Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Description of Procedure or Service

Definitions
Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by mutations in one of three genes, low-density lipoprotein receptor (LDLR), apolipoprotein B-100 (APOB), and proprotein convertase subtilisin-like kexin type 9 (PCSK9). It is characterized by severe lifelong elevations in low-density lipoprotein cholesterol and increased risk of premature coronary heart disease.(Ahmad et al., 2016; Goldberg et al., 2011).

Related Policies
Laboratory Procedures Reimbursement Policy – AHS – R2162

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will provide coverage for genetic testing for familial hypercholesterolemia when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Familial Hypercholesterolemia is covered

1. Genetic testing to establish a molecular diagnosis of Familial Hypercholesterolemia is considered medically necessary when BOTH of the following criteria are met:
   A. When FH is clinically suspected (based on clinical features, family history, physical exam, lipid levels, etc.) and a definitive diagnosis is required.
   B. The result of the test will directly impact the treatment being delivered to the member.
2. Genetic testing of children of individuals with FH to determine future risk of disease is considered medically necessary when a known pathogenic mutation is present in a parent.

When is not covered
Genetic testing to confirm a diagnosis of FH is considered investigational in all other situations.
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Note: For 5 or more gene tests run on the same platform, such as multi-gene panel next generation sequencing, please refer to the Laboratory Procedures Reimbursement Policy – AHS – R2162

Policy Guidelines

Background

Mutations in the APOB, LDLR, and PCSK9 genes cause between 70-95% of familial hypercholesterolemia. It is estimated that 2%-3% of myocardial infarctions in individuals younger than age 60 years are due to FH (Youngblom, Pariani, & Knowles, 2014). Although affected individuals have a 20-fold increased risk of premature atherosclerotic cardiovascular disease (Austin, Hutter, Zimmern, & Humphries, 2004), early diagnosis and treatment with lipid-lowering drugs reduces the risk of coronary heart disease (CHD) to rates comparable to the general population (Ahmad et al., 2016; Knowles et al., 2014; Versmissen et al., 2008).

Three current diagnostic criteria have been developed (Simon Broome, Dutch Lipid Clinic Network (DLCN), and the US Make Early Diagnosis to Prevent Early Death (MEDPED)) and can identify patients with FH-causing mutations with >80% sensitivity or specificity (Civeira, 2004; Marks, Thorogood, Neil, & Humphries, 2003; Williams et al., 1993). However, <10% of FH cases are identified (Neil, Hammond, Huxley, Matthews, & Humphries, 2000; O'Brien et al., 2014), despite an estimated prevalence of 1:200 to 1:500 (Ahmad et al., 2016; De Backer et al., 2015; Do et al., 2015; Nordestgaard et al., 2013).

The Familial Hypercholesterolemia Foundation established the CASCADE SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE FH) Registry as a national, multicenter initiative to identify US FH patients, track their treatment, and patient-reported outcomes over time. (O'Brien et al., 2014). This first results from this study demonstrated the heterogeneity in the application of FH diagnostic criteria in the United States (Ahmad et al., 2016).

The American Heart Association published a scientific statement in 2015 (Gidding et al., 2015) which proposed new diagnostic criteria:

FH Diagnostic Categories

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<thead>
<tr>
<th>ICD-10 Category</th>
<th>Clinical Criteria</th>
<th>With Genetic Testing Performed</th>
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<tbody>
<tr>
<td>Heterozygous FH</td>
<td>LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)</td>
<td>Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C &lt;160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes</td>
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<td>Genetic Testing for Familial Hypercholesterolemia AHS – M2137</td>
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<td><strong>Homozygous FH</strong></td>
<td>Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C &lt;160 mg/dL (4 mmol/L)</td>
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<td>LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH</td>
<td>Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type</td>
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<td>If LDL-C &gt;560 mg/dL (14 mmol/L) or LDL-C &gt;400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at &lt;20 y of age, homozygous FH highly likely</td>
<td>Occasionally, homozygotes will have LDL-C &lt;400 mg/dL (10 mmol/L)</td>
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<tr>
<td>Family history of FH</td>
<td>LDL-C level not a criterion; presence of a first-degree relative with confirmed FH</td>
<td>Genetic testing not performed</td>
</tr>
</tbody>
</table>

apoB indicates apolipoprotein B; FH, familial hypercholesterolemia; ICD-10, *International Classification of Diseases, 10th Revision*; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

Wald et al (2016) assessed the efficacy and feasibility of Child-parent screening for familial hypercholesterolemia in primary care practice and found that “Child-parent screening was feasible in primary care practices at routine child immunization visits. For every 1000 children screened, 8 persons (4 children and 4 parents) were identified as having positive screening results for familial hypercholesterolemia and were consequently at high risk for cardiovascular disease.”

**Guidelines and Recommendations:**

Rosensen and Durrington (2017) stated that “testing for mutations in the LDLR, APOB, and PCSK9 genes may be offered to individuals with xanthomata and/or a clinical diagnosis of homozygous FH.” A negative genetic score does not necessarily imply the lack of a genetic defect. The authors noted that “in homozygotes, genetic testing may help with decision making regarding PCSK9 agents.” Regarding genetic testing in adults clinically suspected to have heterozygous FH, the authors stated that it “does not contribute substantially to clinical decision-making, and its role is not established. Genetic testing should be performed in consultation with a lipid specialist and/or geneticist.

Cuchel et al (2014) published position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society that stated that the diagnosis of homozygous familial hypercholesterolemia (HoFH) can be made on clinical or genetic criteria.
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While genetic testing may provide a definitive diagnosis of HoFH, in some patients genetic confirmation remains elusive despite exhaustive investigation. The authors recommended genetic analysis should be considered to:

- Confirm the clinical diagnosis
- Facilitate testing of family members (reverse cascade screening)
- Assist in diagnosis where clinical presentation is borderline between that of HoFH and heterozygous FH

Norgestgaard et al (2013) published a consensus statement on Familial Hypercholesterolemia from the European Atherosclerosis Society. The authors stated that “in cases of probable or definite FH, cascade screening using LDL cholesterol measurement in the family should be conducted and the subject referred for genetic testing if available, with subsequent cascade testing in the family if a causative mutation is found. Initial family members to be tested are biological first-degree relatives, namely parents, siblings, and children.” The authors further stated “the DLCN criteria are recommended in order to establish the clinical diagnosis of FH. Among individuals with a definite or probable diagnosis of FH (DLCN > 5), and particularly those with an obvious clinical diagnosis with xanthoma and/or high cholesterol plus a family history of premature CHD, molecular genetic testing is strongly recommended. When a causative mutation is found in the index case, a genetic test should be offered to all first-degree relatives.”

Practice Guidelines and Position Statements

American Heart Association

In 2015, the AHA released a scientific statement on familial hypercholesterolemia that stated that “identification of all patients with FH is critical, but the optimal screening strategy has not been determined, and the complementary roles of genetic testing, family history, and LDL-C need to be further defined, particularly for children” (Gidding et al, 2015). AHA noted that “In healthcare systems that are less cohesive such as the US system, genetic testing is controversial for individuals in confirming diagnosis, and implementing cascade screening will be more difficult. In most countries, genetic testing remains relatively expensive and has limited availability. A reduction in costs and improved efficiency of genetic testing is likely to increase its broader application in screening families for FH.” Regarding testing for family members of patients with FH, AHA stated that “Consenting family members should be offered a standard plasma lipid profile and a genetic test if the family mutation is known and DNA testing is available.” The AHA also recommended that “Genetic counseling for FH can help patients and their families complete their pedigree and understand the inheritance of FH and the personal and familial implications of the diagnosis.”

National Lipid Society

In 2011, the National Lipid Society (Goldberg et al., 2011) published clinical guidelines for screening, diagnosis and management of FH that stated:

“Universal screening for elevated serum cholesterol is recommended. FH should be suspected when untreated fasting LDL cholesterol or non-HDL cholesterol levels are at or above the following: B Adults (≥20 years): LDL cholesterol ≥190 mg/dL or non-HDL cholesterol ≥220 mg/dL; B Children, adolescents and young adults (<20 years): LDL cholesterol ≥160 mg/dL or nonHDL cholesterol ≥190 mg/dL.”

“Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain. Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment. Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods.”
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In 2014, the National lipid Society published guidelines for the management of dyslipidemia (Jacobson et al., 2014, 2015) which reaffirmed:

“If LDL-C is ≥190 mg/dL, consider severe hypercholesterolemia phenotype, which includes familial hypercholesterolemia.”

American College of Cardiology/American Heart Association

The 2013 American College of Cardiology/American Heart Association (Goff et al., 2014) guidelines on the treatment of blood cholesterol suggest to consider FH in all patients with LDL-C >190 mg/dL.

American Association of Clinical Endocrinologists and American College of Endocrinology

The 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease recommend (Jellinger et al., 2017):

- Screening guidelines for dyslipidemia vary by age group;
- Although ASCVD risk in young adults is low, adults older than 20 years should be evaluated for dyslipidemia every 5 years as part of a global risk assessment
- Middle-aged individuals (Men Aged 45-65 Years, Women Aged 55-65 Years) should be screened for dyslipidemia at least every 1 to 2 years. More frequent lipid testing is recommended when multiple global ASCVD risk factors are present.
- Because many older individuals (over 65 years) may benefit from lipid-lowering therapy, even those with 0 to 1 ASCVD risk factors should be screened for dyslipidemia annually
- In children at risk for familial hypercholesterolemia (e.g., family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18
- Screen adolescents older than 16 years every 5 years or more frequently if they have ASCVD risk factors, have overweight or obesity, have other elements of the insulin resistance syndrome, or have a family history of premature ASCVD
- Use a fasting lipid profile to ensure the most precise lipid assessment; this should include total cholesterol, LDL-C, TG, and non-HDL-C

US Preventive Services Task Force

The 2017 USPSTF Task Force Recommendations include (Bibbins-Domingo et al., 2017; Chou et al., 2016):

Periodic assessment of cardiovascular risk factors from ages 40 to 75 years, including measurement of total cholesterol, LDL-C, and HDL-C levels. The optimal intervals for cardiovascular risk assessment are uncertain. Based on other guidelines and expert opinion, reasonable options include annual assessment of blood pressure and smoking status and measurement of lipid levels every 5 years. Shorter intervals may be useful for persons whose risk levels are close to those warranting therapy, and longer intervals are appropriate for persons who are not at increased risk and have repeatedly normal levels.

The USPSTF found insufficient evidence that screening for dyslipidemia before age 40 years has an effect on either short- or longer-term cardiovascular outcomes, and no studies that evaluated the effects of screening vs no screening, treatment vs no treatment, or delayed vs earlier treatment
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in adults in this age group. Thus, the USPSTF recommends neither for nor against screening for dyslipidemia in this age group. Insufficient evidence to assess the balance of benefits and harms of screening for dyslipidemia in children and adolescents.

The USPSTF found in 2009 that: “The USPSTF found inadequate direct evidence on the benefits of screening for familial hypercholesterolemia or multifactorial dyslipidemia.”(USPSTF, 2009)

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81401, 81403, 81405, 81406, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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From the American Heart Association. Circulation, 132(22), 2167-2192.
doi:10.1161/cir.0000000000000297


doi:10.1016/j.jacl.2011.04.003

doi:10.1016/j.jacl.2014.07.007


Knowles, J. W., O'Brien, E. C., Greendale, K., Wilemon, K., Genest, J., Sperling, L. S.,

doi:10.1016/j.ahj.2014.09.001


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Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing for familial hypercholesterolemia when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)


10/29/19 No change to policy statements. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

12/10/2019 Reviewed by Avalon 3rd Quarter 2019 CAB. Added Related Policies to Description section and “Note” to When Not Covered section of policy. Medical Director review 11/2019. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.