DRAFT Medical Coverage Policy | Invasive Prenatal (Fetal) Diagnostic Testing

EFFECTIVE DATE: 01|01|2024
POLICY LAST UPDATED: 09|06|2023

OVERVIEW

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 molecular diagnosis of single-gene disorders, and next-generation sequencing.

The following test(s) are addressed in this policy:

- IriSight™ Prenatal Analysis – Proband (Variantyx, Inc.) CPT code 0335U
- IriSight™ Prenatal Analysis – Comparator (Variantyx, Inc.) CPT code 0336U

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

IriSight™ Prenatal Analysis – Proband (CPT code 0335U) and Genomic Unity® Exome Plus Analysis – Comparator (CPT code 0336U)

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

OR

- For autosomal recessive conditions with one of the following:
  - 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.

OR

- 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.

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for the following tests:

- IriSight™ Prenatal Analysis – Proband CPT code 0335U
- IriSight™ Prenatal Analysis – Comparator CPT code 0336U

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following tests may be considered medically necessary when the medical criteria above have been met:

- IriSight™ Prenatal Analysis – Proband CPT code 0335U
- IriSight™ Prenatal Analysis – Comparator CPT code 0336U

The use of next-generation sequencing in the setting of invasive prenatal testing is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable benefits/coverage.

BACKGROUND

Prenatal Genetic Testing Methodologies

The focus of this evidence review is the use of certain invasive prenatal genetic testing methodologies in the prenatal (fetal) setting to provide a framework for evaluating the clinical utility of diagnosing monogenic disorders in this setting. The purpose of prenatal genetic testing is to identify conditions that might affect the fetus, newborn, or mother to inform pregnancy management (eg, prenatal treatment, decisions about delivery location and personnel, or pregnancy termination).

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

This evidence review only addresses the following:

- the diagnosis of copy number variants (CNVs) using CMA technology

- the diagnosis of single-gene disorders, most of which are due to single nucleotide variants (SNVs) or very small deletions, and use molecular methods to diagnose (mainly PCR but also multiplex ligation-dependent probe amplification)
- Next-generation sequencing

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. Both procedures increase the risk of miscarriage. Chorionic villus sampling utilizes placental cells that are derived from the same fertilized egg as the fetus. The chorionic villi are collected for genetic evaluation under ultrasound guidance without entering the amniotic sac. During amniocentesis, a small sample of the fluid that surrounds the fetus is removed. This fluid contains cells that are shed primarily from the fetal skin, bladder, gastrointestinal tract, and amnion. Typically, CVS is done at earlier gestation than amniocentesis. Most times only one procedure is done; however, sometimes CVS has ambiguous results from maternal cell contamination or placental mosaicism such that amniocentesis might additionally be needed for clarification. Invasive prenatal procedures are usually performed in pregnancies of women 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. For confirming positive cell-free DNA results, amniocentesis might be preferred over CVS to avoid potential false-positive results due to confined placental mosaicism1,2,.

Chromosomal Microarray Testing

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 testing, including the detection of variants of uncertain significance (VUS) and the fact that it cannot detect certain types of chromosomal abnormalities, including balanced rearrangements.

CMA analyzes abnormalities at the chromosomal level and measures gains and losses of DNA (known as CNVs) throughout the genome. CMA testing detects CNVs by comparing a reference genomic sequence ("normal") with the corresponding patient sequence. Each sample has a different fluorescent label so that they can be distinguished, and both are cohybridized to a sample of a specific reference (also normal) DNA fragment of the known genomic locus. If the patient sequence is missing part of the normal sequence (deletion) or has the normal sequence plus additional genomic material within that genomic location (eg, a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, standard CMA (non-SNVs, see the following) cannot detect balanced CNVs (equal exchange of material between chromosomes) or sequence inversions (the same sequence is present in reverse base-pair order) because the fluorescence intensity would not change.

CMA analysis uses thousands of cloned or synthesized DNA fragments of known genomic loci immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. The prepared sample and control DNA is hybridized to the fragments on the slide, and CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. Array resolution is limited only by the average size of the fragment used and by the chromosomal distance between loci represented by the reference DNA fragments on the slide. High-resolution oligonucleotide arrays are capable of detecting changes at a resolution of up to 50 to 100 Kb.

Types of Chromosomal Microarray Technologies

There are differences in CMA technology, most notably in the various types of microarrays. They can differ first by construction; the earliest versions used DNA fragments cloned from a bacterial artificial chromosome. They have been largely replaced by oligonucleotide (oligos; short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of SNVs across the genome have some advantages as well. An SNV is a DNA variation in which a single nucleotide in the genomic sequence is altered.

This variation can occur between 2 different individuals or between paired chromosomes from the same individual and may or may not cause disease. Oligo/SNV hybrid arrays have been constructed to merge the advantages of each.

The 2 types of microarrays both detect CNVs but they identify different types of genetic variation. The oligo arrays detect CNVs for relatively large deletions or duplications, including whole chromosome duplications (trisomies) but cannot detect triploidy. SNV arrays provide a genome-wide copy number analysis and can detect consanguinity, as well as triploidy and uniparental disomy.

Microarrays may be prepared by the laboratory using the technology, or more commonly by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of in-house developed and commercially available platforms prompted the American College of Medical Genetics and Genomics to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

At this time, no guidelines have shown whether targeted or genome-wide arrays should be used or what regions of the genome should be covered. Both targeted and genome-wide arrays search the entire genome for CNVs, however, targeted arrays are designed to cover only clinically significant areas of the genome. The American College of Medical Genetics guidelines for designing microarrays has recommended probe enrichment in clinically significant areas of the genome to maximize the detection of known abnormalities. Depending on the laboratory that develops a targeted array, it can include as many or as few microdeletions and microduplication syndromes as thought to be needed. The advantage, and purpose, of targeted arrays, is to minimize the number of VUS.

Whole-genome CMA analysis has allowed for the characterization of several new genetic syndromes, with other potential candidates currently under study. However, whole-genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and, to some extent, made available in public reference databases to aid in clinical interpretation relevance.

Clinical Relevance of Chromosomal Microarray Findings and Variants of Uncertain Significance
CNVs are generally classified as pathogenic (known to be disease-causing), benign, or a VUS.

A CNV that is considered a VUS:

- has not been previously identified in a laboratory's patient population, or
- has not been reported in the medical literature, or
- is not found in publicly available databases, or
- does not involve any known disease-causing genes.

To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (eg, fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, PCR).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic.
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication).
- The laboratory may establish a size cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 300 kilobases to 1 megabase.

- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign variants whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue.

The International Standards for Cytogenomic Arrays (ISCA) Consortium (2008) was organized; it established a public database containing de-identified whole-genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including intellectual disability, autism, and developmental delay. As of July 2018, nearly 10500 "expert reviewed" variants are listed in the ClinVar database. Data are currently hosted on ClinGen.

Use of the database includes an intralaboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other variants, as well as any inconsistency with the ISCA "known" pathogenic and "known" benign lists. The intralaboratory conflict rate was initially about 3% overall; following the release of the first ISCA curated track, the intralaboratory conflict rate decreased to about 1.5%. A planned interlaboratory curation process, whereby a group of experts curates reported CNVs/variants across laboratories, is currently in progress.

The consortium proposed "an evidence-based approach to guide the development of content on chromosomal microarrays and to support the interpretation of clinically significant copy number variation." The proposal defines levels of evidence (from the literature and/or ISCA and other public databases) that describe how well or how poorly detected variants or CNVs correlate with phenotype.

ISCA is also developing vendor-neutral recommendations for standards for the design, resolution, and content of cytogenomic arrays using an evidence-based process and an international panel of experts in clinical genetics, clinical laboratory genetics, genomics, and bioinformatics.

Single-Gene (Mendelian) Disorders

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.

Most Mendelian disorders are caused by SNVs or very small deletions or duplications. Monogenic variants are diagnosed by molecular methods, mainly PCR for SNVs but also other methods like multiplex ligation-dependent probe amplification for very small deletions and duplications. Approximately 5000 known disorders are inherited in this fashion. Diagnostic tests are currently available for most of the common monogenic disorders, as well as for a number of the more rare disorders. For most single-gene disorders, testing in the prenatal setting requires knowledge of the familial variants.

Next-Generation Sequencing

Next-generation sequencing has been used to identify pathogenic variants in disease-associated genes in many Mendelian disorders. Approximately 85% of known disease-causing variants occur within 1% of the genome that encodes for proteins (exome). Therefore, whole-exome sequencing can cost-effectively capture the majority of protein-coding regions. However, concerns remain about technical complexity, coverage, bioinformatics, interpretation, VUSs, as well as ethical issues.4,

Commercially Available Tests

Many academic and commercial laboratories offer CMA testing and single-gene disorder testing. Many laboratories also offer reflex testing, which may be performed with microarray testing added if karyotyping is normal or unable to be performed (due to no growth of cells). The test should be cleared or approved by the

U.S. Food and Drug Administration, or performed in a Clinical Laboratory Improvement Amendment-certified laboratory.

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.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing and who receive 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 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 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 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 (ie, 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.

CODING

Medicare Advantage Plans and Commercial Products
The following CPT code(s) are covered for Medicare Advantage Plans and Commercial Products when medical criteria above are met:

This code can be used for IriSight™ Prenatal Analysis – Proband (Variantyx, Inc.)

0335U Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants

This code can be used for IriSight™ Prenatal Analysis – Comparator (Variantyx, Inc.)

0336U Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)

RELATED POLICIES

Biomarker Testing Mandate
Proprietary Laboratory Analyses (PLA)

PUBLISHED

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