

Corporate Medical Policy

Genetic Testing for Familial Hypercholesterolemia AHS – M2137

File Name: genetic_testing_for_familial_hypercholesterolemia
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Description of Procedure or Service

Definitions

Familial hypercholesterolemia (FH) is a genetic condition that results in premature atherosclerotic cardiovascular disease due to lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C) levels (Sturm et al., 2018). FH encompasses multiple clinical phenotypes associated with distinct molecular etiologies. The most common 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*) (Ahmad et al., 2016; Goldberg et al., 2011). Rare autosomal recessive disease results from mutation in low-density lipoprotein receptor adaptor protein (*LDLRAP*) (Garcia et al., 2001).

Related Policies

Genetic Markers for Assessing Risk of Cardiovascular Disease AHS - M2180

*****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 (FH) is considered medically necessary when BOTH of the following criteria are met:
 - A. 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 for a known familial mutation associated with FH is considered medically necessary in asymptomatic close relatives (i.e., first-, second-, or third-degree relative) of an affected individual.

When is Genetic Testing for Familial Hypercholesterolemia is not covered

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Genetic testing to confirm a diagnosis of FH is considered not medically necessary in all other situations.

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

Familial Hypercholesterolemia (FH) is considered the most common inherited cardiovascular disease, affecting up to 1 in 200 people. FH's signature clinical sign is extremely elevated levels of low-density lipoprotein (LDL) cholesterol, which often leads to early-onset atherosclerotic cardiovascular disease (ASCVD) (Rosenson & Durrington, 2020). FH likely accounts for up to 3% of myocardial infarctions for individuals under 60 (Youngblom et al., 2016). Although affected individuals have a 20-fold increased risk of premature ASCVD (Austin et al., 2004), early diagnosis and treatment with lipid-lowering drugs can reduce 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).

The primary pathogenic mechanism of FH is the impairment of LDL-receptor mediated catabolism of LDL. Mutations in any of the three main genes (APOB, LDLR, PCSK9) typically cause this impairment, and mutations can be detected in up to 80% of patients with “definite” FH and up to 30% with “possible” FH. Of the three mutations, LDLR is the most common, composing 85-90% of the total mutations. PCSK9 consists of 2-4% of the total, and APOB consists of 1-12%. The severity of clinical phenotype depends on the extent to which LDL metabolism is affected. LDLR mutations reduce the efficacy of LDL receptors to clear LDL particles, APOB mutations impair binding of LDL particles to the LDL receptor, and PCSK9 mutations lead to decreased LDLR expression (fewer LDL receptors). Other factors (unrelated genetic conditions, diet, et al.) may affect LDL levels as well (Rosenson & Durrington, 2020). Several proprietary gene panels exist for assessment of FH. These typically include the three primary genes, but they may also include rarer genes, such as LDLRAP (Ambry, 2020; Invitae, 2020). Some panels intended for broader conditions, such as hyperlipidemia, may also include FH-related genes, such as BluePrint Genetics' 20 gene panel (BluePrint, 2022).

At least 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]). These criteria have been able to identify patients with FH-causing mutations with >80% sensitivity or specificity (Civeira, 2004; Marks et al., 2003; Williams et al., 1993). The Simon Broome and DLCN diagnostic criteria consider DNA-based evidence of mutations in any of APOB, LDLR, or PCSK9 to be suitable evidence for a “definite” diagnosis of FH (Rosenson & Durrington, 2020).

However, <10% of FH cases are identified (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). Ahmad et al. noted the heterogeneity of clinical application of FH diagnostic criteria, observing that the most commonly used formal criteria was Simon–Broome only (21%), followed by multiple diagnostic criteria (16%), MEDPED only (7%), DLCN only (1%), and other (0.5%) (Ahmad et al., 2016).

Clinical Utility and Validity

Wald et al. (2016) assessed the efficacy and feasibility of child-parent screening for familial hypercholesterolemia in primary care practice. 10095 children provided capillary blood samples, and the authors measured their cholesterol. Children were considered positive for FH if their levels were at or above the 99.2% percentile (1.53 times the median level). 28 (0.3%) children were considered positive for FH, and 20 children were classified as carriers of an FH mutation. Another

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17 children with levels under the 1.53 median were found to have an FH mutation. Overall, the mutation prevalence was 1/273 children (37/10095). The authors concluded 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” (Wald et al., 2016).

Khera et al. (2016) evaluated the prevalence of an FH mutation among those with “severe” hypercholesterolemia and determined whether coronary artery disease (CAD) risk varies with mutation status. Three genes causative of FH (LDLR, APOB, and PCSK9) were sequenced in 26025 patients from 7 case-control studies (5540 with CAD, 8577 controls without) and 5 prospective cohort studies (n = 11908). Out of the 20485 prospective cohort and CAD-free patients, 1386 were found to have LDL cholesterol levels of ≥ 190 mg/dL, and only 24 of these carried an FH mutation. Patients with LDL cholesterol ≥ 190 mg/dL and no FH mutation were found to have a 6-fold higher risk for CAD compared to patients with LDL < 130 mg/dL, but patients with both LDL cholesterol ≥ 190 mg/dL and an FH mutation were found to have a 22-fold higher risk (Khera et al., 2016).

Braamskamp et al. (2017) performed a study assessing the effect of “2-year treatment with rosuvastatin on carotid intima-media thickness (IMT) in children with heterozygous familial hypercholesterolemia (HeFH). 197 children with HeFH were provided rosuvastatin for 2 years, and carotid IMT was assessed at baseline, 1 year, and 2 years. The authors noted that at baseline, carotid IMT was greater in HeFH than affected siblings, but rosuvastatin treatment resulted in “significantly less progression of increased carotid IMT in children with HeFH than untreated unaffected siblings”, even suggesting that “no difference in carotid IMT could be detected between the 2 groups after 2 years of rosuvastatin”. The authors concluded that “these findings support the value of early initiation of statin treatment for low-density lipoprotein cholesterol reduction in children with HeFH” (Braamskamp et al., 2017).

Elbitar et al. (2018) showed the identification new mutations in FH through use of exome sequencing of LDLR, APOB, PCSK9, and APOE. 13 French families with “autosomal dominant hypercholesterolemia” had an exome sequencing performed. Several new mutations were identified, such as “p.Arg50Gln mutation in the APOB gene, a p.Ala3396Thr mutation of APOB, and one patient with a severe phenotype carrying also a mutation in PCSK9: p.Arg96Cys”. The authors stated that this study provided the first known case of a compound heterozygote with a mutation in APOB and PCSK9 and suggested that identifying these new mutations “lead to better diagnosis and treatment of ADH” (Elbitar et al., 2018).

Lee et al. (2019) performed a meta-analysis on the impact of genetic testing for FH on “1) diagnosis of 'definite familial hypercholesterolemia', 2) initiation and adherence of lipid-lowering therapy and 3) risk of ASCVD.” The authors included 56 studies. Genetic testing was found to have provided confirmation of FH in 28-80% of cases over clinical criteria alone. The authors also identified a 76751-individual cohort that indicated that an FH-causing variant was found in only 1.7%-2.5% of subjects with LDL > 190 mg/dL. Molecular diagnosis was found to increase lipid-lowering therapy adherence (4181 definite FH subjects). A loss-of-function LDLR variant was found to increase risk of myocardial infarction by 6.77-fold, and even a milder pathogenic LDLR variant still increased risk by 4.4-fold. The authors concluded that “DNA sequencing confirms the diagnosis of FH but has a poor yield in unselected patients whose sole criterion is an elevated LDL-C. Initiation and adherence to treatment is improved. The risk of ASCVD is 4.4- to 6.8-fold increased in patients with an FH-causing variant compared with controls, depending on the severity of the DNA change” (Lee et al., 2019).

Trinder et al. (2019) evaluated the risk of premature (defined as < 55 years old) cardiovascular events in patients with clinically diagnosed familial hypercholesterolemia. Monogenic (defined as mutations in LDLR, APOB, or PCSK9, comprising up to 80% of cases) and polygenic causes of FH were compared. 626 patients were included, and both targeted sequencing and genetic variant analysis were performed to identify patients for both cohorts. Patients with polygenic scores above

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the 80th percentile were considered to have polygenic FH. Risk of several cardiovascular events (unstable angina, myocardial infarction, coronary revascularization, or stroke) were assessed. Monogenic causes of FH were associated with a 1.96-fold increase of CVD, whereas the polygenic cohort saw no significant increase compared to patients without any genetic cause of FH at all. The authors also found that an elevated low-density lipoprotein polygenic risk score increased the CVD risk for monogenic patients to 3.06-fold. The authors concluded that “genetic testing for FH provides important prognostic information that is independent of LDL-C levels” (Trinder et al., 2019).

Trinder et al. (2020) compared the risk of CVD events between three cohorts; monogenic FH (277 patients), polygenic FH (2379), and hypercholesterolemia with “undetermined cause” (2232). The authors defined polygenic FH as a “polygenic score >95th percentile based on 223 single-nucleotide variants”. The authors found that patients with monogenic FH were three times more likely than polygenic FH to experience a CVD event before age 55 (6.1% vs 2.0%) and that both genetically-based types of FH were more likely to experience a CVD event compared to patients with hypercholesterolemia of unknown cause. The authors concluded that “genetic determinants of LDL-C levels may impose additional risk of CVD” and that “understanding the possible genetic cause of hypercholesterolemia may provide important prognostic information to treat patients” (Trinder et al., 2020).

Sturm et al. (2021) conducted a cross-sectional study comparing limited-variant screening and comprehensive next-generation (NGS) genetic testing for diagnosing FH. In the patient cohort, the researchers found that the limited-variant screen would have only yielded a positive detection rate of 8.4%, compared to the 27.0% positive detection rate with the comprehensive test, meaning that 68.9% of individuals with a FH-associated gene would be missed by the limited screen. Individuals of self-reported Black/African American and Hispanic descent were more likely to be missed by the limited-variant screen. This demonstrates the need to conduct a full evaluation via genetic screening, and how it is a useful modality for diagnosing FH (Sturm et al., 2021).

Reeskamp et al. (2020) performed a study that investigated the role of NGS in clinical FH. For the diagnostic yield of NGS, the researchers stated that an “FH-causing genetic variant was identified in only 14.9% of FH patients with LDL-cholesterol levels of 5 mmol/L or greater;” the mutations being considered were from LDLR (80.2%), APOB (14.5%), or PCSK9 (5.3%). “This percentage increased to more than 50% when patients were stratified according to either higher LDL-cholesterol levels or more stringent diagnostic FH criteria ascertained by the DLCN [Dutch Lipid Clinic Network] criteria; 4.8% of FH-mutation negative patients were heterozygous carriers of a pathogenic variant in a minor FH gene.” Though this study overall had a lower diagnostic yield using NGS in comparison to other studies, the researchers propose that “stringent use of clinical criteria algorithms is warranted to increase this yield” and thus maximize the clinical utility of NGS (Reeskamp et al., 2020).

Vallejo et al. (2021) conducted a cross-sectional assessment of 42,617 adults 18 years and older with a clinical or genetic diagnosis of heterozygous familial hypercholesterolaemia. The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration provided a global registry of individuals with FH in World Health Organization regions. Cardiovascular risk factors varied by age and World Health Organization region. The authors found that, “among patients taking lipid-lowering medications, 2.7% had LDL cholesterol lower than 1.8 mmol/L; the use of combination therapy, particularly with three drugs and with proprotein convertase subtilisin-kexin type 9 inhibitors, was associated with a higher proportion and greater odds of having LDL cholesterol lower than 1.8 mmol/L.” In addition, the authors advocated for earlier detection and the use of combination therapies (as opposed to single-drug therapy) to achieve guideline-recommended LDL concentrations.

Guidelines and Recommendations

European Atherosclerosis Society (EAS)

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Cuchel et al. (2014) published a position paper from the Consensus Panel on Familial Hypercholesterolemia of the EAS that stated that the diagnosis of homozygous familial hypercholesterolemia (HoFH) can be made on clinical or genetic criteria. 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

Wiegman et al. (2015) published a position paper from the EAS regarding FH in children. In it, they state that “DNA testing establishes the diagnosis,” and that “detection of a pathogenic mutation, usually in the LDLR gene, is the gold standard for diagnosis of FH.” The EAS also observes that “It is best practice to first genetically test a phenotypically affected parent or a second-degree relative in the absence of a parent. If a mutation is identified, genetic testing and counselling should be offered to all family members” (Wiegman et al., 2015).

The EAS published an update in 2019. In it, they recommend that genetic testing should be performed to confirm clinically suspicious cases of FH. The EAS lists the following criteria as evidence for FH:

- “TC \geq 8 mmol/L (\geq 310 mg/dL) without treatment in an adult or adult family member (or $>$ 95th percentile by age and gender for country);
- Premature CHD in the patient or a family member;
- Tendon xanthomas in the patient or a family member; or
- Sudden premature cardiac death in a family member.”

The EAS also recommends that cascade testing be performed when a causative mutation is known in an index case of heterozygous FH (Mach et al., 2019).

American Heart Association (AHA)

In 2015, the AHA released a scientific statement on FH 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.” 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” (Gidding et al., 2015).

The American Heart Association also proposed new diagnostic criteria (Gidding et al., 2015).

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ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C \geq 160 mg/dL (4 mmol/L) for children and \geq 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)	<p>Presence of 1 abnormal LDL-C-raising (LDL receptor, APOB or PCSK9) gene defect</p> <p>Diagnosed as heterozygous FH if LDL-C-raising defect positive and LDL-C <160 mg/dL (4 mmol/L)</p> <p>Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes</p> <p>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 <160 mg/dL (4 mmol/L)</p>
Homozygous FH	LDL-C \geq 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	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
	If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely	Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

National Lipid Association (NLA)

In 2011, the NLA released guidelines for screening, diagnosing, and managing familial hypercholesterolemia among pediatric and adult patients. This was last reaffirmed in August 2020. With regards to genetic testing/screening, the NLA stated the following:

- “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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On cascade screening, the NLA stated the following:

- “Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.
- As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
- Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol-lowering treatment is begun in all those identified.”

However, in terms of diagnosis of FH, the NLA states:

- “Untreated fasting lipid levels at which FH may be suspected in children, adolescents, and young adults (<20 years) are LDL cholesterol concentration ≥ 160 mg/dL or non-HDL cholesterol ≥ 190 mg/dL. These levels are supported by family studies of affected individuals.
- A second lipid profile should be performed to assess response to diet management, to account for regression to the mean, and to accurately classify those with levels close to classification thresholds” (Goldberg et al., 2011).

In 2015, the NLA published guidelines for the management of dyslipidemia (Jacobson et al., 2015) which reaffirmed in August 2020:

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

The NLA also published a statement on genetic testing for dyslipidemia in 2020. This statement has been reaffirmed in June 2021. The FH-related recommendations are listed below:

- “Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone.”
- “Cascade screening for FH either by lipid profile or genetic testing is recommended in all first-degree relatives (children and siblings) of an individual who has tested genetically positive for FH.”
- “Cascade testing [for general genetic dyslipidemias] should begin with first-degree relatives (parents, siblings, and children) and then extend to second- and third-degree relatives.”

The Association also remarks that genetic testing for FH can predict clinical outcomes and that identifying particular mutations (such as LDLR) may guide targeted therapy in the future. No “polygenic risk scores” have been identified as a “gold standard” (Brown et al., 2020).

American College of Cardiology/American Heart Association

The 2018 statement (Sturm et al., 2018) on clinical genetic testing for familial hypercholesterolemia recommends:

Proband (index case)

Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient’s clinical and/or family histories. This index of suspicion includes the following:

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- “Children with persistent* LDL-C levels ≥ 160 mg/dl or adults with persistent LDL-C levels ≥ 190 mg/dl without an apparent secondary cause of hypercholesterolemia and with at least 1 first-degree relative similarly affected or with premature CAD[‡] or where family history is not available (e.g., adoption)”
- “Children with persistent* LDL-C levels ≥ 190 mg/dl or adults with persistent LDL-C levels ≥ 250 mg/dl without an apparent secondary cause of hypercholesterolemia, even in the absence of a positive family history”

Genetic testing for FH may be considered in the following clinical scenarios:

- “Children with persistent* LDL-C levels ≥ 160 mg/dl (without an apparent secondary cause of hypercholesterolemia[†]) with an LDL-C level ≥ 190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD”
- “Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD”
- “Adults with persistent LDL-C levels ≥ 160 mg/dl (without an apparent secondary cause of hypercholesterolemia) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD”

*Two or more measurements, including assessment after intensive lifestyle modification

[†]Hypothyroidism, diabetes, renal disease, nephrotic syndrome, liver disease, medications.

If LDL-C values are unavailable, total cholesterol values ≥ 320 , 260, and 230 mg/dl (corresponding to LDL-C levels ≥ 250 , 190, and 160 mg/dl, respectively) could be used.

At-risk relatives

Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified.

They recommend that “Genetic testing for patients with suspected FH should, at a minimum, include analysis of LDLR, APOB, and PCSK9. This analysis should include for LDLR and PCSK9 sequencing of all exons and exon/ intron boundaries, as well as LDLR deletion/duplication analysis, and for APOB the exons encoding the LDLR ligand-binding region... Larger, more inclusive, lipid disorder NGS panels are also available that provide evaluation of not only the main FH genes but also the genes causing conditions with phenotypic overlap previously described. These expanded panels should be considered to improve the diagnosis of patients with these ‘phenocopy’ conditions that may require specific therapies, and they should include the following genes: LDLR, APOB, PCSK9, LDLRAP1, LIPA, ABCG5, ABCG8, and APOE” (Sturm et al., 2018).

This set of guidelines was endorsed by the FH Foundation (Fountain, 2022).

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 include some items regarding FH. These guidelines include the following (Jellinger et al., 2017):

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- For children at risk (such as family history) for FH,
 - screening should be at 3 years of age
 - repeated once between ages 9 and 11 years
 - repeated again at age 18
- “Individuals should be screened for familial hypercholesterolemia (FH) when there is a family history of premature ASCVD (definite MI or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative)”
- Individuals should be screened if they have “Elevated cholesterol levels (total, non-HDL and/ or LDL) consistent with FH”
- The authors note, “While genetic testing may identify FH, it is not commonly used in the U.S. due to cost and lack of payer coverage” (Jellinger et al., 2017).

US Preventive Services Task Force (USPSTF)

According to the 2016 USPSTF guidelines, “Screening can detect FH in children, and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. There is no evidence for the effect of screening for FH in childhood on lipid concentrations or cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood” (Lozano et al., 2016).

National Institute for Health and Care Excellence

NICE published an update on FH in 2019, and their relevant recommendations include the following:

- “Carry out cascade testing using DNA testing to identify affected first- and second- and, when possible, third-degree biological relatives of people with a genetic diagnosis of FH.”
- “Healthcare professionals should consider a clinical diagnosis of homozygous FH in adults with a low-density lipoprotein cholesterol (LDL-C) concentration greater than 13 mmol/l and in children/young people with an LDL-C concentration greater than 11 mmol/l.”
- “Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings.”
- “Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5” (NICE, 2019).

Hyperlipidaemia Education and Atherosclerosis Research Trust United Kingdom (HEART UK)

This guideline focuses on homozygous FH. For diagnosis of homozygous FH, HEART-UK recommends that mutation analysis “should be by comprehensive DNA sequencing of introns and exons of the *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* gene loci [in an accredited laboratory]” (France et al., 2016).

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International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel

The panel notes that in addition to the main three genes, mutations in *APOE* or *STAP1* may result in the heterozygous FH phenotype. However, the panel remarks that “...identification of a causative gene variant is not essential for either diagnosis or treatment decisions, since as mentioned these are more appropriately guided by the LDL-C and not by the genotype” (Santos et al., 2016).

Canadian Cardiovascular Society (CCS)

In 2018, the CCS released a position statement on FH. With regards to genetic testing, screening and diagnosis of FH, the CCS included the following relevant recommendations:

- **Diagnosis of FH**
 - “We recommend that FH be defined using the DLCNC [Dutch Lipid Clinic Network Criteria], Simon Broome Registry, or FH Canada definition (Strong Recommendation, High-Quality Evidence).”
- **Screening for FH**
 - “We recommend that cascade screening (lipid profile) protocols be implemented at the local, provincial, and national level in Canada and offered to first-degree relatives of patients with FH (Strong Recommendation, Moderate-Quality Evidence).”
- **Genetics**
 - “We recommend that genetic testing be offered, when available, to complement a diagnosis of FH and enable cascade screening (Strong Recommendation, High Quality Evidence). The decision to request genetic screening should be made by the treating physician after discussion with the patient.”
- **ASCVD [atherosclerotic cardiovascular disease] and FH**
 - “We suggest that if available, genetic testing should be used to stratify the ASCVD risk in patients with FH (Weak Recommendation, Moderate-Quality Evidence).
 - Values and preferences. An FH-causing genetic variant increases ASCVD risk, beyond that associated with an elevated LDL-C level. Patients should be informed on the high lifetime risk of ASCVD associated with FH.”
- **Homozygous FH**
 - “We recommend that patients with HoFH be referred to a specialized lipid clinic and undergo complete evaluation for genetic analysis, presence of ASCVD, and aggressive lipid-lowering therapies, including consideration for extracorporeal LDL-C removal, lomitapide, and PCSK9 inhibitors (Strong Recommendation, Moderate-Quality Evidence)” (Brunham et al., 2018).

State and Federal Regulations, as applicable

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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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, 81405, 81406, 81407, 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

Ahmad, Z. S., Andersen, R. L., Andersen, L. H., O'Brien, E. C., Kindt, I., Shrader, P., Vasandani, C., Newman, C. B., deGoma, E. M., Baum, S. J., Hemphill, L. C., Hudgins, L. C., Ahmed, C. D., Kullo, I. J., Gidding, S. S., Duffy, D., Neal, W., Wilemon, K., Roe, M. T., . . . Knowles, J. W. (2016). US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. *J Clin Lipidol*, 10(5), 1223-1229. <https://doi.org/10.1016/j.jacl.2016.07.011>

Ambry. (2020). FHNNext®. <https://www.ambrygen.com/clinician/genetic-testing/13/cardiology/fhnnext>

Austin, M. A., Hutter, C. M., Zimmern, R. L., & Humphries, S. E. (2004). Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol*, 160(5), 421-429. <https://doi.org/10.1093/aje/kwh237>

Braamskamp, M., Langslet, G., McCrindle, B. W., Cassiman, D., Francis, G. A., Gagne, C., Gaudet, D., Morrison, K. M., Wiegman, A., Turner, T., Miller, E., Kusters, D. M., Raichlen, J. S., Martin, P. D., Stein, E. A., Kastelein, J. J. P., & Hutten, B. A. (2017). Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). *Circulation*, 136(4), 359-366. <https://doi.org/10.1161/circulationaha.116.025158>

Brown, E. E., Sturm, A. C., Cuchel, M., Braun, L. T., Duell, P. B., Underberg, J. A., Jacobson, T. A., & Hegele, R. A. (2020). Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. *J Clin Lipidol*. <https://doi.org/10.1016/j.jacl.2020.04.011>

Brunham, L. R., Ruel, I., Aljenedil, S., Rivière, J. B., Baass, A., Tu, J. V., Mancini, G. B. J., Raggi, P., Gupta, M., Couture, P., Pearson, G. J., Bergeron, J., Francis, G. A., McCrindle, B. W., Morrison, K., St-Pierre, J., Henderson, M., Hegele, R. A., Genest, J., . . . Brophy, J. (2018). Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018. *Can J Cardiol*, 34(12), 1553-1563. <https://doi.org/10.1016/j.cjca.2018.09.005>

Civeira, F. (2004). Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis*, 173(1), 55-68. <https://doi.org/10.1016/j.atherosclerosis.2003.11.010>

Cuchel, M., Bruckert, E., Ginsberg, H. N., Raal, F. J., Santos, R. D., Hegele, R. A., Kuivenhoven, J. A., Nordestgaard, B. G., Descamps, O. S., Steinhagen-Thiessen, E., Tybjærg-Hansen, A., Watts, G. F., Averna, M., Boileau, C., Borén, J., Catapano, A. L., Defesche, J. C., Hovingh, G. K., Humphries, S. E., . . . Chapman, M. J. (2014). Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper

Genetic Testing for Familial Hypercholesterolemia AHS – M2137

from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*, 35(32), 2146-2157. <https://doi.org/10.1093/eurheartj/ehu274>

De Backer, G., Besseling, J., Chapman, J., Hovingh, G. K., Kastelein, J. J., Kotseva, K., Ray, K., Reiner, Z., Wood, D., & De Bacquer, D. (2015). Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. *Atherosclerosis*, 241(1), 169-175. <https://doi.org/10.1016/j.atherosclerosis.2015.04.809>

Do, R., Stitzel, N. O., Won, H. H., Jorgensen, A. B., Duga, S., Angelica Merlini, P., Kiezun, A., Farrall, M., Goel, A., Zuk, O., Guella, I., Asselta, R., Lange, L. A., Peloso, G. M., Auer, P. L., Girelli, D., Martinelli, N., Farlow, D. N., DePristo, M. A., . . . Kathiresan, S. (2015). Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*, 518(7537), 102-106. <https://doi.org/10.1038/nature13917>

Elbitar, S., Susan-Resiga, D., Ghaleb, Y., El Khoury, P., Peloso, G., Stitzel, N., Rabes, J. P., Carreau, V., Hamelin, J., Ben-Djoudi-Ouadda, A., Bruckert, E., Boileau, C., Seidah, N. G., Varret, M., & Abifadel, M. (2018). New Sequencing technologies help revealing unexpected mutations in Autosomal Dominant Hypercholesterolemia. *Sci Rep*, 8(1), 1943. <https://doi.org/10.1038/s41598-018-20281-9>

France, M., Rees, A., Datta, D., Thompson, G., Capps, N., Ferns, G., Ramaswami, U., Seed, M., Neely, D., Cramb, R., Shoulders, C., Barbir, M., Pottle, A., Eatough, R., Martin, S., Bayly, G., Simpson, B., Halcox, J., Edwards, R., . . . Soran, H. (2016). HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*, 255, 128-139. <https://doi.org/10.1016/j.atherosclerosis.2016.10.017>

Garcia, C. K., Wilund, K., Arca, M., Zuliani, G., Fellin, R., Maioli, M., Calandra, S., Bertolini, S., Cossu, F., Grishin, N., Barnes, R., Cohen, J. C., & Hobbs, H. H. (2001). Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science*, 292(5520), 1394-1398. <https://doi.org/10.1126/science.1060458>

Gidding, S. S., Champagne, M. A., de Ferranti, S. D., Defesche, J., Ito, M. K., Knowles, J. W., McCrindle, B., Raal, F., Rader, D., Santos, R. D., Lopes-Virella, M., Watts, G. F., & Wierzbicki, A. S. (2015). The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation*, 132(22), 2167-2192. <https://doi.org/10.1161/cir.0000000000000297>

Goldberg, A. C., Hopkins, P. N., Toth, P. P., Ballantyne, C. M., Rader, D. J., Robinson, J. G., Daniels, S. R., Gidding, S. S., de Ferranti, S. D., Ito, M. K., McGowan, M. P., Moriarty, P. M., Cromwell, W. C., Ross, J. L., & Ziajka, P. E. (2011). Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*, 5(3 Suppl), S1-8. <https://doi.org/10.1016/j.jacl.2011.04.003>

Invitae. (2020). Invitae Familial Hypercholesterolemia Panel. <https://www.invitae.com/en/physician/tests/02401/>

Jacobson, T. A., Ito, M. K., Maki, K. C., Orringer, C. E., Bays, H. E., Jones, P. H., McKenney, J. M., Grundy, S. M., Gill, E. A., Wild, R. A., Wilson, D. P., & Brown, W. V. (2015). National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol*, 9(2), 129-169. <https://doi.org/10.1016/j.jacl.2015.02.003>

Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., Grunberger, G., Guerin, C. K., Bell, D. S. H., Mechanick, J. I., Pessah-Pollack, R., Wyne, K., Smith, D., Brinton, E. A., Fazio, S., & Davidson, M. (2017). AMERICAN ASSOCIATION OF

Genetic Testing for Familial Hypercholesterolemia AHS – M2137

CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr Pract*, 23(Suppl 2), 1-87.

<https://doi.org/10.4158/ep171764.appgl>

Khera, A. V., Won, H. H., Peloso, G. M., Lawson, K. S., Bartz, T. M., Deng, X., van Leeuwen, E. M., Natarajan, P., Emdin, C. A., Bick, A. G., Morrison, A. C., Brody, J. A., Gupta, N., Nomura, A., Kessler, T., Duga, S., Bis, J. C., van Duijn, C. M., Cupples, L. A., . . . Kathiresan, S. (2016). Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol*, 67(22), 2578-2589.

<https://doi.org/10.1016/j.jacc.2016.03.520>

Knowles, J. W., O'Brien, E. C., Greendale, K., Wilemon, K., Genest, J., Sperling, L. S., Neal, W. A., Rader, D. J., & Khoury, M. J. (2014). Reducing the burden of disease and death from familial hypercholesterolemia: a call to action. *Am Heart J*, 168(6), 807-811.

<https://doi.org/10.1016/j.ahj.2014.09.001>

Lee, S., Akioyamen, L. E., Aljenedil, S., Riviere, J. B., Ruel, I., & Genest, J. (2019). Genetic testing for familial hypercholesterolemia: Impact on diagnosis, treatment and cardiovascular risk. *Eur J Prev Cardiol*, 26(12), 1262-1270. <https://doi.org/10.1177/2047487319829746>

Lozano, P., Henrikson, N. B., Dunn, J., Morrison, C. C., Nguyen, M., Blasi, P. R., Anderson, M. L., & Whitlock, E. P. (2016). Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*, 316(6), 645-655. <https://doi.org/10.1001/jama.2016.6176>

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., Chapman, M. J., De Backer, G. G., Delgado, V., Ference, B. A., Graham, I. M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T. R., Riccardi, G., Richter, D. J., Sabatine, M. S., Taskinen, M.-R., . . . Group, E. S. C. S. D. (2019). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*, 41(1), 111-188. <https://doi.org/10.1093/eurheartj/ehz455>

Marks, D., Thorogood, M., Neil, H. A., & Humphries, S. E. (2003). A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis*, 168(1), 1-14.

NICE. (2019). Familial hypercholesterolaemia: identification and management.

<https://www.nice.org.uk/guidance/cg71/chapter/Recommendations>

Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., Descamps, O. S., Wiklund, O., Hegele, R. A., Raal, F. J., Defesche, J. C., Wiegman, A., Santos, R. D., Watts, G. F., Parhofer, K. G., Hovingh, G. K., Kovanen, P. T., Boileau, C., Averna, M., Boren, J., . . . Tybjaerg-Hansen, A. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*, 34(45), 3478-3490a.

<https://doi.org/10.1093/eurheartj/ehz273>

O'Brien, E. C., Roe, M. T., Fraulo, E. S., Peterson, E. D., Ballantyne, C. M., Genest, J., Gidding, S. S., Hammond, E., Hemphill, L. C., Hudgins, L. C., Kindt, I., Moriarty, P. M., Ross, J., Underberg, J. A., Watson, K., Pickhardt, D., Rader, D. J., Wilemon, K., & Knowles, J. W. (2014). Rationale and design of the familial hypercholesterolemia foundation CAscade SCReening for Awareness and DEtection of Familial Hypercholesterolemia registry. *Am Heart J*, 167(3), 342-349.e317.

<https://doi.org/10.1016/j.ahj.2013.12.008>

Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Reeskamp, L. F., Tromp, T. R., Defesche, J. C., Grefhorst, A., Stroes, E. S., Hovingh, G. K., & Zuurbier, L. (2020). Next-generation sequencing to confirm clinical familial hypercholesterolemia. *Eur J Prev Cardiol*, 2047487320942996. <https://doi.org/10.1177/2047487320942996>

Rosenson, R., & Durrington, P. (2020, September 21). Familial hypercholesterolemia in adults: Overview. <https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-overview>

Santos, R. D., Gidding, S. S., Hegele, R. A., Cuchel, M. A., Barter, P. J., Watts, G. F., Baum, S. J., Catapano, A. L., Chapman, M. J., Defesche, J. C., Folco, E., Freiburger, T., Genest, J., Hovingh, G. K., Harada-Shiba, M., Humphries, S. E., Jackson, A. S., Mata, P., Moriarty, P. M., . . . Yamashita, S. (2016). Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*, 4(10), 850-861. [https://doi.org/10.1016/s2213-8587\(16\)30041-9](https://doi.org/10.1016/s2213-8587(16)30041-9)

Sturm, A. C., Knowles, J. W., Gidding, S. S., Ahmad, Z. S., Ahmed, C. D., Ballantyne, C. M., Baum, S. J., Bourbon, M., Carrié, A., Cuchel, M., Ferranti, S. D. d., Defesche, J. C., Freiburger, T., Hershberger, R. E., Hovingh, G. K., Karayan, L., Kastelein, J. J. P., Kindt, I., Lane, S. R., . . . Foundation, C. b. t. F. H. (2018). Clinical Genetic Testing for Familial Hypercholesterolemia. *Journal of the American College of Cardiology*, 72(6). <https://doi.org/10.1016/j.jacc.2018.05.044>

Sturm, A. C., Truty, R., Callis, T. E., Aguilar, S., Esplin, E. D., Garcia, S., Haverfield, E. V., Morales, A., Nussbaum, R. L., Rojahn, S., Vatta, M., & Rader, D. J. (2021). Limited-Variant Screening vs Comprehensive Genetic Testing for Familial Hypercholesterolemia Diagnosis. *JAMA Cardiology*, 6(8).

Trinder, M., Francis, G. A., & Brunham, L. R. (2020). Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease. *JAMA Cardiology*, 5(4), 390-399. <https://doi.org/10.1001/jamacardio.2019.5954>

Trinder, M., Li, X., DeCastro, M. L., Cermakova, L., Sadananda, S., Jackson, L. M., Azizi, H., Mancini, G. B. J., Francis, G. A., Frohlich, J., & Brunham, L. R. (2019). Risk of Premature Atherosclerotic Disease in Patients With Monogenic Versus Polygenic Familial Hypercholesterolemia. *J Am Coll Cardiol*, 74(4), 512-522. <https://doi.org/10.1016/j.jacc.2019.05.043>

Versmissen, J., Oosterveer, D. M., Yazdanpanah, M., Defesche, J. C., Basart, D. C., Liem, A. H., Heeringa, J., Witteman, J. C., Lansberg, P. J., Kastelein, J. J., & Sijbrands, E. J. (2008). Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *Bmj*, 337, a2423. <https://doi.org/10.1136/bmj.a2423>

Wald, D. S., Bestwick, J. P., Morris, J. K., Whyte, K., Jenkins, L., & Wald, N. J. (2016). Child-Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med*, 375(17), 1628-1637. <https://doi.org/10.1056/NEJMoal602777>

Wiegman, A., for the European Atherosclerosis Society Consensus, P., Gidding, S. S., for the European Atherosclerosis Society Consensus, P., Watts, G. F., for the European Atherosclerosis Society Consensus, P., Chapman, M. J., for the European Atherosclerosis Society Consensus, P., Ginsberg, H. N., for the European Atherosclerosis Society Consensus, P., Cuchel, M., for the European Atherosclerosis Society Consensus, P., Ose, L., for the European Atherosclerosis Society Consensus, P., Averna, M., for the European Atherosclerosis Society Consensus, P., Boileau, C., for the European Atherosclerosis Society Consensus, P., Borén, J., . . . Ginsberg, H. N. (2015). Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*, 36(36), 2425-2437. <https://doi.org/10.1093/eurheartj/ehv157>

Genetic Testing for Familial Hypercholesterolemia AHS – M2137

Williams, R. R., Hunt, S. C., Schumacher, M. C., Hegele, R. A., Leppert, M. F., Ludwig, E. H., & Hopkins, P. N. (1993). Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol*, 72(2), 171-176.

Youngblom, E., Pariani, M., & Knowles, J. W. (2016). Familial Hypercholesterolemia [Text]. GeneReviews. <https://www.ncbi.nlm.nih.gov/books/NBK174884/>

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Medical Director review 10/2022

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)
- 8/13/19 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (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)
- 12/10/19 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)
- 7/28/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)
- 8/11/20 Minor revision to “Last Review” date for clarification. (jd)
- 11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Background, policy guidelines, and references updated. Related policies section revised. When Not Covered section, statement 1 revised removing “investigational” and replacing with “not medically necessary”. CPT code 81479 removed and 81407 added to the Billing/Coding section. Medical Director review 10/2020. (jd)
- 9/7/21 Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)
- 11/16/21 Reviewed by Avalon 3rd Quarter 2021 CAB. Policy guidelines and references updated. Medical Director review 10/2021. (jd)
- 12/30/22 Reviewed by Avalon 3rd Quarter 2022 CAB. Background, Policy Guidelines, and References updated. Related policies section revised. When Covered section, criteria 2 stating “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

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in a parent” removed and replaced with “Genetic testing for a known familial mutation associated with FH is considered medically necessary in asymptomatic close relatives (i.e., first-, second-, or third-degree relative) of an affected individual”. CPT code 81403 removed and 81479 added to the Billing/Coding section. Medical Director review 10/2022. (tm)

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