# Corporate Medical Policy

# Invasive Prenatal (Fetal) Diagnostic Testing

| | |
|---|---|
| **File Name:** | invasive_prenatal_(fetal)_diagnostic_testing |
| **Origination:** | 12/2014 |
| **Last CAP Review:** | 3/2018 |
| **Next CAP Review:** | 3/2019 |
| **Last Review:** | 3/2018 |

## Description of Procedure or Service

The focus of this policy is on the use of certain invasive diagnostic testing methodologies in the prenatal (fetal) setting and to provide a framework for evaluating the clinical utility of diagnosing monogenic disorders in this setting.

Invasive fetal diagnostic testing can include obtaining fetal tissue for karyotyping, fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA) testing, quantitative polymerase chain reaction (qPCR), next-generation sequencing (NGS), and multiplex ligation-dependent probe amplification (MLPA).

This policy will only address the following:

- the diagnosis of copy number variants using CMA technology
- the diagnosis of single-gene disorders, most of which are due to point mutations or very small deletions and use molecular methods to diagnose (mainly PCR, but also MLPA)
- next-generation sequencing (NGS)

This policy applies only if there is not a separate medical policy that outlines specific criteria for diagnostic testing. If a separate policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy (see list of related policies).

Genetic disorders are generally categorized into 3 main groups: chromosomal, single gene, and multifactorial. Single-gene disorders (also known as monogenic) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural.

Invasive prenatal testing refers to the direct testing of fetal tissue, typically by chorionic villus sampling (CVS) or amniocentesis. Invasive prenatal procedures are typically performed during pregnancy in those who have been identified as having a fetus at increased risk for a chromosomal abnormality, or if there is a family history of a single-gene disorder.

CMA technology has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping) and, therefore, can result in higher rates of detection of pathogenic chromosomal abnormalities. However, there are disadvantages to CMA analysis, including the detection of variants of uncertain significance (VUS) and the fact that it cannot detect certain types of chromosomal abnormalities, including balanced rearrangements.

Single-gene (Mendelian) disorders include those with an inheritance mode of autosomal dominant or recessive, X-linked dominant or recessive. Women may be identified as being at increased risk for having a fetus with an inherited genetic condition because of previously affected pregnancies,

a family history in a suggestive pattern of inheritance, or being a member of a subpopulation with elevated frequencies of certain autosomal recessive conditions.

NGS has been used to identify pathogenic variants in disease-associated genes in many Mendelian disorders. Approximately 85% of known disease-causing variants occur within the 1% of the genome that encodes for proteins (exome). Therefore, whole exome sequencing can cost-effectively capture the majority of protein-coding regions. However, there remain concerns about technical complexity, coverage, bioinformatics, interpretation, VUSs, as well as ethical issues.

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

**Related Policies**
- Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
- Carrier Testing for Genetic Disease
- Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss Fetal Surgery for Malformations
- Maternal and Fetal Diagnostics
- Noninvasive Prenatal Testing for Fetal Aneuploidies Using Cell-Free Fetal DNA

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

**BCBSNC will provide coverage for invasive prenatal (fetal) diagnostic testing when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

**The use of next-generation sequencing in the setting of invasive prenatal testing is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When invasive prenatal (fetal) diagnostic testing is covered

**Chromosomal Microarray**
In patients who are undergoing invasive diagnostic prenatal (fetal) testing, chromosome microarray analysis 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:

1. For autosomal dominant conditions, at least 1 of the parents has a known pathogenic mutation.
2. 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.
3. For X-linked conditions: A parent is suspected to be or is a known carrier AND, ALL of the following are met:
    a. 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
    b. The disease has high penetrance, AND
    c. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, AND
    d. An association of the marker with the disorder has been established.

## When invasive prenatal (fetal) diagnostic testing is not covered

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

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

## Policy Guidelines

**Chromosomal Microarray**
The American College of Obstetricians and Gynecologists (ACOG) recommends CMA testing be performed in patients who are undergoing invasive prenatal diagnostic testing and that if:

- Prenatal CMA analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasound examination and who is undergoing invasive prenative diagnosis. CMA testing typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either karyotyping or a CMA analysis can be performed.

**Fetal Structural 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; CNS: anencephaly, hydrocephalus, myelomeningocele; facial clefts; body wall: omphalocele/gastroschisis; 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 family-specific mutation 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.

**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.

**Summary**

Invasive prenatal (fetal) diagnostic testing may be used to confirm the presence of a pathogenic abnormality after it has been determined by prenatal screening that the fetus is at increased risk for one of these conditions.

The evidence for chromosomal microarray analysis (CMA) testing in patients who are undergoing invasive diagnostic prenatal (fetal) testing includes a systematic review and meta-analysis and prospective cohort and retrospective analyses of the diagnostic yield compared with karyotyping. Relevant outcomes are test accuracy and validity and changes in reproductive decision making. CMA testing has been shown to have a higher rate of detection of pathogenic chromosomal abnormalities than karyotyping. CMA testing is associated with a certain percentage of results that have unknown clinical significance; however, this can be minimalized 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 regarding continuation of the pregnancy, enabling for 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 recommends CMA testing in those who are undergoing an invasive diagnostic procedure. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for testing for single-gene disorders in patients who are undergoing invasive diagnostic prenatal (fetal) testing includes rare case series that generally report which disorders are detected. Relevant outcomes are test accuracy and validity and changes in reproductive decision making. The analytic validity in the diagnosis of single-gene disorders depends on the individual mutation tested. In general, it is necessary to identify the particular mutation(s) in the affected parent(s) so that the particular mutation(s) can be sought for prenatal diagnosis. When a family-specific mutation is known, the analytic validity of testing for this mutation is expected to be high, approaching 100% accuracy. For clinical validity, when there is a known pathogenic family-specific mutation, the sensitivity and specificity for testing for the mutation in other family members is expected to be very high. Changes in reproductive decision making could include decisions regarding continuation of the pregnancy, enabling for timely treatment of a condition that could be treated medically or surgically either in utero or immediately after birth and birthing decisions. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for next-generation sequencing (NGS) in patients who are undergoing invasive diagnostic prenatal (fetal) testing is lacking. Relevant outcomes are test accuracy and validity and changes in reproductive decision making. There are concerns about interpretation of data generated by NGS and the data's clinical relevance. Analytic and clinical validity of NGS in the prenatal setting are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

The following codes might be used for chromosomal microarray testing: *81228, 81229*

*Applicable codes: 81405, 81470, 81471*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

The use of chromosomal microarray analysis in prenatal diagnosis. Committee Opinion No. 581. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1374-1377.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.116, 10/9/2014

Specialty Matched Consultant Advisory Panel – 9/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.116, 10/15/2015

Specialty Matched Consultant Advisory Panel – 3/2016

Committee Opinion No.682. Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. Dec 2016; 128(6):e262-e268. PMID 27875474

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.116, 4/13/2017

## Policy Implementation/Update Information

| | |
|---|---|
| 12/30/14 | New policy created. Invasive prenatal (fetal) diagnostic testing is medically necessary using CMA and for single-gene disorders when criteria for each category are met. NGS is considered investigational. Notification given 12/30/2014 for effective date 3/10/2015. (sk) |
| 10/30/15 | Specialty Matched Consultant Advisory Panel review 9/30/2015. (sk) |
| 12/30/15 | Reference added. Policy Guidelines updated. (sk) |
| 4/29/16 | Specialty Matched Consultant Advisory Panel review 3/30/2016. Policy statement unchanged. (an) |

12/30/16 Minor changes in description section. Policy statement unchanged. (an)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (an)

4/27/18 Description and Policy Guidelines sections updated. References added. Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (an)