CLINICAL MEDICAL POLICY	
Policy Name:	Non-Oncologic Genetic Testing Panels
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Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 19

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary non-oncologic Genetic Testing Panels.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

DEFINITIONS

Genetic Testing Panel – A laboratory test that evaluates multiple genes simultaneously compared to sequential testing of individual genes. There are multiple uses of the testing results including but not limited to: to establish a clinical diagnosis, confirmation of a specific clinical diagnosis, the diagnosis of a hereditary disorder, to determine when a known cancer diagnosis is part of a hereditary cancer syndrome, or to assist in the identification of a cancer type/subtype and in the selection of the most appropriate treatment of a cancer type/subtype.

Germline Mutation – An alteration in the DNA that is transmissible from parent to offspring.

Panel Testing Technology – A genetic testing method that examines multiple genes or mutations simultaneously. Testing methods can include next-generation sequencing and chromosomal microarray.

Next-Generation Sequencing (NGS) – Non-Sanger-based high-throughput DNA sequencing technologies. Billions of DNA strands can be sequenced in parallel, yielding substantially more throughput and minimizing the need for the fragment-cloning methods that are often used in Sanger sequencing of genomes.

Chromosomal Microarray Analysis (CMA) – A technique that identifies chromosomal abnormalities, including submicroscopic abnormalities that are too small to be detected by conventional karyotyping.

Variant of Unknown/Uncertain Significance (VUS) – An allele, or variant form of a gene, that has been identified via genetic testing. The significance of the finding is not established, and the connection to a human disease has not been identified.

Clinical Utility – How likely the testing is to significantly improve patient outcomes that reflect the balance between health-related benefits and/or harms that can ensue from using the information made available from the testing.

Genetic Counseling – A service that is provided by a Clinical Geneticist, Certified Genetic Counselor, or other approved medical provider who is independent and not employed by any clinical or genetic laboratory, who bears no conflict of interest with the entity performing the testing.

PROCEDURES

This policy applies only if there is no separate Highmark Health Options medical policy that addresses criteria for specific non-oncologic genetic testing.

The ordering provider must validate the clinical utility by considering:

- Will the panel testing offer significant advantages compared to sequential analysis of individual genes (i.e., a genetic testing panel that addresses the disorder in question, rather than the disorder in question plus other disorders, has been considered and discussed)
- How will the panel testing results be used in patient care decision making
- Will the ancillary findings lead to further testing or management changes
- Is there reliable evidence in the peer-reviewed scientific literature that health outcomes will be improved as a result of treatment decisions based on molecular genetic testing findings

1. Medical Necessity Guidelines
   A. All genetic testing panels must be performed in a Clinical Laboratory Improvement Amendment (CLIA) licensed lab; AND
   B. Genetic testing panels are to be ordered or recommended by a physician specialist such as a hematologist, a physician with expertise in the treatment of the targeted disease, or a geneticist; AND
   C. The ordering provider must not be employed or contracted by a commercial genetic testing laboratory; AND
   D. A recommendation for the genetic testing is confirmed by either:
      1) An American Board of Medical Genetics or American Board of Genetic Counselor; OR
      2) An independent Board Certified or Board eligible medical geneticist; AND
   E. All components of the specific genetic testing panel must demonstrate positive clinical utility for the medical condition being evaluated; AND
   F. All components of panel testing offer substantial advantages in efficiency compared to sequential analysis of individual genes; AND
   G. Genetic testing panels should be considered when clinical evaluation suggests a particular diagnosis, the disorder cannot be identified through clinical evaluation and/or other testing, and not when the diagnosis is unclear or uncertain; AND
   H. The provider has had a discussion with the patient regarding the scope of the genetic testing panel being ordered and the impact of variants of unknown significance; AND
   I. Documentation Requirements:
      - Brief explanation of how the results of genetic testing are necessary to guide treatment decisions relevant to the patient's personal medical history for positive patient outcome (i.e., whether to perform surgery, determine chemotherapy treatment, choose between medication options, etc.); AND
      - Diagnose an illness when signs/symptoms are displayed; OR
      - Rule out a diagnosis when signs/symptoms are displayed; OR
      - Medical records relevant to the testing being performed are to include:
         a. A thorough history and physical examination by the referring physician; AND
         b. Conventional testing and outcomes; AND
         c. A three-generation pedigree analysis result; AND
         d. Conservative treatment provided, if applicable.

J. The following information is required:
    1) The specific name of the test or panel; AND
    2) Name of performing CLIA-accredited laboratory; AND
    3) The exact gene(s) and/or mutations being tested; AND
    4) Correct CPT and/or HCPCS code(s); AND
    5) Estimated cost/quote sheet for the genetic testing panel ordered; AND
K. An informed consent must be signed by the patient prior to testing. The consent must include a statement that the patient agrees to post-test counseling, and the consent must be made available upon request; AND
L. Pre-test genetic counseling has been performed and post-test genetically counseling by an independent genetic professional is planned.

2. When genetic testing panels are not covered
   Broad-based genetic testing panels are considered not medically necessary when individual components are sufficient for treatment/management of the patient. Testing for multiple genes or multiple conditions, in cases where a tiered approach/method is clinically available, will be covered only for the number of genes or tests that are reasonable to obtain necessary therapeutic decision making and NOT the entire panel.

   More than one multi-gene panel is considered not medically necessary at the same time.

   Infant and adolescent genetic testing to predict adult onset of diseases is considered not medically necessary.

   In the absence of specific information regarding advances in the knowledge of mutation characteristics for a particular disorder, the current literature indicates that genetic tests for inherited disease only need to be conducted once per lifetime for the patient.

   If a genetic testing panel was previously performed for medically necessary indications, and a larger panel is developed and requested, only the testing for previously untested genes will be considered medically necessary.

3. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

4. Place of Service
   The place of service for genetic testing panel is outpatient.

5. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the patient and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician with experience in cancer genetics
- A physician with experienced with the suspected medical condition (e.g., neurologist)

GOVERNING BODIES APPROVAL

Three federal agencies play a role in the regulation of genetic tests: CMS, FDA, and the Federal Trade Commission (FTC). The Centers for Medicare and Medicaid Services is responsible for regulating all clinical laboratories performing genetic testing, ensuring their compliance with the Clinical Laboratory Improvement Amendments of 1988. The FDA has the broadest authority in terms of regulating the safety and effectiveness of genetic tests as medical devices under the Federal Food, Drug, and Cosmetic Act. Compared to the FDA and CMS, the Federal Trade Commission's regulatory authority is rather narrow and is limited to how tests are advertised. The Commission has the authority to regulate advertising that delivers health-related information to consumers to ensure that it is not false or misleading.

Genetic testing panels are typically laboratory derived tests that are not subject to the United States Food and Drug Administration (FDA) approval.

CLIA
The genetic testing panels are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

Additional information is available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm

*__NOTE__: This policy may not apply to multi-gene panel testing for indications that are addressed in test-specific policies. For genetic test-specific policies, please see the following link:
https://highmarkhealthoptions.com/providers/MedicalAndPaymentPolicy
The following is a list of existing Highmark Health Options genetic testing policies:

- BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
- BRCA 1 & 2 Genetic Mutation Testing and Related Genetic Counseling
- Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)
- Fetal Aneuploidy Testing using Noninvasive Cell-Free Fetal DNA
- Genetic Testing for Colorectal Cancer Susceptibility
- Genetic Testing for Cystic Fibrosis
- Genetic Testing for Warfarin
- Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
- Molecular Tumor Markers for Non-Small Cell Lung Cancer
- Testing for Genetic Disease
- Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

CODING REQUIREMENTS

Procedure Codes

CPT Codes	Description
0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 Antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant
81242	FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A>T)
81243	FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81244	FMR1 (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)
81245	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G>A)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (egg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P)
81261	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (e.g., polymerase chain reaction)
81262	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (e.g., Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264	IGK@ (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
81267	Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)
81290	MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
81302	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variants
81304	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variants
81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variants
81324	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variants
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)

81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)
81400	Molecular pathology procedure, Level 1
81401	Molecular pathology procedure, Level 2
81402	Molecular pathology procedure, Level 3
81403	Molecular pathology procedure, Level 4
81404	Molecular pathology procedure, Level 5
81405	Molecular pathology procedure, Level 6
81406	Molecular pathology procedure, Level 7
81407	Molecular pathology procedure, Level 8
81408	Molecular pathology procedure, Level 9
81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome);duplication/deletion analysis panel, must include analysis for GFBR1, TGFBR2, MYH11, and COL3A1
81412	Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81413	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2 CASQ2, CAV3M KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, AND SCNSA
81414	Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81434	Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C1orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, AND TYMP

81442	Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score
88299	Unlisted cytogenetic study
88380	Microdissection (i.e., sample preparation of microscopically identified target); laser capture

NOTE: If a procedure code other than those listed above is requested, the request must be sent to a Medical director for individual consideration.

Diagnosis Codes

ICD-10 Codes	Description
D66	Hereditary factor VIII deficiency [hemophilia A/VWF]
D67	Hereditary factor IX deficiency [hemophilia B]
D68.2	Hereditary deficiency of other clotting factors [deficiency of factor II (prothrombin), 20210A mutation]
D69.42	Congenital and hereditary thrombocytopenia purpura
D70.0	Congenital agranulocytosis [congenital neutropenia] [cyclic]
D70.4	Cyclic neutropenia [congenital]
E23.0	Hypopituitarism [Kallman's syndrome] (FGFR1)
E25.0	Congenital adrenal hyperplasia
E31.21	Multiple endocrine neoplasia [MEN] type I
E70.0	Classical phenylketonuria
E70.30	Albinism, unspecified
E70.310	X-linked ocular albinism
E70.311	Autosomal recessive ocular albinism
E70.318	Other ocular albinism
E70.319	Ocular albinism, unspecified
E71.0	Maple syrup urine disease
E71.311	Medium chain acyl CoA dehydrogenase deficiency [MCAD]
E74.04	McArdle's disease
E74.20	Disorders of galactose metabolism
E74.21	Galactosemia
E74.29	Other disorders of galactose metabolism
E75.02	Tay-Sachs disease
E75.21	Fabry (-Anderson) disease
E75.22	Gaucher disease

E75.240	Niemann-Pick disease type A
E75.241	Niemann-Pick disease type B
E75.242	Niemann-Pick disease type C
E75.243	Niemann-Pick disease type D
E75.248	Other Niemann-Pick disease
E75.249	Niemann-Pick disease, unspecified
E75.29	Other sphingolipidosis
E83.110	Hereditary hemochromatosis
E85.2	Heredofamilial amyloidosis, unspecified [hereditary amyloidosis (TTR variants)]
E88.01	Alpha-1-antitrypsin deficiency
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
F81.81	Disorder of written expression
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive development disorders
F84.9	Unspecified disorder of psychological development
G10	Huntington's disease
G11.0	Congenital nonprogressive ataxia
G11.1	Early-onset ataxia
G11.2	Late-onset cerebellar ataxia
G11.3	Cerebellar ataxia with defective DNA repair
G11.4	Hereditary spastic paraplegia
G11.8	Other hereditary ataxia
G11.9	Hereditary ataxia, unspecified
G12.0	Infantile spinal muscular atrophy, Type 1
G12.1	Other inherited spinal muscular atrophy
G12.20	Motor neuron disease, unspecified
G12.21	Amyotrophic lateral sclerosis
G12.22	Progressive bulbar palsy
G12.23	Primary lateral sclerosis
G12.24	Familial motor neuron disease
G12.25	Progressive spinal muscular atrophy
G12.29	Other motor neuron disease
G12.8	Other spinal muscular atrophies; and related syndromes
G12.9	Spinal muscular atrophy, unspecified
G13.0	Paraneoplastic neuromyopathy and neuropathy
G13.1	Systemic atrophy primarily affecting central nervous system in neoplastic disease
G13.2	Systemic atrophy primarily affecting central nervous system in myxedema
G13.8	Systemic atrophy primarily affecting central nervous system in other diseases classified elsewhere
G24.1	Genetic torsion dystonia [primary TOR1A (DYT1]

G31.82	Leigh's disease
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, without status epilepticus
G47.35	Congenital central alveolar hypoventilation syndrome
G60.0	Hereditary motor and sensory neuropathy [Charcot-Marie-Tooth disease]
G71.0	Muscular dystrophy
G71.2	Congenital myopathies
G71.11	Myotonic muscular dystrophy
G71.12	Myotonic congenita
G71.13	Myotonic chondrodystrophy
G71.14	Drug induced myotonic
G71.19	Other specified myotonic disorders
G72.89	Other specified myopathies
G90.1	Familial dysautonomia [Riley-Day]
H35.52	Pigmentary retinal dystrophy [retinitis pigmentosa]
H47.22	Hereditary optic atrophy [Leber's optic atrophy (LHON)]
I42.1	Obstructive hypertrophic cardiomyopathy
I42.2	Other obstructive hypertrophic cardiomyopathy
I42.8	Other cardiomyopathies [arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)]
I78.0	Hereditary hemorrhagic telangiectasia
N04.0	Nephrotic syndrome with minor glomerular abnormality
N04.1	Nephrotic syndrome with focal and segmental glomerular lesions
N04.2	Nephrotic syndrome with diffuse membranous glomerulonephritis
N04.3	Nephrotic syndrome with diffuse mesangial proliferative glomerulonephritis
N04.4	Nephrotic syndrome with diffuse endocapillary proliferative glomerulonephritis
N04.5	Nephrotic syndrome with diffuse mesangiocapillary glomerulonephritis
N04.6	Nephrotic syndrome with dense deposit disease
N04.7	Nephrotic syndrome with diffuse crescentic glomerulonephritis
N04.8	Nephrotic syndrome with other morphologic changes
N04.9	Nephrotic syndrome with unspecified morphologic changes
Q04.3	Other reduction deformities of brain [lissencephaly (classical)] [Joubert syndrome]
Q61.5	Medullary cystic kidney [nephronopthisis]
Q61.9	Cystic kidney disease, unspecified [Meckel-Gruber syndrome]
Q75.0	Craniosynostosis
Q75. 1	Craniofacial dysostosis
Q75.2	Hypertelorism
Q75.3	Macrocephaly
Q75.4	Mandibulofacial dysostosis
Q75.5	Oculomandibular dysostosis
Q75.8	Other specified congenital malformations of skull and face bones

Q75.9	Congenital malformation of skull and face bones, unspecified
Q77.1	Thanatophoric short stature
Q77.4	Achondroplasia
Q78.0	Osteogenesis imperfecta
Q79.6	Ehlers-Danlos syndrome
Q79.8	Other congenital malformations of musculoskeletal system [Jackson-Weiss syndrome] [Muencke syndrome (FGFR2)]
Q82.2	Other specified congenital malformations of skin [Bloom syndrome]
Q85.01	Neurofibromatosis, type 1 [von Recklinghausen's disease] [neurofibromin] [not covered for Legius syndrome]
Q85.02	Neurofibromatosis, type 2 [acoustic neurofibromatosis] [Merlin]
Q85.8	Other phakomatoses, not elsewhere classified [von Hippel Lindau syndrome (VHL)] [Cowden syndrome]
Q87.0	Congenital malformation syndrome predominantly affecting facial appearance [acrocephalosyndactyly] [Pfeiffer syndrome (FGFR1)]
Q87.1	Congenital malformation syndromes predominantly associated with short stature [Prader-Willi syndrome] [GABRA, SNRPN] [Noonan syndrome]
Q87.40	Marfan's syndrome, unspecified
Q87.410	Marfan's syndrome with aortic dilation
Q87.418	Marfan's syndrome with other cardiovascular manifestations
Q87.42	Marfan's syndrome with ocular manifestations
Q87.43	Marfan's syndrome with skeletal manifestations
Q93.5	Other deletions of part of a chromosome [Angelman syndrome (GABRA, SNRPN)]
Q99.2	Fragile X chromosome [Fragile X syndrome]
R62.52	Short stature (child) [SHOX-related]

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

Examples of Genetic Testing Panels, not all inclusive

Name of Test
ARUP Laboratories
Agammaglobulinemia Panel
Amyotrophic Lateral Sclerosis Pane
Aortopathy Panel
Ashkenazi Jewish Diseases Panel
Autism Panel
Biotinidase Deficiency (BTD) 5 Mutation
Brugada Syndrome Panel
Cardiomyopathy and Arrhythmia Panel
Cystic Fibrosis (CFTR) 32 Mutations Panel
Mitochondrial Disorders Panel
Noonan Spectrum Disorders Panel
Periodic Fever Syndromes Panel
Retinitis Pigmentosa/Leber Congenital Amaurosis Panel

Solid Tumor Mutation Panel Next Generation Sequencing
Vascular Malformation Syndromes
Emory Genetics Laboratories
ACOG/ACMG Carrier Screen Targeted Mutation Panel
Anophthalmia/ Microphthalmia/ Anterior Segment Dysgenesis/ Anomaly: Sequencing Panel
Arrhythmias Deletion/Duplication Panel
Arrhythmias Sequencing Panel
Autism Spectrum Disorders
Cardiomyopathy Panel
Ciliopathies Panel
Congenital Glycosylation Disorders
Early Onset IBD Sequencing and Del/Dup Panels
Epilepsy
Eye Disorders
Expanded Neuromuscular Disorders
Hereditary Hemolytic Anemia Sequencing 28 Genes
Noonan Syndrome and Related Disorders
Osteogenesis Inperfecta and Osteopenia Sequencing Panel
Short Stature Panel
Sudden Cardiac Arrest Panel
X-linked Intellectual Disability
Ambry Genetics
BreastNext™
CancerNext™
ColoNext™
FHNext
HCMNext
Marfan, Aneurysm and Related Disorders Panel
OvaNext™
Pan Cardio Panel
PancNext
RenalNext
TAADNext
X-linked Intellectual Disability
Athena
Alzheimer's Disease
Amyotrophic Lateral Sclerosis Advanced Evaluation Gene Panel
Ataxia, Comprehensive Evaluation
Autosomal Recessive Ataxia Evaluation
Common Mitochondrial Disorder Evaluation
Complete Ataxia Evaluation Panel
Complete Hereditary Spastic Paraplegia Evaluation Panel
Early Infantile Epileptic Encephalopathy
Hemiplegic Migraine Profile
Hereditary Renal Tubular Disorder Panel
Intellectual Disability
Mitochondrial Disease Associated with Mitochondrial Depletion Syndrome

Myotonic Syndrome Advanced Evaluation Panel
Periodic Paralysis Advanced Sequencing Evaluation Panel
Progressive External Ophthalmoplegia Evaluation Panel
Idiopathic Hypogonadotropic Hypogonadism/Kallmann Syndrome
Baylor College of Medicine
Cobalamin Metabolism Comprehensive Panel
CoQ10 Comprehensive Panel
GeneAware
Glycogen Storage Disorders Panel
Low Bone Mass Panel
Mitochondrial Disorders Panel
Myopathy/Rhabdomyolysis Panel
Progressive External Ophthalmoplegia Panel
Pyruvate Dehydrogenase Deficiency and Mitochondrial Respiratory Chain Complex V Deficiency Panel
Retinitis Pigmentosa Panel
Usher Syndrome Panel
GeneDx
Autism/ID Xpanded Panel
Breast/Ovarian Cancer Panel
Cardiomyopathy Panel
Colorectal Cancer Panel
Combined Cardiac Panel
Combined Mito Genome Plus Mito Nuclear Gene Panel
Comprehensive Hereditary Cancer Panel
Comprehensive Arrhythmia Panel
Comprehensive Cancer Panel
Comprehensive Epilepsy Panel
Comprehensive Mitochondrial Nuclear Gene Panel
Congenital Ichthyosis XomeDxSlice Panel
Congenital Myopathy and Congenital Muscular Dystrophy Panel
Dilated Cardiomyopathy (DCM) Left Ventricular Non-Compaction (LVNC)
Endometrial Cancer Panel
EpiXpanded Panel
Heterotaxy Panel
High-Moderate Risk Panel
Hyper-IgE Syndromes Panel
Hypertrophic Cardiomyopathy (HCM) Panel
Marfan Syndrome/TAAD Sequencing Panel
Noonan RASopathies Panel
Noonan Syndrome Panel
Pancreatic Cancer Panel
Prenatal Noonan Spectrum Disorders
Prenatal Skeletal Dysplasia Panel
Progressive External Ophthalmoplegia (PEO)/Optic Atrophy Nuclear Gene Panel
Rett/Angelman Syndrome Panel
Syndromic Macrocephaly Overgrowth Panel

XomeDxPlus (whole exome sequencing [WES] + mtDNA Sequencing and Deletion Testing
Medical Neurogenetics
Leigh Disease Panel
Spastic Paraplegia Next Generation Sequencing
Partners Healthcare
Isolated Non-syndromic Congenital Heart Defects Panel
Noonan Spectrum Panel *Pan Cardiomyopathy Panel*
Usher Syndrome Panel
Mayo Medical Laboratories
Arrhythmogenic Right Ventricular Cardiomyopathy Panel
Bacterial Typing by whole Genome Sequencing
Brugada Syndrome
Comprehensive Cardiomyopathy Multi-Gene Panel
Congenital Disorders Chromosome Analysis (CDCA)
Dilated Cardiomyopathy Panel
Hereditary Colon Cancer Syndromes
Hypertrophic Cardiomyopathy Panel
Long QT Syndrome
Marfan Syndrome Panel
Noonan Syndrome Panel
Signature Genomics
Signature Prenatal Microarray
Counsyl Genomics
Counsyl Panel
GoodStart Genetics
GoodStart Select

SUMMARY OF LITERATURE

The role of genetic testing in the medical profession has continued to grow rapidly. With the completion of the Human Genome Project (HGP) and continued advances in the field of genomics, the use of genetic testing has become widespread. The World Health Organization (WHO) has published criteria to be met for any genetic test to be considered valuable: the disease is an important health problem, the risk in mutation carriers is high in the general population (not just in a high-risk group), mutations for the disease can be accurately identified, and effective interventions exist.

Genetic testing was first introduced as a clinical tool in the 1960s with chromosomal karyotyping (Satya-Murti et al. 2013). More advanced testing includes: Chromosomal microarray analysis or comparative genomic hybridization (array CDG) testing, fluorescence-in-situ-hybridization (FISH), letter-by-letter sequencing of specific genes (Sanger technology), and the new technology where huge panels of genes as large as the entire exome can be sequenced (NexGen technology).

Genetic testing includes the following:

- Single gene-targeted mutation/sequence analysis, deletion/duplication testing
- Gene Panels

- Whole Exome Sequencing (WES) – sequencing of exome but interpretation focus on genes related to phenotype
- Whole Genome Sequencing (WGS) – sequences all genetic material

Genetic testing uses next-generation sequencing (NGS) technology, massive parallel sequencing, or chromosomal microarray analysis (CMA) testing to perform genetic panels. NGS and CMA are new genetic technologies. The intended use for genetic panels is variable. Existing genetic testing panels are available for the following areas: cancer, cardiovascular disease, neurologic disease, psychiatric conditions, and for reproductive testing. As of October 10, 2017, the Genetic Testing Registry listed more than 2,600 diagnostic testing panels representing three laboratories.

When scientists test for mutations in large numbers of genes with a single test, known as a gene panel, they are virtually guaranteed to find at least one VUS, says Colleen Caleshu, a genetic counselor at Stanford University's Center for Inherited Cardiovascular Disease. "The more genes you look at, the more variation you'll find," she adds. "We all have tons of variations in our genes, most of which are extremely rare and, by the very nature of rarity, uninterpretable." In short, there isn't enough data to know what you are seeing (https://arstechnica.com/science/2017/07/the-uncertain-future-of-genetic-testing/).

Several methods can be used for genetic testing:

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Advantages of genetic testing panels

- The potential for overall greater sensitivity which can provide a comprehensive analysis for multiple diagnoses;
- Enhanced sensitivity over Sanger sequencing

Disadvantages

- There is no standardization in the makeup of genetic panels. The panel compositions are variable with different set of genes for the same condition. This genetic panel composition is determined by the specific lab that developed the test.
- The gene selection of genetic panels is subject to change based on scientific discovery.
- Because of the large number of mutations contained in expanded panels, it is not possible to determine clinical validity for the panels as a whole.
- The risk for uncertain and incidental findings with the large numbers of genes on the panels.
- Large percentage of VUS.

An example of the number of genes for the same clinical indications is as follows: There are at least four clinical laboratories offering the epilepsy gene panels. The number of genes being tested range from 70 to 377 (Xue et al. 2015). It is suggested that the rationale for the obvious difference in the number of genes tested is that some laboratories may prefer to include all possible genes that are even remotely associated with the phenotype being evaluated in order to procure a higher diagnostic yield. Other laboratories elect to take a conservative approach by only including the genes that have support for association with a disorder. However, it is the responsibility of the clinician and the laboratory geneticist to determine the medically appropriate gene selection for the panels. The clinician needs to be able to understand the results in relation to the clinical case at hand.

For many genes, clear risk reduction strategies for mutation carriers are not established. A major concern is the increased likelihood of identifying results of uncertain clinical significance. Uncertain results occur when a rare variant is identified whose impact on protein function is unknown. Uncertainty can also arise from the identification of a clearly deleterious mutation in a gene of uncertain clinical significance. The more genes that are tested, the greater the chances are of such uncertain results. Clinical management should not be dictated by these uncertain variants; rather, family history should guide recommendations in these cases. However, clinicians may misinterpret uncertain results, treating patients as if a deleterious mutation is present, leading to unnecessary interventions. Given the increased variety of testing options and potential complexity of genetic results with cancer gene panels, genetic counselors or knowledgeable medical professionals should carefully discuss the pros and cons with patients.

Types of Testing

- Testing of affective/symptomatic individual (diagnostic, prognostic, and therapeutic)
- Testing asymptomatic individual to determine risk
- Testing individual to benefit family
- Testing of DNA from cancer cells (diagnostic, prognostic, treatment responses)

While cost is not a primary concern—most panel tests are comparable in price to testing for individual genetic tests—some genetics professionals question the inclusion of emerging-risk genes or variants of undetermined significance on panels, and whether collecting that information is clinically beneficial or possibly harmful to patients.

Current research indicates that multi-gene panel testing can provide information in a small subset of patients, however, additional studies are necessary to address if clinical interventions are of any benefit to positive less well studied mutations. In addition, there is paucity in the information in addressing the large numbers of variants of uncertain significance generated by multi-gene panels.

Multi-gene panels are commonly used when:

- When the family mutation is unknown in a symptomatic patient; OR
- When there are multiple candidate genes, and no single gene is significantly more likely than the others; OR
- When personal and family history are suggestive of more than one hereditary syndrome; OR
- When the suspected diagnosis cannot be unequivocally diagnosed otherwise.

Targeted Gene Sequencing

Targeted gene sequencing are focused panels that contain a select number of genes or gene regions that are known or are suspected as associates of the disease or phenotype. These panels can be designed with preselected content or custom designed. Next-generation sequencing also evaluates targeted genes of interest, however, multiple genes can be assessed.

Shashi and colleagues (2014) noted that it remains unclear which patients should be analyzed with a specific genetic test and in which stage during the evaluation. In a study to assess the diagnostic yield of the traditional comprehensive clinical evaluation and targeted genetic testing, the authors retrospectively analyzed a cohort of 500 unselected consecutive patients. These patients had received traditional genetic diagnostic evaluations at a tertiary facility. The diagnosis rate, number of visits to diagnosis, genetic tests, and the cost of testing was calculated. The authors concluded that nearly half of the patients tested with traditional approaches were diagnosed in the initial visit. It is logical that the remaining patients that were undiagnosed may benefit from next-generation sequencing. The use of next-generation sequencing utilized after the first clinical visit could result in a higher rate of genetic diagnoses and at a considerable cost savings.

The American Academy of Neurology (AAN) has issued recommendations for genetic testing that is "guided by the clinical phenotype, inheritance patter (if available), and electrodiagnostic features." As an example, the AAN does not support complete panels of all known Charcot-Marie Tooth genes but rather recommends a stepwise evaluation method to improve genetic screening efficiency.

Multiple research documents report that a thorough clinical evaluation is a major step in choosing the best genetic test for the patient's condition.

POLICY SOURCE(S)

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Policy History

Date	Activity
11/15/2017	Initial policy developed
03/13/2018	QI/UM Committee approval
04/20/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables under CODING REQUIREMENTS
05/15/2018	Provider effective date
09/11/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C; Title changed to Nononcologic Genetic Testing Panels; Added reference to several related medical policies; Added multiple nononcologic procedure codes as eligible in Attachment B; Multiple oncologic related procedure codes in Attachment B were deleted and nononcologic procedure codes were added.
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date