Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP325

Section: Medical Benefit Policy

Subject: Genetic Testing for Familial Hypercholesterolemia

Applicable line of business:

Commercial	**x**	**Medicaid**	**x**
Medicare	**x**	**ACA**	**x**
CHIP	**x**		

I. Policy: Genetic Testing for Familial Hypercholesterolemia

II. Purpose/Objective:

To provide a policy of coverage regarding Genetic Testing for Familial Hypercholesterolemia

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

Commercial

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicare

Geisinger Gold Medicare Advantage HMO, PPO, and HMO D-SNP plans are offered by Geisinger Health Plan/Geisinger Indemnity Insurance Company, health plans with a Medicare contract. Continued enrollment in Geisinger Gold depends on contract renewal. Geisinger Health Plan/Geisinger Indemnity Insurance Company are part of Geisinger, an integrated health care delivery and coverage organization.

CHIP

Geisinger Health Plan Kids (GHP Kids) is a Children's Health Insurance Program (CHIP) offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Medicaid

Geisinger Health Plan Family (GHP Family) is a Medical Assistance (Medicaid) insurance program offered by Geisinger Health Plan in conjunction with the Pennsylvania Department of Human Services (DHS). Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment
Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION:
Familial hypercholesterolemia is an inherited genetic condition that results in a >20-fold increase in risk for premature or "early-onset" atherosclerotic cardiovascular disease events (ASCVD) due to lifelong exposure to elevated low-density lipoprotein cholesterol (LDL-C). The condition encompasses a spectrum of clinical phenotypes with a broad range of pathogenic variants.

A 2024 review of >21K individuals, across six prospective cohorts, identified a causative FH variant was found in individuals across all ages in the following LDL-C categories: 2.2% positive rate with >190mg/dL, 0.6% positive rate in 160-189mg/dL, 0.2% positive rate in 130-159mg/dL, and 0.1% <130mg/dL.

Disease-specific panels may change from year to year based on available evidence and technological advancements. Germline multigene panel testing (MGPT) for moderate and high-penetrance familial hypercholesterolemia susceptibility genes should include LDLR, APOB, and PCSK9. Test methodology should include sequencing and full deletion and duplication analysis (i.e., detection of large genomic rearrangements) with a benefit of once per lifetime, dependent upon advances in testing technology.

INDICATIONS:
Genetic Testing for Familial Hypercholesterolemia or inherited dyslipidemias will be considered medically necessary in a member when any of the following criteria are met:

1. The member meets diagnostic criteria per MedPed, Simon Broome, or Dutch Lipid Clinic tools (below)

OR

2. Elevated LDL-C level, defined as:
   1 An LDL-C level of >160mg/dL in a member at any age without an apparent secondary cause, **OR**
   2 A post-treatment LDL-C level of >130mg/dl with no pre-treatment LDL-C available at any age, **OR**
   3 Failure to achieve LDL-C goal with at least one line of acceptable therapy
   4 An LDL-C level of >130mg/dL at any age, with ≥1 close relative(s) with known or suspected FH.

OR

3. Elevated total cholesterol, defined as:
   1 A total cholesterol level of >230mg/dL in a member <18y, without an apparent secondary cause, **OR**
   2 A pre-treatment total cholesterol level of >310mg/dL, in a member >18y, without an apparent secondary cause.

OR

4. A personal history of premature coronary artery disease (CAD) such as myocardial infarction or obstructive CAD requiring intervention or other cardiovascular disease (e.g., ischemic stroke, peripheral vascular disease) in:
   1 A <55y assigned-male at birth member, OR
   2 A <65y in assigned-female at birth member, OR
   3 A member without personal history of CAD but reports with 2 or more close relatives on the same side of the family meeting the above criteria.

OR

5. A personal history of 1 or more physical features:
   1. corneal arcus reported before age 45y
   2. xanthoma(s) or xanthelasma(s)

OR

6. A family history of molecularly confirmed FH with a variant in APOB, LDLR, PCSK9 in a first, second, or third degree relative and directed (targeted variant) testing is unable to be performed.

LDLR, APOB, PCSK9 multi-gene panels, or FH multi-gene panels, are the preferred approach for evaluation of FH, unless there is a known familial variant.

A familial hypercholesterolemia panel is considered medically necessary when all of the following criteria are met:
- The member meets ANY of the above listed criteria for evaluation of familial hypercholesterolemia (FH); and
- Clinical consultation and genetic counseling by an appropriate provider has been completed; and
- Member has not had previous LDLR, APOB, or PCSK9 sequencing or deletion/duplication testing, and
- There is no known LDLR, APOB, or PCSK9 mutation in the family,

LDLR, APOB, PCSK9, LDLRAP1 Known Familial Mutation Testing is considered medically necessary when all of the following criteria are met:
- LDLR, APOB, or PCSK9 mutation has been identified in a 1st, 2nd or 3rd degree biological relative; and
- Genetic counseling by an appropriate provider has been completed in the member, or if the member is <18, genetic counseling has been provided to the parent or legal guardian(s); and
- The member has not had previous genetic testing of LDLR, APOB, or PCSK9; and
- The result of the test will directly impact the treatment timeline and/or options for the member.

Diagnostic Criteria Tables

MEDPED DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA [1-3]				
	FH is diagnosed if total cholesterol exceeds these cutpoints in mg/dL (mmol/L)			
Age (years)	First degree relative with FH	Second degree relative with FH	Third degree relative with FH	General population
<20	220 (5.7)	230 (5.9)	240 (6.2)	270 (7.0)
20 – 29	240 (6.2)	250 (6.5)	260 (6.7)	290 (7.5)
30 – 39	270 (7.0)	280 (7.2)	290 (7.5)	340 (8.8)
≥40	290 (7.5)	300 (7.8)	310 (8.0)	360 (9.3)

[1]Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420.
[2]Haase A, Goldberg AC. Identi cation of people with heterozygous familial hypercholesterolemia. Current opinion in lipidology. 2012;23:282-289.
[3]Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. The American journal of cardiology. 1993;72:171-176..

SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1]	
Point	**Criteria**

1	Total cholesterol levels > 290mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) if ≤ 16 yrs
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
5	Family history of elevated total cholesterol > 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated total cholesterol > 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.
DIAGNOSIS	
Definite familial hypercholesterolemia = 1+2 or 3 Possible familial hypercholesterolemia = 1+4 or 5	

[1] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420.

DUTCH LIPID CLINIC NETWORK DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1-3]	
Criteria	**Point**
Family History	
First-degree relative with known premature* coronary and vascular disease OR First-degree relative with known LDL-C level above the 95th percentile.	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C level above the 95th percentile.	2
Clinical History	
Patient with premature* coronary artery disease.	2
Patient with premature* cerebral or peripheral vascular disease.	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years.	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C >= 330 mg/dL (≥ 8.5)	8
LDL-C 250 – 329 mg/dL (6.5 – 8.4)	5
LDL-C 190 – 249 mg/dL (5.0 – 6.4)	3
LDL-C 155 – 189 mg/dL (4.0 – 4.9)	1
DNA Analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite familial hypercholesterolemia	>8
Probable familial hypercholesterolemia	6 – 8
Possible familial hypercholesterolemia	3 – 5
Unlikely familial hypercholesterolemia	<3

***Premature = < 55 years in men; < 60 years in women**
LDL-C = low density lipoprotein cholesterol; FH, familial hypercholesterolemia.
LDLR = low density lipoprotein receptor
Apo B = apolipoprotein B
PCSK9 = Proprotein convertase subtilisin/kexin type 9

[1]Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420.
[2]Haase A, Goldberg AC. Identi cation of people with heterozygous familial hypercholesterolemia. Current opinion in lipidology. 2012;23:282-289.

[3]Nordestgaard BG, Chapman MJ, Humphries SE, et al. 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. European heart journal. 2013;34:3478-3490a.

SEE ALSO: MPA G2050 Cardiovascular Disease Risk Assessment

EXCLUSIONS:
Genetic testing to confirm a diagnosis of heterozygous FH is considered investigational in all other situations.

Direct-to-consumer genetic tests are not recommended or appropriate for clinical use in dyslipidemia and are considered investigational and NOT covered.

Polygenic scores for dyslipidemias are not yet standardized and are currently not recommended or appropriate for clinical use in dyslipidemia and are considered investigational and NOT covered

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

Medicaid Business Segment:
Any requests for services that do not meet criteria set in the PARP may be evaluated on a case by case basis.

CODING ASSOCIATED WITH: Genetic Testing for Familial Hypercholesterolemia
The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements

81401 APOB (apolipoprotein B) (eg, familial hypercholesterolemia type B), common variants
81403 FH Known Familial Mutation Analysis
81405 LDLR (low density lipoprotein receptor) (eg, familial hypercholesterolemia), duplication/deletion analysis
81406 LDLR (low density lipoprotein receptor) (eg, familial hypercholesterolemia), full gene sequence
PCSK9 (proprotein convertase subtilisin/kexin type 9) (eg, familial hypercholesterolemia), full gene sequence

LINE OF BUSINESS:
Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:
Sturm AC, Knowles JW, Gidding SS, et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol 2018;72:662-680.

Leren TP, Finborud TH, Manshaus TE, Ose L, Berge KE. Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetic screening. Community Genet. 2008;11(1):26-35

Bouhairie, VE, Goldberg, AC. Familial hypercholesterolemia. Endocrinology and metabolism clinics of North America. 2016 Mar;45(1):1-16

Wald, D. S., Bestwick, J. P., Morris, J. K., Whyte, K., Jenkins, L., & Wald, N. J. (2016). ChildParent Familial Hypercholesterolemia Screening in Primary Care. N Engl J Med, 375(17), 16281637

Knowles JW, Rader DJ, Khourey MJ. Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing. JAMA. 2017;318(4):381-382.

Migliara G, Baccolini V, Rosso A, et al. Familial hypercholesterolemia: a systematic review of guidelines on genetic testing and patient management. Front Public Health. Oct 2017;5:252.

Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of dyslipidemia and prevention of cardiovascular disease - executive summary. Endocr Pract. Apr 2 2017;23(4):479497.

Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. Jun 07 2016;67(22):2578-2589

Familial Hypercholesterolemia Foundation. Diagnostic Criteria for Familial Hypercholesterolemia. https://thefhfoundation.org/diagnostic-criteria-for-familia-hypercholesterolemia?gclid=EAIaIQobChMI9YK5iIn66QIVFkWGCh27lwJYEAAYASAAEgJiNPD_BwE

Bilen, O, Pokharel, Y, Ballantyne, CM. Genetic testing in hyperlipidemia. Endocrinology and metabolism clinics of North America. 2016 Mar;45(1):129-40.

Sturm AC, Knowles JW, Gidding SS, et al. Clinical Genetic Testing for Familial Hypercholesterolemia. J Am Coll Cardiol. 2018;72(6):662-680.

C Lee, M Rivera-Valerio, H Bangash, L Prokop, IJ Kullo. New Case Detection by Cascade Testing in Familial Hypercholesterolemia: A Systematic Review of the Literature. Circ Genom Precis Med. 2019;12(11):e002723.

EE Brown, AC Sturm, M Cuchel, et al. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. Journal of clinical lipidology. 2020;14(4):398-413.

Musunuru K, Hershberger RE, Day SM, et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association..Aug 2020; 13(4): e000067

Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. Apr 16 2020; 382(16): 1520-1530

Ajufo E, deGoma EM, Raper A, et al. A randomized controlled trial of genetic testing and cascade screening in familial hypercholesterolemia. Genet Med. Sep 2021; 23(9): 1697-1704

Brown EE, Sturm AE, Cuchel M, et al., Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. Journal of Clinical Lipidology (2020) 14, 398–413

Abifadel M, Boileau C. Genetic and molecular architecture of familial hypercholesterolemia. J Intern Med. 2023;293(2):144-165.

Zhang Y, de Ferranti SD, Moran AE. Genetic testing for familial hypercholesterolemia. Curr Opin Lipidol. 2024;35(2):93-100.

Sustar U, Kordonouri O, Mlinaric M, et al. Universal screening for familial hypercholesterolemia in 2 populations. Genet Med. 2022;24(10):2103-2111.

Abifadel M, Boileau C. Genetic and molecular architecture of familial hypercholesterolemia. J Intern Med. 2023 Feb;293(2):144-165. Epub 2022 Oct 17. PMID: 36196022.

Anagnostis P, Antza C, Florentin M, Kotsis V. Familial hypercholesterolemia and its manifestations: Practical considerations for general practitioners. Kardiol Pol. 2023;81(11):1081-1088. Epub 2023 Nov 8. PMID: 37937357.

van den Bosch SE, Hutten BA, Corpeleijn WE, Kusters DM. Familial hypercholesterolemia in children and the importance of early treatment. Curr Opin Lipidol. 2024 Jun 1;35(3):126-132. PMID: 38363694.

Suryawanshi YN, Warbhe RA. Familial Hypercholesterolemia: A Literature Review of the Pathophysiology and Current and Novel Treatments. Cureus. 2023 Nov 20;15(11):e49121. PMID: 38125244.

This policy will be revised as necessary and reviewed no less than annually.

Devised: 7/20

Revised: 7/23, 7/24 (revise LDL-C criteria to >160mg/dL)

Reviewed: 7/21, 7/22, 6/25

CMS UM Oversight Committee Approval: 12/23, 7/24, 8/25

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.
Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at https://www.geisinger.org/health-plan/providers/ghp-clinical-policies