Medical Policy:  
Genetic Testing (Non-Prenatal)  

**Policy Number:**  
**Title:** Non-Prenatal Genetic Testing  
**Department:** Medical  
**Unit:**  
**Effective Date:** 01/01/2014  
**Revision Date:**  

**PURPOSE**  
To establish criteria for coverage of non-prenatal genetic testing.  

**POLICY**  
Coverage of genetic testing in a non-prenatal setting shall be determined using the algorithm shown on the last page unless otherwise specified below.  

A) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer suspected to be hereditary, or patients at increased risk to due to family history.  
1) Services are provided according to the Comprehensive Cancer Network Guidelines.  
   a) Lynch syndrome (hereditary colorectal and endometrial cancer) services (CPT 81292-81300, 81317-81319) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. V.1.2013 (4/13/13). [www.nccn.org](http://www.nccn.org)  
   b) BRCA1/BRCA2 testing services (CPT 81211-81217) for women without a personal history of breast and/or ovarian cancer should be provided to high-risk women:  
      • Having a strong family history of breast cancer, defined as one of the following:  
          o Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative);  
          o Three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative);  
          o Four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative);  
          o One relative with ovarian cancer at any age and, on the same side of the family, either one first-degree relative (including the relative with ovarian cancer) or second-degree
relative diagnosed with breast cancer at younger than age 50 years, or two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years, or another ovarian cancer at any age;
- One first-degree relative with cancer diagnosed in both breasts at younger than an average age of 50 years;
- One first-degree or second-degree relative diagnosed with bilateral breast cancer and one first-degree or second-degree
- A relative diagnosed with breast cancer at younger than an average age of 60 years; or,
- A male relative with breast cancer at any age and, on the same side of the family, at least one first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years, or two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years.
- A history of LCIS with a family history of breast cancer
- A history of treatment with thoracic radiation between ages of 10 and 30.

c) BRCA1/BRCA2 testing services (CPT 81211-81217) for women with a personal history of breast and/or ovarian cancer and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V.1.2011 (4/7/11). www.nccn.org
d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V.1.2013 (5/13/13). www.nccn.org.

2) Genetic counseling should precede genetic testing for hereditary cancer. Very rarely, it may be appropriate for a genetic test to be performed prior to genetic counseling for a patient with cancer. If this is done, genetic counseling should be provided as soon as practical.
   a) Pre- and post-test genetic counseling by the following providers should be covered:
      i) Medical Geneticist (M.D.) -- Board Certified or Active Candidate Status from the American Board of Medical Genetics
      ii) Clinical Geneticist (Ph.D.) -- Board Certified or Active Candidate Status from the American Board of Medical Genetics
      iii) Genetic Counselor -- Board Certified or Active Candidate Status from the American Board of Genetic Counseling, or Board Certified by the American Board of Medical Genetics
      iv) Advance Practice Nurse in Genetics -- Credential from the Genetic Nursing Credentialing Commission
3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).

4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer are not covered.

B) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index < 70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder or multiple congenital anomalies:

1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies or Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.

2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies or Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected or (b) uniparental disomy is suspected or (c) another mechanism is suspected that is not detected by the copy number variant test alone. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.

3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.

4) A visit with the appropriate specialist (often genetics, developmental pediatrics or child neurology), including physical exam, medical history and family
history, is covered. Physical exam, medical history and family history by the appropriate specialist, prior to any genetic testing, is often the most cost-effective strategy and is encouraged.

C) Related to other tests with specific CPT codes:

1) The following tests are not covered:
   a) CPT 81225, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
   
   
   c) CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
   
   d) CPT 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
   
   e) CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
   
   f) CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)
   
   g) CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variants (e.g., -1639/3673)
   
2) The following tests are covered only if they meet the criteria for the Non-Prenatal Genetic Testing Algorithm AND the specified situations:
   a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g., Maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal.
   
   b) Diagnostic testing for cystic fibrosis (CF)
      i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for
cystic fibrosis, or for clients who have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.

c) Carrier testing for cystic fibrosis
   i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered.

d) CPT 81240. F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

e) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

f) CPT 81256, HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first-degree family member has treatable iron overload from HFE.

g) CPT 81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle-age individual with unexplained dyspnea. Generic testing or the anpha-1 phenotype test is appropriate if the protein test is
abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

3) Do not cover a more expensive genetic test (generally one with a wider scope or more detailed testing) if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

NON-PRENATAL GENETIC TESTING ALGORITHM

Initial screening indicates genetic testing may be indicated.

Pretest genetic risk assessment and/or clinical evidence indicate chance of genetic abnormality ≥ 10% and results would do at least one of the following:
- Change treatment,
- Change health monitoring,
- Provide prognosis, or
- Provide information needed for genetic counseling for patient, or patient's parents, siblings, or children.

No

Yes

No

Yes

Genetic test is not covered

1. Examples of initial screening: physical exam, medical history, family history, laboratory studies, imaging studies.