Genetic Testing
Clinical Coverage Criteria

Overview

Genetic testing refers to the laboratory analysis of DNA. Compared to other types of laboratory testing, genetic testing is unique in that it can provide a diagnosis and/or a prediction of the likelihood of developing a particular disease before symptoms even appear; it can also reveal if a person is carrying a specific gene that could be passed on to his or her children. While genetic testing holds great potential, it also has many limitations:

- Genetic tests may predict the chances of developing a particular disease. Such results may leave a person wondering what to do with the results, particularly if there are treatments available that may change the course of the disease.
- While genetic tests may reveal if a mutation exists, it does not guarantee that the disease will develop, nor can it predict how severely the disease will manifest in the person carrying the mutation, e.g., some individuals with cystic fibrosis have mild symptoms, while others develop debilitating lung disease and pancreatitis.
- Many genetic tests cannot detect all mutations that can cause disease, and thus, while a positive result can be informative, a negative result is ”not always conclusive” or ”may be inconclusive.”
- Many diseases are the result of an interaction between genes and environment, and the way these interactions cause disease is not clearly understood.
- There are many legal and social issues that must be considered.

Because of these limitations, it is essential that individuals are thoroughly informed before undergoing any type of genetic testing. Results of genetic testing can have implications not only for an individual, but for an individual’s family as well. Genetic counseling is advised to communicate the limitations of genetic testing and to also counsel patients about the results.

Massachusetts law Chapter 111, Section 70G, requires prior written consent before genetic testing. The consent form must be signed by the person who is the subject of the test or, if that person lacks capacity to consent, signed by the person authorized to consent for such person. Prior written consent must include:

1. A statement of the purpose of the test;
2. A statement that prior to signing the consent form, the consenting person discussed with the medical practitioner ordering the test the reliability of positive or negative test results and the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease;
3. A statement that the consenting person was informed about the availability and importance of genetic counseling and provided with written information identifying a genetic counselor or medical geneticist from whom the consenting person might obtain such counseling;
4. A general description of each specific disease or condition tested for (inclusive of a description of the specific genes being tested); and
5. The person or persons to whom the test results may be disclosed.

Definitions

First-degree relative: A blood relative with whom an individual shares approximately 50% of his or her genes, including parents, full siblings and children.
Second-degree relative: A blood relative with whom an individual shares approximately

25% of his/her genes, including grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.
DEX Z-Code™ Identifiers: DEX Z-Code™ Identifiers are unique and proprietary 5-character alpha-numeric codes assigned to molecular diagnostic tests by the DEX™ Diagnostics Exchange (https://dexzcodes.com/). The DEX™ Diagnostics Exchange is a molecular diagnostic (MDx) test identification and policy management solution that connects payers and labs to bring clarity to MDx testing. DEX Z-Codes™ are not publicly visible.

Policy

This Policy applies to the following Fallon Health products:
☒ Commercial
☒ Medicare Advantage
☒ MassHealth ACO
☒ NaviCare
☒ PACE

Fallon Health requires prior authorization (approval in advance) for genetic testing.

Prior authorization requests for genetic testing should be submitted to Fallon Health by the ordering provider. Requests should include: (1) the DEX Z-Code™ Identifier assigned to the test by the DEX™ Diagnostics Exchange, (2) all recent clinical information such as the most recent physical examination, lab work, and (3) any other relevant clinical information to support this request (see Guidelines for Genetic Testing below). Failure to provide this information will result in a denial of the request.

Medicare Advantage plan members

Fallon Health follows guidance from the Centers for Medicare and Medicaid Services (CMS) for organization (coverage) determinations for Medicare Advantage plan members. National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and guidance in the Medicare manuals are the basis for coverage determinations. When there is no NCD, LCD, LCA or manual guidance, Fallon Health clinical coverage criteria are used for coverage determinations.

With respect to genetic testing, when the test results will directly impact treatment or management of the plan member's disease/condition, the following hierarchy will apply:

1. *NCD*
   a. *If the test is listed within an NCD as being not covered, the test will not be covered.*
2. *LCD or LCA with test-specific criteria*
   a. *If the test is listed within an LCD or LCA as being not covered, the test will not be covered.*
3. *If there are no applicable NCDs, LCDs or LCAs, or if the applicable NCD, LCD or LCA does not include test-specific criteria, then Fallon Health clinical coverage criteria will be applied (Fallon Health uses InterQual criteria for genetic testing).*

Screening services such as carrier screening or pre-symptomatic genetic testing used to detect an undiagnosed disease or disease predisposition are not a Medicare benefit and are not covered.

Laboratory developed tests - A laboratory developed test (LDT) is a type of diagnostic laboratory test that is designed, manufactured and used within a single independent laboratory. Medicare has a system whereby contractors, called Medicare Administrative Contractors (MAC), perform various administrative duties including processing claims and establishing coverage policy where none exists nationally. Medicare jurisdiction of LDTs, except where indicated in §50.5.1 and §50.5.2, lies with the Part B MAC serving the area in which the laboratory test is performed (i.e., where the laboratory is physically located). Jurisdiction is not affected by whether or not the laboratory uses a central billing office and whether or not the laboratory provides services to

customers outside its service area. With respect to LDTs furnished by independent laboratories, Fallon Health will follow an LCD or LCA written by the MAC with jurisdiction over a specific LDT.

MolDX Program - Medicare Administrative Contractors (MACs) may choose to participate in Molecular Diagnostic Services Program (MolDX), a program designed and operated by Palmetto GBA to identify and establish coverage on existing tests, newly developed laboratory developed tests (LDTs), tests using pathology NOC codes, and other molecular diagnostic tests that fall within the scope of the Palmetto Molecular Diagnostic Test LCD (L35025). In addition to Palmetto GBA, the following contractors have implemented the MolDX Program: Noridian Healthcare Solutions, CGS Administrators, and Wisconsin Physicians Service (WPS). At this time, the Medicare Jurisdiction K A/B MAC, National Government Services, Inc., has not implemented the MolDX Program.

NCDs

Medicare has two NCDs related to genetic testing (MCD search 01/24/2022):

- ***Pharmacogenomic Testing for Warfarin Response (90.1)***
  Nationally Covered Indications: Pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:
  - *have not been previously tested for CYP2C9 or VKORC1 alleles; and*
  - *have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and*
  - *are enrolled in a prospective, randomized, controlled clinical study when that study meets the standards specified in the Decision Memorandum.*

  The approved clinical studies are listed on the CMS Coverage with Evidence Development (CED) website at: https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Pharmacogenomic-Testing-for-Warfarin-Response. [1]
  Nationally Non-Covered Indications: Outside of the context of a CED clinical study, CMS believes that the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries outside the context of CED, and is therefore not reasonable and necessary under §1862(a)(1)(A) of the Act.
- ***Next Generation Sequencing (NGS) (90.2)***
  This NCD is only applicable to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) cancers.
  Nationally Covered Indications:
  1. *Somatic (Acquired) Cancer - Effective for services performed on or after March 16, 2018, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:*
     a. Patient has:
     i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
     ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
     iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

[1] *When billing for CYP2C9 and/or VKORC1 gene testing for warfarin response, report HCPCS code G9143 (Warfarin responsiveness testing by genetic technique using any method, any number of specimens) and 1 unit of service. Claims must be submitted with ICD-10-CM code: Z00.6 (Examination of participant in clinical trial) and HCPCS modifier QO (Investigational clinical service provided in a clinical research study that is in an approved clinical research study). Do not report CPT codes 81227 and/or 81355 when billing for CYP2C9 and/or VKORC1 gene testing for warfarin response. See Medicare Claims Processing Manual, Chapter 32, Section 250 – Pharmacogenomic Testing for Warfarin Response for additional information.*

b. The diagnostic laboratory test using NGS must have:
i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic;[2] and,
ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

2. Germline (Inherited) Cancer - Effective for services performed on or after January 27, 2020, CMS has determined that NGS as a diagnostic laboratory test is reasonable and necessary and covered nationally for patients with germline (inherited) cancer, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:
a. Patient has:
i. ovarian or breast cancer; and,
ii. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
iii. a risk factor for germline (inherited) breast or ovarian cancer; and
iv. not been previously tested with the same germline test using NGS for the same germline genetic content.
b. The diagnostic laboratory test using NGS must have all of the following:
i. FDA-approval or clearance; and,
ii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Nationally Non-Covered Indications:

1. Somatic (Acquired) Cancer
Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with acquired (somatic) cancer are non-covered if the cancer patient does not meet the criteria noted in section 1.a., above.
Other:

1. *Somatic (Acquired Cancer) - Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of NGS as a diagnostic test for patients with advanced cancer, only when the test is ordered by the treating physician, performed in a CLIA-certified laboratory and when the patient has:*
   a. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   b. not been previously tested with the same test using NGS for the same cancer genetic content, and
   c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
2. *Germline (Inherited) Cancer - Effective for services performed on or after January 27, 2020, MACs may determine coverage of NGS as a diagnostic test for other inherited cancer, only when the test is ordered by the treating physician, performed in a CLIA-certified laboratory, when results are provided to the treating physician for management of the patient and when the patient has:*
   a. any cancer diagnosis; and,
   b. a clinical indication for germline (inherited) testing of hereditary cancers; and,
   c. a risk factor for germline (inherited) cancer; and,
   d. not been previously tested with the same germline test using NGS for the same germline genetic content.

LCDs
National Government Services, Inc., the MAC with jurisdiction in our service area has three LCDs related to genetic testing (MCD search 01/24/2022):

- ***Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms*** *(L37810, Revision Effective Date 10/03/2019) and associated LCA, Billing and Coding:*

[2] *List of Cleared or Approved Companion Diagnostic Lab Tests is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.*

Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (A56867, Revision Effective Date 10/03/2019).

- *National Government Services, Inc. covers targeted genomic sequence analysis panels (CPT 81445)[3] in the evaluation of solid tumor tissue in the following clinical circumstances:*
  - *Newly diagnosed patients with advanced (stage IIIB or IV) non-small cell lung cancer (NSCLC), who are not treatable by resection or radiation with curative intent, and who are suitable candidates for therapy at the time of testing.*
  - *Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have not responded to at least one systemic therapy, or who have progressed following resection. The patient must be a candidate for treatment at the time of testing.*
  - *Previously diagnosed patients with advanced (stage IIIB or IV) NSCLC, who have been resistant to at least one targeted therapy, are able to undergo tumor tissue biopsy for testing, and who are suitable candidates for additional treatment at the time of testing.*
- *National Government Services, Inc. also covers targeted genomic sequence analysis panels (CPT 81445)[4] when the test is performed in a CLIA-certified laboratory qualified to perform high complexity testing, ordered by a treating physician, and the patient has:*
  - *Metastatic colorectal cancer; and*
  - *Is a candidate for intensive chemotherapy with an anti-EGFR biologic agent; and*
  - *Has not had prior RAS/BRAF testing (except after initiation of anti-EGFR therapy with evidence of acquired resistance).*

- ***Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases** (L37606, Revision Effective Date 10/03/2019), and associated LCA, Billing and Coding: Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (A56793, Revision Effective Date 10/03/2019). National Government Services, Inc. covers targeted genomic sequence analysis panels (CPT 81450)[5] of blood or bone marrow samples for acute myelogenous leukemia, myelodysplastic syndromes and myeloproliferative neoplasms:*
  - *Acute myelogenous leukemia (AML)*
    - *Newly diagnosed patients with AML who are undergoing induction therapy, and who are suitable candidates for post-induction transplantation or consolidation therapy at the time of testing, and meet one of the following cytogenetic criteria:*
      - *normal karyotype*

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[3] *Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (CPT 81445) may be used as long as the panel contains, at a minimum, 5 or more gene tests for molecular biomarkers determined to meet Medicare coverage criteria. Gene alterations for which a targeted therapeutic agent is available and the use of which meets Medicare coverage requirements (outside of a clinical trial) include ALK, EGFR, ROS 1, KRAS, BRAF, and MET.*

[4] *Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (CPT 81445) may be used as long as the panel contains, at a minimum, 5 or more gene tests for molecular biomarkers determined to meet Medicare coverage criteria. The genetic factors with strong evidence for clinical decision-making (both prognostic and predictive of chemotherapy efficacy) are BRAF and RAS mutations along with MMR status. Other biomarkers prognostic and predictive of anti-EGFR efficacy include: Extended RAS testing, KRAS/NRAS exon 2, codons 12/13, KRAS/NRAS exon 3, codons 59/61, KRAS/NRAS exon 4, codons 117/146, and BRAF (V600E) mutation*.

[5] *Targeted genomic sequence analysis panel, hematolymphoid neoplasm, DNA analysis, 5-50 genes (CPT 81450) is a useful representation of the aggregate of these gene tests, and may be used as long as the panel contains, at a minimum, 5 or more gene tests for molecular biomarkers determined to meet Medicare coverage criteria listed in L37606:*

- *AML: CEBPA, FLT3, KIT, NPM1, TP53, and RUNX1 (additional biomarkers that can be assessed by either targeted genomic sequence panel or cytogenetics are listed in L37606)*
- *MDS: TP53, EZH2, ETV6, ASXL1, RUNX1, and SF3B1*
- *MPNs: JAK2, CALR, MPL, triple negative, ASXL1, EXH2, IDH1/2, SRSF2, and TP53.*

        - *core binding factor*
    - *Previously diagnosed patients with AML, who have not responded to induction chemotherapy, or who have progressed following induction. The patient must be a candidate for transplantation at the time of the testing.*
    - *Patients with AML, who have responded to treatment, either chemotherapy or transplantation, with evidence of relapse.*
  - *Myelodysplastic syndromes (MDS)*
    - *Patients with clinical signs or symptoms of MDS or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN), in who clinical, laboratory, and pathologic assessment are nondiagnostic.*
    - *Newly diagnosed MDS or MDS/MPN patients either*
      - *stratified by the IPPS or IPPS-R as intermediate risk, or*
      - *in MDS with ringed sideroblasts/RARS.*
  - *Myeloproliferative neoplasms (MPN)*
    - *Diagnosis: Clinical signs or symptoms of MPN or MDS/MPN when*
      - *Clinical, laboratory, and pathologic assessment are nondiagnostic, and*
      - *CML excluded (BCR-ABL1 negative)*
    - *Risk stratification: Newly diagnosed primary myelofibrosis (PMF) not already classified as high-risk by Dynamic International Prognostic Scoring System (DIPSS) Plus*
    - *Monitoring: Higher-risk MF (INT-1, INT-2, High Risk) with progression on therapy*
- ***Molecular Pathology Procedures** (L35000, Revision Effective Date 07/01/2020) and associated LCA: Billing and Coding: Molecular Pathology Procedures (A56199, Revision Effective 01/01/2022). Molecular pathology procedures (Tier 1 and Tier 2) may be eligible for coverage when ALL of the following criteria are met:*
  - *Alternative laboratory or clinical tests to definitively diagnose the disorder/identify the condition are unavailable or results are clearly equivocal; AND*
  - *Availability of a clinically valid test, based on published peer reviewed medical literature; AND*
  - *Testing assay(s) are Food and Drug Administration (FDA) approved/cleared or if LDT (lab developed test) or LDT protocol or FDA modified test(s) the laboratory documentation should support assay(s) of analytical validity and clinical utility; AND*
  - *Results of the testing must directly impact treatment or management of the Medicare beneficiary; AND*
  - *For testing panels, including but not limited to, multiple genes or multiple conditions, and in cases where a tiered approach/method is clinically available, testing would be covered ONLY for the number of genes or test that are reasonable and necessary to obtain necessary information for therapeutic decision making; AND*
  - *Individual has not previously received genetic testing for the disease/condition. (In general, diagnostic genetic testing for a disease should be performed once in a lifetime.) Exceptions include clinical scenarios whereby repeat testing of somatically-acquired mutations (for example, pre- and post- therapy) may be required to inform appropriate therapeutic decision-making.*

  Refer to LCD Indications and Limitations Coverage by specific gene and LCA for Indications and Limitations of Coverage by CPT Code.

NaviCare and PACE plan members

For plan members enrolled in NaviCare, Fallon Health follows Medicare guidance for coverage determinations. In situations where there is no Medicare guidance or if the plan member does not meet coverage criteria in Medicare guidance, Fallon Health Clinical Coverage Criteria are used for coverage determinations. Fallon Health's clinical coverage criteria are developed in accordance with the definition of Medical Necessity in 130 CMR 450.204 and are therefore no more restrictive than MassHealth Medical Necessity Guidelines.

Each PACE plan member is assigned to an interdisciplinary team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the

interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Guidelines for Genetic Testing

Fallon Health utilizes InterQual Criteria for genetic testing when available. All of the Guidelines for Genetic Testing listed below and the disease specific InterQual Criteria must be met to satisfy coverage requirements for genetic testing:

1. The test is to be used for the diagnosis or determination of risk for a suspected disease for a plan member who is either:
   - Symptomatic (e.g., exhibiting signs and symptoms of a disease), or;
   - Presymptomatic, but at an increased risk of disease, as determined by current scientific literature which may be due to family history, ethnicity, or gender.
2. The results of the test will be clinically useful to the medical management of the patient (e.g., initiate a new course of therapy, alter an existing therapy, or determine level of surveillance).
3. There is a sufficient amount of evidence in the scientific literature to support the validity and predictive accuracy of the test.
4. The patient/family has consulted with a genetic practitioner to discuss their questions and concerns about the test and how the results will be used.
5. Prior written consent has been obtained.
6. All testing must be at a contracted facility when available.
7. Current clinical records inclusive of the most recent exam and lab work.

If the test is only for Cystic Fibrosis or Spinal Muscular Atrophy (not part of panel test) for member's who are attempting to become pregnant or in the early stages of pregnancy the test will be covered once per lifetime.

The above Guidelines for Genetic Testing apply to all genetic testing whether or not InterQual Criteria are available. Coverage for other genetic tests are managed on an individual basis.

Refer to the Infertility Clinical Coverage Criteria for coverage of pre-implantation genetic testing.

In regards to panel testing, if any tests included in the panel do not meet criteria the entire panel will be denied.

DEX Z-Code™ identifiers are unique 5 digit alpha-numeric codes assigned to specific molecular tests based on the uniqueness of the specific test. Effective January 1, 2017 for independent laboratory claims and April 1, 2017 for hospital-based lab claims, the provider is required to submit the applicable DEX Z-Code™ on the claim.

Exclusions

- Genetic Testing performed that does not meet the above or InterQual criteria.
- Repeat genetic testing is not covered.
- Fallon Health does not cover direct-to-consumer genetic testing, including, but not limited to, "home-testing kits" or genetic tests ordered by patients over the telephone or Internet. The American College of Medical Genetics recommends that genetic testing should only be provided by a qualified health care professional who is responsible for both ordering and interpreting the genetic tests as well as pretest and post-test counseling of individuals and families regarding the medical significance of the test results and the need for follow-up, if any.

References

1. Centers for Medicare & Medicaid Services, Inc. (CMS). National Coverage Determination (NCD) Pharmacogenomic Testing for Warfarin Response (90.1). Version 1. Effective Date of

this Version: 08/03/09. Accessed 01/24/2022.CMS. NCD Next Generation Sequencing (90.2). Version 2. Effective Date of this Version 01/27/2020. Accessed 01/24/2022.
2. National Government Services, Inc. Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (L37810), Revision Effective Date 10/03/2019. Accessed 01/24/2022.
3. National Government Services, Inc. Billing and Coding: Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (A56867). Revision effective Date 10/03/2019. Accessed 01/24/2022.
4. National Government Services, Inc. Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (L37606). Revision Effective Date 10/03/2019. Accessed 01/24/2022.
5. National Government Services, Inc. Billing and Coding: Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (A56793). Revision Effective Date 10/03/2019. Accessed 01/24/2022.
6. National Government Services, Inc. Molecular Pathology Procedures (L35000). Revision Effective Date 07/01/2020. Accessed 01/24/2022.
7. National Government Services, Inc. Billing and Coding: Molecular Pathology Procedures (A56199). Revision Effective 01/01/2022. Accessed 01/24/2022.

Policy history

Origination date:	05/2002
Approval(s):	Technology Assessment Committee: 05/23/2006, 11/06/2013, 01/28/2015 (updated template, added language regarding panel testing) 01/27/2016 (added requirement that all requests come directly from the ordering provider) 01/25/2017 (added language regarding Z-Code submission on claims), 01/24/2018(clarified panel testing will be denied if one test does not meet criteria), 01/23/2019 (annual review, no updates), 02/27/2019 (added information regarding cystic fibrosis testing in relation to pregnancy), 03/27/2019 (added language in relation to spinal muscular atrophy testing related to pregnancy). *02/01/2022 (Added clarifying language related to Medicare Advantage, NaviCare and PACE under Policy section; added references).*

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.