BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.116 Invasive Prenatal (Fetal) Diagnostic Testing

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Related Policies:

2.04.102 - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
2.04.107 - Carrier Screening for Genetic Diseases
2.04.122 - Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss
2.04.59 - Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies
4.01.21 - Noninvasive Prenatal Screening for Fetal Aneuploidies, Microdeletions, Single-Gene Disorders, and Twin Zygosity Using Cell-Free Fetal DNA
4.02.05 - Preimplantation Genetic Testing

Invasive Prenatal (Fetal) Diagnostic Testing

Description

Description

Invasive prenatal (fetal) diagnostic testing may be used to identify pathogenic genetic alterations in fetuses at increased risk based on prenatal screening or in women who choose to undergo diagnostic testing due to other risk factors. This evidence review only addresses the use of chromosomal microarray (CMA) testing, molecular diagnosis of single-gene disorders, and next-generation sequencing.

OBJECTIVE

The objective of this evidence review is to evaluate evidence on approaches used to identify genetic alterations when prenatal screening (eg, cell-free DNA, ultrasound, or maternal biomarkers) indicates a fetus is at increased risk or when women choose to undergo diagnostic testing due to other risk factors.

POLICY STATEMENT

Chromosomal Microarray Testing

In individuals who are undergoing invasive diagnostic prenatal (fetal) testing, chromosome microarray testing may be considered **medically necessary** as an alternative to karyotyping (see Policy Guidelines).

Single-Gene Disorders

Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders may be considered **medically necessary** when a pregnancy has been identified as being at high risk:

- For autosomal dominant conditions, at least one of the parents has a known pathogenic variant.
- For autosomal recessive conditions:
    - Both parents are suspected to be carriers or are known to be carriers, OR
    - One parent is clinically affected and the other parent is suspected to be or is a known carrier.
- For X-linked conditions: A parent is suspected to be or is a known carrier.

AND, ALL of the following are met:

- The natural history of the disease is well-understood, and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state, AND
- Any variants have high penetrance, AND
- The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, AND
- An association of the marker with the disorder has been established.

If the above criteria for molecular analysis of single-gene disorders are not met, invasive diagnostic prenatal (fetal) testing is considered **investigational**.

Next-Generation Sequencing

The use of next-generation sequencing in the setting of invasive prenatal testing is considered **investigational**.

POLICY GUIDELINES

Fetal Malformations

Fetal malformations identified by ultrasound, characterized as major or minor malformations, whether isolated or multiple, may be part of a genetic syndrome, despite a normal fetal karyotype.

Major malformations are structural defects that have a significant effect on function or social acceptability. They may be lethal or associated with possible survival with severe or moderate immediate or long-term morbidity. Examples by organ system include: genitourinary: renal agenesis (unilateral or bilateral), hypoplastic/cystic kidney; cardiovascular: complex heart malformations; musculoskeletal: osteochondrodysplasia/osteogenesis imperfecta, clubfoot, craniosynostosis; central nervous system: anencephaly, hydrocephalus, myelomeningocele; facial clefts; body wall: omphalocele/gastroschisis; and respiratory: cystic adenomatoid lung malformation.

Single-Gene Disorders

An individual may be suspected of being a carrier if there is a family history of or ethnic predilection for a disease. Carrier screening is not recommended if the carrier rate is less than 1% in the general population.

In most cases, before a prenatal diagnosis using molecular genetic testing can be offered, the familial variant must be identified, either in an affected relative or carrier parent(s). Therefore, panel testing in this setting would not be considered appropriate.

In some cases, the father may not be available for testing, and the risk assessment to the fetus will need to be estimated without knowing the father's genetic status.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing and who receive chromosomal microarray (CMA) testing, the evidence includes a systematic review and meta-analysis and prospective cohort and retrospective analyses comparing the diagnostic yield of CMA testing with that of karyotyping. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. CMA testing has a higher detection rate of pathogenic chromosomal alterations than karyotyping. CMA testing can yield results that have uncertain clinical significance; however, such results can be minimized by the use of targeted arrays, testing phenotypically normal parents for the copy number variant, and the continued accumulation of pathogenic variants in international databases. The highest yield of pathogenic copy number variants by CMA testing has been found in fetuses with malformations identified by ultrasound. Changes in reproductive decision-making could include decisions on the continuation of a pregnancy, enabling timely treatment of a condition that could be treated medically or surgically either in utero or immediately after birth, and birthing decisions. The American College of Obstetricians and Gynecologists has recommended CMA testing in women who are undergoing an invasive diagnostic procedure. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing and who receive molecular testing for single-gene disorders, the evidence includes case series that may report disorders detected and test validity. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. For clinical validity, when there is a known pathogenic familial variant, the sensitivity and specificity of testing for the variant in other family members are expected to be very high. Changes in reproductive decision-making could include decisions on the continuation of the pregnancy, facilitating timely treatment of a condition medically or surgically either in utero or immediately after birth, decisions concerning the place of delivery (i.e., tertiary care center), and route of delivery. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing and who receive next-generation sequencing, the evidence is lacking. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. There are concerns about the interpretation of data generated by next-generation sequencing and the data's clinical relevance. The clinical validity of next-generation sequencing in the prenatal setting is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine

In 2016, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine offered recommendations on the use of chromosomal microarray (CMA) testing and next-generation sequencing in prenatal diagnosis (Committee Opinion Number 682)[25,]:

- "Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities.
- Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.
- Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Comprehensive patient pretest and posttest genetic counseling from an obstetrician-gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential.
- Chromosomal microarray analysis should not be ordered without informed consent, which should include a discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.
- The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

This Committee Opinion was reaffirmed in 2023.

International Society for Prenatal Diagnosis, et al.

In 2018, the International Society for Prenatal Diagnosis, the Society for Maternal-Fetal Medicine, and the Perinatal Quality Foundation released a joint position statement on the use of prenatal exome and genome-wide sequencing for fetal diagnosis.[26,] This initial position statement was replaced in 2022.[27,] The 2022 position statement provides suggestions for clinical use, as described in the clinical indications below:

1. "The current existing data support that prenatal sequencing is beneficial for the following indications:
    1. A current pregnancy with a fetus having a major single anomaly or multiple organ system anomalies:
        1. For which no genetic diagnosis was found after CMA and a clinical genetic expert review considers the phenotype suggestive of a possible genetic etiology.
        2. For which the multiple anomaly 'pattern' strongly suggests a single gene disorder with no prior genetic testing. As pES [prenatal exome sequencing] is not currently validated to detect all CNVs [copy number variants], CMA should be run before or in parallel with pES in this scenario.
    2. A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single or multiple anomalies:

1. With a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA for the current or prior undiagnosed pregnancy. Point a.i. above also applies in these circumstances.

2. When such parents present for preconception counseling and no sample is available from the affected proband, or if a fetal sample cannot be obtained in an ongoing pregnancy, it is considered appropriate to offer sequencing for both biological parents to look for shared carrier status for autosomal recessive mutations that might explain the fetal phenotype. However, where possible, obtaining tissue from a previous abnormal fetus or child for pES is preferable.

2. There is currently no evidence that supports routine testing (including upon parental request) on fetal tissue obtained from an invasive prenatal procedure (amniocentesis, CVS, cordocentesis, other) for indications other than fetal anomalies.

    1. There may be special settings when prenatal sequencing in the absence of a fetal phenotype visible on prenatal imaging can be considered, such as with a strong family history of a recurrent childhood-onset severe genetic condition with no prenatal phenotype in previous children for whom no genetic evaluation was done and is not possible. Such scenarios should be reviewed by an expert multidisciplinary team preferentially in the context of a research protocol. If sequencing is done for this indication, it must be done as trio sequencing, using an appropriate analytical approach."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through June 30, 2023; no references added. Policy statement unchanged. 2024 FEP Benefit changes. New FEP Policy