CYTOGENETICS TESTING

Policy Number: CMP-030
Effective Date: January 21, 2017

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BACKGROUND
Cytogenetics is the study of chromosomes. Chromosomal abnormalities are associated with infertility, miscarriage, birth defects, mental retardation, and cancer. The clinical application of cytogenetics offers the potential to predict disease susceptibility, to diagnose disease early, and to monitor treatment response.¹

Prenatal Diagnosis

Structural or genetic birth defects can be identified in 3% of all births in the United States.² When chromosomal syndromes result in a live birth, the phenotype commonly includes mental retardation, growth retardation, dysmorphic facial features, and heart defects. The field of prenatal diagnosis moved forward after the discovery of an additional chromosome 21 in Down syndrome in 1959. Although Down syndrome is the chromosomal
abnormality most often diagnosed by prenatal screening, many other abnormalities can be detected. The other
trisomies that can be seen in liveborn children are trisomy 13 (cleft lip, polydactyly, heart defects, and brain or
spinal cord abnormalities) and trisomy 18 (intrauterine growth retardation and defects of the heart and other
organs). Tay-Sachs disease, cystic fibrosis, retinoblastoma, sickle cell anemia, and Huntington disease all arise
from point mutations and can be diagnosed prenatally.

In the past, prenatal screening for aneuploidy and other chromosomal abnormalities was routinely offered to
women over the age of 35, but recommendations have changed. Maternal age is no longer deemed a good
screening criterion. According to the American College of Obstetricians and Gynecologists, diagnostic testing
should be available to all women before 20 weeks gestation regardless of maternal age. The recommendations
further state that when screening identifies women with an increased risk of fetal aneuploidy, invasive testing
(chorionic villus sampling or second-trimester amniocentesis) should be offered. The American College of
Medical Genetics recommends all women be given the option of invasive diagnostic testing; those who do not
wish to undergo invasive testing should have the option of noninvasive screening regardless of their age. Non-
invasive prenatal screening includes a fetal ultrasound and maternal serum testing for proteins whose titers can
be used to assess the risk of aneuploidy or a neural tube defect; however, these tests do not provide
information about the full complement of maternal or fetal chromosomes. If an abnormality is detected,
invasive prenatal testing may be recommended. Invasive prenatal testing encompasses conventional
amniocentesis at 15-20 weeks gestation and chorionic villus sampling, after 9 weeks gestation. These
techniques can provide a full fetal karyotype and yield a cytogenetic accuracy of >99%. Prenatal screening and
testing should be distinguished from newborn screening. Newborn screening is a state-based public health
effort that detects treatable conditions in babies before disease manifestations occur. This testing is carried out
in the hospital after a baby is born with blood obtained by a heel stick. The newborn’s blood is analyzed for
proteins diagnostic of selected genetic diseases and generally not subjected to a full cytogenetic study.

The American College of Medical Genetics was commissioned by the Maternal and Child Health Bureau to
make recommendations for state newborn screening programs. In 2006, the ACMG published a list of 29
conditions it believes should be mandated. The list includes genetic disorders such as cystic fibrosis and
hemoglobinopathies.

Clinical Oncology

In hematologic malignancies, chromosomal analysis can be performed on peripheral blood in addition to bone
marrow and lymph node biopsy specimens. The National Comprehensive Cancer Network (NCCN) recommends
cytogenetics for the diagnosis and treatment of acute lymphoblastic leukemia, acute myeloid leukemia, and
multiple myeloma. Conventional bone marrow cytogenetics are recommended before treatment and to assess
response to treatment in patients with chronic myelogenous leukemia. The NCCN also recommends
cytogenetics by standard karyotyping for the initial evaluation of myelodysplastic syndromes. Genome-wide
conventional cytogenetics or FISH is essential for some, but not all, lymphoma diagnoses. For some types of
lymphoma it is considered useful under certain circumstances. Some types of lymphoma can be diagnosed with
adequate immunophenotyping.

Familial Genetic Assessment
Cytogenetic studies can assess the familial risk of heritable diseases, both neoplastic and nonneoplastic. Family ethnicity is related to risk for genetic disease. Because familial genetics can be a consideration for family planning, some couples choose to undergo genetic counseling before conception. For Caucasians of European or Ashkenazi Jewish descent, cystic fibrosis is the most common autosomal recessive disorder causing a decrease in life span, and the carrier rate in this population is 1:25.\textsuperscript{13} Since the disease occurs in all ethnic groups, the American College of Obstetricians and Gynecologists recommends prenatal screening for cystic fibrosis for all women of reproductive age but notes that screening is most efficacious in the non-Hispanic white and Ashkenazi Jewish populations.\textsuperscript{14} The genetic disorders clustering in individuals of Ashkenazi Jewish or Eastern European descent are collectively called the “Jewish Genetic Disorders.” These disorders include Tay-Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Niemann-Pick type A, Bloom syndrome, mucolipidosis IV, and Gaucher disease.

The American College of Medical Genetics recommends carrier screening should be offered to all Ashkenazi Jewish couples for these disorders. The ACMG further notes that one Jewish grandparent is sufficient cause to offer testing.\textsuperscript{15}

Bloom syndrome and Fanconi anemia are familial syndromes that are characterized by mutations in genes required for DNA repair. Other examples of autosomal recessive disorders with genomic instability are ataxia-telangectasia, the Nijmegen breakage syndrome, xeroderma pigmentosum, and Werner syndrome. Individuals with these disorders have an increased risk of developing cancer.

Familial cancers can derive from single-gene traits, as is the case with retinoblastoma. Retinoblastoma is the most common intraocular tumor in children. When an autosomal dominant mutation causes these tumors, often both eyes are affected. This inherited mutation causes 40% of cases of retinoblastoma; the remaining sporadic cases tend to occur later in life and only in one eye. Other familial cancers require mutations in more than one gene or chromosome, such as those associated with adenomatous polyposis of the colon.

The most common familial genetic cancer predisposition is Lynch syndrome, characterized by faulty DNA repair. The inheritance is autosomal dominant, and the lifetime risk of colorectal cancer in persons carrying mutations associated with Lynch syndrome is 80%. Lynch syndrome accounts for 2-3% of all cases of colorectal carcinoma. Immunohistochemistry can be used to detect mismatch repair gene proteins in paraffin-embedded material from sections of colorectal cancer to screen for Lynch syndrome, and the patients’ family members can subsequently undergo genetic testing and/or increased surveillance for colorectal cancer according to guidelines authored by the National Comprehensive Cancer Network, if indicated.\textsuperscript{16} Other familial genetic cancer syndromes include hereditary breast-ovarian cancer syndrome, Cowden syndrome, and Peutz-Jeghers syndrome.

The following clinical findings would be cause to recommend genetic counseling:

- The family has a known or suspected genetic disorder.
- There are multiple affected relatives with the same or related disorders.
- The age of disease onset is earlier than usually seen in the general population.
- Someone in the family has an intellectual disability.
• A diagnosis is made in the less-often-affected sex.

• Tumor location is multifocal or bilateral in paired organs.

• One or more major malformations are identified in a fetus or baby.

• A disease occurs in the absence of risk factors or in spite of preventive measures.

• Growth abnormalities are noted.

• Two or more pregnancy losses occur.

• The parents are related to each other.

• The family’s ethnicity is associated with certain genetic disorders.

• There are many cases of cancer within a family.

• Cancer arises in an individual with birth defects.

**POLICY**

For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

*Table 1. HCPCS Codes (Alphanumeric, CPT® AMA)*

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>88230</td>
<td>Tissue culture for non-neoplastic disorders; lymphocyte</td>
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<tr>
<td>88233</td>
<td>Tissue culture for non-neoplastic disorders; skin or other solid tissue biopsy</td>
</tr>
<tr>
<td>88235</td>
<td>Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells</td>
</tr>
<tr>
<td>88237</td>
<td>Tissue culture for non-neoplastic disorders; bone marrow, blood cells</td>
</tr>
<tr>
<td>88239</td>
<td>Tissue culture for non-neoplastic disorders; solid tumor</td>
</tr>
<tr>
<td>88240</td>
<td>Cryopreservation, freezing and storage of cells, each cell line</td>
</tr>
<tr>
<td>88241</td>
<td>Thawing and expansion of frozen cells, each aliquot</td>
</tr>
<tr>
<td>88245</td>
<td>Chromosome analysis for breakage syndromes; baseline sister chromatid exchange, 20-25 cells</td>
</tr>
<tr>
<td>88248</td>
<td>Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, fanconi anemia, fragile X)</td>
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<tr>
<td>88249</td>
<td>Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (e.g., diepoxybutane, mitomycin C, ionizing radiation, UV radiation)</td>
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<tr>
<td>88261</td>
<td>Chromosome analysis; count 5 cells, 1 karyotype, with banding</td>
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<tr>
<td>88262</td>
<td>Chromosome analysis; count 15-20 cells, 2 karyotype, with banding</td>
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<tr>
<td>HCPCS Code</td>
<td>Description</td>
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<tr>
<td>88263</td>
<td>Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding</td>
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<tr>
<td>88264</td>
<td>Chromosome analysis; analyze 20-25 cells</td>
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<tr>
<td>88267</td>
<td>Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding</td>
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<tr>
<td>88269</td>
<td>Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding</td>
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<td>88271</td>
<td>Molecular cytogenetics; DNA probe, each (e.g., FISH)</td>
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<td>88272</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers)</td>
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<tr>
<td>88273</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)</td>
</tr>
<tr>
<td>88274</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells</td>
</tr>
<tr>
<td>88275</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells</td>
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<tr>
<td>88280</td>
<td>Chromosome analysis; additional karyotypes, each study</td>
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<tr>
<td>88283</td>
<td>Chromosome analysis; additional specialize banding technique (e.g., Nor, C-banding)</td>
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<tr>
<td>88285</td>
<td>Chromosome analysis; additional cells counted, each study</td>
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<tr>
<td>88289</td>
<td>Chromosome analysis; additional high resolution study</td>
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<td>88291</td>
<td>Cytogenetics and molecular cytogenetics, interpretation and report</td>
</tr>
<tr>
<td>88299</td>
<td>Unlisted cytogenetic study</td>
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ICD-10 Diagnosis Codes (Proven)
REFERENCES


7. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2007;129:S25-S85.


POLICY HISTORY/REVISION HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
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<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ ICD10 PDF files.</td>
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