed in an individual's affected first- or second-degree blood relative **and** the affected relative has not had genetic testing and is unavailable for testing.

XVI. Carrier screening for other genetic conditions not listed above is considered **not medically necessary and not covered** when criterion XV., above is not met.

Expanded Genetic Panel Testing for Carrier Screening

XVII. Carrier screening using multi-gene panels (also known as expanded carrier screening) may be considered **medically necessary** when Genetic Counseling general criteria have been met if the individual meets medical necessity criteria applicable for the genes/conditions addressed above.

XVIII. Carrier screening using multi-gene panels are considered **not medically necessary and not covered** when medical necessity criteria above are not met.

Preimplantation Genetic Testing

- XIX. [Preimplantation genetic diagnostic \(PGD\)](#) testing to determine whether a specific genetic condition is present in the fetus may be considered **medically necessary** when Genetic Counseling general criteria have been met and **any one** of the following criteria (A.-D.) are met:
- A. One partner is a known carrier of a pathogenic mutation causing a single gene autosomal dominant disorder; **or**
 - B. Both partners are known carriers of a pathogenic mutation causing a single gene autosomal recessive disorder; **or**
 - C. One partner is a known carrier of a pathogenic mutation causing a single gene X-linked disorder; **or**
 - D. One partner carries a known balanced chromosomal translocation, inversion, or other structural chromosomal rearrangement.
- XX. Preimplantation genetic diagnostic (PGD) testing is considered **not medically necessary and is not covered** for sex selection.
- XXI. Preimplantation genetic diagnostic (PGD) testing is considered **not medically necessary and not covered** for all other indications, including but not limited to:
- A. When the above criterion (XIX.) is not met.
 - B. Testing solely to determine if an embryo is a carrier of an autosomal recessively inherited disorder.
 - C. Testing for a multifactorial condition. A multifactorial condition is a condition caused by a combination of one or more genes and environmental factors (e.g., type II Diabetes)
 - D. When testing for a variant of uncertain significance (VUS).
- XXII. [Preimplantation genetic screening \(PGS\)](#) to assess whether an individual is at an increased risk of having a fetus affected by a genetic condition is considered **not medically necessary and not covered** for all indications, including but not limited to:
- A. To enhance delivery rates in advanced reproductive technologies.
 - B. To improve in vitro fertilization success rates.
 - C. In women with advanced maternal age (over 35 years).
 - D. History of failed in vitro fertilization (IVF) cycles.
 - E. Recurrent pregnancy loss.

Noninvasive Prenatal Screening (NIPS/NIPT)

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- XXIII. Noninvasive prenatal screening using cell-free DNA may be considered **medically necessary** for screening of trisomy 13, 18 and 21 in a viable, single gestation pregnancy \geq 10 weeks gestation.
- XXIV. Noninvasive prenatal screening using cell-free DNA is considered **not medically necessary and not covered** for the following indications:
- A. Fetal sex determination.
 - B. History of miscarriage without a history of aneuploidy.
 - C. Twin zygosity (i.e., differentiating between identical and fraternal twins).
- XXV. Noninvasive prenatal screening using cell-free DNA is considered **not medically necessary and not covered** in all other situations, including but not limited to:
- A. When above criterion (XXIII.) is not met.
 - B. Multiple-gestation pregnancies.
 - C. Screening for single-gene disorders, including X-linked disorders such as Duchenne muscular dystrophy.
 - D. Presence of a vanishing twin or empty second gestational sac.
 - E. Aneuploidies of other autosomes (e.g., 7, 9, 16, 22).
 - F. Sex chromosome aneuploidies (X and/or Y).
 - G. Microdeletions.
 - H. Whole genome DNA screening (e.g., MaterniT[®] GENOME).
 - I. Screening of non-pregnant individuals.

Pregnancy Loss

- XXVI. Evaluation of chromosomal abnormalities for pregnancy loss may be considered **medically necessary** when Genetic Counseling general criteria have been met and when using either fluorescence in situ hybridization (FISH), karyotype analysis, or chromosomal microarray analysis in **either** (A. or B.) of the following situations:
- A. For the evaluation of recurrent pregnancy loss (defined as a history of two or more consecutive failed pregnancies) via **one or both** of the following methods:
 - 1. Analysis of peripheral blood of one or both of the biological parents; **or**
 - 2. Analysis of fetal tissue (e.g., amniotic fluid, placenta or products of conception) when there is a maternal history of recurrent miscarriage; **or**
 - B. Analysis of fetal tissue when pregnancy loss occurs at 20 weeks or later of gestation (stillbirth).
- XXVII. Evaluation of chromosomal abnormalities for pregnancy loss is considered **not medically necessary and not covered** when the above criteria are not met.

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XXVIII. Genetic testing to evaluate pregnancy loss using sequencing-based tests (e.g., single mutation or single gene testing, or multi-gene panel testing) is considered **not medically necessary and not covered**.

Genetic Panel Testing

XXIX. Genetic panel testing for reproductive planning and prenatal testing is considered **not medically necessary and not covered** if any component of the panel is considered investigational.

Link to [Policy Summary](#)

POLICY GUIDELINES

*Standard CFTR Mutation Panel

The following 25 mutations are the most common CF-causing mutations according to the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG):¹

- ΔF508 • N1303K • A455E • R347P • 2789+5G>A
- ΔI507 • R553X • R560T • 711+1G>T • 3569delC
- G542X • 621+1G>T • R1162X • 1898+1G>A • 3120+1G>A
- G551D • R117H • G85E • 2184delA • I148delT
- W1282X • 1717-1G>A • R334W • 3849+10kbC>T • 1078delT

Genetic Conditions in Individuals of Ashkenazi Jewish (Eastern and Central European) Descent

The list conditions and causal genes which may meet medical necessity criteria above for carrier testing for individuals of Ashkenazi Jewish descent have been endorsed by a number of guidance documents published by the American College of Obstetrician and Gynecologists and the American College of Medical Genetics.²⁻⁵

In the context of this policy, *clinical utility* is defined as the likelihood that a genetic test will lead to improved health outcomes, specifically: aiding in current and future reproductive decision-making as well as pregnancy management decisions (e.g. the need for additional testing, fetal monitoring, mode of delivery, in utero treatment options, management recommendations, including fetal surveillance, and referral to other specialists).

BILLING GUIDELINES

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Carrier Screening

Testing for carrier screening of asymptomatic parents is limited to once per each condition per lifetime.

If a request is received for testing for an individual gene variant for carrier screening purposes that is addressed by a specific code (such as CPT codes for Cystic Fibrosis), and receives a negative test result, this does not preclude a request from being approved for testing of other specific gene variants.

Testing fetal DNA for the purpose of diagnostic prenatal testing is limited to once per pregnancy to diagnosis the fetus.

CPT 81507 is a proprietary test that should only be billed for Harmony Prenatal Test (Ariosa Diagnostics). CPT 81420 should never be billed with CPT 81507.

When no specific CPT or HCPCS code exists for the panel, the provider is required to bill using an unlisted code. It is not appropriate for the provider to bill any of the tests in a panel separately as if they were performed individually. This is a misrepresentation of services performed and is not appropriate based on either CPT or CMS guidelines. In a “Healthcare Fraud Prevention Partnership” white paper published in May, 2018, CMS identified unbundling of lab panels as an example of fraudulent billing.

CPT/HCPCS CODES

Genetic testing for reproductive planning and in the prenatal setting may include but is not limited to any of the CPT/HCPCS codes listed below. Additional codes may apply.

All Lines of Business Except Medicare	
Prior Authorization Required	
0009M	Fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
0124U	Fetal congenital abnormalities, biochemical assays of 3 analytes (free beta-hCG, PAPP-A, AFP), time-resolved fluorescence immunoassay, maternal dried-blood spot, algorithm reported as risk scores for fetal trisomies 13/18 and 21
0168U	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma without fetal fraction cutoff, algorithm reported as a risk score for each trisomy
0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions

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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
0233U	FXN (frataxin) (eg, Friedreich ataxia), 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
0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
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
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed
81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed)
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
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

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81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant
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)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
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)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

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81244	FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), 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)
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygoty testing, or maternal cell contamination of fetal cells)
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
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)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
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)

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81290	MCOLN1 (mucopolipin 1) (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
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
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
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
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

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81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
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)
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A

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81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolipidosis 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,

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	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
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
No Prior Authorization Required	
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
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
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 variants, comparative genomic hybridization [CGH] microarray analysis
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)])
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding

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88263	Chromosome analysis; count 45 cells for mosaicism, 2 Karyotypes, with banding
88264	Chromosome analysis; analyze 20-25 cells
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
88289	Chromosome analysis; additional high resolution study
88291	Cytogenetics and molecular cytogenetics, interpretation and report
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 preimplantation genetic diagnosis); greater than 5 embryo(s)
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
Not Covered	
0252U	Fetal aneuploidy short (tandem)
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)

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81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing. If an unlisted code is billed related to services addressed in this policy then prior-authorization is required.	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
88299	Unlisted cytogenetic study
89398	Unlisted reproductive medicine laboratory procedure

DESCRIPTION

Genetic Counseling

The National Society of Genetic Counselors (NSGC) defines genetic counseling as the following:⁶

“The process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. Education about inheritance, testing, management, prevention, resources and research. Counseling to promote informed choices and adaptation to the risk or condition.”

Carrier Screening

Carrier screening is genetic testing performed on an asymptomatic individual to determine whether that person has a mutation in a gene that is associated with a particular inherited disorder. Carrier screening can be performed for one specific condition or for multiple disorders and traditionally has been based on family history and ethnic background. Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening. Expanded carrier screening panels offered by laboratories may include options to screen for a focused subset of conditions (five-ten) to as many as several hundred conditions.³

Preimplantation Testing

Preimplantation genetic testing involves the removal of one or more nuclei from oocytes (polar bodies) or embryos (blastomeres or trophoctoderm cells) during the in vitro fertilization (IVF) process to test for genetic mutations or aneuploidy before transfer. Preimplantation genetic diagnosis (PGD) is genetic testing that occurs when one or both parents carry a known gene mutation or a balanced chromosomal rearrangement and the testing is performed to determine whether that specific genetic alteration has

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been transmitted to the oocyte or embryo. Preimplantation genetic screening (PGS) is genetic testing that occurs when the parents are known or presumed to be chromosomally normal and their embryos are screened for aneuploidy.⁷

Noninvasive Prenatal Screening

Noninvasive prenatal screening (NIPS; also referred to as noninvasive prenatal testing [NIPT]) was developed as an advanced screening test designed to detect the most common fetal aneuploidies in a noninvasive manner. These assays involve the analysis of cell-free fetal DNA (cffDNA, in some cases, also referred to as cfDNA) that is present in a mother’s blood during pregnancy in order to detect chromosomal aneuploidies. They use recently developed (“next-generation”) molecular techniques, such as massively parallel sequencing (MPS; i.e., the sequence analysis of millions of DNA fragments at the same time), that allow for an evaluation of fetal DNA in the cell-free component of the mother’s blood (i.e., plasma). Although each NIPT assay is different with respect to its exact methodology and algorithms for data analysis, they are all considered roughly equal in terms of detection and false-positive rates.

Pregnancy Loss

Recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies. There is a very high frequency of sporadic karyotypic abnormalities in products of conception while the incidence of karyotypic abnormalities in the parents is low. However, parents with unknown chromosomal abnormalities have a high risk of passing it on to their children. Of the examined products of conception, approximately 60% of early pregnancy losses are associated with sporadic chromosomal anomalies, primarily trisomies that are, in part, age related. However, in recurrent pregnancy loss, the risk of aneuploidy is just as high, but is less likely to be influenced by maternal age.⁸

Stillbirth, also known as intrauterine fetal demise, is defined as fetal death at 20 weeks or greater of gestation. An abnormal karyotype can be found in approximately 8–13% of stillbirths. The rate of karyotypic abnormalities exceeds 20% in fetuses with anatomic abnormalities or in those with growth restriction, but the rate of chromosomal anomalies found in normally formed fetuses is approximately 5%.⁹

REVIEW OF EVIDENCE

This policy is based on the most current clinical practice guidelines published by the following U.S.-based professional associations: American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics (ACMG), American Society of Reproductive Medicine (ASRM) and the Society of Maternal Fetal Medicine (SMFM). Please refer to the Clinical Practice Guidelines Section below for more details.

Since many of the genetic tests listed in the Policy Criteria section above are now considered standard of care by way of accepted practice guidelines from major medical societies; the evidence summary

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described below will focus on the indications for which genetic testing for reproductive planning and in the prenatal setting are still considered investigational. A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted and below is a review of evidence identified through January 2021.

Carrier Screening for Genetic Conditions

Carrier screening for genetic disease in the general population lacks support from both evidence- and consensus-based clinical practice guidelines from major medical societies. In addition, there is no direct evidence of clinical utility of carrier screening in the general population, as the published studies have reported prevalence, and not whether the results from the screening test impact reproductive decision-making.

Testing for screening or diagnostic purposes for a genetic disease when a family member has been found to have a variant of uncertain significance (VUS) is not considered to have clinical utility for any indication. No studies were identified for any genetic condition that reported on how testing for a VUS impacted clinical, medical management, or reproductive decisions; or how the results of these tests improved health outcomes.

Preimplantation Genetic Testing

The use of preimplantation genetic screening (PGS) in the asymptomatic general population has been studied for a number of years and as a result, the body of evidence for PGS consists of a number of RCTs that have been published over the past decade. Therefore, the evidence reviewed below will focus on recent systematic reviews that have evaluated RCTs of PGS and any RCTS not included in the reviews.

Systematic Reviews

In 2015, Dahdouh et al. published a systematic review of RCTs utilizing new PGS methods which assess the whole chromosome complement by way of microarray, NGS or quantitative polymerase chain reaction (qPCR), known as PGS-v2 or PGS-CCS.¹⁰ The review included three RCTs that compared women undergoing in vitro fertilization (IVF) with PGS-v2 techniques on trophectodermic blastocyst cells to standard IVF care without PGS. Of the included studies, one RCT used comparative genomic hybridization microarray (aCGH) while the other two used qPCR to assess chromosomal complement. One RCT used fresh tissue, one used fresh and frozen, and one used frozen tissue only. Although the reviewers reported that PGS-v2 is associated with higher clinical implantation rates, and higher ongoing pregnancy rates, compared with embryo selection based on morphology criteria alone in good-prognosis patients, they stated their results might be neither valid nor generalizable to poorer prognosis patients.

In 2015 Dahdouh et al. published a meta-analysis that assessed whether PGS-v2 improved clinical and sustained implantation rates (IR) (>20 weeks) compared with routine care for embryo selection in IVF, including the same three studies analyzed in the systematic review by the same group, described above.¹¹ Although the included RCTs used different tissue types and different platforms to assess

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chromosomal complement, they reported that the heterogeneity between studies was low. Analysis of the RCTs (three studies; n = 659) showed that PGS-v2 was associated with a significantly higher clinical IR, with a pooled RR of 1.29 (95% CI 1.15-1.45), as well as a significantly higher sustained IR, with a pooled RR of 1.39 (95% CI 1.21-1.60). Limitations of these RCTs included the fact that two of the RCTs came from the same IVF laboratory, one RCT was a pilot study, and the randomization for one RCT was carried out in a non-blinded fashion that may have introduced bias. The reviewers concluded that larger, more robust RCTs are needed in both poor- and good-prognosis populations to determine the utility of PGS.

Also in 2015, Chen et al. published a meta-analysis on PGS-v2 methods, including four RCTs and seven cohort studies.¹² Three of the included RCTs were also included in the systematic review and meta-analysis by Dahdouh group above.^{10,11} Within the four RCTs (N = 776) that compared PGS-v2 and traditional morphological-based selection, the PGS-v2 group showed a higher implantation rate than the control group (RR 1.32; 95% CI 1.18–1.47). A pooled analysis of two RCTs did not find clinical or ongoing pregnancy rates, or miscarriage rates to be significantly better in the PGS-v2 group compared to controls. The authors concluded that better designed RCTs were required to provide sufficient evidence regarding the efficiency of PGS-v2 compared to other methods used to evaluate preimplantation embryo viability.

Randomized Controlled Trials

In 2015, Yang et al. performed a pilot study that randomly compared next-generation sequencing (NGS) and aCHG for PGS.¹³ Phase I retrospectively evaluated NGS for aneuploidy screening in 38 samples from previous IVF PGS samples. Phase II compared clinical pregnancy and implantation outcomes between 86 patients undergoing PGS with 86 patients undergoing PGS with aCGH. In phase I, NGS detected all types of aneuploidies accurately and was 100% concurrent with aCGH in terms of comprehensive chromosomal analysis (all 24 chromosomes). Pregnancy rates were similar between blastocysts screened with NGS versus aCGH (74.7 % vs. 69.2 %, respectively, p = 0.56). Observed implantation rates were also comparable between the NGS and aCGH groups (70.5 % vs. 66.2 %, respectively, p = 0.56). Limitations of this RCT include the fact that the results may not be generalizable to higher-risk/poorer-prognosis patients, such as those with advanced maternal age.

Noninvasive Prenatal Screening (NIPS)

The use of noninvasive prenatal screening has been clinically validated for the common trisomies. However, testing labs are now offering NIPS testing for a number of indications that have not been validated in the clinic or through studies published in peer-reviewed journals. The use of NIPS to screen for aneuploidies of chromosomes (other than 13/18/21), including sex chromosomes, as well as for microdeletion syndromes and for testing of multi-gestational pregnancies has been reported in many studies over the past decade.¹⁴ However, aneuploidies other than 13/81/21 as well as microdeletions are so rare that meaningful conclusions regarding test performance difficult to be drawn from many of the individual studies.

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Common Trisomies: Low-Risk and General Obstetric Populations only

Several studies have been published on the clinical validity of NIPT tests. These studies are described below. Of note, the two largest cohort studies published recently by Zhang et al.¹⁵ and Norton et al.¹⁶ have been included in the two systematic reviews below,^{17,18} but the individual studies are described in detail below.

In 2016, Taylor-Phillips et al. published the results of a systematic review which assessed the accuracy of NIPT testing for detection of trisomies 13, 18 and 21, including case-control and cohort studies that recruited women who had been given NIPT and a reference standard.¹⁸ The review reported test performance statistics for both high-risk population and the general obstetrics populations. Pooled sensitivity, calculated by from bivariate random-effects regression, was applied to populations of pregnant women taking the test to estimate the positive predictive values for each population. In the high-risk population, the positive predictive values were 91%, 84% and 87% for Down, Edwards, and Patau syndromes, respectively. In the general obstetric population, the positive predictive values were 82%, 37% and 49% for Down, Edwards, and Patau syndromes, respectively. The reviewers reported significant heterogeneity between included studies and most studies had a high risk of bias.

In 2017, Iwarsson et al. published a systematic review which assessed NIPT assays for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population.¹⁷ The reviewers reported that in a general pregnant population (six studies, 62,201 patients), the pooled sensitivity for trisomy 21 was 99.3% (95% CI 95.5-99.9%) and specificity was 99.9% (95% CI 99.8-99.9%). Pooled sensitivity and specificity for T13 and T18 was not calculated in the general pregnant population due to the low number of studies. In a high-risk pregnant population, the pooled sensitivities for T21 and T18 were 99.8% (95% CI 98.1-99.9%) and 97.7% (95% CI 95.8-98.7%) respectively, and the pooled sensitivity for T13 is 97.5 (95% CI 81.9-99.7%), although there was limited quality of evidence for trisomy 13.

In 2017 (reviewed in 2019), Hayes published a review which evaluated the clinical utility for use NIPT screening for fetal trisomy 21, 18, and 13 in low-risk women with singleton or multiple gestation pregnancies, including 15 studies (five observational and 10 health economic modelling studies).¹⁹ The review reported that, based on the results published by 10 modelling studies, that universal cfDNA screening in singleton pregnancies detects more cases of trisomy 21, 18, and 13 with fewer procedure-related miscarriages compared with conventional screening. However the body of evidence for clinical utility in general was found to be of very-low to low quality and the health economic modelling studies included in the review are not direct clinical utility studies. No studies were found that directly compared clinical outcomes for cfDNA screening with routine screening strategies in this population. As such the included studies have several limitations including variability in fetal abnormalities considered, heterogeneity in the conventional screen evaluated for comparison, assumptions that all patients with positive cfDNA screening would elect diagnostic testing, and treatment of cfDNA test failures. In addition, there was insufficient evidence to draw conclusions regarding cfDNA screening for trisomy 21, 18, and 13 in multiple gestation pregnancies. The review concluded that additional larger directly comparing clinical outcomes of cfDNA screening with those of routine screening strategies for low-risk or general obstetric patients are needed.

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In 2019, the Washington State Health Care Authority published a systematic review addressing the clinical utility of cell-free DNA prenatal screening for chromosomal aneuploidies.²⁰ On the basis of results from 1 RCT, 9 test accuracy studies and 8 economic studies, investigators concluded that universal screening with cfDNA appears to be more accurate than conventional screening for the common trisomies (T21, T18, and T13) in the general obstetric population.

Nonrandomized Comparative Studies

In 2015 Norton et al. published the results from a blinded, prospective industry-sponsored study that compared standard first-trimester screening versus the Ariosa cell-free DNA test (Harmony) in a population of average risk, single gestation women who received routine obstetric care at centers in the USA, Canada and Europe.¹⁶ The researchers assigned pregnant women presenting for aneuploidy screening at 10 to 14 weeks of gestation to undergo both standard screening (with measurement of nuchal translucency and the maternal serum screen including three analytes) and cell-free DNA testing. Participants received the results of standard screening, however; the results of cell-free DNA testing were blinded. Determination of the birth outcome was determined using diagnostic genetic testing or newborn examination. A total of 18,955 individuals were enrolled in the study and 15,841 were available for analysis. Cell-free fetal DNA testing identified all 38 cases (100% [95% CI, 90.7 to 100]) of trisomy 21 identified in the study, while standard screening identified only 30 of these cases (78.9% CI, 62.7 to 90.4; p=0.008). False positive rates were 0.06% (95% CI, 0.03 to 0.11) in the cell-free DNA group versus 5.4% (95% CI, 5.1 to 5.8) in the standard-screening group (p<0.001). The positive predictive value of screening with cell-free DNA was 80.9% (66.7 to 90.9) versus 3.4 (2.3 to 4.8) for standard screening (p<0.001). Among the 11,994 women with low-risk pregnancies on the basis of a maternal age under 35 years, cfDNA testing identified 19 of 19 women with trisomy 21, with 6 false positive results. The positive predictive value for cfDNA testing was 76.0% (95% CI, 54.9 to 90.6) for women under the age of 35 years. Overall, cell-free DNA testing for trisomy 21 outperformed standard screening using nuchal translucency measurement plus maternal triple serum screen, regardless of maternal age.

Nonrandomized Non-Comparative Studies

In 2015, Zhang et al. published an industry-sponsored prospective study evaluating the clinical performance of an NGS-based NonInvasive Fetal Trisomy (NIFTY) test in detecting trisomies 21, 18 and 13 in over 147,000 Chinese samples and compared its performance in both, low-risk and high-risk pregnancies.¹⁵ A patient was classified as high risk for aneuploidy if they met any one of the following criteria: advanced maternal age (> 35 years), a positive conventional Down syndrome screening test, abnormal sonographic markers, and family history of aneuploidy or a previous pregnancy with a trisomic fetus. Patients with none of the high-risk factors were defined as low risk for aneuploidy. Results from the NIPT test were confirmed using karyotyping or follow-up clinical analysis. Of the 146,958 samples tested, results were available in 112,669 (76.7%). Aneuploidy was confirmed in 720/781 of the cases with positive NIPT results for trisomy 21, 167/218 of the cases positive for trisomy 18 and 22/67 of the cases positive for trisomy 13. The sensitivity of NIPT was 99.17%, 98.24% and 100% for trisomies 21, 18 and 13, respectively. The specificity was 99.95%, 99.95% and 99.96% for trisomies 21, 18 and 13,

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respectively. There were no significant differences in test performance between the 72,382 high-risk participants and the 40,287 low-risk participants in terms of sensitivity (99.21% vs 98.97%; p=0.82) or specificity (99.95% vs 99.95%; p=0.98). A limitation of this study was the incomplete follow-up of NIPT results, which may have led to bias in terms of test performance. Thirty three percent of patients were lost to follow-up, with the majority of women being lost because they declined to provide clinical outcomes (17.9%) or they elected pregnancy termination (13.0%).

In 2016, Chitty et al. published the results of a prospective cohort study designed to assess the impact of offering NIPT testing as part of the United Kingdom (UK) National Health Services maternity care pathway.²¹ Eight maternity units across the UK participated, and included all pregnant women with a current Down’s syndrome risk on screening of at least 1/1000, including 3175 pregnant women (934 of which [29%] were considered high risk). The positive predictive value was 92% (81% to 97%) in the overall cohort, 94% (83% to 99%) in the high risk group and 82% (48% to 98%) in the intermediate risk group.

In 2017 Palomaki et al. published a prospective multi-center cohort study which assessed the clinical validity of the Panorama screening test (Natera, Inc.) in a general pregnancy population, including 2,691 women, 564 of which (21%) were 35 years or older.²² Of the 2685 women who underwent the test, 314 (12%) were indicated to be high risk. Among 2,681 reports, 16 women (0.6%) were screen-positive for trisomy 21, 18, or 13. Twelve were confirmed (positive predictive value (PPV), 75%; 95% CI, 48–93%) and four were false-positives (0.15%). The size of the group tested did not allow for a confident estimate of other test performance measures. Limitations is this study include the following: pregnancies reported as true-positive were not confirmed by karyotype, the percent of women electing diagnostic testing was not reported, inclusion criteria were not explicitly stated and test failures were excluded from the analysis.

Evidence Summary

Prior to 2015, there were a paucity of studies that assessed NIPT test performance and clinical validity in low- to average-risk populations. As a result, the positive predictive value (PPV) of NIPT published in the 2015 Hayes review for average-risk populations (reported at below 50% for all three common aneuploidies) was based on one 2014 study. In 2015, two large nonrandomized studies (n= 19,000 and 147,000) published test performance measures. One study reported PPVs of 81% and 76% for high-risk women and average-risk women (over the age of 35), respectively. The larger study did not publish PPVs, but reported the sensitivity to be 98-100% for all three common aneuploidies in over 40, 000 women with no risk factors. As United Kingdom and the U.S. have started implementing NIPT into standard maternal care pathways, studies have begun to emerge on clinical validity of NIPT in “general obstetric” populations, allowing for more generalizable results. These initial studies (n=2685 and 3175) have reported PPVs of 75-92%, but have also reported higher false positive rates. It is anticipated that as more regions implement NIPT testing into routine care, that additional studies will be published on the impact of NIPT testing in the general obstetric population.

Sex Chromosome Aneuploidies (SCAs)

Systematic Reviews

In 2015, Gil et al. published a systematic review and meta-analysis of NIPT for the screening of fetal aneuploidies, including sex chromosome aneuploidies (SCAs).²³ For monosomy X, 16 case series were included (N=177 singleton pregnancies with monosomy X and 9079 without). These studies reported anywhere from 0-47 cases of monosomy X per study. For SCAs other than monosomy X, 12 studies were included (N= 56 singleton pregnancies with SCAs and 6699 without). These studies reported between one to nine cases of SCA per study. The reviewers found that the studies included for SCAs had high risk of bias in terms of the index test used and the reference standard, raising concerns regarding applicability of screening to the general population. Weighted pooled detection rates (DR) and false-positive rates (FPR) in singleton pregnancies were 90.3% (95% CI, 85.7-94.2%) and 0.23% (95% CI, 0.14-0.34%) for monosomy X and 93.0% (95% CI, 85.8–97.8%) and 0.14% (95% CI, 0.06–0.24%) for sex chromosome aneuploidies other than monosomy X, indicating that screening performance measures for SCAs are substantially worse than those reported for common aneuploidies. In studies that reported no-call rates separately for common aneuploidies and SCAs (n=four studies), the no-call rate for SCAs was significantly greater than the no-call rate for the common aneuploidies (6.9% versus 17.2%, $p < 0.0001$). The reviewers found a number of limitations, including that the studies included for SCAs were small in number and size, there was high risk of bias in terms of the initial screening test and the reference standard used, and lack of clarity around the patients risk status in some studies, raising concerns regarding applicability of screening to the general population.

In 2017 (reviewed in 2020), Hayes published a review which evaluated the clinical utility for use NIPT screening for fetal SCAs, including seven studies published between 2013 and 2017 (three retrospective and four prospective).²⁴ The review reported that although some women with singleton pregnancies and positive cfDNA screening results for SCA elect diagnostic testing and use the results for pregnancy management decisions, these rates vary between studies, likely due, in part, to the small number of positive cases per study (very low quality evidence). None of the studies included were deemed to be of good quality. No studies were identified that reported clinical utility of SCA testing for multiple gestation pregnancies. The review noted that one benefit of NIPT screening for SCAs is that false-positive results, which indicate additional follow-up testing can lead to diagnosis of maternal chromosome aneuploidy, which is relevant to future pregnancy screening. The review noted several additional limitations of the included studies: small and heterogeneous patient populations, limited patient follow-up, excluded failed tests from analysis, and test failure and fetal fraction not reported.

Multiple Gestation Pregnancies

Meta-analysis

In the meta-analysis by Gil et al. described above, analyses on NIPT screening for common trisomies in twin pregnancies were also reported, including five case series ranging anywhere from 12 to 178 twin pregnancies (N= 31 trisomy-21 cases and 399 twin pregnancies).²³ The reviewers reported that the

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pooled detection rate (DR) was 93.7% (95% CI, 83.6–99.2%) and the false positive rate (FPR) was 0.23% (95% CI, 0.00–0.92%). Nine trisomy-18 pregnancies and two trisomy-13 pregnancies were also found and classified correctly. The reviewers concluded that performance of NIPS in multi-gestation pregnancies requires further evaluation.

In 2019, Dyr and colleagues conducted a retrospective study assessing the cfDNA screening in 30,000 multifetal pregnancies.²⁵ Maternal plasma samples from multifetal gestations were subjected to DNA extraction and library preparation followed by massively parallel sequencing. Sequencing data were analyzed to identify autosomal trisomies and other subchromosomal events. Fetal fraction requirements were adjusted in proportion to fetal number. Outcome data, when voluntarily received from the ordering provider, were collected from internal case notes. Feedback was received in 50 cases. The positivity rate in multifetal samples for trisomy 21 was 1.50%, 0.47% for trisomy 18, and 0.21% for trisomy 13. Average total sample fetal fraction was 12.2% at a mean gestational age of 13 weeks 6 days. Investigators concluded that cfDNA screening for multiple gestation pregnancies performs comparably to cfDNA screening for singleton pregnancies. Study limitations included a lack of outcome data by which clinical validity and clinical utility could be determined; and authorial conflicts of interest with the test manufacturer.

Fetal Sex Determination

Systematic Reviews

In 2011, Devaney et al. published results from a systematic review the test performance of noninvasive prenatal sex determination; including 57 studies (80 datasets representing 3524 male-bearing pregnancies and 3017 female-bearing pregnancies).²⁶ The reviewers reported that despite inter-study variability, test performance was high using maternal blood after 20 weeks. Overall performance of the test to detect Y chromosome sequences had high sensitivity, 95.4% (95% CI; 94.7%–96.1%) and specificity, 98.6% (95% CI; 98.1%–99.0%), but DNA methodology and gestational age had large effects on test performance. Methodology test characteristics were area under the curve (AUC) 0.988 (95% CI; 0.979–0.993) for polymerase chain reaction (PCR) and 0.996 (95% CI; 0.993–0.998) for real-time quantitative PCR (RTQ-PCR) (p=0.02). Testing after 20 weeks (sensitivity, 99.0%; specificity, 99.6%) outperformed testing prior to 7 weeks (sensitivity, 74.5%; specificity, 99.1%), testing at 7 through 12 weeks (sensitivity, 94.8%; specificity, 98.9%), and 13 through 20 weeks (sensitivity, 95.5%; specificity, 99.1%). The authors conceded that many of the studies included here were relatively small and that a large, prospective, randomized, blinded clinical trial would be beneficial to help validate test performance for sex determination.

In 2012, Wright et al. published a systematic review to evaluate the diagnostic test accuracy for fetal sex using NIPS, including 90 studies incorporating 9,965 pregnancies and 10,587 fetal sex results.²⁷ Overall mean sensitivity was 96.6% (95% CI; 95.2% to 97.7%) and mean specificity was 98.9% (95% CI; 98.1% to 99.4%). The authors indicated that their study did not have the ability to properly evaluate inconclusive or uncertain results and that the fact that there is obvious publication bias in the field due to the suppression of unwanted findings was a possible limitation.

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Microdeletion Syndromes

In 2015, Wapner et al. reported on a large case series to determine if NIPS can be used to detect fetal microdeletion syndromes, including 496 samples tested with Natera’s single nucleotide polymorphisms (SNP)-based NIPS test.²⁸ The study assessed detection rates of five microdeletion syndromes: 22q11.2, 1p36, cri du chat, Prader-Willi, and Angelman. The evaluation included six positive controls, 362 negative controls and 111 artificial DNA mixtures that mimicked the fetal fraction found in cfDNA from pregnant plasma and were enriched with microdeletions. The analytic detection rate was 97.8% for 22q11.2 deletions and 100% for each of the other microdeletions. False-positive rates were 0.76% for 22q11.2 deletion syndrome and 0.24% for cri-du-chat syndrome. No false positives occurred for Prader-Willi (0/428), Angelman (0/442), or 1p36 deletion syndromes (0/422). Limitations of this study include the fact that the population studied was not a clinical population and the samples tested were artificially constructed, the number of positive samples was very small, and not all negative controls received the standard test for microdeletions.

In 2022, Jacobsen and colleagues published a prospective trial assessing the performance of a single nucleotide polymorphism- based, prenatal cell-free DNA screening for detection of 22q11.2 deletion syndrome.²⁹ The primary outcome was sensitivity, specificity, positive predictive value, and negative predictive value of cell-free DNA screening for the detection of all deletions, including the classical deletion and nested deletions that are 500 kb, in the 22q11.2 low-copy repeat A-D region. Secondary outcomes included the prevalence of 22q11.2 deletion syndrome and performance of an updated cell-free DNA algorithm that was evaluated with blinding to the pregnancy outcome. Of the 20,887 women enrolled, a genetic outcome was available for 18,289 (87.6%). A total of 12 22q11.2 deletion syndrome cases were confirmed in the cohort, including 5 (41.7%) nested deletions, yielding a prevalence of 1 in 1524. In the total cohort, cell-free DNA screening identified 17,976 (98.3%) cases as low risk for 22q11.2 deletion syndrome and 38 (0.2%) cases as high risk; 275 (1.5%) cases were nonreportable. Overall, 9 of 12 cases of 22q11.2 were detected, yielding a sensitivity of 75.0%; specificity of 99.84% positive predictive value of 23.7%, and negative predictive value of 99.98%. None of the cases with a nonreportable result was diagnosed with 22q11.2 deletion syndrome. The updated algorithm detected 10 of 12 cases (83.3%) with a lower false positive rate and a positive predictive value of 52.6%.

Pregnancy Loss

The majority of the studies published on the genetics of pregnancy loss are moderate to large-sized association studies. However, the evidence review below will focus on studies reporting measures of clinical utility of genetic testing for recurrent pregnancy loss and stillbirth.

CLINICAL PRACTICE GUIDELINES

Due to the fast-paced nature of genetic testing for reproductive purposes and prenatal genetic testing, professional societies are updating guidelines at a rapid pace. Therefore, only the most recent clinical practice guideline for U.S.-based professional societies will be described below.

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Carrier Screening for Genetic Conditions

American College of Obstetricians and Gynecologists (ACOG)

In 2019, the American College of Obstetricians and Gynecologists (ACOG) reaffirmed two Committee Opinions ([#690](#) and [#691](#)) that were published in 2017 regarding carrier screening for genetic conditions.^{3,30} These documents provided recommendations for a set of specific conditions, including cystic fibrosis, spinal muscular atrophy, fragile X syndrome and Tay-Sachs disease. In addition, recommendations were provided for ethnicity specific screening, other targeted screening and expanded screening (including expanded cystic fibrosis panels and multigene panels for complex disorders). Lastly, guidance regarding genetic counseling was provided.

Preimplantation Testing

American College of Obstetricians and Gynecologists (ACOG)

In 2018, ACOG reaffirmed a 2016 Practice Bulletin ([#162](#)) on prenatal diagnostic testing for genetic disorders, making evidence-based recommendations for preimplantation genetic diagnosis (PGD).³¹ The panel stated that PGD can be used for most genetic conditions in which a mutation has been identified in the family. In addition, the panel stated that because PGD uses only one or a few cells from the early embryo and errors are possible, confirmation of results with CVS or amniocentesis is recommended.

American Society of Reproductive Medicine (ASRM)

In 2008, the American Society of Reproductive Medicine (ASRM) published a Committee Opinion on preimplantation genetic testing.⁷ The panel recommended indications for which PGD was appropriate, as well as guidance on genetic counseling. However, the panel felt there were no indications for which preimplantation genetic screening (PGS) was appropriate. In 2018, the ASRM published an expert committee opinion regarding preimplantation genetic testing for aneuploidy (PGT-A) as a screening test for in vitro fertilization (IVF).³² The committee concluded that the value of PGT-A in IVF has yet to be determined.

Noninvasive Prenatal Screening (NIPS)

American College of Medical Genetics (ACMG)

In July of 2016, the American College of Medical Genetics (ACMG) published an update of their 2013 position statement regarding noninvasive prenatal screening for fetal aneuploidy.³³ The panel stated the following:

- “Based on objective measures of clinical utility, NIPS can replace conventional screening for syndromes associated with chromosome 13/18/21 aneuploidy

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- NIPS testing is supported across the maternal age spectrum and continuum of gestational age beginning at 9–10 weeks
- There is an absolute need for pretest counseling
- Despite the lack of clinical utility studies, NIPS can be expanded beyond chromosome 13/18/21 to potentially include screening for sex chromosome aneuploidies and select microdeletions “when the live birth frequency of conditions reaches or exceeds that of currently screened conditions and when test metrics meet or exceed those of well-established approaches to prenatal screening.”²⁰

American College of Obstetricians and Gynecologists (ACOG)

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued a new practice bulletin, [\(#226\)](#), replacing Bulletin #163, which addressed screening for fetal chromosomal abnormalities.³⁴

The panel made the following Level A recommendations (“good and consistent scientific evidence”):

- Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing.
- Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cfDNA testing is not equivalent to diagnostic testing

The panel also made the following Level B recommendations (“limited or inconsistent scientific evidence”):

- The use of cell-free DNA screening as followUp for patients with a screen positive serum analyte screening test result is an option for patients who want to avoid a diagnostic test. However, patients should be informed that this approach may delay definitive diagnosis and will fail to identify some fetuses with chromosomal abnormalities.
- Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13.

Society of Maternal Fetal Medicine (SMFM)

In June 2015, the Society of Maternal Fetal Medicine (SMFM) published a consult document (#36) to aid clinicians in counseling their patients regarding cell-free DNA testing for aneuploidies.³⁵ A follow-up statement was published in December of the same year, with the sole purpose to clarify that the SMFM does not recommend that cfDNA aneuploidy screening be offered to all pregnant women.³⁶

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The original publication made the following strong recommendations, which were based on moderate quality evidence:

“Optimal candidates for routine cfDNA aneuploidy screening are women with:

- Maternal age ≥ 35 years at delivery.
- Fetal ultrasound finding that indicates an increased risk of aneuploidy, specifically for trisomies 13, 18, or 21.
- History of previous pregnancy with a trisomy detectable by cfDNA screening (trisomies 13, 18, or 21).
- Positive screening results for aneuploidy that include a first-trimester, sequential, integrated, or quadruple screen.
- Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21.”

Additional strong recommendations included:

- Routine screening for microdeletions with cfDNA is not recommended.
- For women who desire comprehensive testing for chromosomal disorders, diagnostic testing should be offered.”

In addition, the following recommendations were made based on clinical consensus:

- Formal genetic posttest counseling by maternal-fetal medicine subspecialist, geneticist, or genetic counselor after a positive cfDNA test is recommended.
- Chorionic villous sampling or amniocentesis should be offered after a positive cfDNA screen to confirm the diagnosis.
- Traditional aneuploidy screening and cfDNA aneuploidy screening should not be performed at the same time.

Pregnancy Loss

American College of Obstetricians and Gynecologists (ACOG)

The Committee Opinion ([#682](#)) published by ACOG, described above, on the use of chromosomal microarray analysis (CMA) in obstetrics and gynecology, addressed the use of CMA to evaluate stillbirths.³⁷ The panel recommended the use of CMA of fetal tissue for the evaluation of stillbirth (defined as pregnancy loss at or after 20 weeks gestation). The panel concluded that CMA was superior to karyotyping for stillbirth evaluation because it had a better likelihood of obtaining results and yields improved detection of causative abnormalities.

This recommendation was based on a study published by the NICHD Stillbirth Collaborative Research Network in 2012 that reported an analysis of samples from 532 stillbirths.³⁸ In this series, microarray analysis yielded results more often than did karyotype analysis (87.4% vs. 70.5%, $P < 0.001$) and provided

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better detection of genetic abnormalities (aneuploidy or pathogenic copy-number variants, 8.3% vs. 5.8%; P=0.007).

The guideline also stated that the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis was not recommended outside of the context of clinical trials.

POLICY SUMMARY

Carrier Screening

There is sufficient evidence that carrier testing, including testing for a known familial mutation, targeted mutation analysis, gene sequencing and deletion/duplication analysis in certain circumstances leads to improved health outcomes in selected individuals with risk of a genetic condition and allows prospective parents to make informed reproductive choices. In addition, clinical practice guidelines support carrier testing in select situations for certain well-defined conditions. However, for individuals that do not meet the medical necessity criteria outlined above, carrier screening for single-gene conditions is investigational due to insufficient evidence and lack of support from clinical practice guidelines. There is sufficient evidence that carrier screening for certain disorders in individuals of Ashkenazi Jewish descent improves health outcomes in this population. It has been established that the disorders listed in the medical necessity criteria above occur with substantially greater frequency in Ashkenazi Jewish descendants compared to the general population. In addition, clinical practice guidelines support carrier screening for these indications. There is insufficient evidence and lack of support from clinical practice guidelines for the genetic testing of any other conditions for Ashkenazi Jewish descendants.

Carrier screening of adult-onset conditions is not medically necessary as these conditions typically have a highly variable age of onset and the large majority have complex symptoms and are poorly understood. Current American College of Obstetricians and Gynecologists guidance recommends against screening for these conditions.

There is insufficient evidence that carrier screening impacts clinical decision-making or improves health outcomes when used for general population screening. In addition, there is a lack of support from clinical practice guidelines for carrier screening of the general population.

There is insufficient evidence of both clinical validity and clinical utility of multi-gene (also referred to as “expanded”) carrier screens. It has not been demonstrated that expanded carrier screens result in reductions of the number of births with an inherited disorder or impacts family planning decisions. In addition, there is a lack of consensus from specialty associations identifying appropriate population to undergo screening using these tests or which genes should be included in the panels.

Preimplantation Testing

There is sufficient evidence to support the use of preimplantation genetic diagnostic (PGD) testing for individuals who are known carriers of specific pathogenic disease-causing mutations, as outlined in the

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medical policy criteria above. PGD testing for these individuals leads to an increased likelihood of successful live births of healthy unaffected newborns. There is also sufficient evidence to support the use of PGD testing for individuals who are known carriers of balanced chromosomal translocations, as PGD testing leads to decrease risk of spontaneous abortion and increased likelihood of achieving a live birth. In addition, clinical practice guidelines support the use of PGD in these clinical situations. There is insufficient evidence to support the use of preimplantation genetic diagnostic testing (PGD) in other situations not identified in the medical necessity policy criteria above. It is unclear if PGD leads to improved health outcomes for these indications. In addition, there is a lack of support from clinical practice guidelines for the use of PGD in these clinical situations.

There is insufficient evidence that preimplantation genetic screening (PGS) improves live birth rates, regardless of the presence of risk factors. In fact, newer PGS methods such as microarray do not appear to improve health outcomes in women with risk factors such as advanced maternal age or history of failed in-vitro fertilization cycles. In addition, major medical association guidelines have indicated that there are no proposed indications for which PGS is recommended.

Noninvasive Prenatal Screening

There is sufficient evidence to support the use of noninvasive prenatal screening (NIPS or NIPT) for common trisomies (chromosome 13, 18, and 21) in pregnant individuals with specific risk factors and under the clinical circumstances outlined in the medically necessary policy criteria. NIPT in these circumstances has been reported to have a high positive predictive value and negative predictive value and evidence indicates testing may improve pregnancy outcomes. In addition, there is support from several clinical practice guidelines for the use of NIPT in certain clinical situations, including when an individual has one or more risk factors that increase the risk of fetal aneuploidy.

The use of NIPT for the purposes of sex determination is considered not medically necessary as the current standard method of fetal sex determination is by routine prenatal ultrasound.

There is insufficient evidence to support the use of NIPT in individuals that are not considered to be at high risk of fetal aneuploidy, such as women that do not have any of the risk factors listed in the policy criteria or for the general obstetric population. There have been limited studies published on the performance of the NIPT test in these populations, and even fewer studies on whether NIPT improves health outcomes in these populations. In addition, the Society of Maternal Fetal Medicine state that optimal candidates for NIPT are individuals with one or more risk factors.

There is insufficient evidence to support the use of NIPT in all other clinical situations, including but not limited to multi-gestational pregnancy, screening for microdeletions, and screening for aneuploidies other than chromosome 13, 18 and 21. In addition, several clinical practice guidelines recommend against the use of NIPT to screen for aneuploidies other than those involving chromosomes 13, 18, and 21, including sex chromosomes (X and/or Y).

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Pregnancy Loss

There is sufficient evidence that evaluation of chromosomal abnormalities for pregnancy loss in certain situations, through specific testing methodologies outlined in the criteria above, alters reproductive decision-making and changes diagnostic testing strategies for future pregnancies. While direct clinical utility for traditional techniques such as fluorescence in situ hybridization (FISH) and karyotype analysis has been established; for chromosomal microarray, the potential for clinical utility parallels that of traditional techniques as it is much more sensitive than its predecessors. Due to insufficient evidence of clinical utility and lack of support from clinical practice guidelines, genetic testing for pregnancy loss is investigational, when individuals do not meet medical necessity criteria as outlined above, or when sequencing based tests are used.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

MEDICAL POLICY CROSS REFERENCES

- Genetic Counseling (All Lines of Business Except Medicare)
- Genetic Testing: Reproductive Planning and Prenatal Testing (Medicare Only)
- Genetic Testing: Whole Exome, Whole Genome and Proteogenomic Testing
- Direct-to-Consumer Testing

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