Chromosome Analysis for Reproductive Disorders, Prenatal Testing, and Developmental Disorders

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is a chromosome abnormality

Definition

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes.\(^1\)

Humans typically have 23 pairs of chromosomes. Each chromosome has a characteristic appearance that should be the same in each person.\(^1\)

Chromosome abnormalities can lead to a variety of developmental and reproductive disorders. Common chromosome abnormalities include Down syndrome (trisomy 21), trisomy 18, trisomy 13, Turner syndrome, and Klinefelter syndrome.

Chromosome abnormalities occur in approximately 1 in 150 live births.\(^2\) A higher percentage of pregnancies are affected but lost during pregnancy. According to the American College of Obstetricians and Gynecologists (ACOG), “Fetuses affected with Down syndrome often do not survive pregnancy; between the first trimester and full term, an estimated 43% of pregnancies end in miscarriage or stillbirth.”\(^2\)

Chromosome abnormalities are also seen in pregnancy losses. Balanced reciprocal translocations and Robertsonian translocations are observed in approximately 2-5% of couples with recurrent pregnancy loss.\(^3\) Individuals with balanced translocations will typically not experience any outward symptoms of the chromosome abnormality. However, they may conceive pregnancies with an unbalanced rearrangement, resulting in an increased risk for miscarriage, stillbirth, and live-born children with developmental disorders. Offspring who inherit the balanced translocation are usually asymptomatic, but will have the same reproductive risks as their parent.

Test information

Introduction

Chromosome analysis can be done on blood or tissue. This testing can also be performed prenatally on fetal cells from amniotic fluid (amniocentesis) or placenta (chorionic villus sampling, CVS).

Chromosome analysis, also called karyotyping, requires stimulating cells to divide, arresting cell division at metaphase when the chromosomes can be seen microscopically, and staining to visualize the banding patterns. Routine chromosome analysis allows visualization of about 400-550 bands per karyotype.\(^4\) High resolution chromosome analysis allows visualization of finer details and up to 1000 bands per karyotype.\(^4\)

Once the chromosomes are prepared, chromosome analysis will identify any differences from normal that can be seen under the microscope. This includes entire missing or extra chromosomes, deletions or duplications within a chromosome that are large enough to be seen by microscope, and rearrangements including translocations and inversions.
Chromosome analysis will not detect submicroscopic abnormalities, such as Y chromosome microdeletions that cause 16% of azoospermia and severe oligospermia. Specific probes or array comparative genomic hybridization (CGH) is required.

Chromosome analysis also cannot detect single-gene disorders (such as cystic fibrosis, Tay-Sachs, etc.).

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to chromosome analysis for purposes of prenatal testing, reproductive purposes, and developmental disorders.

Prenatal Testing

Prenatal diagnosis through amniocentesis and CVS is standard of care in obstetrics practice.

American College of Obstetricians and Gynecologists

Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2016) recommend that:

- “All pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors.”
- “Prenatal genetic testing cannot identify all abnormalities or problems in a fetus, and any testing should be focused on the individual patient’s risk, reproductive goals, and preferences.”
- “Genetic testing should be discussed as early as possibly in pregnancy, ideally at the first obstetrics visit, so that first trimester options are available.”

Society for Assisted Reproductive Technology and American Society for Reproductive Medicine

Practice Committee opinion from the Society for Assisted Reproductive Technology (SART) and American Society for Reproductive Medicine (ASRM, 2008) indicates that “Prenatal diagnostic testing to confirm the results of PGD is encouraged strongly because the methods used for PGD have technical limitations that include the possibility for a false negative result.”

Society of Obstetricians and Gynaecologists of Canada

The Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2006) indicate, “Couples considering IVF-ICSI for male-factor infertility should receive information, and if necessary formal genetic counseling,
about the increased risk of de novo chromosomal abnormalities (mainly sex chromosomal anomalies) associated with their condition. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis should be offered to these couples if they conceive. (Evidence level II-2A).”

Reproductive Disorders

**American Society for Reproductive Medicine**

The ASRM (2015)\(^8\) did not include chromosome analysis in their recommendations for the routine evaluation of female infertility.

In a later guideline for the evaluation of male infertility, the ASRM (2015)\(^9\) reaffirmed their previous recommendation for karyotype and Y-chromosome analysis in men with nonobstructive azoospermia or severe oligospermia prior to ICSI.

**American Society for Reproductive Medicine and Society for Male Reproduction and Urology**

In 2008, the American Society for Reproductive Medicine (ASRM) and Society for Male Reproduction and Urology issued the following recommendation for the evaluation of azoospermia: “[…] men with nonobstructive azoospermia or severe oligospermia should be karyotyped before their sperm are used for ICSI.”\(^{10}\)

**American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (ACOG, 2014) guidelines on ovarian insufficiency recommend the following for diagnosis:\(^{11}\)

- “Menstrual irregularity for at least 3 consecutive months”
- “Follicle-stimulating hormone and estradiol levels (two random tests at least 1 month apart)”
- “Prolactin and thyroid function test”
- If the diagnosis is confirmed, karyotype is among the tests recommended for further evaluation.

**National Institute for Health and Clinical Excellence**

In 2004 (updated 2017), the National Institute for Health and Clinical Excellence (NICE) made the following recommendations regarding the evaluation of infertility:\(^{12}\)

- “Where a specific genetic defect associated with male infertility is known or suspected, couples should be offered appropriate genetic counseling and testing.”
- “Where the indication for ICSI is a severe deficit of semen quality or nonobstructive azoospermia, the man’s karyotype should be established.”
American Society for Reproductive Medicine

ASRM (2012) guidelines state that evaluation of recurrent pregnancy loss can proceed after two consecutive clinical pregnancy losses, and should include peripheral karyotype of the parents.\textsuperscript{3}

The ASRM 2008 guideline for the evaluation of amenorrhea states:\textsuperscript{13}

- “The history and physical examination should include a thorough assessment of the external and internal genitalia.”
- “When the physical examination is normal (the majority of cases), the initial investigations should exclude pregnancy and estimate FSH and prolactin concentrations.”
- “Ovarian failure is confirmed by documenting an FSH level persistently in the menopausal range. In women under 30 with ovarian failure, a karyotype should be obtained to rule out sex chromosome translocation, short arm deletion, or the presence of an occult Y chromosome, which is associated with an increased risk of gonadal tumors.”

American College of Obstetricians and Gynecologists

ACOG (2002) guidelines on recurrent pregnancy loss state, “Parental cytogenetic analysis should be offered to all couples with recurrent pregnancy loss. In addition, all couples in which one partner has been found to have a balanced translocation or inversion should be offered prenatal genetic diagnosis because of the increased risk of a karyotypic abnormality in the conceptus.”\textsuperscript{14}

Developmental Disorders

American Academy of Pediatric

The American Academy of Pediatrics (2014)\textsuperscript{15} published recommendations for the evaluation of children with intellectual disability (ID) or global developmental delay (GDD). They state the following:

- “CMA now should be considered a first tier diagnostic test in all children with GDD/ID for whom the causal diagnosis is not known.”
- “G-banded karyotyping historically has been the standard first-tier test for detection of genetic imbalance in patients with GDD/ID for more than 35 years. CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies.”

American Academy of Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (AACAP, 2014) states that as a clinical standard, clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD. This includes the following:\textsuperscript{16}
“All children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood’s lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray.”

“Unusual features in the child (e.g., history of regression, dysmorphology, staring spells, family history) should prompt additional evaluations… Genetic or neurologic consultation, neuroimaging, EEG, and additional laboratory tests should be obtained when relevant, based on examination or history (e.g., testing for the MECP2 gene in cases of possible Rett’s disorder).”

American College of Medical Genetics and Genomics

American College of Medical Genetics and Genomics (2013) included a list of first tier tests in the evaluation of an individual with autism spectrum disorder. These are outlined in the guideline and include the following:

- Three-generation family history with pedigree analysis
- Initial evaluation to identify known syndromes or associated conditions
  - Examination with special attention to dysmorphic features
  - If specific syndromic diagnosis is suspected, proceed with targeted testing
  - If appropriate clinical indicators present, perform metabolic and/or mitochondrial testing (alternatively, consider a referral to a metabolic specialist)
- Chromosomal microarray: oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array
- DNA testing for fragile X (to be performed routinely for male patients only).

American College of Medical Genetics and Genomics (2005) published recommendations for cytogenetic evaluation for developmental delay. The final recommendations stated:

- For any child with unexplained MR/DD, even in the absence of dysmorphic facial features, other clinical features or positive family history, routine chromosome analysis (minimum 550-band resolution) is indicated.
- For children with clinical features of known chromosomal abnormality syndromes (e.g., Down syndrome), cytogenetic analysis should be performed. The identification of a translocation may affect the family’s recurrence risk.
- High-resolution chromosome analysis is not routinely indicated unless a specific chromosomal region is to be investigated or there is a family history of a particular abnormality. These studies should be limited in focus and used when FISH is not available.”
For children with clinical features suggestive of a particular microdeletion/microduplication syndrome, FISH or other molecular techniques should be performed prior to or concurrently with chromosome analysis.

If chromosome analysis is normal at 550-band resolution, subtelomere FISH testing may be considered.

Criteria

Introduction

Requests for chromosome analysis are reviewed using the following criteria.

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous chromosomal microarray (CMA) testing on the individual or the fetus, and
  - No previous chromosome analysis performed on the individual or the fetus, AND

- Prenatal Testing:
  - The member has sufficient risk of fetal aneuploidy to justify invasive prenatal diagnosis. (It is important to note that invasive procedures such as chorionic villus sampling and amniocentesis are associated with risks; the provider and patient must have determined that the associated benefits outweigh the risks), OR

- Testing for Individuals with Reproductive Disorders:
  - Males with azoospermia or severe oligozoospermia, defined as <5 million sperm per mL, without obstruction or congenital absence of the vas deferens, or
  - Females with ovarian failure (cessation of menses with elevated FSH) prior to age 30, or
  - Evidence of gonadal dysgenesis on physical examination or ultrasound, or
  - Two or more spontaneous, unexplained pregnancy losses conceived by the member, or
  - Abnormal chromosome arrangement (e.g. translocation or inversion) in a first-, second-, or third-degree biologic relative, OR

- Diagnostic Testing for Symptomatic Individuals with Developmental Disorders:
  - Testing is performed on living child or adult, and
- Diagnosis cannot be made on clinical evaluation alone, and
- Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is a suspected diagnosis

**Note** This guideline only addresses chromosome analysis for prenatal testing, reproductive disorders, and developmental disorders. This guideline does not address chromosome analysis for cancer. Please see the guideline Chromosome Analysis for Blood, Bone Marrow, and Solid Tumor Cancers for this indication.

**Billing and Reimbursement Considerations**

Chromosomal microarray (CMA) is considered a first-tier test in the evaluation of postnatal developmental disorders. Therefore, it often is not necessary to perform chromosome analysis or FISH in conjunction with CMA. The following claims will be subject to review:

- Claims for chromosome analysis (CPT 88230), in conjunction with all other billed cytogenetics codes (CPT 88230-88291), will require medical necessity documentation and review if CMA (CPT 81228, 81229) has already been paid for the member on any date of service.
- Claims for CMA (CPT 81228, 81229) will require medical necessity documentation and review if chromosome analysis (88230) has already been paid for the member on any date of service.

If routine karyotype and CMA are ordered simultaneously, only the most appropriate test based on clinical history will be considered for reimbursement.

Full karyotype in addition to CMA is considered excessive. However, a limited 5 cell analysis may be approved in addition to CMA if criteria for CMA are met. This approval may be subject to claims review to ensure that the appropriate procedure code for a limited 5 cell analysis is billed (CPT 88261 x 1).

**References**

**Introduction**

This guideline cites the following references.


