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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are undergoing invasive prenatal (fetal) testing	Interventions of interest are: • Chromosomal microarray testing	Comparators of interest are: • Karyotyping	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making
Individuals: • Who are undergoing invasive prenatal (fetal) testing	Interventions of interest are: • Molecular testing for single-gene disorders	Comparators of interest are: • No molecular testing	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making
Individuals: • Who are undergoing invasive prenatal (fetal) testing	Interventions of interest are: • Next-generation sequencing	Comparators of interest are: • Chromosomal microarray • Molecular testing for single-gene disorders	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making

DESCRIPTION

Invasive prenatal (fetal) diagnostic testing may be used to identify pathogenic genetic alterations in fetuses at increased risk based on prenatal screening or on 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.

SUMMARY OF EVIDENCE

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing 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 par-

ents 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 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 a meaningful 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 is 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 (i.e., tertiary care center), and route of delivery. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing 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 the effects of the technology on health outcomes.

POLICY

CHROMOSOMAL MICROARRAY ANALYSIS

In patients 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:

1. For autosomal dominant conditions, at least one of the parents has a known pathogenic variant.
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. Any variants have 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.

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 protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Genome Project, the HUMAN Genome Organization, and by 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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

MEDICARE ADVANTAGE

For Medicare Advantage, the following genetic testing procedures are unlikely to impact therapeutic decision-making in the clinical management of the patient and will be considered **not medically necessary**:

- Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis);
- interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities;
- X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2.
- X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2.

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 – e.g., 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 (MLPA).

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 MLPA)
- Next-generation sequencing.

This evidence review applies only if there is not a separate evidence review that outlines specific criteria for diagnostic testing. If a separate evidence review exists, then the criteria in it supersede the guidelines herein. This evidence review does NOT cover the use of:

- prenatal carrier testing (Carrier Screening for Genetic Diseases Protocol)
- preimplantation genetic diagnosis or screening (Preimplantation Genetic Testing Protocol)
- noninvasive prenatal testing (Genetic Testing for Noninvasive Prenatal Testing Protocol)
- testing in the setting of fetal demise (Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss Protocol).

Genetic disorders are generally categorized into three 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 or amniocentesis. 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.

CMA 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 co-hybridized 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 (e.g., 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 frag-

ments on the slide. High-resolution oligonucleotide arrays are capable of detecting changes at a resolution of up to 50 to 100 Kb.

Types of CMA 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 two 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 two 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 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 CMA Findings and VUS

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 (e.g., fluorescence in situ hybridization, MLPA, 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.¹

Use of the database includes an intra-laboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other variants, as well as any inconsistent with the ISCA “known” pathogenic and “known” benign lists. The intra-laboratory conflict rate was initially about 3% overall; following the release of the first ISCA curated track, the intra-laboratory 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 MLPA for very small deletions and duplications. Approximately 5,000 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 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, concerns remain about technical complexity, coverage, bioinformatics, interpretation, VUSs, as well as ethical issues.²

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 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.

RELATED PROTOCOLS

Carrier Screening for Genetic Diseases

Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Genetic Testing for Developmental Delay and Autism Spectrum Disorder

Genetic Testing for Noninvasive Prenatal Testing

Preimplantation Genetic Testing

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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