Genetic Cancer Susceptibility Using Next Generation Sequencing

Policy Description

Next generation sequencing (NGS) is a type of DNA sequencing technology that sequences many small fragments of DNA in parallel. This has been used for conditions such as cancer that may be caused by many different gene variants (Hulick, 2020).

Related Policies

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<thead>
<tr>
<th>Policy Number</th>
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<tr>
<td>AHS – M2145</td>
<td>General Genetic Testing, Germline Disorders</td>
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<td>AHS - M2146</td>
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<tr>
<td>AHS – M2032</td>
<td>Whole Genome Whole Exome Sequencing</td>
</tr>
</tbody>
</table>

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Pre-test genetic counseling is required and **MEETS COVERAGE CRITERIA**; and counselor intends to engage in post-test follow-up counseling.

2. Genetic cancer susceptibility panels* (see Notes 1 & 2) using next generation sequencing **MEETS COVERAGE CRITERIA** when all the following criteria are met:
   a. Individual displays clinical features and/or has a family history consistent with a hereditary cancer syndrome as listed in the policies for BRCA (AHS-M2003), Lynch syndrome (AHS-M2004), and Familial Adenomatous Polyposis (AHS-M2024)
   b. All genes in the panel are relevant based on the personal and family history for the individual being tested
   c. Specific mutation(s) in the genes on the panel contain(s) AMA CPT coding guideline required genes at a minimum
   d. The results of the genetic test will impact the medical management of the individual with surveillance as treatment and likely improve health outcomes
3. All other genetic panels that do not meet all of the above-mentioned criteria ARE CONSIDERED NOT MEDICALLY NECESSARY because the current scientific evidence is not yet sufficient to establish how test results from panels which include a broad number of genes may be used to direct treatment decisions and improve health outcomes associated with all components of the panels.

Note 1: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

Note 2: Concurrent ordering of multi-gene panel tests for a specific condition IS STRICTLY PROHIBITED; only one multi-gene panel test may be ordered at a time for a specific condition.

**Scientific Background**

NGS allows for the rapid sequencing of multiple strands of DNA. It is not limited to one specific type of test; rather it encompasses numerous technologies that produce swift and high-volume sequencing. NGS can be used to sequence multiple genes, the exome, or even the entire genome. This is opposed to the traditional Sanger sequencing, which is more useful for sequencing a specific gene (ACMG, 2012; Hulick, 2020).

The NGS procedure typically includes the following steps: first the patient’s DNA is prepared to serve as a template, then DNA fragments are isolated (on solid surfaces such as small beads) where sequence data is generated, then these results are compared against a reference genome. Any DNA sample may be used if the quality and quantity of that sample are sufficient, but the methods of library generation and data analysis often vary from panel to panel. Evaluating the results of a gene panel typically requires some expertise in bioinformatics. Since NGS reports data on any variants found, great care must be taken to evaluate these gene variants, especially variants of unknown significance (VUS) and secondary findings (Hulick, 2020; Rehm et al., 2013).

Panels that sequence multiple, specified genes are referred to as “targeted panels” and may range from 5 to over 1000 genes. Targeted panels are generally more cost-effective than whole exome or whole genome sequencing and are useful for conditions where many different genes may cause a disease phenotype. For example, nonsyndromic hearing loss may be caused by variants in over 60 genes and sequencing each gene individually would not be cost effective. Many companies have developed a wide variety of gene panels. From the FDA-approved MSK-IMPACT to well-validated proprietary panels, many different options of panel testing are available (Hulick, 2020).

Exome and genome sequencing may be necessary. The exome represents all the protein-encoding genes, and at least 85% of pathogenic mutations are found in the exome. The exome only represents approximately 1.5%-2% of the genome, thereby making it more cost effective than genome sequencing. The entire exome includes about 30 megabases compared to the genome’s 3.3 gigabases. However, sequencing an entire genome may be useful as a pathogenic mutation may be in a non-coding region of the genome, such as gene regulation dysfunction. Most clinical NGS testing uses targeted panels or whole exome sequencing, and whole genome sequencing is only used in select cases (Hulick, 2020).

Clinical genomics play a significant part in treatment, diagnosis, and understanding of cancer. Assessment of multiple pathogenic genes has become a widely used technique with the rise of NGS technologies, and the NCCN often recommends genetic panels in certain clinical situations. Some panels may also test for other genetic defects, such as microsatellite instabilities or expression levels of specific proteins. Evaluation of genomic information (somatic changes, inherited germline changes, and so on) is widely prevalent in treatment and diagnosis of numerous types of cancer (Hulick, 2020).
Clinical Validity and Utility

Findings such as pathogenic variants are traditionally confirmed by Sanger sequencing, which is considered the gold standard of gene sequencing (>99.99% accuracy). NGS has been shown to compare favorably to Sanger sequencing. In a study performed by Strom et al, 110 single-nucleotide variants (SNVs) were found by NGS, with 103 of those SNVs meeting the minimum quality score threshold of 500 set by the lab and 7 falling below this threshold. However, 109 of the 110 total SNVs were validated by Sanger sequencing (Strom et al., 2014). Another study focusing on the agreement between Sanger sequencing and NGS results found only 2 variants out of 5800 that did not have cross-method agreement. Overall, the agreement rate was 99.965%. The authors concluded that a single round of Sanger sequencing was “more likely to incorrectly refute a true-positive variant from NGS than to correctly identify a false-positive variant from NGS” (Beck, Mullikin, & Biesecker, 2016).

D’Haene et al designed and validated a custom NGS panel for routine diagnosis of gliomas. 14 genes were included, which are as follows: H3F3A, ACVR1, IDH1, PDGFRA, TERT, HIST1H3B, HIST1H3C, EGFR, BRAF, CDKN2A, PTEN, IDH2, TP54, and ATRX. The 1p/19q codeletion was also included. The panel was first validated to 52 known glioma samples and then applied to 91 unknown brain lesions. For these brain lesions, a sensitivity of 99.4% and specificity of 100% was achieved. “Orthogonal” methods (such as in situ hybridization and immunohistochemistry) demonstrated high concordance with the panel (D’Haene et al., 2019).

NGS has utility in numerous clinical scenarios. For example, NGS may be useful in situations where:

- multiple genes cause the same phenotype
- other candidate genes were found to be normal
- sequencing individual genes would not be timely or cost effective (Hulick, 2020).

Discussions of utility may also revolve around what is done with the findings of a gene panel. For instance, a study by Zehir et al focused on the MSK-IMPACT gene panel. This panel of 410 cancer-related genes was used to sequence 10945 tumors from 10336 patients. 36.7% (3792/10336) of these patients were found to have a “clinically actionable” gene variant, such as TP53 and KRAS. Of these, 527 patients were enrolled in clinical trials (Zehir et al., 2017). NGS has also helped provide diagnostic information to patients. A study focusing on 382 patients with a previously undiagnosed condition used NGS technology to diagnose 98 patients with exome or genome sequencing, allowing for changes in diagnostic testing, treatment, and genetic counseling. A total of 31 new syndromes were defined as well (Splinter et al., 2018).

Surrey et al evaluated the clinical utility of a custom NGS panel for pediatric tumors. Sequencing was performed on 367 pediatric cancer samples. The authors found that results from the panel testing were “incorporated successfully into clinical care” for 88.7% of leukemias and lymphomas, 90.6% of central nervous system (CNS) cancers, and 62.6% of non-CNS solid tumors. A diagnosis change occurred in 3.3% of cases, and 19.4% of patients had variants requiring further germline testing (Surrey et al., 2019).

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

Numerous gene panels have been recommended by the NCCN. Cancers, such as breast, ovarian, and leukemia, may be caused by many different gene variants, and the NCCN recommends panels in genetic testing for these conditions. These conditions are as follows:

Acute Lymphoblastic Leukemia (ALL):
The NCCN notes that NGS assays used to detect leukemia-specific fusion genes are in development, but are not recommended for MRD quantification outside a clinical trial (NCCN, 2020a).

**Acute Myeloid Leukemia (AML):**

The NCCN states that NGS analysis may be used to obtain “a more comprehensive prognostic assessment” of gene mutations involved with AML such as TP53 (NCCN, 2019a).

**Breast Cancer:**

NCCN notes that NTRK mutations may be detected with NGS (NCCN, 2020c).

**Central Nervous Cancers:**

Evaluation of IDH1 and IDH2 mutations is highly recommended. The most common mutation of IDH1 of R132H is reliably screened by immunohistochemistry, but sequencing (through Sanger or NGS-based assays) of IDH1 and IDH2 may also be highly recommended in the appropriate contexts. NGS is included as a “standard sequencing method” (NCCN, 2019b).

**Colon and Rectal Cancer:**

NCCN recommends that sequencing for RAS and BRAF genes be performed if a patient is suspected or proven to have a metastatic synchronous adenocarcinoma. The NCCN does not recommend any sequencing method over another, but lists NGS and Sanger sequencing as possible methods (NCCN, 2019c, 2019l).

**Multiple Myeloma:**

NCCN notes NGS as a valid method for informing treatment decisions. For instance, NGS is listed as a way to assess minimum residual disease (MRD) and categorize responses to treatment. However, this criterion is based on recommendations from the International Myeloma Working Group.

In Version 2.2020 of the Multiple Myeloma guidelines, the NCCN commented that NGS panels may be “useful in certain circumstances” for bone marrow samples in the initial diagnostic workup stage (NCCN, 2019f).

**Myelodysplastic Syndromes:**

NCCN recommends that evaluation of mutations should include panels incorporate the 21 most frequently mutated genes, which are as follows: TET2, DNMT3A, ASXL1, EZH2, SF3B1, SRSF2, U2AF1, ZRSR2, RUNX1, TP53, STAG2, NRAS, CBL, NF1, JAK2, CALR, MPL, ETV6, GATA2, DDX41, IDH1, IDH2, SETBP1, PHF6, BCO, FLT3, WT1, NPM1, STAT3, and PPM1D (NCCN, 2019g).

**Myeloproliferative Neoplasms:**

NCCN states that NGS may be useful in establishing clonality in selected circumstances, such as the “triple negative” of non-mutated JAK2, CALR, and MPL. The NCCN also notes that workup may include a multi-gene NGS panel that includes all three of JAK2, CALR, and MPL (NCCN, 2019h).

**Ovarian Cancer:**

The NCCN recommends NGS for BRCA1/2 somatic mutations, as clinically indicated (NCCN, 2019j).

**Pancreatic Adenocarcinoma:**
The NCCN states that NGS may be used to detect “actionable somatic findings”, such as ALK, NRG1, NTRK, ROS1, BRAF, BRCA1/2, HER2, KRAS, PALB2, and MMR deficiency-related genes (NCCN, 2019k).

**B-Cell Lymphomas:**

NCCN states that NGS may be used if a high suspicion of clonal process remains but other techniques have not clearly identified a clonal process. The NCCN states that an NGS panel including TNFRSF14 and STAT6 may be useful “under certain circumstances” for Follicular Lymphoma. NGS may also be useful for “treatment selection” (NCCN, 2020b).

**T-Cell Lymphomas:**

NCCN states that “NGS will usually identify clonal rearrangement of T-cell receptor genes”. The NCCN also states that “genetic testing, including…NGS that detect[s] somatic gene abnormalities are often informative and in some cases essential for an accurate and precise diagnostic and prognostic assessment of T-cell lymphomas”. The NCCN further notes TET2, IDH1, IDH2, RH0A, DNMT3A, STAT3, and STAT5B as mutations that may be detected with sequencing methods (NCCN, 2020e).

**Non-Small Cell Lung Cancer (NSCLC):**

The NCCN recommends that testing be performed in a “panel-based approach, most typically performed by next-generation sequencing (NGS)”, if feasible. RNA-based NGS should be considered in patients without identifiable driver oncogene mutations, “especially in never smokers”. The NCCN mentions NGS as a commonly used method for mutations such as EGFR and BRAF. However, the NCCN notes that NGS may be considered in biomarker analysis but cautions that not all types of alterations will be detected and to be aware of the nuances of NGS (NCCN, 2019i).

**Soft Tissue Sarcoma:**

NGS is mentioned among the techniques used to identify genetic aberrations in soft tissue sarcoma (NCCN, 2020d).

**Systemic Mastocytosis:**

NCCN recommends against NGS panels for detection of KIT D816V, citing their low sensitivity (approximately 5%). However, a myeloid mutation panel should be performed on bone marrow (although testing can be done on peripheral blood). Prognostically relevant mutations include TET2, SRSF2, CBL, ASXL1, RUNX1, JAK2, and RAS (NCCN, 2018).

**Genetic/Familial High-Risk Assessment for Colorectal Cancer:**

NCCN states that there are numerous scenarios in which multi-gene testing may be more effective. For example, it may be useful for an NGS panel to be used if a condition may be caused by more than one gene, or if a patient has tested negative for a single syndrome but is suspicious but for another inherited condition.

The NCCN notes certain cons associated with panel testing, such as higher chance of identifying variants of unknown significance, unactionable variants, or variants that do not have a clear course of treatment. The NCCN also identifies two examples of clinical scenarios in which multi-gene testing should not be considered: “an individual from a family with a known pathogenic variant and no other reason for multi-gene testing, and as first-line testing when the family history is strongly suggestive of a known hereditary syndrome.”

Overall, the NCCN acknowledges the significant benefits of panel testing, such as value compared to single gene sequencing, as well as providing more information for causes of illnesses, but states that choice of panel and testing is critical.
As a final aside, the NCCN is in agreement with the 2015 ASCO recommendations (NCCN, 2019e).

**Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic Cancer:**

The NCCN notes the following genes as “could potentially be included in a multi-gene test” for breast cancer: **BRCA1/2, ATM, BARD1, CHEK2, PALB2, TP53, PTEN, STK11, and CDH1**. For ovarian cancer, the following genes are mentioned: **BARD1, BRIP1, MRE11A, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D, and TP53** (NCCN, 2019d).

**American Society of Clinical Oncology (ASCO)**

ASCO released guidelines discussing tumor testing for epithelial ovarian cancer. In it, they recommend germline sequencing of **BRCA1/2** “in the context of a multigene panel” that includes “at minimum” the following genes: **BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2, and PALB2** (Konstantinopoulos et al., 2020).

ASCO published guidelines regarding evaluating susceptibility to pancreatic cancer. In it, they recommend that germline genetic testing be performed using a multigene panel that includes the following genes: **APC, ATM, BRCA1/2, CDKN2A, MLH1, MSH2, MSH6, PMS2, EPCAM, PALB2, STK11, TP53**. An exception is if a genetic diagnosis has been previously confirmed in a family member; a panel should not be used in this case. Further, ASCO recommends that every patient diagnosed with pancreatic adenocarcinoma should undergo a risk assessment for hereditary syndromes associated with increased risk of pancreatic adenocarcinoma (Stoffel et al., 2018).

In 2015, ASCO published a policy statement update on genetic and genomic testing for cancer susceptibility that included recommendations for multi-gene panel testing for cancer susceptibility. ASCO recognizes that panel testing “may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient’s personal or family history of cancer”. ASCO notes that panel testing will identify variants of uncertain significance (VUSs) often, but that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility (Robson et al., 2015).

ASCO states that there is little consensus as to which genes should be on gene panels and that clinical utility is “the fundamental issue with respect to testing for mutations in moderate-penetrance genes”. At this time (2015) there is insufficient evidence to “conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations” and that until these questions are answered, testing should be limited to mutations of established clinical utility (Robson et al., 2015).

**American College of Medical Genetics (ACMG)**

The ACMG published guidelines on inclusion criteria for genes with “various gene-disease evidence levels”. For confirming a clinical diagnosis, the ACMG stated to include any gene associated (with a “moderate”, “strong” or “definitive” association) with the disease, as long as the primary method of diagnosis was a “Disease-focused multigene panel or other non-sequencing-based ancillary assays”. Genes with no emerging evidence or without evidence at all were to be excluded. Genes with emerging evidence should “typically” be excluded, although the ACMG notes some inclusions that may be “meaningful”. The ACMG also states that genes with this level of evidence should be reported with a statement that disease association and inheritance has not been established.

For panels intended to “Establish genetic diagnosis for clinically complex cases” and that are used for conditions primarily diagnosed through exome/genome sequencing, genes that have evidence levels of “definitive”, “strong” and “moderate” should be included. Genes of unknown significance should be qualified with a statement that disease association and inheritance have not been completely established (Bean et al., 2019).
The ACMG recommends that the selection of genes and transcripts in any given panel be limited to genes with “sufficient scientific evidence for a causative role in the disease”. Genes without clear evidence of association with the disease should not be included.

ACMG recommends validating diagnostic testing through another method such as Sanger sequencing.

ACMG cannot recommend a minimum threshold for “coverage” as many factors of the platform and assay may influence minimum coverage. However, the ACMG recommends that each laboratory independently validate their panel tests (Rehm et al., 2013).

**Center for Medical Technology Policy (CMTP, 2015): Green Park Collaborative**

In 2015, the Green Park Collaborative recommended that panels containing from 5 to 50 genes should be covered when the following criteria are met:

A subset of at least 5 constituent genes or variants is cited in the label of an FDA-approved companion diagnostic indicated for treatment, designated as standard of care for the underlying condition by molecular testing committees of at least 3 National Cancer Comprehensive Network (NCCN) member institutions, or recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the NCCN or other guidelines that meet the IOM criteria for clinical guidelines.

OR

“The provider has submitted two peer-reviewed journal articles of studies designed to demonstrate the safety and effectiveness of using the genomic information in question for clinical management of the patient’s diagnosis and support the conclusion that use of the information is reasonably likely to provide a health benefit for the patient.”

AND, in all cases:

“The cost of analysis by NGS does not exceed the cost of individual sequencing of the target genes by other methods, AND the laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing (CMTP, 2015).

The Collaborative proposed panels over 50 genes that “should be considered” for coverage if providers have sought prior authorization demonstrating the following diagnoses:

- Stage IV adenocarcinoma of the lung
- Carcinoma of unknown primary site
- Stage IV rare or uncommon solid tumors for whom no systemic treatment exists in clinical care guidelines and/or pathways;
- Stage IV solid tumors where the median overall survival is less than two years (such as pancreatic cancer)
- Stage IV solid tumors and has exhausted established guideline-driven systemic therapy options and requisite molecular testing and maintains functional status (ECOG score 0-2)
  OR
  newly diagnosed hematologic malignancies with limited treatment options in defined clinical care guidelines (CMTP, 2015).

**Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists (2017)**

The Joint Commission recommended that somatic variants be categorized by and reported based on their impact on clinical care. The Joint Commission notes that somatic variants include indels, SNVs, fusion genes from genomic rearrangements, and CNVs and should focus on their impact on clinical care. Any variant may be considered a biomarker if it predicts response to
therapy, influences prognosis, diagnosis, treatment decisions, or the gene function itself. The Joint Commission proposes four levels for these biomarkers which are as follows:

1. Level A, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors;

2. Level B, biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on well-powered studies with expert consensus;

3. Level C, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (i.e., off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies;

4. Level D, biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus.”

The Joint Commission also includes variants in different tiers based on the amount of evidence there is to support its significance. For example, tier 1 variants include significance of levels A and B and tier 2 includes significance of levels C and D. Tier 3 is variants of unknown significance (VUS), such as variants in cancer genes that haven’t been reported in any other cancers. These variants are not typically seen in significant frequencies in the general population. When evaluating these variants, the type of mutation and gene function should be considered. Tier 4 is benign variants or likely benign variants. These alleles are often observed in significant amounts in general populations. Tier 3 variants should be reported while ensuring that the most important information is communicated to the patient (Li et al., 2017).

State and Federal Regulations, as applicable

A search of the FDA Device database on 02/05/2020 for “gene panel” yielded 4 results, last updated 11/30/2017. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

On November 30, 2017, the FDA approved FoundationOne CDx, by Foundation Medicine, Inc. This device is a next generation sequencing-based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens (FDA, 2017a).

On June 29, 2017, the FDA approved Praxis Extended RAS Panel, by Illumina, Inc. The Praxis™ Extended RAS Panel is a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples (FDA, 2017b).

On June 22, 2017, the FDA approved Oncomine Dx Target Test, by Life Technologies Corporation. The Oncomine Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants
(SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM Dx System (FDA, 2017c).

On December 19, 2016, the FDA approved FoundationFocus CDxBRCA, by Foundation Medicine, Inc. The FoundationFocus CDxBRCA is a next generation sequencing based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. The FoundationFocus CDxBRCA assay detects sequence alterations in BRCA1 and BRCA2 (BRCA1/2) gene (FDA, 2016).

### Applicable CPT/HCPCS Procedure Codes

<table>
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<th>Code Number</th>
<th>Code Description</th>
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<tr>
<td>81432</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53</td>
</tr>
<tr>
<td>81433</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</td>
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<tr>
<td>81434</td>
<td>Hereditary retinal disorders (eg, 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</td>
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<tr>
<td>81435</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11</td>
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<tr>
<td>81436</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11</td>
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<td>81437</td>
<td>Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL</td>
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<tr>
<td>81438</td>
<td>Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL</td>
</tr>
<tr>
<td>81442</td>
<td>Noonan spectrum disorders (eg, 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,</td>
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<td>Code</td>
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<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
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<tr>
<td>81455</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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<tr>
<td>0101U</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])</td>
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<tr>
<td>0102U</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])</td>
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<td>0103U</td>
<td>Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])</td>
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</tbody>
</table>


Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**


Sequencing Panel for Routine Diagnosis in Gliomas. *Cancers (Basel)*, 11(6).
doi:10.3390/cancers11060773

FDA. (2016). FoundationFocus CDxBRCA. Retrieved from
https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=389050

FDA. (2017a). FoundationOne CDx. Retrieved from
https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=407172


