

Clinical Appropriateness Guidelines

Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis

EFFECTIVE MARCH 6, 2022



8600 West Bryn Mawr Avenue
South Tower - Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

Appropriate.Safe.Affordable
© 2022 AIM Specialty Health
GEN03-0322.1

Table of Contents

Scope	3
Appropriate Use Criteria	3
Carrier Screening	3
<i>Familial Disease</i>	3
<i>Fragile X</i>	3
<i>Cystic Fibrosis</i>	3
<i>Spinal Muscular Atrophy</i>	4
<i>Hemoglobinopathies</i>	4
<i>Ashkenazi Jewish Carrier Screening</i>	4
<i>Other Ethnicities</i>	5
Carrier Screening Not Clinically Appropriate	5
Preimplantation Genetic Testing of Embryos	5
Prenatal Cell-Free DNA Screening	6
Prenatal Molecular Genetic Testing of a Fetus	7
Reproductive Genetic Testing for Pregnancy Loss	7
Reproductive Genetic Testing for the Diagnosis of Infertility	7
CPT Codes	8
Background	10
Reproductive Carrier Screening	10
Preimplantation Genetic Testing	11
Prenatal Cell-Free DNA Testing	13
Prenatal Diagnosis via Karyotype or Microarray	14
Reproductive Genetic Testing for Pregnancy Loss	14
Fertility Evaluation	14
Professional Society Guidelines	15
Selected References	18
Revision History	19

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

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: Chromosomal Microarray Analysis, Whole Exome and Whole Genome Sequencing.

Appropriate Use Criteria

Carrier Screening

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

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- Patient has a family history of cystic fibrosis and the P/LP variant is not known
- For testing of parents when there is a high clinical suspicion of cystic fibrosis in a pregnancy, e.g., fetal echogenic bowel
- Patient is of an ancestry where common variants are less likely, 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 and a definitive diagnosis remains uncertain
- A definitive diagnosis is known but specific P/LP variant identification is necessary for reproductive options/interventions, e.g., preimplantation genetic testing or 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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- Niemann-Pick disease, type A
- Bloom syndrome
- Mucopolidosis 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

Multi-gene panel testing is medically necessary when the individual's personal and/or family history meets one or more criteria above for all of the genes on the panel.

Carrier Screening Not Clinically Appropriate

The following tests are not medically necessary for carrier screening in the general population:

- 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)

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- 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
- Pre-implantation genetic testing for aneuploidy (PGT-A) by any testing methodology for any indication

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 (including recurrent pregnancy loss) 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)

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- Prenatal cell-free DNA testing for single gene conditions (e.g., 81479)
- Prenatal cell-free DNA testing for twin zygosity (e.g., 0060U)

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.

Prenatal molecular genetic testing in a fetus for familial variants of unknown significance is not medically necessary.

Reproductive Genetic Testing for Pregnancy Loss

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

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.

Genetic testing (using single gene or multi-gene panel assays) for genes associated with thrombophilia, e.g., F2, F5, MTHFR, is not medically necessary.

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.)

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

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)

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1

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

81479 or SensiGene[®]

81403

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

Codes that do not meet medical necessity criteria:

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81422 Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood

81443 Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolysaccharidosis 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.

0060U Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood

0236U SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- 0252U Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy
- 0253U Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)
- 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
- ANY vanadis® NIPT

CPT® (Current Procedural Terminology) is a registered trademark of the American Medical Association (AMA). CPT® five digit codes, nomenclature and other data are copyrighted by the American Medical Association. All Rights Reserved. AMA does not directly or indirectly practice medicine or dispense medical services. AMA assumes no liability for the data contained herein or not contained herein.

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.

Cystic fibrosis (CF) was the first condition targeted by pan-ethnic universal carrier screening using molecular technology in 2001 following joint recommendations from 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 irregardless 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. ACMG does not recommend CFTR deletion/duplication analysis for carrier screening indications (Deignan et al. 2020). ACMG and ACOG have also historically endorsed a pan-ethnic approach to carrier screening for spinal muscular atrophy (SMA).

Large pan-ethnic carrier screening panels are now available. These panels typically include hundreds of genes and are intended to be used for general population carrier screening. These panels often include

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

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). In response, ACMG recently published a practice resource on carrier screening for autosomal recessive and X-linked conditions during pregnancy and preconception. In this resource, it is recommended that all individuals currently pregnant or planning pregnancy be offered screening for 97 autosomal recessive conditions and 16 X-linked conditions (Gregg et al. 2021). The authors state that a concern for equity in this space is a driver for the expansion of reproductive carrier screening. While equity is a growing concern and focus in the genetics and medical communities at large, this practice resource fails to address the complexities of equitable access related not only to availability of this testing but the potentially relevant follow-up resources and services it may lead to. The resource group also cites that the decreasing cost of genetic testing allows for this broadened recommendation. Although the cost of next generation sequencing based testing has declined, the downstream financial impact of this intervention at the population level has not been proven with real public health data. Robust cost-effectiveness analysis is needed to determine if the benefits of expanded carrier screening are truly worth the cost to the healthcare system and increased out-of-pocket expenses for consumers. Measuring the clinical utility of large panel tests is complex. More work is needed to address larger public health ramifications, including potential harms.

Preimplantation Genetic Testing

Preimplantation genetic testing (PGT) 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, this practice is no longer considered safe given evidence that these early biopsies reduce implantation and live birth rates (Scott et al. 2007; Dahdouh et al. 2015). Microarray and next generation sequencing technology have become more common in the last few years, as has testing multiple cells from the trophectoderm at the blastocyst stage (Brezina et al. 2016). NGS is more sensitive than microarray, but is associated

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

with an increased incidence of mosaic results. Some caution is needed as the technological capabilities within the realm of PGT-A advance. It is not well understood whether the trophoctoderm biopsy may have a damaging effect on implantation and/or embryo development, and the safety of prolonged embryo culturing and cryopreservation have also been called into question (Practice Committees of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology 2018; Verpoest et al. 2018; Guzman et al. 2018).

Due to the apparent frequency of mosaicism with newer NGS technology, multiple researchers have called into question the accuracy of testing trophoctoderm biopsies to determine the aneuploidy status of the entire embryo (Maxwell et al. 2016; Gleicher and Orvieto 2017). Trophoctoderm 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. In addition, the degree of mosaicism in an embryo is a poor predictor of pregnancy success (Kushnir et al. 2018). Therefore, using PGT-A to eliminate embryos with detected chromosome abnormalities in the trophoctoderm may in fact lead to discarding embryos that still have the potential to develop into healthy, liveborn infants (Gleicher et al. 2016). Further studies looking at the specifics of a mosaic result (including prenatal and postnatal chromosome testing) would need to be done to determine if prenatal or postnatal mosaicism can be applied to predict outcomes for mosaic embryos (ASRM 2020; Gleicher et al. 2021). Additionally, other technologies for evaluating embryos that do not include trophoctoderm biopsy, such as noninvasive PGT of the blastocoel fluid and spent culture media are emerging; randomized trials are required to elucidate its validity and cost effectiveness across patient populations (Li et al. 2021).

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.

Given the limitations of published studies, the utility of PGT-A continues to be a subject of debate (Gleicher et al. 2021). The Practice Committees of ASRM 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. ACOG expressed a similar opinion, Number 799, that additional future research is needed to establish the

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

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, ACOG acknowledged that any woman may choose to have NIPT, just as any woman may choose to have invasive diagnostic testing. In 2016, ACMG reiterated its stance that NIPT should be available to women of all risk groups as one of many options. SMFM, 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 microarray technology to screen for copy number variants across the genome. Cell-free DNA microdeletion studies have not been clinically validated and are not recommended by ACOG, the European and American Societies for Human Genetics, or SMFM (ACOG 2020; Dondorp et al. 2015; SMFM 2016).

ACOG (2020) recognizes that NIPT is the only screening test with the ability to identify fetal sex and sex chromosome aneuploidy, and several large validation studies have demonstrated the sensitivity and specificity of NIPT for determining fetal sex and sex chromosome aneuploidies such as Turner syndrome (45,X) and Klinefelter syndrome (47,XXY). However, these studies have indicated that screening for XY chromosome aneuploidy has a significantly lower positive predictive value than other chromosomes-only about 26% for monosomy X (ACOG & SMFM 2016; Bianchi 2019). 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 ACMG recommends that patients should be discouraged from choosing screening for the sole purpose of fetal sex determination (Gregg et al. 2016).

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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

13. 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

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).

Reproductive Genetic Testing for Pregnancy Loss

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.

ACOG and 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. ACMG 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; 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

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

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 [reaffirmed 2020]) 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 Committee Opinion No. 605. Primary Ovarian Insufficiency in Adolescents and Young Women. *Obstet Gynecol.* 2014 Jul [reaffirmed 2020];124(1):193-197. PubMed PMID: 24945456.

ACOG Committee Opinion No. 682. Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstet Gynecol.* 2016 Dec [reaffirmed 2020];128(6): e262-8. PubMed PMID: 27875474.

ACOG Committee Opinion No. 690. Carrier Screening in the Age of Genomic Medicine. *Obstet Gynecol.* 2017 Mar [reaffirmed 2020];129(3): e35-40. PubMed PMID: 28225425.

ACOG Committee Opinion No. 691. Carrier Screening for Genetic Conditions. *Obstet Gynecol.* 2017 Mar [reaffirmed 2020];129(3): e41-55. PubMed PMID: 28225426.

ACOG Committee Opinion No. 799. Preimplantation Genetic Testing. *Obstet Gynecol.* 2020 Mar;135(3): e133-e137. PubMed PMID: 32080053.

ACOG Committee Opinion No. 816. Consumer Testing for Disease Risk. *Obstet Gynecol.* 2021 Jan 1;137(1):e1-e6. PubMed PMID: 33399428.

ACOG Practice Bulletin No. 78. Hemoglobinopathies in Pregnancy. *Obstet Gynecol.* 2007 Jan [reaffirmed 2018];109(1):229-37. PubMed PMID: 17197616.

ACOG Practice Bulletin No. 197. Inherited Thrombophilias in Pregnancy. *Obstet Gynecol* 2018;132: e18-34. PubMed PMID: 23963422.

ACOG Practice Bulletin No. 200. Early Pregnancy Loss. *Obstet Gynecol* 2018;132. PubMed PMID: 30157093.

ACOG Practice Bulletin No. 231. Multifetal Gestations Twin Triplet and Higher-Order Multifetal Pregnancies. *Obstet Gynecol* 2021 Jun 1; 137(6). PubMed PMID: 34022891.

ACOG Practice Advisory. Cell-free DNA to Screen for Single-Gene Disorders.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

ACOG Committee on Genetics, Hoskovec J, Russo M. February 2019 [reaffirmed 2020 March]. Available at: www.acog.org. Accessed on 2/11/2021.

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.

Fertil Steril. 2020 Aug;114(2):246-254. PubMed PMID: 32741460.

ASRM Evaluation and Treatment of Recurrent Pregnancy Loss. A Committee Opinion.

Fertil Steril. 2012 Nov;98(5):1103-11. Epub 2012 Jul 24. PubMed PMID: 22835448.

ASRM Definitions of Infertility and Recurrent Pregnancy Loss. A Committee Opinion.

Fertil Steril. 2020 Mar;113(3):533-535. Epub 2020 Feb 27. PubMed PMID: 32115183.

American College of Medical Genetics and Genomics (ACMG)

ACMG Clinical Practice Resource. Lack of Evidence for MTHFR Polymorphism Testing.

Hickey SE, Curry CJ, Toriello HV. *Genet Med.* 2013 Feb [reaffirmed 2020];15(2):153-6. PubMed PMID: 23288205.

ACMG Points to Consider Statement for Programs and Sponsoring Organizations: DNA-Based Screening and Population Health.

Murray M, Giovanni M, Doyle D, et al. *Genet Med.* 2021 Mar 16. Epub ahead of print. PubMed PMID: 33727704.

ACMG Points to Consider Statement for Individuals and Health Care Providers. DNA-Based Screening and Personal Health.

Bean L, Scheuner M, Murray M, et al. *Genet Med.* 2021 Jun;23(6):979-988. PubMed PMID: 33790423.

ACMG Position Statement. Noninvasive Prenatal Screening for Fetal Aneuploidy, 2016 update.

Gregg AR, Skotko BG, Benkendorf JL, et al. *Genet Med.* 2016 Oct;18(10):1056-65. Epub 2016 Jul 28. PubMed PMID: 27467454.

ACMG Position Statement. Direct-to-Consumer Prenatal Testing for Multigenic or Polygenic Disorders.

Genet Med. 2021 Jun 28. PubMed PMID: 34183790.

ACMG Practice Guideline. Array-based Technology and Recommendations for Utilization in Medical Genetics Practice for Detection of Chromosomal Abnormalities.

Manning M, Hudgins L. *Genet Med.* 2010 Nov;12(11):742-5. PubMed PMID: 20962661.

ACMG Practice Guideline. Carrier screening in Individuals of Ashkenazi Jewish Descent.

Gross SJ, Pletcher BA, Monaghan KG. *Genet Med.* 2008 Jan;10(1):54-6. PubMed PMID: 18197057.

ACMG Practice Guideline. Carrier Screening for Spinal Muscular Atrophy.

Prior, TW. *Genet Med.* 2008 Nov;10(11):840-2. PubMed PMID: 18941424.

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

Sherman S, Pletcher BA, Driscoll DA. *Genet Med.* 2005 Oct;7(8):584-7. PubMed PMID: 16247297.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

ACMG Technical Standards. CFTR Variant Testing.

Deignan J, Astbury C, Cutting G, et al. Genet Med. 2020 Aug;22(8):1288-1295. PubMed PMID: 32404922.

ACMG Technical Standards. Venous Thromboembolism Laboratory Testing (factor V Leiden and factor II c.*97G>A), 2018 update.

Genet Med. 2018 Dec;20(12):1489-1498. PubMed PMID: 30297698.

ACMG Technical Standard. Laboratory Testing for Fragile X, 2021 revision.

Spector E, Behlmann A, Kronquist K, et al. Genet Med. 2021 May;23(5):799-812. PubMed PMID: 33795824.

International Society for Prenatal Diagnosis (ISPD)

Position Statement. Cell Free (cf)DNA Screening for Down Syndrome in Multiple Pregnancies.

Palomaki GE, Chiu RWK, Pertile MD, et al. Prenat Diagn. 2020 Oct 5. doi: 10.1002/pd.5832. Epub ahead of print. PMID: 33016373.

National Society of Genetic Counselors (NSGC)

NSGC Practice Guideline. Genetic Counseling and Testing for FMR1 Gene Mutations.

Finucane B, Abrams L, Cronister A, et al. J Genet Couns. 2012 Dec;21(6):752-60. Epub 2012 Jul 14. PubMed PMID: 22797890.

Joint Statements

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

Obstet Gynecol. 2019 Jan [reaffirmed 2020];133(1):e78-e89. PubMed PMID: 30575679.

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

Obstet Gynecol 2019 [reaffirmed 2020];133:e377-84. PubMed PMID: 31135764

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

Obstet Gynecol. 2020 Mar;135(3):e110-e132. PubMed PMID: 32080052.

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

Obstet Gynecol. 2016 May [reaffirmed 2021];127(5):e108-22. PubMed PMID: 26938573.

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

Obstet Gynecol 2020 Oct;136(4):859-867. PubMed PMID: 32976375.

Diagnosis and Treatment of Infertility in Men: American Urology Association/ASRM Guideline.

Schlegel PN, Sigman M, Collura B, et al. Available at: <https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/diagnosis-and-treatment-of-infertility-in-men-aaa-asrm.pdf>. Accessed on January 27, 2021.

Evaluation of the Azoospermic Male. A Committee Opinion. Practice Committee of the ASRM in Collaboration with the Society for Male Reproduction and Urology.

Fertil Steril. 2018 May;109(5):777-782. PubMed PMID: 29778371.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

Expanded Carrier Screening in Reproductive Medicine-Points to Consider: A Joint Statement of the ACMG, ACOG, NSGC, Perinatal Quality Foundation, and SMFM.

Edwards JG, Feldman G, Goldberg J, et al. *Obstet Gynecol.* 2015 Mar;125(3):653-62. PubMed PMID: 25730230.

The Use of Preimplantation Genetic Testing for Aneuploidy (PGT-A): A Committee Opinion. Practice Committees of the ASRM and the Society for Assisted Reproductive Technology.

Fertil Steril. 2018 Mar;109(3):429-436. PubMed PMID: 29566854.

Selected References

- 1 Bean LJH, Funke B, Carlston CM, Gannon JL, Kantarci S, Krock BL, Zhang S, Bayrak-Toydemir P, on behalf of the ACMG Laboratory Quality Assurance Committee. Diagnostic gene sequencing panels: from design to report- a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2019 Nov 16. PubMed PMID: 31732716.
- 2 Bender, W and Dugoff, L. Screening for aneuploidy in multiple gestations: the challenges and options. *Obstet Gynecol Clin North Am.* 2018 Mar;45(1):41-53. PubMed PMID: 29428285.
- 3 Benn P, Borrell A, Chiu R, et al. Position statement from the Chromosome Abnormality Screening Committee on behalf of the board of the International Society for Prenatal Diagnosis. *Prenat Diagn.* 2015;35(8):725-734. PubMed PMID: 25970088.
- 4 Bianchi DW, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med.* 2014 Feb 27;370(9):799-808. PubMed PMID: 24571752.
- 5 Brezina PR, Anchan R, Kearns WG. Preimplantation genetic testing for aneuploidy: what technology should you use and what are the differences? *J Assist Reprod Genet.* 2016 Jul;33(7):823-32. Epub 2016 Jun 14. PubMed PMID: 27299602.
- 6 Chibuk J, Rafalko J, Boomer T, McCullough R, McLennan G, Wyatt P, Almasri E. Cell-free DNA screening in twin pregnancies: A more accurate and reliable screening tool. *Prenat Diagn.* 2020 Jul 16. PubMed PMID: 32677048.
- 7 Committee Opinion No. 640: Cell-Free DNA Screening For Fetal Aneuploidy. *Obstet Gynecol.* 2015 Sep;126(3):e31-7. PubMed PMID: 26287791.
- 8 Cornel MC, Rigger T, Jansen ME, Henneman L. Neonatal and carrier screening for rare diseases: how innovation challenges screening criteria worldwide. *J Community Genet.* 2020 Oct 19. Epub ahead of print. PMID: 33074550.
- 9 Cuckle H, Benn P, Pergament E. Cell-free DNA screening for fetal aneuploidy as a clinical service. In: *Circulating Nucleic Acids, a Clinical Biochemistry Special Issue*, Editors Chiu R and Oudejans C. *Clin Biochem* 2015 Oct;48(15):932-41. PubMed PMID: 25732593.
- 10 Debrock S, Melotte C, Spiessens C, et al. Preimplantation genetic screening for aneuploidy of embryos after in vitro fertilization in women aged at least 35 years: a prospective randomized trial. *Fertil Steril.* 2010 Feb;93(2):364-73. Epub 2009 Feb 26. PubMed PMID: 19249029.
- 11 Devaney SA, Palomaki GE, Scott JA, et al. Noninvasive fetal sex determination using cell-free fetal DNA: a systematic review and meta-analysis. *JAMA.* 2011 Aug 10;306(6):627-36. PubMed PMID: 21828326.
- 12 Dhillon RK, Hillman SC, Morris RK, et al. Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. *BJOG.* 2014 Jan;121(1):11-21. Epub 2013 Jul 17. PubMed PMID: 23859082.
- 13 Di Renzo GC, Bartha JL, Bilardo CM. Expanding the indications for cell-free DNA in the maternal circulation: clinical considerations and implications. *Am J Obstet Gynecol.* 2019 Jun;220(6):537-542. PubMed PMID: 30639383.
- 14 Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. *Eur J Hum Genet.* 2015 Nov;23(11):1438-50. Epub 2015 Mar 18. PubMed PMID: 25782669
- 15 Dyr B, Boomer T, Almasri EA, Wardrop JL, Rafalko J, Chibuk J, McCullough RM. A new era in aneuploidy screening: cfDNA testing in >30,000 multifetal gestations: Experience at one clinical laboratory. *PLoS One.* 2019 Aug 8;14(8):e0220979. PubMed PMID: 31393959.
- 16 Familiari A, Boito S, Rembouskos G, Ischia B, Accurti V, Fabietti I, Volpe P, Persico N. Cell-free DNA analysis of maternal blood in prenatal screening for chromosomal microdeletions and microduplications: a systematic review. *Prenat Diagn.* 2021 Mar 12. PubMed PMID: 33710639.
- 17 Gil MM, Accurti V, Santacruz B, Plana MN, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol.* 2017 Sep;50(3):302-314. Update in: *Ultrasound Obstet Gynecol.* 2019 Jun;53(6):734-742. PubMed PMID: 28397325.
- 18 Gil MM, Galeva S, Jani J, Konstantinidou L, Akolekar R, Plana MN, Nicolaides KH. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. *Ultrasound Obstet Gynecol.* 2019 Jun;53(6):734-742. PubMed PMID: 31165549.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

- 19 Gleicher N, Orvieto R. Is the hypothesis of preimplantation genetic screening (PGS) still supportable? A review. *Journal of Ovarian Research*. 2017 Mar;10(1):21. PubMed PMID: 28347334.
- 20 Gleicher N, Patrizio P, and Brivaniou A. Preimplantation Genetic Testing for Aneuploidy- a Castle Built on Sand. *Trends Mol Med*. 2021 Jan 11:S1471-4914(20)30313-0. PubMed PMID 33446425.
- 21 Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2016;18(10):1056-1065. PubMed PMID: 27467454.
- 22 Gregg AR, Aarabi M, Klugman S, et al.; ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021 Jul 20. PubMed PMID: 34285390.
- 23 Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ; Subcommittee on Cystic Fibrosis Screening, Accreditation of Genetic Services Committee, ACMG. American College of Medical Genetics. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med*. 2001 Mar-Apr;3(2):149-54. PubMed PMID: 11280952.
- 24 Health Quality Ontario. Noninvasive Prenatal Testing for Trisomies 21, 18, and 13, Sex Chromosome Aneuploidies, and Microdeletions: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2019;19(4):1-166. Published 2019 Feb 19. PubMed PMID: 30847010.
- 25 Hui AS, Chau MHK, Chan YM, Cao Y, Kwan AH, Zhu X, Kwok YK, Chen Z, Lao TT, Choy KW, Leung TY. The role of chromosomal microarray analysis among fetuses with normal karyotype and single system anomaly or nonspecific sonographic findings. *Acta Obstet Gynecol Scand*. 2021 Feb;100(2):235-243. PubMed PMID: 32981064.
- 26 Laurino MY, Bennett RL, Saraiya DS, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. *J Genet Counsel* 2005 Jun;14(3):165-81. PubMed PMID: 15959648.
- 27 Lee E, Illingworth P, Wilton L, et al. The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): systematic review. *Hum Reprod*. 2015 Feb;30(2):473-83. Epub 2014 Nov 28. PubMed PMID: 25432917.
- 28 Maxwell SM, Colls P, Hodes-Wertz B, et al. Why do euploid embryos miscarry? A case-control study comparing the rate of aneuploidy within presumed euploid embryos that resulted in miscarriage or live birth using next-generation sequencing. *Fertil Steril*. 2016 Nov;106(6):1414-9. Epub 2016 Sep 28. PubMed PMID: 27692437.
- 29 Munné S, Blazek J, Large M, et al. Detailed investigation into the cytogenetic constitution and pregnancy outcome of replacing mosaic blastocysts detected with the use of high-resolution next-generation sequencing. *Fertil Steril*. 2017 Jul;108(1):62-71. Epub 2017 Jun 1. PubMed PMID: 28579407.
- 30 Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. *Fertil Steril*. 2015 May;103(5):1215-20. Epub 2015 Mar 13. PubMed PMID: 25772770.
- 31 Nicolaides KH, Syngelaki A, Gil M, et al. Validation of targeted sequencing of single-nucleotide polymorphism for non-invasive prenatal detection of aneuploidy of chromosomes 13, 18, 21, X and Y. *Prenat Diagn*. 2013 June; 33(6), 575-9. Epub 2013 Apr 24. PubMed PMID: 23613152.
- 32 Okun N, Sierra S. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can*. 2014 Jan;36(1):64-83. PubMed PMID: 24444289.
- 33 Orvieto R, Shuly Y, Brengauz M, Feldman B. Should pre-implantation genetic screening be implemented to routine clinical practice? *Gynecol Endocrinol*. 2016 Jun;32(6):506-8. Epub 2016 Feb 12. PubMed PMID: 26872945.
- 34 Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. *Fertil Steril*. 2015 Mar;103(3):e18-25. PMID: 25597249.
- 35 Sherman S, Pletcher BA, Driscoll DA. ACMG Standards and Guidelines. Fragile X syndrome: Diagnosis and Carrier Testing. *Genet Med*. 2005 Oct;7(8):584-7. PubMed PMID: 16247297.
- 36 Silver J and Norton M. Expanded Carrier Screening and the Complexity of Implementation. *Obstet Gynecol*. 2021 Feb 1;137(2):345-350. PubMed PMID: 33416279.
- 37 Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Electronic address: pubs@smfm.org. #36: Prenatal aneuploidy screening using cell-free DNA. *Am J Obstet Gynecol*. 2015 Jun;212(6):711-6. PubMed PMID: 25813012.
- 38 Turley P, Meyer M, Wang N, et al. Problems with Using Polygenic Scores to Select Embryos. *N Engl J Med*. 2021 Jul 1;385(1):78-86. PubMed PMID: 34192436.
- 39 Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med*. 2004 Sep-Oct;6(5):387-91. PubMed PMID: 15371902.
- 40 Zhu X, Chen M, Wang H, Guo Y, Chau MHK, Yan H, Cao Y, Kwok YKY, Chen J, Hui ASY, Zhang R, Meng Z, Zhu Y, Leung TY, Xiong L, Kong X, Choy KW. Clinical utility of expanded non-invasive prenatal screening and chromosomal microarray analysis in high-risk pregnancy. *Ultrasound Obstet Gynecol*. 2021 Mar;57(3):459-465. PubMed PMID: 32198896.

Revision History

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

Medical Advisory Board Review:

- v1.2022 09/20/2021: Approved
- v2.2021 03/12/2021: Approved
- v1.2021 11/13/2020: Approved
- v3.2020 11/13/2020: Approved
- v2.2020 05/08/2020: Reviewed
- v1.2020 11/04/2019: Approved
- v2.2019 05/23/2019: No Criteria Changes
- v1.2019 11/07/2018: Reviewed
- v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

- v1.2021 08/23/2021: Approved
- v2.2021 02/22/2021: Approved
- v1.2021 10/13/2020: Approved
- v3.2020 10/13/2020: Approved
- v2.2020 04/06/2020: Approved
- v1.2020 10/11/2019: Approved
- v2.2019 04/03/2019: Approved
- v1.2019 10/03/2018: Approved
- v1.2018 02/28/2018: Approved
- v2.2017 03/08/2017: Approved
- v1.2017 01/25/2017: Approved

Revisions:

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

Version	Date	Editor	Description
v1.2022 GEN03-0322.1	8/16/2021	Melissa Burns, MS, CGC and Carrie Langbo, MS, CGC	Semi-annual review. SensiGene® criteria was added. All revisions to criteria represent formatting changes for clarification and do not reflect any changes in coverage stance. CPT codes, professional society guidelines, background and references were updated.
v2.2021 GEN03-0921.1	2/15/2021	Melissa Burns, MS, CGC and Carrie Langbo, MS, CGC	Semi-annual review. Criteria for cystic fibrosis, NIPT in twins, prenatal cell-free DNA screening and prenatal molecular genetic testing was clarified. Criteria for SensiGene® was removed because the test is no longer commercially available. CPT codes, professional society guidelines, background and references were updated.
v1.2021	9/11/2020	Carrie Langbo, MS, CGC, Kay LeChien, MS, CGC, and Tricia Page, MS, CGC	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.
v3.2020	10/9/2020	Carrie Langbo, MS, CGC and Kay LeChien	Interim update: criteria added for NIPT in twin pregnancies. Background, professional society guidelines and references were updated.
v2.2020	03/13/2020	Melissa Burns, MS, CGC and Nancy Herrig, MS, CGC	Semi-annual review. Preimplantation Genetic Testing criteria was updated with no impact on coverage. CPT codes, professional society guidelines, background and references were updated.

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

v1.2020	09/11/2019	Melissa Burns, MS, CGC	Semi-annual review. Criteria was added for SensiGene [®] . CPT codes, background and references were updated.
v2.2019	4/03/2019	Melissa Burns, MS, CGC	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.
v1.2019	10/03/2018	Heather Dorsey, MS, CGC	Semi-annual review. Clarified language regarding appropriate use of microarray for stillbirth fetuses. Updated guidelines and reference section. Reformatted CPT code list. PMID added.
v1.2018	03/31/2018	Kate Charyk, MS, CGC	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.
v3.2017	10/26/2017	Kate Charyk, MS, CGC	Quarterly Review. Added simultaneous screening to indications for which cfDNA is not

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.

			medically necessary. Added additional background evidence and references for PGS.
v2.2017	09/11/2017	Megan Czarniecki, MS, CGC	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.
v2.2017	06/20/2017	Kate Charyk, MS, CGC	Quarterly review. No criteria changes. Reorganized carrier screening criteria under new header. Updated references. Approved by Policy Lead.
v2.2017	04/19/2017	Kate Charyk, MS, CGC	Quarterly review. Added updated ACOG committee opinions #690 and 691 per 3/8/17 CSC approval. Updated references.
v2.2017	03/08/2017	Kate Charyk, MS, CGC	Expanded criteria of SMA to general population carrier screening.
v1.2017	01/23/2017	Kate Charyk, MS, CGC	Quarterly review. No criteria changes. Added paragraph to background regarding prenatal WES. Updated references. Renumbered to 2017 version.
v1.2016	08/01/2016	Gwen Fraley, MS, CGC	Expanded criteria NIPT to average-risk population. Updated references.
v1.2015	04/19/2015	Gwen Fraley, MS, CGC	Original version

Original Effective Date: 4/19/2015

Primary Author: Gwen Fraley, MS, CGC

PROPRIETARY

Guidelines developed by, and used with permission from, Informed Medical Decisions, Inc. © 2015-2022 Informed Medical Decisions, Inc. All Rights Reserved.