Clinical Appropriateness Guidelines

Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis

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Scope

This document addresses genetic testing in the reproductive setting, including both testing of parents (carrier screening) and testing of fetal or embryonic DNA (prenatal diagnosis, preimplantation genetic testing, cell-free DNA). All tests listed in these guidelines may not require prior authorization; please refer to the health plan. For whole exome sequencing as a technology for prenatal testing, please refer to the Clinical Appropriateness Guidelines: Whole Exome and Whole Genome Sequencing.

Appropriate Use Criteria

Carrier Screening for Familial Disease

Single gene reproductive carrier screening for hereditary conditions is medically necessary when any of the following criteria are met:

- An individual’s reproductive partner is a known carrier of a disease-causing pathogenic or likely pathogenic (P/LP) variant for a recessively-inherited condition
- A diagnosis of a genetic disorder has been confirmed in an affected relative, and one of the following:
  - A genetic P/LP variant has been identified, and testing is targeted to the known familial P/LP variant
  - The affected relative has not had genetic testing and is unavailable for testing, or the specific P/LP variant is unavailable

Fragile X

Preconception or prenatal genetic testing for Fragile X syndrome (FMR1) is medically necessary for the following indications:

- Family history of unexplained intellectual disability/developmental delay or autism in a blood relative
- Female patient with a personal or family history of premature ovarian insufficiency

Carrier Screening for Genetic Diseases

Cystic Fibrosis

Cystic fibrosis (CF) carrier screening with a targeted test for common variants (CPT code 81220) is medically necessary one time when testing has not been previously performed.

CFTR full gene sequencing (81223) is medically necessary one time for any of the following indications:
- Patient’s reproductive partner is a known carrier of a cystic fibrosis P/LP variant
- Patient has a family history of cystic fibrosis but the P/LP variant is not known
- Testing is for prenatal diagnosis when there is a high clinical suspicion of cystic fibrosis, e.g. fetal echogenic bowel
- Common variants are less likely based on ancestry, e.g. Asian, African American, Hispanic

Deletion/duplication testing (81222) is not medically necessary for routine carrier screening.

Known familial P/LP variant analysis (81221) must be pursued if the patient has a family history of cystic fibrosis and the specific P/LP variant is known.

**Spinal Muscular Atrophy**

Spinal muscular atrophy (SMA) carrier screening by SMN1 dosage/deletion analysis (81329) is medically necessary when testing has not been previously performed.

- For those with a family history of SMA, pre- and post-test genetic counseling is recommended to discuss testing strategy due to the complex inheritance of this condition

**Hemoglobinopathies**

Hemoglobinopathy genetic carrier screening is medically necessary when any of the following criteria are met:

- Clinical or laboratory features (e.g. CBC, hemoglobin electrophoresis) are suggestive of a hemoglobinopathy
- Results of testing by conventional studies (e.g., electrophoresis, liquid chromatography, isoelectric focusing) yield equivocal results
- A definitive diagnosis remains uncertain or a definitive diagnosis is known but specific P/LP variant identification is necessary for prenatal diagnosis

**Ashkenazi Jewish Carrier Screening**

Ashkenazi Jewish carrier screening by targeted P/LP variant analysis for the following conditions is medically necessary when an individual or their reproductive partner has Ashkenazi Jewish ancestry:

- Cystic fibrosis
- Familial dysautonomia
- Tay-Sachs disease
- Canavan disease
- Fanconi anemia group C
- Niemann-Pick disease, type A
• Bloom syndrome
• Mucolipidosis type IV
• Gaucher disease, type 1

Other Ethnicities
Carrier screening for additional conditions may be considered medically necessary if the patient is at increased risk to be a carrier based on their ethnicity, including but not limited to:

• Tay-Sachs carrier screening for individuals with French Canadian ancestry
• Maple syrup urine disease (MSUD) screening for individuals with Mennonite ancestry

Carrier Screening Not Clinically Appropriate
The following tests are not medically necessary for carrier screening in the general population:

• Expanded carrier screening panels
• Thrombophilia screening
• Whole exome sequencing

Preimplantation Genetic Testing of Embryos
Note: Coverage of genetic testing of embryos may be dependent upon health plan fertility benefits.

Preimplantation genetic testing, including the embryo biopsy procedure if applicable, is medically necessary for the following indications:

Preimplantation Genetic Testing for Monogenic Disease (PGT-M)

• Both biologic parents are carriers of a single gene autosomal recessively-inherited disorder
• One biologic parent is a known carrier of a single gene autosomal dominantly-inherited disorder or a single X-linked disorder
• One biologic parent is a potential carrier based on family history of a single gene autosomal dominantly-inherited disorder or a single X-linked disorder and is requesting non-disclosure testing
• A previous pregnancy or child has been diagnosed with a genetic disease and familial P/LP variant(s) are known

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR)

• One biologic parent is a carrier of a chromosomal rearrangement

Preimplantation genetic testing is not medically necessary for any other indication, including but not limited to the following:
- Human leukocyte antigen (HLA) typing of an embryo to identify a future suitable stem-cell tissue or organ transplantation donor
- Testing solely to determine if an embryo is a carrier of an autosomal recessively-inherited disorder
- Testing for a multifactorial condition
- Testing for variants of unknown significance
- Nonmedical gender selection
- Nonmedical traits

**Preimplantation Genetic Testing for Aneuploidy**

Preimplantation genetic testing for aneuploidy (PGT-A) by any testing methodology is not medically necessary for any indication, including but not limited to the following:

- Advanced maternal age (i.e., age ≥ 35 years)
- Repeated in vitro fertilization (IVF) failures
- Recurrent spontaneous abortions

**Prenatal Cell-Free DNA Screening**

Prenatal cell-free DNA screening (cfDNA) (coded with only one CPT code, i.e. 81507 or 81420) is medically necessary for single or twin pregnancies.

Prenatal cell-free DNA screening is not medically necessary for the following indications:

- High-order multiple gestations (i.e. triplets or higher)
- Multiple gestation pregnancies with fetal demise, vanishing twin, one or more anomalies detected in one fetus
- Miscarriage or fetal demise

SensiGene® (81479 or 81403) testing is medically necessary in a single gestation pregnancy when all of the following criteria are met:

- A maternal anti-D antibody has been identified
- The paternal Rh genotype is determined to be heterozygous or is unknown
- The results will impact antenatal care

The following tests are not medically necessary:

- Screening for copy number variants (e.g. 22q11.2, Cri-du-chat, whole genome, microdeletions, etc.) (e.g. 81422, 81479)
• Screening for autosomal trisomies other than 13, 18, and 21 (e.g. 81479)
• Prenatal cell-free DNA testing for single gene conditions (e.g. 81479)

Concurrent screening for aneuploidy using multiple screening tests is not considered medically necessary.

**Prenatal Molecular Genetic Testing of a Fetus**

*Note: The criteria below do not apply to cytogenetic testing (e.g. karyotype, chromosome analysis.)*

Single gene, multi-gene, or chromosomal microarray prenatal genetic testing is medically necessary when the results of the genetic test will impact clinical decision-making and the requested method is scientifically valid for the suspected condition.

Chromosomal microarray (CMA) testing on products of conception is medically necessary for:

• Evaluation of recurrent pregnancy loss*
• Evaluation of intrauterine fetal demise (IUFD) or stillbirth after 20 weeks of gestational age
• Evaluation of a pregnancy loss with one or more major structural anomalies

*Recurrent pregnancy loss is defined by two or more unexplained pregnancy losses.

**Reproductive Genetic Testing for Recurrent Pregnancy Loss**

*Note: The criteria below do not apply to cytogenetic testing (e.g. karyotype, chromosome analysis).*

Single or multi-gene panel testing for the evaluation of recurrent pregnancy loss is not medically necessary, including but not limited to the following

• F2
• F5
• MTHFR

**Reproductive Genetic Testing for the Diagnosis of Infertility**

*Note: The criteria below do not apply to cytogenetic testing (e.g. karyotype, chromosome analysis).*

The following tests are medically necessary when performed to establish the underlying etiology of infertility:

• Cystic fibrosis testing for males with either congenital bilateral absence of vas deferens or azoospermia or severe oligospermia (i.e., < five million sperm/milliliter) with palpable vas deferens
• Y-chromosome microdeletion testing in males with nonobstructive azoospermia or severe oligospermia (i.e., < five million sperm/milliliter)

(See above for Fragile X testing criteria related to premature ovarian insufficiency.)
CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

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

81228  Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

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

81243  FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

81244  FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)

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

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
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

SensiGene®

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

Codes that do not meet medical necessity criteria:

MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood

Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)

Policy Interpretation: This test is performed for the genomic analysis of at least 15 genes for carrier screening of individuals with inherited conditions. Specimen type varies. Methodology is a multiplex PCR-based assay.

Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood

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

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

Myriad Foresight® Carrier Screen (Myriad® Women’s Health, Inc.)
ANY Preparent Global Panel (Progenity®)
ANY Horizon™ Carrier Screen (Natera, Inc.)
ANY Inheritest® Carrier Screen, Comprehensive Panel (LabCorp)

Background

Reproductive Carrier Screening

Historically carrier screening in the prenatal or preconception period has been driven primarily by the knowledge of specific autosomal recessive conditions known to be more prevalent in individuals of particular ancestral backgrounds, e.g. Ashkenazi Jewish ancestry. The ACMG recommends carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, Tay-Sachs disease, Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, and Gaucher disease for all individuals of Ashkenazi Jewish descent who are pregnant or considering pregnancy. These disorders all have significant health impacts on an affected infant. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Genetics and Genomics (ACMG) acknowledge the complexities of race, ethnicity, ancestry and coupling patterns (ACOG 690; ACOG 691; Edwards 2015; Grody 2011).

Cystic fibrosis (CF) was the first condition targeted by pan-ethnic universal carrier screening using molecular technology in 2001 following joint recommendations from the ACMG and ACOG (Deignan et al. 2020). The ACMG Technical Standard released in 2020 highlights the racial disparity in detection rates when carrier screening utilizes the original targeted panel of the 23 most common P/LP variants and states that carrier screening using next generation sequencing allows for screening of clinically relevant CFTR variants irrespective of ethnicity (Deignan et al. 2020). The Technical Standard addresses the advances in knowledge that allow for expanded CFTR variant analysis, e.g. refinement of the variant classification system, better characterization of classic/non-classic CF phenotypes, and recognition of variants contributing to clinically relevant non-classic CF disease. The ACMG does not recommend CFTR deletion/duplication analysis for carrier screening indications (Deignan et al. 2020).

Additionally, preconception and prenatal screening for spinal muscular atrophy (SMA) across all ethnicities is recommended by ACOG and ACMG regardless of family history. Guidance for additional conditions is limited or conflicting. General population reproductive carrier screening for X-linked conditions, excluding Fragile X syndrome, is not addressed by ACOG or ACMG. Fragile X carrier screening is recommended for women with a personal or family history of premature ovarian insufficiency as well as a family history of Fragile X-related disorders, autism, unexplained intellectual disability or developmental delay (ACOG 691). While carrier screening for Fragile X syndrome in the general population is complicated by concerns around genetic counseling for complex information and the potential for psychosocial harms, ACOG Committee Opinion 762 authored in conjunction with the Society for Maternal Fetal Medicine (ACOG 2019) states Fragile X carrier screening may be performed in patients without risk factors after informed consent.
Large pan-ethnic expanded carrier screening panels are now available. These panels typically include hundreds of genes and are intended to be used for general population carrier screening. There are no standard guidelines regarding which disease genes and P/LP variants to include on an expanded carrier screening panel of this size. These panels often include diseases that are present with increased frequency in specific populations, as well as a large number of diseases for which the carrier frequency in the general population is low in the absence of a known family history. Multiple professional societies have called for guidelines to be developed that would limit genes on these panels based on standard criteria, such as only including severe, childhood-onset genetic diseases, and only genes for which P/LP variant frequencies are known and prognosis can be predicted based on genotype (Grody et al. 2013; Edwards et al. 2015).

**Preimplantation Genetic Testing**

Preimplantation genetic testing (PGT), previously referred to as preimplantation genetic screening and diagnosis, is a procedure that involves testing an embryo for a genetic condition before the embryo is placed into the uterus for implantation. PGT can be further categorized into preimplantation genetic testing for aneuploidy (PGT-A), preimplantation genetic testing for monogenic disease (PGT-M), and preimplantation genetic testing for structural rearrangements (PGT-SR). PGT is available for a variety of single gene conditions and chromosome rearrangements, but requires the following:

- Genetic testing on one or both parents: the diagnosis in the family needs to be confirmed via genetic testing and the specific causative variant(s) must be known
- In Vitro Fertilization (IVF): PGT can only be done in the context of IVF

Methods used for PGT vary, and may depend on the specific type of P/LP variant or chromosome change. Linkage analysis is still required in many cases despite advances in testing methodologies.

**Preimplantation Genetic Testing for Aneuploidy**

Preimplantation genetic testing for aneuploidy (PGT-A) involves testing for chromosome abnormalities in biopsied cells from IVF-created embryos. Historically, PGT-A was performed using FISH for common aneuploidies on single cells from cleavage stage embryos; however, microarray technology has become more common in the last few years, as has testing multiple cells from the trophectoderm at the blastocyst stage (Brezina et al. 2016). Microarray allows testing for aneuploidies in all 23 chromosomes, but cannot detect triploidy. Many other technical methods (e.g. qPCR) are used or are in development for PGT.

Despite these advances, multiple researchers have called into question the accuracy of testing trophectoderm biopsies to determine the aneuploid status of an embryo due to the apparent frequency of mosaicism (Maxwell et al. 2016; Gleicher and Orvieto 2017). Trophectoderm mosaicism has been reported to be as high as 70-90% in cleavage- and blastocyst-stage embryos, and approximately 3-20% with more sensitive assays such as next generation sequencing (ASRM 2020). Increasing evidence suggests mosaicism may be a normal phenomenon. Therefore, using PGT-A to eliminate embryos with detected chromosome abnormalities in the trophectoderm may in fact lead to discarding embryos that still have the potential to develop into healthy, liveborn infants.

Studies evaluating the effectiveness of PGT-A include prospective nonrandomized and randomized controlled trials. While several small studies suggest that PGT-A outcomes may be improving, there is no consensus about when to use the technology or for which populations. Limited data is available on
the pregnancy outcomes after transfer of an embryo with mosaicism, but approximately 100 documented live births have been reported as of mid-2019 (ASRM 2020). No adverse events (e.g. congenital anomalies, pregnancy complications, abnormal prenatal or postnatal karyotypes) related to the transfer of an embryo with mosaic PGT-A results have been reported in the literature (ASRM 2020), but there are several limitations with this data including a lack of chromosomal microarray and uniparental disomy data, a lack of formal outcome studies on the health of the newborns including no longitudinal studies, possible delayed recognition of syndrome phenotypes, and the relatively small number of reported live births (ASRM 2020). Published, peer-reviewed scientific literature does not support the use of PGT-A in couples undergoing IVF procedures for infertility with a history of recurrent pregnancy loss, repeated IVF failures and/or advanced maternal age in order to improve IVF success rates.

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology released a committee opinion in 2018 detailing the limitations of the current data on the topic, and noting that the value of PGT-A as a screening test for all IVF patients has yet to be determined. In a 2020 Committee Opinion on clinical management of PGT-A mosaicism, ASRM still does not endorse nor suggest that PGT-A is appropriate for all cases of IVF. At this time, there is insufficient evidence to suggest that PGT-A is medically necessary to improve fertility outcomes. The American College of Obstetricians and Gynecologists (ACOG) expressed a similar opinion, Number 799, that additional future research is needed to establish the clinical utility of PGT-A including the appropriate subset of patients that may benefit from testing, the residual risk for aneuploidy and the clinical significance of mosaicism.

**Prenatal Cell-Free DNA Testing**

Prenatal cell-free DNA screening, also called non-invasive prenatal testing (NIPT), are highly sensitive DNA sequencing-based tests that screen for common fetal aneuploidy, including trisomy 21/18/13 and sex chromosome abnormalities. NIPT, which tests a maternal blood sample, may be used as a sophisticated screening test to help determine who might benefit from invasive diagnostic testing for fetal aneuploidy using chorionic villus sampling (CVS) or amniocentesis.

NIPT for trisomies 13, 18 and 21 has a significantly higher testing performance than traditional prenatal aneuploidy screening tests (e.g. maternal serum screening). While not equivalent to diagnostic testing since positive predictive values are lower in younger women due to their lower baseline risk and false negatives are possible, NIPT is the most sensitive and specific screen for Trisomies 13, 18 and 21 (ACOG 2020). Detection rates for these common trisomies range from 98 to >99% (Gil et al. 2017; ACOG 2020). In a 2020 Committee Opinion, the American College of Obstetricians and Gynecologists (ACOG) acknowledged that any woman may choose to have NIPT, just as any woman may choose to have invasive diagnostic testing. In 2016, the American College of Medical Genetics and Genomics (ACMG) reiterated its stance that NIPT should be available to women of all risk groups as one of many options. The Society for Maternal Fetal Medicine, however, states that the best candidates for NIPT are those at high risk for aneuploidy but temper this statement by adding, “when guided by patient autonomy, the option should be available to women who request additional testing beyond what is currently recommended by professional societies” (2015).

Several laboratories have added common microdeletions such as 22q11.2 to their NIPT testing platforms, and some labs now offer evaluation of cell free DNA for copy number changes greater than 7Mb across the genome. Cell-free DNA microdeletion studies have not been clinically validated and are
not recommended by the American College of Obstetricians and Gynecologists, the European and American Societies for Human Genetics, or the Society for Maternal Fetal Medicine (ACOG 2020; Dondorp et al. 2015; SMFM 2016).

The ACOG (2020) recognizes that NIPT is the only screening test with the ability to identify fetal sex and sex chromosome aneuploidy; however, the meta-analysis cited on performance of NIPT for chromosome aneuploidy, Gil et al. (2017) could not report on the detection rate for sex chromosome aneuploidy due to the small study population. In addition, the phenotype associated with these conditions is highly variable. Both the European and the American Societies of Human Genetics have issued recommendations that sex chromosome screening by cfDNA not be performed (Dondorp et al. 2015), and the ACMG recommends that patients should be discouraged from choosing screening for the sole purpose of fetal sex determination (Gregg et al. 2016).

The ACOG (2020) recommends that NIPT can be performed in twin pregnancies based limited or inconsistent evidence, and the summary of evidence-based practices issued by the International Society for Prenatal Diagnosis (2020) states, with a moderate rating, that the use of cfDNA screening for common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence revealing high detection and low false positive rates with high predictive values (Palomaki et al. 2020). Research suggests that NIPT may be accurate for Trisomy 21 screening in twin pregnancies, however data is limited making it difficult to determine accurate detection rates in particular for Trisomy 18 and 13. The ACOG (2020) recommendation was based on a prospective analysis pooled with data from a meta-analysis by Gil et al. (2017). This analysis was updated in 2019 and included 997 twin pregnancies combined with datasets from seven studies identified by literature review. The analysis revealed a pooled weighted detection rate (DR) and false-positive rate (FPR) for Trisomy 21 twin pregnancies (n=56) of 98.2\% (95\% CI, 83.2-99.8\%) and 0.05\% (95\% CI, 0.01-0.26\%); for Trisomy 18 twin pregnancies (n=18) the DR was 88.9\% (95\% CI, 64.8-97.2\%) and FPR was 0.03\% (95\% CI, 0.00-0.33\%); and for Trisomy 13 twin pregnancies there were only three cases, two (66.7\%) detected by NIPT at a FPR of 0.19\%. Larger prospective trials to provide more data regarding the performance of NIPT technology in multiple gestation pregnancies in particular for Trisomy 18 and 13 are needed (Gregg et al. 2016; Bender and Dugoff 2018; Gil et al. 2019).

### Prenatal Diagnosis via Karyotype or Microarray

The American College of Obstetricians and Gynecologists (ACOG) recommends prenatal chromosomal microarray (CMA) on CVS or amniocentesis samples for patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination. They also state that in patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or CMA can be performed (regardless of maternal age).

In the setting of intrauterine fetal demise or stillbirth, CMA is recommended on the products of conception in place of karyotype for genetic evaluation, due to its higher yield of results with nondividing cells and increased detection of chromosomal abnormalities. ACOG does not recommend routine CMA analysis on structurally normal pregnancy losses less than 20 weeks gestation.

### Recurrent Pregnancy Loss Testing

The American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) both recommend chromosomal analysis via karyotyping when a couple has a history of recurrent pregnancy loss (two or more unexplained losses). Karyotypic analysis can be
performed on either the products of conception or on both parents when a history of recurrent pregnancy loss is identified. The American College of Medical Genetics and Genomics states that chromosomal microarray (CMA) should NOT be used to evaluate parents with a history of recurrent pregnancy loss, as this technology cannot detect balanced chromosomal rearrangements.

See Clinical Appropriateness Guidelines for Pharmacogenomic Testing and Genetic Testing for Thrombotic Disorders for discussion of F5, F2, and MTHFR testing.

**Fertility Evaluation**

Infertility is defined as the failure to achieve a pregnancy after 12 months of regular unprotected intercourse (Agency for Healthcare Research and Quality (AHRQ) 2008; American Society of Reproductive Medicine (ASRM) 2013). Infertility can affect one or both reproductive partners. Some underlying factors are reversible through medical intervention; the major underlying causes of infertility include: ovulatory, tubal, cervical, uterine/endometrial, and male partner factors. There are some genetic factors responsible for male factor infertility, including chromosome abnormalities, Y-chromosome microdeletions, and mild/non-classical cystic fibrosis.

All men with severe oligozoospermia or azoospermia (sperm count < 5 million/hpf) should be offered genetic counseling, karyotype assessment for chromosomal abnormalities, and Y-chromosome microdeletion testing prior to initiating in vitro fertilization with intracytoplasmic sperm injection (Okun and Sierra 2014). Cystic fibrosis testing is also indicated for males with obstructive azoospermia.

ACOG Committee Opinion 781 (Infertility Workup for the Women’s Health Specialist, 2019) states thrombophilia testing is not appropriate for inclusion in the battery of tests routinely ordered to determine the etiology of infertility.

**Professional Society Guidelines**

**American College of Obstetricians and Gynecologists (ACOG)**


ACOG Practice Bulletin No. 78. Hemoglobinopathies in Pregnancy. 


American Society for Reproductive Medicine (ASRM) 
ASRM Clinical Management of Mosaic Results from Preimplantation Genetic Testing for Aneuploidy (PGT-A) of Blastocysts. A Committee Opinion.


American College of Medical Genetics and Genomics (ACMG) 


ACMG Position Statement. Prenatal/Preconception Expanded Carrier Screening. 


ACMG Practice Guideline. Carrier screening in Individuals of Ashkenazi Jewish Descent. 
ACMG Practice Guideline. Carrier Screening for Spinal Muscular Atrophy.


ACMG Standards and Guidelines. Fragile X syndrome: Diagnosis and Carrier Testing.

ACMG Technical Standards. CFTR Variant Testing.


International Society for Prenatal Diagnosis (ISPD)
Position Statement. Cell Free (cf)DNA Screening for Down Syndrome in Multiple Pregnancies.

National Society of Genetic Counselors (NSGC)

Joint Statements
ACOG Committee Opinion 762. Pre-Pregnancy Counseling. ACOG and SMFM.

ACOG Committee Opinion No. 781. Infertility Workup for the Women’s Health Specialist. ACOG and ASRM.

ACOG Obstetric Care Consensus No. 10. Management of Stillbirth. ACOG and SMFM.

ACOG Practice Bulletin No. 162. Prenatal Diagnostic Testing for Genetic Disorders. ACOG Committee on Practice Bulletins—Obstetrics; Committee on Genetics; SMFM.

ACOG Practice Bulletin No. 226. Screening for Fetal Chromosomal Abnormalities. ACOG and SMFM.

Selected References


Revision History

Medical Advisory Board Review:

v1.2021 11/13/2020: Approved
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v2.2020 05/08/2020: Reviewed
v1.2020 11/04/2019: Approved
v2.2019 05/23/2019: No Criteria Changes
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<td>Carrie Langbo, MS, CGC, Kay LeChien, MS, CGC, and Tricia Page, MS, CGC</td>
<td>Semi-annual review. Carrier screening for cystic fibrosis was expanded. Criteria for carrier screening that is not clinically appropriate was updated. CPT codes, Professional Society Guidelines, Background and References were updated.</td>
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<td>Melissa Burns, MS, CGC</td>
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<td>Version</td>
<td>Date</td>
<td>Author</td>
<td>Notes</td>
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<tr>
<td>v2.2019</td>
<td>4/03/2019</td>
<td>Melissa Burns, MS, CGC</td>
<td>Semi-annual review. Revised language for preimplantation genetic screening and diagnostic testing of embryos, prenatal cell-free DNA screening, prenatal molecular genetic testing of a fetus, and reproductive genetic testing for recurrent pregnancy loss. Updated background.</td>
</tr>
<tr>
<td>v1.2018</td>
<td>03/31/2018</td>
<td>Kate Charyk, MS, CGC</td>
<td>Semi-annual review. Revised language for prenatal cell-free DNA screening, prenatal molecular testing of a fetus, reproductive genetic testing for recurrent pregnancy loss and the diagnosis of infertility, familial variant testing and cystic fibrosis, hemoglobinopathy, Ashkenazi Jewish testing for carrier screening. Removed recommendation for genetic counseling following unclear SMA result. Expanded carrier screening to include rare variants common in other ethnicities. Removed 10 week gestational age limit and vanishing twin exclusion for NIPT. Added disclaimer sentence to Scope. Added additional background evidence and reference for NIPT in multiple gestations.</td>
</tr>
<tr>
<td>v3.2017</td>
<td>10/26/2017</td>
<td>Kate Charyk, MS, CGC</td>
<td>Quarterly Review. Added simultaneous screening to indications for which cfDNA is not medically necessary. Added additional background evidence and references for PGS.</td>
</tr>
<tr>
<td>v2.2017</td>
<td>09/11/2017</td>
<td>Megan Czarniecki, MS, CGC</td>
<td>Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Added disclaimer to PGD testing coverage. Approved by Policy Lead.</td>
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<td>Version</td>
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<tr>
<td>v2.2017</td>
<td>06/20/2017</td>
<td>Kate Charyk, MS, CGC</td>
<td>Quarterly review. No criteria changes. Reorganized carrier screening criteria under new header. Updated references. Approved by Policy Lead.</td>
</tr>
<tr>
<td>v2.2017</td>
<td>04/19/2017</td>
<td>Kate Charyk, MS, CGC</td>
<td>Quarterly review. Added updated ACOG committee opinions #690 and 691 per 3/8/17 CSC approval. Updated references.</td>
</tr>
<tr>
<td>v2.2017</td>
<td>03/08/2017</td>
<td>Kate Charyk, MS, CGC</td>
<td>Expanded criteria of SMA to general population carrier screening.</td>
</tr>
<tr>
<td>v1.2017</td>
<td>01/23/2017</td>
<td>Kate Charyk, MS, CGC</td>
<td>Quarterly review. No criteria changes. Added paragraph to background regarding prenatal WES. Updated references. Renumbered to 2017 version.</td>
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<tr>
<td>v1.2016</td>
<td>08/01/2016</td>
<td>Gwen Fraley, MS, CGC</td>
<td>Expanded criteria NIPT to average-risk population. Updated references.</td>
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<tr>
<td>v1.2015</td>
<td>04/19/2015</td>
<td>Gwen Fraley, MS, CGC</td>
<td>Original version</td>
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**Original Effective Date:** 4/19/2015

**Primary Author:** Gwen Fraley, MS, CGC