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Medical Policy

Subject:	Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling		
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Description/Scope

This document addresses whole genome sequencing, whole exome sequencing, and gene panel testing. For the purposes of this document, a gene panel is defined by five or more genes or gene mutation variants tested on the same day on the same member by the same rendering provider.

This document also addresses multi-biomarker molecular profiling for the evaluation of malignancies in persons who have been diagnosed with cancer. The personalized tumor molecular profiling services or test panels addressed in this document are similar in that they all evaluate tumor tissue to produce a molecular profile intended to guide potential therapies.

Note: Please see the following related documents for additional information:

- CG-GENE-13 Genetic Testing for Inherited Diseases
- CG-GENE-14 Gene Mutation Testing for Solid Tumor Cancer Susceptibility and Management
- CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
- GENE.00010 Panel and other Multi-Gene Testing for Polymorphisms to Determine Drug-Metabolizer Status

Position Statement

Medically Necessary:

~~Molecular profiling is considered **medically necessary** when all of the criteria below are met:~~

~~1. The individual has been diagnosed with stage IV or recurrent non-small cell lung cancer (NSCLC); **and**~~

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~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. .The member's contract benefits in effect on the date that services are rendered must be used. .Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. .Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

~~2. The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy; **and**~~
~~3. The test is performed using a formalin-fixed paraffin-embedded tumor tissue sample.~~

Molecular profiling is considered **medically necessary** for unresectable or metastatic solid tumors when all of the criteria below are met:

1. The test is used to assess ~~-~~tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy; **and**
2. Individual has progressed following prior treatment; **and**
3. Individual has no satisfactory alternative treatment options.

Note: The test should be performed using tumor tissue (not cell-free circulating tumor DNA, also known as liquid biopsy).

Testing for hereditary retinal disorders using gene panels is considered **medically necessary** for an individual with a suspected inherited retinal degenerative disease when results of the panel are likely to guide treatment decisions.

Testing for Ashkenazi Jewish associated inherited disorders using gene panels is considered **medically necessary** for an individual with suspected genetic disease or as part of preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status when the parent or prospective parent is of Ashkenazi Jewish descent and when genetic counseling, which encompasses **all** of the following components, has been performed:

1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
4. Counseling for the psychological aspects of genetic testing.

Testing for Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer) using gene panels is considered **medically necessary** when the panel contains only the following genes: MLH1, MSH2, MSH6, PMS2, and EPCAM ~~*(only)*~~, and an individual meets criteria for *Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer [HNPCC])* genetic testing according to CG-GENE-15.

Investigational and Not Medically Necessary:

Molecular profiling is considered **investigational and not medically necessary** for all other indications, including when the medically necessary criteria above have not been met.

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Testing for hereditary retinal disorders using gene panels is considered **investigational and not medically necessary** for all other indications, including when the medically necessary criteria above have not been met.

Testing for Ashkenazi Jewish associated inherited disorders using gene panels for individuals with suspected genetic disease or as part of preconception or prenatal genetic screening of a parent or prospective parent to determine carrier status when the parent or prospective parent is of Ashkenazi Jewish descent is **considered investigational and not medically necessary** for all other indications, including when the medically necessary criteria above have not been met.

Genetic testing for cancer susceptibility using gene panels (with or without next-generation sequencing) is considered **investigational and not medically necessary** when the medically necessary criteria above have not been met**.**

Genetic testing of the individual's genome for inherited diseases using gene panels (with or without next generation sequencing), including but not limited to whole genome and whole exome sequencing, is considered **investigational and not medically necessary.**

Rationale

Molecular Profiling
Molecular profiling, also called comprehensive genomic profiling, is a method for identifying multiple biomarkers in the malignant tumors of persons who have cancer. The biomarker information can be used to identify treatment options. The personalized tumor molecular profiling services or test panels addressed in this document are similar in that they all evaluate tumor tissue and, from it, produce a molecular profile of the tumor and a list of potential therapies. However, their individual testing methods vary from matching over expressed genes with drugs to more complex systems biology approaches. Large multi-biomarker panels test a variety of markers. It is often the case that not every test in these panels has a proven benefit.

Some commercially available molecular profile panels are listed below:
FoundationOne
FoundationOne uses next generation sequencing (NGS) "to interrogate the entire coding sequence of 236 cancer-related genes (3769 exons) plus 47 introns from 19 genes frequently altered or rearranged in cancer." FoundationOne helps match the genomic alterations present in a tumor with specific targeted therapies or clinical

trials. Recent small studies (Drilon, 2013; Lipson, 2012; Vignot, 2013) have investigated next generation sequencing in individuals with lung cancer. Others have used next generation sequencing in those with breast cancer (Ross, 2013a); colorectal and other gastrointestinal cancers (Dhir, 2017; Gong, 2017; Lipson, 2012), ovarian cancer (Ross, 2013b), and prostate cancer (Beltran, 2013). Limitations of these studies include small sample sizes and lack of randomization.

FoundationOne CDx
On November 30, 2017, the United States Food and Drug Administration (FDA) approved the FoundationOne CDx NGS sequencing test as a companion diagnostic for several drugs including: Gilotrif® (afatinib), Iressa® (gefitinib), Tarceva® (erlotinib), Tagrisso® (osimertinib), Alecensa® (alectinib), Xalkori® (crizotinib), Zykadia® (ceritinib), Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib), Tafinlar® (dabrafenib), Zelboraf® (vemurafenib), Mekinist® (trametinib), Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib), Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), Perjeta® (pertuzumab), Erbitux® (cetuximab), Vectibix® (panitumumab), and Rubraca® (rucaparib). In addition, the test detects substitutions and alterations in 324 genes and is indicated to provide general tumor mutation profiling of solid malignant neoplasms in accordance with professional guidelines in oncology. ~~The FDA Summary of Safety and Effectiveness notes that FoundationOne CDx is a new test that has never been marketed in the United States.~~

The FDA approval was based on concordance studies that compared the Foundation One CDx test to approved specific companion diagnostic tests including the cobas® EGFR Mutation Test (EGFR exon 19 deletions, L858R, EGFR T790M), Ventana ALK CDx Assay (ALK), Vysis ALK Break-Apart FISH Probe Kit (ALK), therascreen® KRAS RGQ PCR Kit (KRAS), Dako HER2 FISH pharmDx® Kit (ERBB2 [HER2]), cobas® BRAF V600 Mutation Test (BRAF V600), THxID™ BRAF kit (BRAF V600), and FoundationFocus CDx_{BRCA} (BRCA1 and BRCA2). The sample size for each biomarker comparison study ranged from 175 to 342, the positive percent agreement ranged from 89.4% to 100%, and the negative percent agreement ranged from 86.1% to 100%. For the BRCA1 and BRCA2 mutation, the FoundationOne CDx was considered concordant based on the previous approval of the FoundationFocus CDx_{BRCA} test. The FDA states, "The clinical concordance studies, with the exception of *ALK* and *EGFR* T790M, were subject to pre-screening bias, therefore the concordance results may be overestimated and the failure rate may be underestimated." For the T790M mutation, there is ongoing research to determine why a subset population with a mutant allele frequency < 5% tested negative with the cobas EGFR Mutation Test v2 but tested positive with the FoundationOne CDx test. The FDA concluded that, overall, the FoundationOne CDx test demonstrated non-inferiority to the corresponding specific companion diagnostic tests (FDA, 2017a). On March 16, 2018, the Centers for Medicare and Medicaid Services (CMS) approved NGS-based in vitro companion diagnostic laboratory tests for national coverage after an FDA-CMS parallel review.

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In 2018, Hellmann and colleagues reported results from the CheckMate 227 study, an open-label, phase 3 trial (NCT02477826) designed to evaluate the efficacy of nivolumab or nivolumab-based regimens as first-line therapy in participants with stage IV or recurrent non-small cell lung cancer (NSCLC) that have not previously received chemotherapy as primary therapy. Trial participants were stratified into PD-L1 expression levels (at least 1% or less than 1%). In addition, tumor mutation burden was determined using the FoundationOne CDx assay. At 1 year, the progression-free survival (PFS) rate for participants with a high tumor mutation burden that received nivolumab in combination with ipilimumab was 42.6% versus 13.2% for the chemotherapy group. The median PFS was 7.2 months (95% confidence interval [CI], 5.5 to 13.2) for participants that received nivolumab in combination with ipilimumab versus 5.5 months for the chemotherapy group (95% CI, 4.4 to 5.8) (HR for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; P<0.001). The authors concluded:

> Progression-free survival was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy alone among patients with NSCLC and a high tumor mutational burden, irrespective of PD-L1 expression level. The results validate the benefit of nivolumab plus ipilimumab in NSCLC and the role of tumor mutational burden as a biomarker for patient selection.

Additional data regarding the CheckMate 227 study was published by Hellmann and colleagues in 2019. The authors reported on the overall survival with nivolumab plus ipilimumab compared to chemotherapy in participants with a tumor PD-L1 expression level of 1% or greater. There were 679 participants who had evaluation of tumor mutation burden which showed a similar degree of overall survival regardless whether they had a high tumor mutation burden or a low tumor mutation burden. The authors conclude:

> …although absolute survival with nivolumab plus ipilimumab was greatest in patients with a high tumor mutational burden, a similar relative benefit of nivolumab plus ipilimumab, as compared with chemotherapy, was seen in patients regardless of tumor mutational burden.

Based on this data showing no difference in survival outcomes between individuals whose tumors had high or low levels of tumor mutation burden, Bristol-Myers Squibb announced its decision in January 2019 to withdraw the supplemental biologics license application with the FDA seeking approval for the combination of nivolumab and ipilimumab for individuals with advanced NSCLC with tumor mutational burden greater than or equal to 10 mutations per megabase.

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The 2020 NCCN guideline for NSCLC notes that the emerging biomarker tumor mutation burden may be helpful to identify eligibility of first-line therapy with nivolumab with or without ipilimumab for those with NSCLC, however there is no consensus regarding how to measure tumor mutation burden.

In June 2020, the FDA updated the label for pembrolizumab (Keytruda® [Merck, Kenilworth, NJ]) to include treatment for individuals with unresectable or metastatic solid tumors with tumor mutation burden-high (defined as greater than or equal to 10 mutations per megabase) when confirmed by an FDA-approved test following progression after prior treatment and no satisfactory alternative treatment options. According to the FDA label, the accelerated approval was based on the Keynote-158 trial (NCT02628067), a multicenter, non-randomized, open-label trial. Efficacy outcomes were tumor response rate and duration of response. Tumor mutation burden was assessed by the Foundation One CDx assay. Of the 1050 subjects enrolled in the efficacy analysis population, tumor mutation burden was analyzed in 790 subjects. There were 102 subjects who had tumors identified as tumor mutation burden-high. With a median follow-up time of 11.1 months, 29% of participants reached an objective response rate, 4% reached a complete response, and 25% reached a partial response. Duration of response was assessed at 57% with a duration of greater than or equal to 12 months and 50% with a duration of greater than or equal to 24 months. Continuation of approval may be contingent on verification and description of clinical benefit in confirmatory trials.

Molecular Intelligence Service or Target Now
A widely used tumor molecular profile has been the Target Now Molecular Profiling Service. According to the Caris Life Sciences website, their tumor profiling service is now being promoted as the Molecular Intelligence™ Service. The published literature addressing these services is limited. Von Hoff and colleagues (2010) evaluated 86 individuals with refractory metastatic cancer. PFS using a treatment regimen selected by Target Now molecular profiling of a malignant tumor was compared with the PFS of the most recent treatment regimen on which the individual experienced progression. A molecular target was detected in 84 of 86 (98%) participants. A total of 66 (78.6%) individuals were treated according to the molecular profile results with 18 of the 66 (27%) having a PFS ratio (defined as PFS on molecular profile–selected therapy or PFS on prior therapy) of greater than or equal to 1.3 (95% CI, 17% to 38%; p=0.007).

An editorial (Doroshow, 2010) accompanying the study reported that the trial had a number of significant limitations, including uncertainty surrounding the achievement of time to progression (the study's primary endpoint), and a lack of a randomized design. Additional limitations include a small number of participants and lack of duplication of study results by an independent dataset.

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Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)
Cheng and colleagues (2015) developed and evaluated the MSK-IMPACT, "a hybridization capture-based assay targeting all coding regions of 341 oncogenes and tumor suppressors." The ability of the assay to detect single nucleotide variants (SNVs) and short insertions and deletions (indels) was assessed in 284 known positive solid tumor samples. Of these, 75 had a matched normal sample available. The authors reported successful detection of known variants in all 284 cases, and ability to achieve high degrees of resolution and levels of coverage to > 500x in tumor samples that allows low-frequency mutations to be detected. On November 15, 2017, the FDA granted marketing authorization for MSK-IMPACT based on a *de novo* request (FDA 2017b).

Other Molecular Profiling
Other molecular profiling such as EXaCT-1 Whole Exome Sequencing, GeneKey, GeneTrails Solid Tumor Panel, MatePair, MyAML, OmniSeq, OnkoMatch, OncInsights, and SmartGenomics have less published validation. To date, there is insufficient peer-reviewed evidence specifically validating these tests.

In 2012, Tsimberidou and colleagues developed a personalized medicine program at a single facility in the context of early clinical trials. Their goal was to observe whether molecular analysis of advanced cancer and use of targeted therapy to counteract the effects of specific aberrations would be associated with improved clinical outcomes. Participants with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. A total of 175 subjects were treated with matched therapy, and the overall response rate was 27%. Of the 116 subjects treated with non-matched therapy, the response rate was 5%. The median time-to-failure was 5.2 months for those on matched therapy versus 2.2 months on non-matched therapy. At a median of 15 months follow-up, median survival was 13.4 months versus 9.0 months in favor of matched therapy.

Jameson and colleagues (2013) performed a small pilot study investigating multi-omic molecular profiling (MMP) for the selection of breast cancer treatment. MMP treatment recommendations were selected in 25 cases and original treatment plans were revised accordingly. Partial responses were reported in 5/25 (20%), stable disease in 8/25 (32%) and 9/25 had no disease progression at 4 months. This study was limited by its small size and non-randomization. A large randomized prospective trial is needed for further evaluation.

Primarily marketed to researchers, Life Technologies Inc. offers several variations of their Ion Torrent™ Next Generation Sequencing Ion AmpliSeq™ panels, according to the company website. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion

AmpliSeq Cancer Hotspot Panel v2 analyzes the "hotspot" regions of 50 cancer-related and tumor suppressor genes.

Studies on Molecular Profiling Therapy

LeTourneau and colleagues (2012, 2015) reported on an open-label, randomized controlled phase II trial of treatment of refractory metastatic solid tumors directed by molecular profiling versus standard of care treatment (SHIVA trial). A total of 195 adults, consisting of 99 in the experimental group and 96 in the control group, were enrolled from eight academic centers in France. The primary outcome was progression-free survival (PFS) analyzed by intention-to-treat. Randomization was stratified by three molecular pathways (hormone receptor pathway, PI3K/AKT/mTOR pathway, and RAF/MEK pathway). Molecular analysis included targeted NGS, gene copy number alterations and hormone expression by immunohistochemistry. The molecularly targeted drugs used in the experimental group were approved for clinical use in France, but were outside their indications. The control group received standard treatment chosen by the physician. Median follow-up was 11.3 months for both the experimental and control groups at the time of primary analysis of PFS. Median PFS was 2.3 months (95% CI, 1.7-3.8) in the experimental group versus 2.0 months (95% CI, 1.7-2.7 months) in the control group (hazard ratio, 0.88; 95% CI, 0.65-1.19; p=0.41). Upon subgroup analysis, there was no statistically significant difference in PFS between the two groups. Objective responses were reported for 4 of 98 (4.1%) assessable subjects in the targeted treatment group versus 3 of 89 (3.4%) assessable subjects in the standard care group. Among the safety population, grade 3-4 adverse events were reported for 43 of the 100 subjects (43%) who received a molecularly targeted agent and 32 (35%) of 91 subjects treated in the control group. The authors suggested that "off-label use of molecularly targeted agents should be discouraged and enrollment in clinical trials should be encouraged to help identify predictive biomarkers of efficacy."

Presley and colleagues (2018) conducted a multicenter, retrospective, cohort study to compare broad-based genomic sequencing to routine EGFR and ALK biomarker testing in individuals with advanced NSCLC (stage IIIB/IV or unresectable nonsquamous). The primary outcomes were the 12-month mortality and overall survival from the start of first-line treatment. The researchers examined the Flatiron Health Database records of 5688 individuals (median age 67 years) who received care for advanced NSCLC between January 1, 2011 and July 31, 2016: 875 received broad-based genomic sequencing (multigene panel testing assay of more than 30 genes) and 4813 received routine EGFR/ALK testing. Subjects were required to have documented broad-based genomic sequencing testing or EGFR testing; if EGFR was negative, ALK testing was required. All subjects received at least one line of systemic antineoplastic treatment. At 12 months, the unadjusted mortality rates were 49.2% for the broad-based group and 35.9% for the EGFR/ALK group. Of the subjects in the broad-based group, 4.5% received targeted treatment based on test results, 9.8% received EGFR/ALK targeted treatment, and 85.1% received no

targeted treatment. When using an instrumental variable analysis, no significant association was found between broad-based genomic sequencing and 12-month mortality (difference in the predicted probability of death at 12 months between the groups: −3.6%; 95% CI, −18.4% to 11.1%; p=0.63). The predicted probability of 12-month mortality was 44.4% (95% CI, 42.9% to 45.9%) in the EGFR/ALK group and 41.1% (95% CI, 27.7% to 54.5%) in the broad-based group. For the propensity score-matched sample, the overall survival was not significantly different between the groups (42.0% vs. 45.1%; 0.92 HR; 95% CI, 0.73 to 1.11; p=0.40). The researchers concluded that "among patients receiving care for advanced NSCLC in the community oncology setting, broad-based genomic sequencing directly informed treatment in a minority of patients and was not independently associated with better survival." Limitations of the study included a relatively small and homogenous sample for the broad-based group and the possible inaccuracy of the electronic health records.

Other Considerations

The 2020 National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) ~~guidelines~~ do not contain recommendations for the general strategy of testing a tumor for a wide range of biomarkers. However, the guidelines do contain recommendations for specific genetic testing for individual cancers, when there is a known drug-biomarker combination that has demonstrated benefits for that particular type of tumor, such as colon or ~~non-small cell lung cancer (~~NSCLC~~)~~. In order to conserve tissue, the current NSCLC guidelines support an FDA approved NGS companion diagnostic test that can simultaneously test for EGFR mutations, BRAF mutations, ROS1 rearrangements, and ALK rearrangements.

A 2018 joint guideline (Lindeman, 2018), *Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors*, from the CAP, International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) states that "multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1" (level of evidence rating: expert consensus opinion - serious limitations in quality of evidence). However, the authors note that "the strength of evidence is inadequate supporting the use of multiplexed genetic sequencing panels compared with single-gene tests."

In summary, there is insufficient published evidence to support the wide use of molecular profiling to guide treatment decisions for malignant tumors. The available published literature consists of one randomized controlled trial, a small number of uncontrolled studies, and non-randomized trials that use imperfect comparators.

Genetic Testing Using Gene Panels

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Until recently, genetic testing for cancer susceptibility was generally carried out by direct sequencing (Sanger) which analyzes a specific gene for a particular mutation. However, next generation sequencing, (including but not limited to massively parallel sequencing and microarray testing) has made it possible to conduct panel testing which involves the analysis of multiple genes for multiple mutations simultaneously. Panel testing has the potential benefit of analyzing multiple genes more rapidly and thereby providing the results of the genetic work-up in a more timely fashion. However, the newer sequencing techniques may be associated with a higher error rate and lower diagnostic accuracy than direct sequencing which could affect the clinical validity of testing. Another potential drawback of the newer technologies is that they may provide information on genetic mutations which is of uncertain clinical significance. In assessing the value of a specific genetic testing panel for susceptibility to a particular malignant condition, consideration should be given to the peer-reviewed, published literature addressing the analytical validity, clinical validity, and clinical utility of the test. Also, evidence demonstrating a positive impact of the panel on the care of individuals with, or at risk for, a specific cancer should be considered. Also, evidence demonstrating a positive impact of the panel on the care of individuals with, or at risk for, a specific cancer should be considered.

In 2015, the American Society of Clinical Oncology (ASCO) issued a policy statement update regarding genetic and genomic testing for cancer susceptibility. The findings and conclusions regarding the current state of the technology are summarized as follows:

- ASCO recognizes that concurrent multigene testing (i.e., 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. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes

of uncertain clinical utility and genes not suggested by the patient's personal and/or family history.

- All of the challenges described here raise the possibility of harm to the individual undergoing panel-based testing, including the potential for inappropriate medical intervention and psychological stress resulting from the incidental identification of a mutation in a gene that was not suggested by family history or from aggressive management of moderate-penetrance mutations (or VUSs) that is not yet supported by evidence.
- There remains an urgent need for more research into the implications of unexpected mutations in high-penetrance genes and mutations in moderate-penetrance genes. Continued research is also necessary to resolve VUSs. ASCO recognizes the complexity of the analysis and interpretation of genetic tests. ASCO supports high-quality standards to help providers and patients understand the accuracy, benefits, and limitation of genetic tests from individual laboratories. ASCO believes that current regulation of tests to detect inherited genetic variants is insufficient. Where tests are considered laboratory-developed or commercial tests, ASCO supports a risk-based approach to US Food and Drug Administration (FDA) regulation. High-risk tests used to identify patients who are at increased risk for cancer should be subject to regulatory review. ASCO also recognizes that regulation must be designed in a manner that does not compromise innovation or limit patient access to testing.
- ASCO supports the development of a rapid approval pathway for tests that address an unmet medical need, with the understanding that more than one test should be available before such a need is considered to have been met (Robson, 2015).

There is limited published evidence for the clinical utility and clinical validity of specific genetic test panels for breast and/or ovarian cancer and colorectal cancer susceptibility. While testing these genes may be appropriate in individuals with clinical or family histories suggestive of a specific syndrome, there is no evidence that mass screening of multiple genes in individuals suspected of having or being at risk for breast and/or ovarian cancer syndrome or a hereditary colorectal cancer improves clinical outcomes. The specific genes included in these test panels and the particular NGS technology utilized may differ between manufacturers. At the present time, there is limited published information on their analytical validity and clinical utility or validity.

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~~The NCCN guideline on genetic/familial high-risk assessment for colorectal cancer states that evidence is well-established for the following colorectal genes that are commonly included in gene panels: APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH biallelic pathogenic variants, PMS2, PTEN, SMAD4, STK11 and TP53.~~

Various laboratories offer next-generation sequencing panels (including but not limited to massively parallel sequencing, and microarray testing), making it possible to conduct panel testing which involves the analysis of multiple genes for multiple mutations simultaneously. The ColoNext™ test (manufactured by Ambry Genetics), which tests for variants in 17 genes, is one such example. Of the 17 genes tested, 12 are considered by the 2020 NCCN guideline on genetic/familial high-risk assessment for colorectal cancer to have well-established evidence of association with colorectal risk. The guideline notes that evidence is well-established for the following colorectal genes that are commonly included in gene panels: APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH biallelic pathogenic variants, PMS2, PTEN, SMAD4, STK11 and TP53.

~~The 2016 American Academy of Ophthalmology (AAO) recommends genetic testing be ordered at the initial visit for individuals with a suspected inherited retinal degenerative disease. The causative mutation can be identified in up to 60-80% of affected individuals, which can guide treatment decisions. The scope of genetic testing recommended varies, multi-gene testing may be necessary when there are multiple causative genes, while single gene analysis might be more appropriate for certain conditions. For diseases such as Leber congenital amaurosis (LCA), which is caused by multiple different genes, it can be more efficient to order a single test which has been designed to specifically evaluate for all of the known causative genes (Stone, 2012).~~

Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair genes or loss of expression of MSH2 due to deletion in the EPCAM gene (previously called TACSTD1). The mismatch repair (MMR) genes that are associated with Lynch syndrome include:

- MLH1 (MutL homolog 1), which is located on chromosome 3p22.2
- MSH2 (MutS homolog 2), which is located on chromosome 2p21-16
- MSH6 (MutS homolog 6), which is located on chromosome 2p16.3
- PMS2 (postmeiotic segregation 2), which are located on chromosome 7p22.1

The 2020 NCCN guideline on genetic/familial high-risk assessment for colorectal cancer also ~~NCCN~~ recommends that testing for Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM sequence analysis) includes individuals who meet the Bethesda guidelines, the Amsterdam II criteria, who have a cancer diagnosis prior to age 50, or have a predicted risk for Lynch syndrome greater than 5% on one of the following prediction models: MMRpredict, MMRpro or PREMM51, ~~2, 6 (NCCN, 2019)~~.

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The 2012 American Academy of Ophthalmology (AAO) recommends genetic testing be ordered at the initial visit for individuals with a suspected inherited retinal degenerative disease. The causative mutation can be identified in up to 60-80% of affected individuals, which can guide treatment decisions. The scope of genetic testing recommended varies, multi-gene testing may be necessary when there are multiple causative genes, while single gene analysis might be more appropriate for certain conditions. For diseases such as Leber congenital amaurosis (LCA), which is caused by multiple different genes, it can be more efficient to order a single test which has been designed to specifically evaluate for all of the known causative genes (Stone, 2012).

Expanded Carrier Screening and Panels

Advances in genetic testing technologies have led to the development and use of large-scale DNA sequencing, including but not limited to expanded carrier panels. Generally, carrier screening guidelines have focused on the assessment of individual conditions and ancestry. However, the effectiveness of this approach can be impacted by limited or inaccurate knowledge of ancestry and an increasingly multiethnic society. Approaches to screening have also been influenced by the recognition that while some genetic conditions occur more frequently in certain populations, genetic disorders are not limited to specific ethnic groups (Edwards, 2015).

According to the American College of Medical Genetics (ACMG):

> The completion of the full human genome sequence, followed by dramatic improvement in the speed and cost of DNA sequencing and microarray hybridization analysis, has enabled the ascertainment of an unprecedented quantity of disease-specific genetic variants in a time frame suited to prenatal/preconception screening and diagnosis. Now it is possible, using new technologies, to screen for mutations in many genes for approximately the same cost as previously required to detect mutations in a single gene or a relatively small number of population-specific mutations in several genes. Commercial laboratories have begun to offer such expanded carrier screening panels to physicians and the public, but there has been no professional guidance on which disease genes and mutations to include (Grody, 2013).

Previously, testing for a specific genetically linked condition typically began by identifying the most commonly associated genetic variants first and, if there was a high degree of suspicion, progressed in a step-wise fashion to identify variants that are less common. However, recent advances in NGS (also known as massively parallel sequencing) technologies permit the sequencing of millions of fragments of DNA in a relatively short period of time and enable the efficient screening of vast numbers of conditions simultaneously. As a result of the advances

made in the area of NGS, researchers have been exploring the use of expanded carrier screening (ECS) tests that utilize NGS technologies to access carrier status for a host of genetic conditions simultaneously. ECS has been described as "the practice of screening all individuals for dozens to hundreds of diseases, some with lower frequencies or severity grades, typically without tailoring to a person's reported ethnicity" (Edwards, 2015; Lazarin, 2015).

Next generation sequencing (NGS) provides information pertaining to conditions beyond those that are currently recommended in screening guidelines. At present, professional practice guidelines recommend offering carrier screening for individual conditions based on the severity of the condition, race or ethnicity, prevalence, carrier frequency, detection rates, and residual risk.

The 2013 ACMG Position Statement on Prenatal/Preconception Expanded Carrier Screening indicates that the proper selection of appropriate disease-causing targets for general population-based carrier screening (that is, absence of a family history of the disorder) should be developed using clear criteria, rather than simply including as many disorders as possible. In order for a particular disorder to be included in carrier screening, the following criteria should be fulfilled:

1. Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
    - The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening. This recommendation is guided by the ethical principle of nonmaleficence.
2. When adult-onset disorders (disorders that could affect the offspring of the individual undergoing carrier screening once the offspring reaches adult life) are included in screening panels, patients must provide consent to screening for these conditions, especially when there may be implications for the health of the individual being screened or other family members.
    - This recommendation follows the ethical principles of autonomy and nonmaleficence.
3. For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.
    - Laboratories should specify in their marketing literature and test results how residual risk was calculated using panethnic population data or a specific race/ethnic group.

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- The calculation of residual risk requires knowledge of two factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors. Laboratories offering expanded carrier screening should keep data prospectively and regularly report findings that allow computation of residual risk estimates for all disorders being offered. When data are inadequate, patient materials must stress that negative results should not be overinterpreted.

4. There must be validated clinical association between the mutation(s) detected and the severity of the disorder.
   - Patient and provider materials must include specific citations that support inclusion of the mutations for which screening is being performed.
5. Compliance with the American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, including quality control and proficiency testing.
   - Quality control should include the entire test process, including preanalytical, analytical, and postanalytical phases. Test performance characteristics should be available to patients and providers accessing testing (Grody, 2013).

The joint statement issued by ACMG, American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine, NSGC, and the Perinatal Quality Foundation stops short of endorsing the use of ECS tests and provides a general overview of the expanded screening paradigm. This collaborative statement points out several limitations of ECS. In the context of ECS, all individuals, regardless of ethnicity or race, are offered screening for the same set of conditions and ECSPs, (also known as expanded carrier screening panels, expanded panels and expanded carrier panels [ECPs]) which may include more than 100 genetic conditions, most of which are rare. Although the majority of conditions on current expanded panels are autosomal-recessive, it is possible that some may be X-linked or autosomal-dominant single-gene conditions. The authors also maintain that while expanded screening panels include most of the conditions recommended in current guidelines, the molecular methods used in ECS are not as accurate as methods recommended in current guidelines for the hemoglobinopathies and Tay-Sachs disease (Edwards, 2015).

While ECS delivers more comprehensive screening, this method presents challenges in clinical management. Traditional methods of carrier screening generally have focused on conditions that have a significant impact on the quality of life as a result of physical or cognitive disabilities, require lifelong medical therapies and have a fetal,

neonatal or early childhood onset as well as a well-defined phenotype. In contrast, the ECPs often include conditions for which carrier screening of the general population is not recommended by current practice guidelines (for example factor V Leiden and hemochromatosis). While some genetic variants on expanded panels have a relatively consistent phenotype, others are less clearly defined. ECPs may also include other conditions that have significant variation in their presentation and variable age of onset. Additionally, expanded panels may include rare conditions for which the precise carrier frequency of condition-causing variants may be unknown (Edwards, 2015; ~~Grody, 2001;~~ Monaghan, 2013~~; USPSTF, 2006~~).

The joint statement includes the following recommendations regarding the use of ECPs:

I. The condition being screened for should be a health problem that encompasses one or more of the following:
   a. Cognitive disability.
   b. Need for surgical or medical intervention.
   c. Effect on quality of life.
   d. Conditions for which a prenatal diagnosis may result in:
      i. Prenatal intervention to improve perinatal outcome and immediate care of the neonate.
      ii. Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care.
      iii. Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth (Edwards, 2015).

Finally, the authors point out that:

> Expanded carrier screening panels may include rare conditions; for such disorders, the precise carrier frequency as well as the proportion of condition-causing variants that can be detected may be unknown. Therefore, calculation of residual risk after a negative screening test may not be possible for all conditions (Edwards, 2015).

The American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) recommend carrier screening for Tay-Sach's disease, Canavan disease, mucolipidosis IV, Neumann Pick Disease Type A, Fanconi anemia group C, Bloom syndrome, Gaucher's disease and familial dysautonomia among individuals of Ashkenazi Jewish descent (ACOG, 2017; Gross, 2008).

Despite the fact that ECS tests are increasingly being utilized, there is currently a lack of guidance from specialty associations and societies identifying the population that is appropriate to undergo screening using these tests or which genes should be included in the panels. While many of the targeted carrier screening tests have reported high analytic validity, the analytic validity of ECSPs is either unknown or cannot be sufficiently assessed due to weakness in assay validation. It is also difficult to determine the clinical validity of carrier screening because by definition, carriers have no symptoms of the diseases being tested, and thus the association of the carrier state is impossible to define. For this reason, it is impossible to determine whether a negative test is a true-negative or a false-negative due to the inability to define the carrier state in clinical terms. Lastly, with regards to clinical utility, there is a lack of evidence demonstrating that expanded carrier testing in individuals who are asymptomatic but at risk for having an offspring with a genetic disease, results in improved clinical outcomes (for example, reduces the number of births with an inherited disorder) or impacts management (for example, changes family planning decisions).

There are currently several commercially available laboratory developed tests for carrier screening. These tests range from tests designed to test for individual diseases, to panels based on ethnicity as recommended in specialty association or society guidelines, to large expanded panels that test for many diseases beyond those recommended in practice guidelines. These panels include but are not necessarily limited to the following:

- Counsyl™ Family Prep Screen (Counsyl, South San Francisco, CA), tests for more than 100 diseases which may lead to shortened life span, intellectual disability, have limited treatment options, or can lead to intellectual disability.
- GeneVu (GoodStart Genetics, Cambridge MA), provides a customized testing panel for each patient based on family history, ethnicity and provider testing preferences.
- Inherigen™ (GenPath Diagnostics, Elmwood Park, NJ) offers a panethnic test for 164 autosomal recessive and X-linked inherited diseases, including Ashkenazi Jewish Diseases. The InheriGen Plus includes these 164 diseases and also screens for Fragile X syndrome, SMA and CF carrier status. The InheriGenTx screens for 67 autosomal recessive and X-linked inherited diseases.
- Inheritest℠ Carrier Screen (LabCorp, Burlington, NC) tests for more than 90 autosomal recessive inherited diseases. The Inheritest Select Carrier Screen evaluates diseases for patients of Ashkenazi Jewish descent.
- Natera® Horizon (Natera, San Carlos, CA) provides screening for up to 274 autosomal recessive and X-linked genetic conditions. Screening can be customized for all of these conditions or for a select few based on ethnic background and the physician's recommendation.

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Clinical laboratories may develop and validate screening tests or panels in-house ("home-brew") and market them as a laboratory service; such tests or panels are subject to the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Whole Genome Sequencing
Whole genome sequencing (WGS), also known as full genome sequencing (FGS), complete genome sequencing, or entire genome sequencing, is a laboratory procedure which seeks to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time. WGS allows researchers to study the 98% of the genome that does not generally contain protein-coding genes. In the clinical setting, this process frequently involves obtaining a DNA sample from the individual (typically from blood, saliva or bone marrow) and sequencing an individual's entire chromosomal and mitochondrial DNA. Because of the large volume of genomic data involved in this process, the genomic information is processed by and stored on microprocessors and computers.

Researchers continue to explore the relationship between mutations in the genomic material and the development or presence of disease. The clinical role of WGS has yet to be established. Research is still being done to determine if WGS can be used to accurately identify the presence of a disease, predict the development of a particular disease in asymptomatic individuals as well as how an individual might respond to pharmacological therapy. It has been theorized that WGS might eventually improve clinical outcomes by preventing the development of disease.

Whole Exome Sequencing
It is estimated that most disease-causing mutations (around 85%) of clinically important sequence variants occur within the regions of the genome that encode proteins. While similar to WGS, whole-exome sequencing (WES) reads only the parts of the human genome that encode proteins, leaving the other regions of the genome unread (Choi, 2009). Since most of the errors that occur in DNA sequences that then lead to genetic disorders are located in the exons, sequencing of the exome is being explored as a more efficient method of analyzing an individual's DNA to discover the genetic cause of diseases or disabilities. It has been theorized that sequencing of the human exome can be used to identify genetic variants in individuals to diagnose diseases without the high cost associated with WGS.

The American College of Medical Genetics and Genomics (ACMG, 2012) published a position statement addressing points to consider in the clinical application of genomic sequencing. The policy statement:

WES developed primarily as an educational resource for clinical and laboratory geneticists to help them provide quality clinical and laboratory genetic services. Adherence to these Points to Consider is voluntary and, in determining the relevance of and weight to be given to any specific point, the clinical and laboratory geneticist should apply his or her own professional judgment to the specific circumstances presented by the individual patient or specimen.

The document contains indications for whole genome and WES as both screening and diagnostic tools. The ACMG states that clinical diagnostic testing using whole genome or WES is indicated for the following phenotypically affected individuals:

A. The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
B. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
C. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
D. A fetus with a likely genetic disorder in which specific genetic tests , including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.
    1. Prenatal diagnosis by genomic (i.e., next-generation whole exome- or whole genome-) sequencing has significant limitations. The current technology does not support short turn-around times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis (2012).

The ACMG document does not include references to peer reviewed literature in support of the recommendations made, or describe the process by which the recommendations were developed.

The ACOG Committee on Genetics in collaboration with the Society for Maternal–Fetal Medicine published a Committee Opinion Summary which states “the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published” (Committee on Genetics, 2016).

WES and WGS present ethical questions about informing individuals about incidental findings that have clinical significance. Ongoing discussions continue to explore whether or not, and how to inform individuals about medically relevant mutations in genes unrelated to the diagnostic question (i.e., mutations of unknown significance, non-paternity and sex chromosome abnormalities). This type of information may not only affect the individual being tested, but may also implicate family members. Also, in light of the small sample sizes and the limited number of studies exploring treatment outcomes, there may be safety considerations if a treatment decision is based on WES or WGS findings.

In 2016, the ACMG updated its recommendations for analyzing and reporting incidental or secondary findings from genome and exome sequencing in the clinical context. The Working Group continues to recommended that clinical diagnostic laboratories conducting exome or genome sequencing report known pathogenic or expected pathogenic variants in a total of 59 medically actionable genes, even when unrelated to the primary medical reason for testing. The conditions included for reporting were those that the Working Group and external reviewers considered most likely to be verifiable by other diagnostic methods and amenable to medical intervention. A complete list of these specified conditions can be found in the ACMG document. It should be noted that the ACMG clarified that the term "secondary" findings is preferred to the term "incidental" findings because " these genes are intentionally being analyzed, as opposed to genetic variants found incidentally or accidentally.' Conditions that were part of routine newborn screening were not addressed because they have their own assessment criteria and are applied in a specific public health framework. The Working Group recommendations also do not address preconception sequencing, prenatal sequencing, newborn sequencing, or sequencing of healthy children and adults (Kalia, 2016).

A potential major indication of WES is the establishment of a molecular diagnosis in individuals with a phenotype that is suspicious for a genetic disorder or for individuals with known genetic disorders that have a large degree of genetic heterogeneity involving substantial gene complexity. Such individuals may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic work-up involving a variety of traditional molecular and other types of conventional diagnostic tests. For some of these individuals, WES, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant.

While some of the potential advantages of WES include the fact that it can be carried out more quickly than traditional genetic testing and it may be less expensive than some other tests (for example, WGS), it is not without limitations. WES typically covers only 85-95% of the exome and has no, or limited coverage of other areas of the genome. Areas of concern with this technology include: (1) gaps in the identification of exons prior to sequencing; (2) the need to narrow the large initial number of variants to manageable numbers without losing the likely

candidate mutation; (3) difficulty identifying the potential causative variant when large numbers of variants of unknown significance are generated for each individual. It is more difficult to detect chromosomal changes, duplications, large deletions, rearrangements, epigenetic changes or nucleotide repeats from WES data compared with other genomic technologies (ACMG, 2012; Teer, 2010[a]; Teer, 2010[b]).

At this time, there are limitations to WES that prohibit its use in routine clinical care. The limited experience with WES on a population level leads to gaps in understanding and interpreting ancillary information and variants of uncertain significance. As a result, the risk/benefit ratio of WES testing is poorly defined. Because the peer-reviewed literature on WES for clinical purposes consists primarily of case reports and small case series, the clinical applications of WES has yet to be established (Bilguvar, 2010; Choi, 2009; Clayton-Smith, 2011, Saitsu, 2011; Vissers, 2011).

Cytogenomic Microarray Analysis
Cytogenomic microarray analysis collectively describes two different laboratory techniques: array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays. While both of these techniques detect copy number variants (CNVs), they identify different types of genetic variation. aCGH allows the detection of gains and losses in DNA copy number across the entire genome without prior knowledge of specific chromosomal abnormalities. SNP arrays allow genotyping based on allele frequency. SNP arrays have additional oligonucleotide probes which analyze thousands of SNPs throughout the genome in order to identify deletions and duplications. The use of cytogenomic microarray analysis is specifically addressed more fully in other documents, including but not limited to GENE.00021 Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability (Intellectual Developmental Disorder) and Congenital Anomalies.

Background/Overview

Molecular Profiling
The use of individual molecular markers in cancer management is well established; however, the use of comprehensive molecular profiling to evaluate malignant tumors is evolving. The rationale for molecular profiling is that more complete knowledge of molecular marker status may alter treatment and possibly improve individual outcomes. Molecular profiling refers to the analysis of DNA, RNA and/or proteins within the tumor cells. The term "molecular profiling" was initially limited to DNA analysis, but has now expanded to include analyses of RNA and proteins as well. Examples of commercially available multiple molecular testing panels are listed above.

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Genetic Testing Using Panels of Genes

NGS addresses any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. NGS is not a specific sequencing technology or a test in itself. Instead, the term emphasizes the difference between the earlier testing methods that involved the sequencing of one DNA strand at a time. NGS includes but is not limited to massively parallel sequencing and microarray analysis.

NGS has led to the development of genetic testing incorporating panels which analyze multiple genes for multiple mutations simultaneously. Researchers are investigating genetic testing using panels of genes as a means to identify genetic mutations that may contribute to the development of hereditary cancers.

Commercially available genetic testing panels for breast and/or ovarian cancers include, but are not limited to: BreastNext® (Ambry Genetics®); OvaNext® (Ambry Genetics®); BREVAGen (Phenogen Sciences); and myRisk Hereditary Cancer test (Myriad Genetics).

- The BreastNext genetic panel evaluates select genes that may be associated with a lifetime risk of breast cancer for individuals who, based on personal and family history, are at high risk for breast cancer and have tested negative for BRCA1 and 2 mutations.
- The OvaNext genetic panel simultaneously analyzes 23 genes that contribute to an increased risk for breast, ovarian and/or uterine cancers.
- The BREVAGen genetic panel assesses the risk for sporadic breast cancer by combining a woman's individual clinical risk factors (Gail score) with seven specific genetic markers.
- The myRisk Hereditary Cancer panel uses next-generation sequencing to examine genes associated with 8 cancer syndromes (breast, colorectal, endometrial, melanoma, pancreatic, gastric, and prostate).

The ColoNext™ test (manufactured by Ambry Genetics) is an example that tests for variants in 14 genes that have been associated with hereditary colorectal cancer, including the genes that cause Lynch syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM) as well as the gene that causes FAP (APC).

There is limited information in the peer-reviewed, published literature addressing the analytical validity, clinical validity, and clinical utility of these tests. There were also no studies identified which demonstrated improved clinical outcomes for individuals at risk for breast and/or ovarian cancer syndrome or colorectal cancers as a result of using the genetic testing panels.

Whole Genome Sequencing
Whole genome sequencing (WGS), also known as full genome sequencing (FGS), complete genome sequencing, or entire genome sequencing, is a laboratory procedure which seeks to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time. The role of WGS in the clinical setting has yet to be established.

Whole Exome Sequencing
While similar to WGS, WES reads only the parts of the human genome that encode proteins. Since most of the errors that occur in DNA sequences that then lead to genetic disorders are located in the exons, sequencing of the exome is being explored as a more efficient method of analyzing an individual's DNA to discover the genetic cause of diseases or disabilities. Researchers are exploring various applications of WES including but not limited to determining if sequencing of the human exome can be used to identify genetic variants in individuals in order to diagnose diseases in individuals without the high cost associated with WGS.

Definitions

Ashkenazi Jewish: Persons related to Jewish settlers of the Rhine Valley in Germany and France in the middle ages.

Cancer Moonshot: A collaborative effort between the public and private sectors (including but not limited to the governments, researchers, healthcare providers, data and technology experts, patients, families, and patient advocates) to make a decade's worth of advances in the understanding, prevention, diagnosis, treatment, and care of cancer.

Checkpoint Inhibition Immunotherapy (or Checkpoint Inhibitors): A type of drug (monoclonal antibody) that blocks certain proteins produced by immune T cells and cancer cells that keep the immune system in check and prevent the T cells from attacking cancer cells. By blocking these proteins, checkpoint inhibitors thus unleash the immune T cells to kill the cancer cells. The following is a list of FDA-approved checkpoint inhibitor drugs.

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)
- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)

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- Durvalumab (Imfinzi®)
- Ipilimumab (Yervoy®)

Copy number variant: An alteration of the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA.

Exome: All the exons in a genome.

Gene panel: When five or more genes are tested on the same day on the same member by the same rendering provider.

Genetic testing: A type of test that is used to determine the presence or absence of a specific gene or set of genes to help diagnose a disease, screen for specific health conditions, and for other purposes.

Genome: An organism's entire set of DNA.

Genomic data: Information derived from the sequencing of DNA or RNA fragments.

Genotype: The genetic structure (constitution) of an organism or cell.

Immunohistochemistry: The process of detecting proteins in the cells of a tissue section.

Indel: A genomic insertion or deletion.

Messenger ribonucleic acid (mRNA): A molecule that results when a cell "reads" a DNA strand.

Molecular profiling services: Laboratory services which catalogue a number of genetic markers in an attempt to select optimal therapy.

Next-generation sequencing: Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes.

Panel testing; Involves the analysis of multiple genes for multiple mutations simultaneously.

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Tumor Mutation Burden: A biomarker used to assess responsiveness to immunotherapy by measuring the total number of mutations per coding area of a tumor genome. Tumor Mutation Burden is typically determined by molecular (genomic) profiling with a large multigene assay/panel.

Whole-exome sequencing: Reads only the parts of the human genome that encode proteins, leaving the other regions of the genome unread.

Whole genome sequencing: A laboratory procedure which seeks to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Molecular profiling ~~for NSCLC~~

When services may be Medically Necessary when criteria are met:

CPT	
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationOne CDx™ (F1CDx); Foundation Medicine, Inc.
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets); Memorial Sloan Kettering Cancer Center
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association

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MI Cancer Seek™ - NGS Analysis, Caris MPI d/b/a Caris Life Sciences, Caris MPI d/b/a Caris Life Sciences
Note: Code effective 10/01/2020

ICD-10 Diagnosis

C00.0-C80.2~~C34.00-C34.92~~	Malignant neoplasms ~~of bronchus and lung~~
~~C78.00-C78.02~~	~~Secondary malignant neoplasm of lung~~
~~Z85.118~~	~~Personal history of other malignant neoplasm of bronchus and lung~~

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

Gene panels, whole genome sequencing, whole exome sequencing
When services may be Medically Necessary when criteria are met:

CPT

81412	Ashkenazi Jewish associated disorders (eg, 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*
81434	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*
81445	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 [when specified as a Lynch Syndrome 5-gene panel test including only *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*]

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81479	Unlisted molecular pathology procedure [when specified as a Lynch Syndrome 5-gene panel test including only *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*]

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:
For the panels listed above when criteria are not met, for the following codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81410	Aortic dysfunction or dilation (eg, 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 (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for *TGFBR1*, *TGFBR2*, *MYH11*, and *COL3A1*
81413	Cardiac ion channelopathies (eg, 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*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *RYR2*, and *SCN5A*
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings)

81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including *CDH23*, *CLRN1*, *GJB2*, *GPR98*, *MTRNR1*, *MYO7A*, *MYO15A*, *PCDH15*, *OTOF*, *SLC26A4*, *TMC1*, *TMPRSS3*, *USH1C*, *USH1G*, *USH2A*, and *WFS1*
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for *STRC* and *DFNB1* deletions in *GJB2* and *GJB6* genes
81432	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 10 genes, always including *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PTEN*, *STK11*, and *TP53*
81433	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*
81435	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*
81436	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*
81437	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*
81438	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*

81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including *BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2,* and *TYMP*
81442	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, RAF1, RIT1, SHOC2,* and *SOS1*
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, *ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH*)
81445	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 [when specified as any panel other than the Lynch Syndrome 5-gene panel test including only *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*]
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*)
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, *BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1*), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81455	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
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection if performed
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including *ARX*, *ATRX*, *CDKL5*, *FGD1*, *FMR1*, *HUWE1*, *IL1RAPL*, *KDM5C*, *L1CAM*, *MECP2*, *MED12*, *MID1*, *OCRL*, *RPS6KA3*, and *SLC16A2*
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including *ARX*, *ATRX*, *CDKL5*, *FGD1*, *FMR1*, *HUWE1*, *IL1RAPL*, *KDM5C*, *L1CAM*, *MECP2*, *MED12*, *MID1*, *OCRL*, *RPS6KA3*, and *SLC16A2*
81479	Unlisted molecular pathology procedure [when specified as a molecular profiling panel other than those listed as medically necessary, or a gene panel such as the following: BREVAGen, CancerNext, Foundation One, GeneKey, GeneTrails Solid Tumor Panel, Invitae Multi-Cancer Panel, Ion Torrent™ Next Generation Sequencing Ion AmpliSeq™ panels, Ion AmpliSeq Comprehensive Cancer Panel, Ion AmpliSeq Cancer Hotspot Panel, Molecular Intelligence Service/Target Now, OncInsights; OnkoMatch, SmartGenomics; VistaSeq Hereditary Cancer panel; Counsyl, GeneVu, GoodStart Select, Inherigen, Inheritest Carrier Screen, Natera Horizon]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a molecular profiling panel other than those listed as medically necessary or a gene panel]
0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s) MatePair Targeted Rearrangements, Congenital, Mayo Clinic
0013U	Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene

	rearrangement(s) MatePair Targeted Rearrangements, Oncology, Mayo Clinic
0014U	Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s) MatePair Targeted Rearrangements, Hematologic, Mayo Clinic
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses EXaCT-1 Whole Exome Testing; Lab of Oncology-Molecular Detection, Weill Cornell Medicine Clinical Genomics Laboratory
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements MyAML NGS Panel; LabPMM LLC, an Invivoscribe Technologies, Inc. Company
0056U	Hematology (acute myelogenous leukemia), DNA, whole genome next generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s) MatePair Acute Myeloid Leukemia Panel; Mayo Clinic
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis RCIGM Rapid Whole Genome Sequencing, Rady Children's Institute for Genomic Medicine (RCIGM)
0101U	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]) ColoNext®, Ambry Genetics®, Ambry Genetics®
0102U	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]) BreastNext®, Ambry Genetics®, Ambry Genetics®

0103U	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]) OvaNext®, Ambry Genetics®, Ambry Genetics®
0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) BRCAplus, Ambry Genetics
0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) +RNAinsight™ for ColoNext®, Ambry Genetics
0131U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) +RNAinsight™ for BreastNext®, Ambry Genetics
0132U	Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) +RNAinsight™ for OvaNext®, Ambry Genetics
0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) +RNAinsight™ for CancerNext®, Ambry Genetics
0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) +RNAinsight™ for GYNPlus®, Ambry Genetics
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as

	presence/absence MyMRD® NGS Panel, Laboratory for Personalized Molecular Medicine, Laboratory for Personalized Molecular Medicine
	Note: the following 6 codes are effective 10/01/2020:
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband Genomic Unity® Whole Genome Analysis - Proband, Variantyx Inc, Variantyx Inc
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling) Genomic Unity® Whole Genome Analysis - Comparator, Variantyx Inc, Variantyx Inc
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband Genomic Unity® Exome Plus Analysis - Proband, Variantyx Inc, Variantyx Inc
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling) Genomic Unity® Exome Plus Analysis - Comparator, Variantyx Inc, Variantyx Inc
0216U	Neurology (inherited ataxias), genomic DNA sequence analysis of 12 common genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants Genomic Unity® Ataxia Repeat Expansion and Sequence Analysis, Variantyx Inc, Variantyx Inc
0217U	Neurology (inherited ataxias), genomic DNA sequence analysis of 51 genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions,

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and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
Genomic Unity® Comprehensive Ataxia Repeat Expansion and Sequence Analysis, Variantyx Inc, Variantyx Inc

ICD-10 Diagnosis

All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/13/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Removed MN indication for molecular profiling for NSCLC. Added MN

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		indication for molecular profiling for unresectable or metastatic solid tumors. Updated Rationale and References sections. Updated Coding section to include 10/01/2020 CPT changes, added 02112U-0217U; added 81448 previously addressed in GENE.00033.
	07/08/2020	Updated Coding section; added 81413 previously addressed in GENE.00007.
	04/01/2020	Updated Coding section with 04/01/2020 CPT changes; added 0171U.
Revised	01/13/2020	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Addition to Position Statement regarding gene panel testing for Lynch Syndrome. Updated Rationale and Coding sections.
New	11/07/2019	MPTAC review. Initial document development. Moved content regarding whole genome sequencing, whole exome sequencing, gene panel tests and molecular profiling from GENE.00001 Genetic Testing for Cancer Susceptibility, GENE.00012 Preconception or Prenatal Genetic Testing of a Parent or Prospective Parent, GENE.00025 Molecular Profiling and Proteogenomic Testing for the Evaluation of Malignancies, GENE.00028 Genetic Testing for Colorectal Cancer Susceptibility, GENE.00029 Genetic Testing for Breast and/or Ovarian Cancer Syndrome, GENE.00030 Genetic Testing for Endocrine Gland Cancer Susceptibility, GENE.00035 Genetic Testing for TP53 Mutations, and GENE.00043 Genetic Testing of an Individual's Genome for Inherited Diseases to this new medical policy document. Updated Coding section to remove 81506, not applicable.

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