Medical Policy
Carrier Screening for Genetic Diseases

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Policy Number: 666
BCBSA Reference Number: 2.04.107
NCD/LCD:
- Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

General Carrier Screening
Carrier screening for genetic diseases is considered MEDICALLY NECESSARY when one of the following criteria is met:
- One or both individuals have a first- or second-degree relative who is affected, OR
- One individual is known to be a carrier, OR
- One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition.*

First-degree relatives include a biological parent, brother, sister, or child; second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.

AND all of the following criteria 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.
- Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing.
- The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood.**
- An association of the marker with the disorder has been established.
*If there is no family history of, risk based or ethnic predilection for a disease, carrier screening is not recommended when the carrier rate is less than 1% in the general population.

**The American College of Medical Genetics and Genomics (ACMG) has recommended testing for specific variants, which will result in carrier detection rate of 95% or higher for most disorders.

**Spinal Muscular Atrophy**
Screening for spinal muscular atrophy (SMA) may be considered MEDICALLY NECESSARY when one of the following criteria is met:
- Women who are considering pregnancy or who are currently pregnant, OR
- Patients with a family history of SMA.

*Molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, SMN1 deletion testing should be recommended for the low risk partner.

**Cystic Fibrosis**
Screening for Cystic Fibrosis (CF) may be considered MEDICALLY NECESSARY when one of the following criteria is met:
- Women who are considering pregnancy or who are currently pregnant, OR
- Couples in which both partners are unaffected but one or both has a family history of CF.

**Hemoglobinopathy**
Screening for hemoglobinopathy may be considered MEDICALLY NECESSARY when one of the following criteria is met:
- Women who are currently pregnant to assess their risk of anemia, OR
- Women who are currently pregnant to assess their risk of hemoglobinopathy.

*A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity. If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed.

All targeted screening not meeting any of the above criteria is considered NOT MEDICALLY NECESSARY.

Expanded carrier screening panels are considered INVESTIGATIONAL.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) (L36089)

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.
Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Prior authorization is not required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare HMO Blue℠</td>
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<tr>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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<td>Prior authorization is not required.</td>
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CPT Codes / HCPCS Codes / ICD Codes

**Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.**

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

**The following codes are included below for informational purposes only; this is not an all-inclusive list.**

The above **medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue, and Medicare PPO Blue:**

### CPT Codes

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)</td>
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<tr>
<td>81209</td>
<td>BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant</td>
</tr>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81241</td>
<td>F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant</td>
</tr>
<tr>
<td>81242</td>
<td>FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A&gt;T)</td>
</tr>
<tr>
<td>81251</td>
<td>GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
</tr>
<tr>
<td>81254</td>
<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
</tr>
<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
</tr>
<tr>
<td>81260</td>
<td>KKBAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+61T&gt;C, R696P)</td>
</tr>
</tbody>
</table>
MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)

Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S3841</td>
<td>Genetic testing for retinoblastoma</td>
</tr>
<tr>
<td>S3842</td>
<td>Genetic testing for Von Hippel-Lindau disease</td>
</tr>
<tr>
<td>S3844</td>
<td>DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness</td>
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<tr>
<td>S3845</td>
<td>Genetic testing for alpha-thalassemia</td>
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<tr>
<td>S3846</td>
<td>Genetic testing for hemoglobin E beta-thalassemia</td>
</tr>
<tr>
<td>S3849</td>
<td>Genetic testing for Niemann-Pick disease</td>
</tr>
<tr>
<td>S3850</td>
<td>Genetic testing for sickle cell anemia</td>
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</tbody>
</table>

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
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<tr>
<th>CPT Codes</th>
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<tr>
<td>81412</td>
<td>Ashkenazi Jewish associated disorders (eg, Bloom syndrome, canavan disease, cystic fibrosis, familial dysautonomia, fanconi anemia group c, gaucher disease, tay-sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1</td>
</tr>
<tr>
<td>81437</td>
<td>Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL</td>
</tr>
<tr>
<td>81438</td>
<td>Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL</td>
</tr>
</tbody>
</table>

**Description**

INHERITED RECESSIVE DISORDERS

There are more than 1300 inherited recessive disorders (autosomal or X-linked) that affect 30 out of every 10,000 children.1 Some diseases have limited impact on either length or quality of life, while others are uniformly fatal in childhood.

**Carrier Screening**

Carrier screening is testing asymptomatic individuals to identify those who are heterozygous for serious or lethal single-gene disorders with the purpose of informing the risk of conceiving an affected child “to provide … information to optimize pregnancy outcomes based on … personal preferences and values.”2
Risk-based carrier screening is performed in individuals having an increased risk based on population carrier prevalence, and personal or family history. Conditions selected for screening can be based on ethnicities at high risk (eg, Tay-Sachs disease in Ashkenazi Jews) or may be pan-ethnic (eg, screening for cystic fibrosis carriers). Ethnicity-based screening for some conditions has been offered for decades and, in some cases, has reduced the prevalence of diseases. For example, a 90% reduction in Tay-Sachs disease followed introduction carrier screening in the 1970s in the United States and Canada.\textsuperscript{3} In addition, the U.S. population has become increasingly ethnically intermarried\textsuperscript{4,5}—a phenomenon the American College of Obstetricians and Gynecologists noted when offering a recommendation in 2005 for pan-ethnic cystic fibrosis carrier screening.\textsuperscript{6}

While methods for carrier screening of conditions individually may have been onerous in the past, contemporary molecular techniques including next-generation sequencing allow simultaneously identifying carriers of a wide range of disorders efficiently and inexpensively.

**Expanded Carrier Screening**

Expanded carrier screening (ECS) involves screening individuals or couples for disorders in many genes (up to 100s). The disorders included may also span a range of disease severity or phenotype. Arguments for ECS include potential issues in assessing ethnicity, ability to identify more potential conditions, efficiency, and cost. Uncertain are the possible downsides of screening individuals at low risk, including a potential for incorrect variant ascertainment and the consequences of screening for rare single-gene disorders in which the likely phenotype may be uncertain (eg, due to variable expressivity and uncertain penetrance). The list of conditions included in ECS panels is not standardized. Although ECS panels would include conditions assessed in risk-based screening, ECS panels include many conditions not routinely evaluated and for which there are no existing professional guidelines.

This evidence review applies only if there is no separate evidence review that outlines specific criteria for carrier screening. If a separate evidence review exists, then criteria for medical necessity in that evidence review supersede the guidelines herein.

**Summary**

Carrier screening is performed to identify individuals at risk of having offspring with inherited single-gene disorders. Carriers are usually not at risk of developing the disease, but can pass pathogenic variants to their offspring. Carrier testing may be performed in the prenatal or preconception periods.

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive risk-based carrier screening, the evidence includes studies supporting analytic validity, clinical validity, and clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic but at risk for having offspring with inherited single-gene disorders who receive expanded carrier screening (ECS), the evidence includes studies on analytic validity, clinical validity, and indirectly clinical utility. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. The analytic validity of ECS panels will depend on the molecular method used; 2 identified studies support the analytic validity for ECS, but variant ascertainment with next generation sequencing requires careful evaluation. Three studies have found that ECS identifies more carriers and potentially affected fetuses. However, evidence to support the clinical validity of ECS beyond risk-based recommendations is limited and accompanied by some concerns including: interlaboratory agreement of variant pathogenicity assessment when sequencing identifies rare variants, the validity of disease severity classifications for rare disorders, and the certainty of predicted risk that the offspring will be affected by a severe phenotype for all the disorders included in a panel. The evidence is insufficient to determine the effects of the technology on health outcomes.
### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


Endnotes