Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: 325

Section: Medical Benefit Policy

Subject: Genetic Testing for Familial Hypercholesterolemia

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.

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 premature atherosclerotic cardiovascular disease 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.

Targeted Populations:

Children (defined as less than age 18 years) with:

- persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia); or
- with an LDL-C level ≥190 mg/dl in ≥1 parent; or
- a family history of hypercholesterolemia and premature CAD.

Adults (defined as 18 years or older) with:

- persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia); and
- a family history of hypercholesterolemia; and
- a personal history **or** a family history of premature CAD

Adults (defined as 18 years or older) with:

- no pretreatment LDL-C levels available; and,
- a personal history of premature CAD; and
- family history of both hypercholesterolemia and premature CAD.

INDICATIONS: Genetic Testing for Familial Hypercholesterolemia will be considered medically necessary when the following criteria are met:

LDLR, APOB, PCSK9 Known Familial Mutation Testing will be considered medically necessary when all of the following criteria are met:

- Clinical consultation and genetic counseling by an appropriate provider has been completed; and
- Member has not had previous genetic testing of LDLR, APOB, or PCSK9; and
- LDLR, APOB, or PCSK9 mutation has been identified in a 1st, 2nd or 3rd degree biological relative; and
- Member has LDL cholesterol of >120 mg/dL in the absence of treatment
- The result of the test will directly impact the treatment being delivered to the member.

LDLR Full Sequence and Deletion/Duplication Analysis will be considered medically necessary when all of the following criteria are met:

- Clinical consultation and genetic counseling by an appropriate provider has been completed; and
- Member has not had previous LDLR sequencing or deletion/duplication testing; and
- There is no known LDLR, APOB, or PCSK9 mutation in the family, and
- The member meets the MEDPED criteria or either the Dutch criteria or the Simon Broome criteria for possible or probable FH; and
- Genetic testing is necessary because there is uncertainty in the clinical diagnosis

APOB Targeted Mutation Analysis or Full Sequence Analysis will be considered medically necessary when all of the following criteria are met:

- Criteria for LDLR sequencing and deletion/duplication analysis is met; and
- No previous full sequence analysis of APOB; and
- No mutations detected in full sequencing or deletion/duplication testing of LDLR or PCSK9 sequencing, if previously performed

PCSK9 Full Sequence Analysis will be considered medically necessary when all of the following criteria are met:

- Criteria for LDLR sequencing and deletion/duplication analysis is met; and
- No previous genetic testing for PCSK9; and
- No mutations detected in full sequencing or deletion/duplication analysis of LDLR or APOB sequencing, if previously performed

LDLR, APOB, PCSK9 multi-gene panels, or FH multi-gene panels, will be considered medically necessary when all of the following criteria are met:

- 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, AND
- The member meets the MEDPED criteria or either the Dutch criteria or the Simon Broome criteria for possible or probable FH, and
- Genetic testing is necessary because there is uncertainty in the clinical diagnosis

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.*

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

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.

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
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.

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

Devised: 7/20

Revised:

Reviewed: 7/21

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