Medical Policy

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

This document addresses gene panel testing (for the purposes of this document, a gene panel is defined by five or more genes or gene variants tested on the same day on the same member by the same rendering provider), whole genome sequencing, whole exome sequencing, and molecular profiling (also called comprehensive genomic profiling).

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

- CG-GENE-10 - Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability and Congenital Anomalies
- 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
- CG-GENE-16 BRCA Genetic Testing
- GENE.00010 Panel and other Multi-Gene Testing for Polymorphisms to Determine Drug-Metabolizer Status
- GENE.00049 Circulating Tumor DNA Panel Testing (Liquid Biopsy)

Position Statement

Medically Necessary:

Gene Panel Testing for Inherited Diseases

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.

Gene Panel Testing for Tumor Cancer Susceptibility and Management

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, and an individual meets criteria for *Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer [HNPCC])* genetic testing according to CG-GENE-15.

Testing for breast cancer susceptibility using gene panels (containing 5-50 genes) is considered **medically necessary** when the panel contains, at a minimum, the following genes: BRCA1, BRCA2, PALB2, BARD1, RAD51C, RAD51D, ATM, and CHEK2, and an individual meets criteria for BRCA genetic testing according to CG-GENE-16.

Testing for prostate cancer using gene panels is **medically necessary** when the criteria below are met:
1. The panel evaluates homologous recombination repair (HRR) gene alterations; **and**
2. The individual is a candidate for treatment using Lynparza® (olaparib).

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

Testing for advanced non-small cell lung cancer using gene panels (containing 5-50 genes) is considered **medically necessary** prior to initiating first-line therapy when the panel contains, at minimum, the following genes (mutations, rearrangements, fusions, or amplifications): EGFR, KRAS, ERBB2 (HER2), ALK, ROS1, BRAF, NTRK, MET and RET.
Note: The test should be performed using tumor tissue (not cell-free circulating tumor DNA, also known as liquid biopsy). For criteria relating to use of circulating tumor DNA panel testing, see GENE.00049.

Whole Exome Sequencing (WES)

Whole exome sequencing is considered **medically necessary** in the evaluation of an individual who meets all of the following criteria 1, 2, and 3:
1. Meets one of the following criteria:
   a. Multiple anomalies not specific to a well-delineated genetic syndrome apparent before 1 year of age; **or**
   b. Apparently non-syndromic developmental delay/intellectual disability with onset prior to 18 years of age; **or**
   c. For the evaluation of a fetus with abnormal fetal anatomic findings which are characteristic of a genetic abnormality; **and**
2. When the results of testing would confirm or establish a clinical diagnosis that may lead to changes in management; **and**
3. Genetic counseling, which encompasses all of the following components, has been performed:
   a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   d. Counseling for the psychological aspects of genetic testing.

Note: WES may include comparator WES testing of the biologic parents or sibling of the affected individual.

Molecular Profiling for the Evaluation of Malignancies

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).

Investigational and Not Medically Necessary:

Testing 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.

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

Whole genome sequencing is considered **investigational and not medically necessary** for all indications**.**

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

Rationale

Gene Panel Testing for Inherited Diseases

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 amarurosis (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).

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).

The American College of Medical Genetics recommend carrier screening in individuals of Ashkenazi Jewish descent (Gross, 2008).

Gene Panel Testing for Tumor Cancer Susceptibility and Management
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. 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).

Breast Cancer Susceptibility
Multi-gene testing for hereditary forms of cancer can analyze a set of genes which are associated with a specific family cancer type. Multi-gene panel testing can impact medical management and can provide an association for prediction of risk of breast cancer. However, not all genes tested show a strong association for breast cancer. It's important to define which genes are most useful clinically as not all genes available on multi-gene tests are clinically actionable.

In the 2022 National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for genetic/familial high-risk assessment: breast, ovarian, and pancreatic, recommendations are made for genetic panel testing using these genes BRCA1, BRCA2, PALB2, BARD1, ATM, CHEK2, and CDH1.

Study among cancer susceptibility genes and breast cancer risk continues. Two case-control studies have been published which analyzed various genes which are susceptible for breast cancer risk. A 2021 study by Dorling and colleagues looked at a panel of 34 susceptible genes from samples of 60,466 individuals with breast cancer and 53,461 controls from 25 countries. The objective was the estimated odds ratios for breast cancer overall and tumor subtypes. Using the Cancer Risk Estimates Related to Susceptibility (CARRIERS) population-based studies of breast cancer in the United States, Hu and colleagues (2021) reported on 17 studies and analyzed 28 genes (predisposed to cancer) in 32,247 participants (case group) with breast cancer compared to 32,544 unaffected participants (control group). The objective was the association between variants in each gene and risk of breast cancer. Significant associations between breast cancer and variants in 8 genes: BRCA1, BRCA2, PALB2, BARD1, RAD51C, RAD51D, ATM, and CHEK2 in both studies. Of note, several genes regarded as having strong evidence of an association with breast cancer risk. For example, CDH1, PTEN, STK11, and TP53 are very rare, and did not show a significant association, presumably given their low prevalence. The majority of mutations among case

patients were BRCA1, BRCA2, and PALB2, and among controls, CHEK2 and ATM, reflecting the higher and lower penetrance of the genes respectively. BRCA1, BRCA2, and PALB2 are associated with a high risk of breast cancer (with odds ratios ranging from 5.0 to 10.6 in the study by Dorling et al.), and of mutations in CHEK2 and ATM, are associated with a moderate risk (with odds ratios ranging from 2.1 to 2.5).

Colorectal Cancer Susceptibility
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 2021 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.

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 2021 NCCN guideline on genetic/familial high-risk assessment for colorectal cancer 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 PREMM5.

Unselected Population Screening
As part of a population health study targeting Nevada's diverse demographics (the Healthy Nevada Project), Grzymski and colleagues (2020) reported on the genetic risk and disease manifestation of three inherited autosomal dominant conditions: BRCA-related hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia. With a cohort of 26,906 participants, the authors identified 214 unique pathogenic or likely pathogenic variants carried by 358 individuals (1.33%). Of the 273 carriers with medical records available for review, 60 participants were identified as having clinical disease relevant to the underlying carrier status (21.9%). There were 135 individuals with hereditary breast and ovarian cancer with records available which revealed 28 individuals with disease who were also carriers (20.7%) compared with 523 individuals with disease who were not carriers (2.6%). Records were available for 66 individuals who were carriers of Lynch syndrome. A diagnosis of colon or other cancer was found in 19 participants (28.8%). The prevalence in non-carriers was 0.5% (92 individuals with disease). The records of 73 individuals with familial hypercholesterolemia were reviewed. The prevalence of hyperlipidemia in carriers was 53.4% compared to 25.7% in non-carriers. Net health outcomes were not assessed. While these results suggest genetic screening for certain conditions has potential in identifying at-risk carriers not detected in medical practice, a population health screening approach could underestimate the impact of preventive screening in larger populations with diverse cohorts. There is potential for overinterpretation of disease

risk along with ethical and social factors. The risk of benefits of population-based screening programs need to be carefully assessed with long-term studies.

Management of Prostate Cancer
In 2020, the FDA updated the label for Lynparza to include prostate cancer with deleterious or suspected deleterious germline or somatic HRR gene-mutated metastatic prostate-resistant prostate cancer who have progressed following previous treatment and for therapy based on an FDA-approved companion diagnostic for Lynparza. The label was updated again in 2021 with no change to the above recommendation. This approval was based on the PROfound trial (NCT02987543). In 2020, de Bono and colleagues reported on a randomized, open-label, phase 3 trial which evaluated the use of olaparib in individuals with metastatic castration-resistant prostate cancer with disease progression while receiving a hormonal agent. All participants had a tumor mutation in one of the genes involved in the homologous recombinant repair (HRR) pathway. Participants were divided into two cohorts; cohort A included 245 participants who had at least one alteration in BRCA1, BRCA2, or ATM. Cohort B included 142 participants who had alterations in any of the other 12 prespecified genes (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A,RAD51B, RAD51C, RAD51D and RAD54L). Primary endpoint was progression-free survival in cohort A. Participants were randomized in a 2:1 fashion to receive either olaparib or hormonal agent (control). The authors report that in cohort A, progression-free survival was a median of 7.4 months for those taking olaparib compared to a median of 3.6 months in the control group. Median overall survival in cohort A was 18.5 months for those taking olaparib compared to a median overall survival of 15.1 months in the control group. The final analysis of overall survival was reported by Hussain and colleagues (2020). In cohort A, median duration of overall survival was 19.1 months with olaparib and was 14.7 months in the control group. In cohort B, median duration of overall survival was 14.1 months with olaparib and 11.5 months in the control group. The overall population (cohorts A and B) had a median duration of overall survival of 17.3 months for those taking olaparib and 14.0 months for those in the control group. The study authors note that the role of PPP2R2A could not be validated as a homologous recombination repair gene based on preclinical data and there was no benefit of overall survival with treatment of olaparib over control therapy in the individuals who had alterations in PPP2R2A. The FDA label also notes that while individuals with gene mutations for PPP2R2A were enrolled in the trial, Lynparza is not indicated for those with this gene mutation due to unfavorable risk-benefit.

Management of Non-Small Cell Lung Cancer
Gene alterations have been identified which can impact selection of therapy. Testing of specimens for gene alterations can help identify potentially effective targeted therapy and avoid therapy unlikely to provide clinical benefit. In the 2021 NCCN Clinical Practice Guidelines in Oncology for non-small cell lung cancer, they recommend molecular testing for actionable biomarkers (with these specified genes EGFR, KRAS, ERBB2 (HER2), ALK, ROS1, BRAF, NTRK, MET and RET) prior to administering first-line therapy.

Whole Exome Sequencing (WES)
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 whole genome sequencing (WGS), 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.

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. Results of WES testing are intended to guide treatment decisions including confirming or establishing a clinical diagnosis that may lead to changes in management (which may in some cases, may obviate the need for further testing, and/or end the diagnostic odyssey).

The 2021 Practice Guideline by the ACMG provides exome sequencing and genome sequencing recommendations for children with congenital anomalies or intellectual disability (Manickam, 2021) based on an assessment of 167 studies, 36 of which had a participant population greater than 20 individuals. The guidelines strongly recommend whole exome/genome sequencing as a first-tier or second-tier test (guided by clinical judgment and often clinician–member/family shared decision making after CMA or focused testing) for individuals with one or more congenital anomalies prior to one year of age or for individuals with developmental delay (DD) or intellectual disability with onset prior to 18 years of age:

> The literature supports the clinical utility and desirable effects of whole exome/genome sequencing on active and long-term clinical management of patients with congenital anomalies, or developmental delay or intellectual disability, and on family-focused and reproductive outcomes with relatively few harms. Compared with standard genetic testing, whole exome/genome sequencing has a higher diagnostic yield.

The guidelines also note that WES, which only evaluates the coding regions of the genome, is widely available, with extensive experience interpreting and comparing test results. At this time, WGS, which provides additional assessment of non-coding regions of the genome is limited to small number of clinics and labs. The ACMG includes WES in their guideline statement merely with the expectation that WES will become more commonly used and available.

For fetal testing, recommendations are made in a 2018 joint position statement from the International Society for Prenatal Diagnosis, the Society for Maternal Fetal Medicine, and the Perinatal Quality Foundation on the use of genome-wide sequencing. For fetal diagnosis, the authors recommend:

> The use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis (CMA), has already been performed and is uninformative or is offered concurrently according to accepted practice guidelines, or for whom expert genetic opinion determines that standard genetic testing is less optimal than sequencing for the presenting fetal phenotype.

Historically, prenatal diagnosis has been performed using G-banded karyotyping to detect chromosomal abnormalities. The yield in this approach results in a diagnosis in 9-19% of fetal anomalies. The use of CMA provides an additional 6% yield. Cause of the majority of fetal anomalies is unknown. Identifying the cause of fetal anomalies can help determine prognosis, inform recurrence risk, and guide clinical management. Prior studies of use of exome sequencing to diagnose unexplained fetal anomalies showed diagnostic yields of 8.5% and 10% (Petrovski, 2019; Lord, 2019). The relatively low yields might be explained by the wide range of structural anomalies which were included. There is limited data regarding the usefulness of exome sequencing for diagnosis of specific, severe prenatal phenotypes. In a 2020 study by Sparks and colleagues the authors reported on the

diagnostic yield of exome sequencing in detecting pathogenic or pathogenic variants in 127 participants with unexplained cases of nonimmune hydrops fetalis (NIHF). The presence of NIHF was defined by fetal ascites, pleural or pericardial effusions, skin edema, cystic hygroma, increased nuchal translucency, or combination of the conditions. There were 37/127 cases in which the authors identified diagnostic genetic variants. Overall there were 25/37 cases in which diagnostic variants were autosomal dominant (12% of those were inherited and 88% were de novo). Autosomal recessive diagnostic variants were found in 10/37 cases (95% inherited and 5% de novo). Potentially diagnostic variants were identified in 12 additional cases.

WES presents 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 (that is, 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.

The 2021 Practice Guideline by the ACMG (Manickam, 2021) notes:

> ES is available widely as a clinical tool with a number of commercial and academic laboratories offering this testing. Best practice includes familial comparators ("trio") if available to help contextualize rare variants, but also can be effectively performed as proband only or duo, with diagnostic yield being slightly reduced compared with trio testing.

While some of the potential advantages of WES include the fact that it can be carried out more quickly than traditional genetic testing, 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]).

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.

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 as a diagnostic tool for congenital anomalies as well as for individuals with unexplained developmental delay (DD), autism spectrum disorder (ASD) or intellectual disability (intellectual developmental delay) is specifically addressed by CG-GENE-10 Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability and Congenital Anomalies.

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 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 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.

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 of 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.

The 2021 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.

Other Tests
Other tests are becoming available on the market. One such example is the Oncotype MAP™ PanCancer Tissue Test (Paradigm Diagnostics, Inc., Phoenix, AZ) in which next-generation sequencing is used to identify genetic alterations among 257 genes to match appropriate targeted therapy for tumor mutation burden of solid tumors.

Whole transcriptome testing can assist in determining how cells normally function and how changes in gene activity can contribute to disease by showing what genes are active in which cells. DNA is the molecule which contains instructions needed to build and maintain cells. In order for the instructions to be read and completed, the DNA has to be read and transcribed (that is, copied into RNA). The testing involves the presence and amount of RNA. By analyzing the RNA, it is possible to count the transcripts to determine the amount of gene activity.

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.

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, 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 2021 NCCN 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 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."

Background/Overview

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. Genetic testing using panels of genes may identify numerous 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).

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. Various applications of WES are being explored 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 processing complexity associated with WGS.

Molecular Profiling
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. At this, only use of molecular profiling as a means of assessing tumor mutation burden has been established as a means of identifying candidates for targeted drug therapy.

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®)
- 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.

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.

Gene panel testing for inherited diseases
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*

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary
For the procedure codes 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*
81419	Epilepsy genomic sequence analysis panel, must include analyses for *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*
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
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*)

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*)
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 gene panel such as the following: Counsyl, GeneVu, GoodStart Select, Inherigen, Inheritest Carrier Screen, Natera Horizon]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a gene panel for inherited disease other than those listed as medically necessary]
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, 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
0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including *ANK2*, *CASQ2*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *RYR2*, and *SCN5A*, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions Genomic Unity® Cardiac Ion Channelopathies Analysis, Variantyx Inc, Variantyx Inc
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid Versiti™ aHUS Genetic Evaluation, Versiti™ Diagnostic Laboratories, Versiti™
0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid Versiti™ Autosomal Dominant Thrombocytopenia Panel, Versiti™ Diagnostic Laboratories, Versiti™

0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid Versiti™ Coagulation Disorder Panel, Versiti™ Diagnostic Laboratories, Versiti™
0271U	Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid Versiti™ Congenital Neutropenia Panel, Versiti™ Diagnostic Laboratories, Versiti™
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive Versiti™ Comprehensive Bleeding Disorder Panel, Versiti™ Diagnostic Laboratories, Versiti™
0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid Versiti™ Fibrinolytic Disorder Panel, Versiti™ Diagnostic Laboratories, Versiti™
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid Versiti™ Comprehensive Platelet Disorder Panel, Versiti™ Diagnostic Laboratories, Versiti™
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid Versiti™ Inherited Thrombocytopenia Panel, Versiti™ Diagnostic Laboratories, Versiti™
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid Versiti™ Platelet Function Disorder Panel, Versiti™ Diagnostic Laboratories, Versiti™
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid Versiti™ Thrombosis Panel, Versiti™ Diagnostic Laboratories, Versiti™

ICD-10 Diagnosis

All diagnoses

Gene Panel Testing for Tumor Cancer Susceptibility and Management

When services may be Medically Necessary when criteria are met:

CPT

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* [when genes *BARD1, RAD51C, RAD51D, ATM,* and *CHEK2* are also included]
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* [when genes *BARD1, RAD51C, RAD51D, ATM,* and *CHEK2* are also included]
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 one of the following]:
- Breast cancer panel test less than 51 genes and including at a minimum *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *RAD51C*, *RAD51D*, *ATM*, and *CHEK2* genes
- Lynch Syndrome 5-gene panel test including only *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes
- NSCLC panel test less than 51 genes and including at a minimum *EGFR*, *KRAS*, *ERBB2* (*HER2*), *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET* and *RET* genes
- Prostate cancer panel to evaluate deleterious germline or somatic homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L)*

81479 Unlisted molecular pathology procedure [when specified as one of the following panels:
- Breast cancer panel test less than 51 genes and including at a minimum *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *RAD51C*, *RAD51D*, *ATM*, and *CHEK2* genes
- Lynch Syndrome 5-gene panel test including only *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes
- NSCLC panel test less than 51 genes and including at a minimum *EGFR*, *KRAS*, *ERBB2* (*HER2*), *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET* and *RET* genes
- Prostate cancer panel to evaluate deleterious germline or somatic homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L)*

0238U Oncology (Lynch syndrome), genomic DNA sequence analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
Genomic Unity® Lynch Syndrome Analysis, Variantyx Inc, Variantyx Inc

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary
For the procedure codes 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

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*
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 breast cancer panel test, the Lynch Syndrome 5-gene panel test, the NSCLC panel test or the prostate cancer panel test for HRR genes listed above]
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
81479	Unlisted molecular pathology procedure [when specified as a gene panel such as the following: BREVAGen, CancerNext, Invitae Multi-Cancer Panel, Ion Torrent™ Next Generation Sequencing Ion AmpliSeq™ panels, Ion AmpliSeq Comprehensive Cancer Panel, Ion AmpliSeq Cancer Hotspot Panel, VistaSeq Hereditary Cancer panel]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a gene panel other than those listed as medically necessary]
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

ICD-10 Diagnosis

All diagnoses

Whole Exome Sequencing

When services may be Medically Necessary when criteria are met:

CPT	
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)

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

ICD-10 Diagnosis

All diagnoses

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

Molecular profiling
When services may be Medically Necessary when criteria are met:

CPT

Including, but not limited to, the following:

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 MI Cancer Seek™ - NGS Analysis, Caris MPI d/b/a Caris Life Sciences, Caris MPI d/b/a Caris Life Sciences
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue Oncotype MAP™ PanCancer Tissue Test, Paradigm Diagnostics, Inc, Paradigm Diagnostics, Inc

0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden PGDx elio™ tissue complete, Personal Genome Diagnostics, Inc, Personal Genome Diagnostics, Inc

ICD-10 Diagnosis

C00.0-C80.2	Malignant neoplasms

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.

CPT

81479	Unlisted molecular pathology procedure [when specified as a molecular profiling panel other than those listed as medically necessary, such as the following: GeneKey, GeneTrails Solid Tumor Panel, Molecular Intelligence Service/Target Now, OmniSeq; OncInsights; OnkoMatch, SmartGenomics]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a molecular profiling panel other than those listed as medically necessary]
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
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalinfixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification Praxis Somatic Whole Genome Sequencing, Praxis Genomics LLC [Note: code effective 01/01/2022]

0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification Praxis Somatic Transcriptome, Praxis Genomics LLC [Note: code effective 01/01/2022]
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification Praxis Somatic Optical Genome Mapping, Praxis Genomics LLC [Note: code effective 01/01/2022]
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping, Praxis Genomics LLC [Note: code effective 01/01/2022]

ICD-10 Diagnosis

All diagnoses

Other panels

When services are Investigational and Not Medically Necessary:

For the following codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

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)
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
81479	Unlisted molecular pathology procedure [when specified as a panel test other than those listed as medically necessary
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a gene panel other than those listed as medically necessary]

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
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)
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
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping Augusta Optical Genome Mapping, Georgia Esoteric and Molecular (GEM) Laboratory, LLC, Bionano Genomics Inc
0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping Praxis Optical Genome Mapping, Praxis Genomics LLC
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants Praxis Whole Genome Sequencing, Praxis Genomics LLC
0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue specific gene expression by whole transcriptome and next-generation sequencing, blood, formalin-fixed paraffin embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes Praxis Transcriptome, Praxis Genomics LLC
0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing Praxis Combined Whole Genome Sequencing and Optical Genome Mapping, Praxis Genomics LLC

ICD-10 Diagnosis

All diagnoses

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Websites for Additional Information

1. American Cancer Society. Available at: http://www.cancer.org. Accessed on October 21, 2021.
2. National Human Genome Research Institute. Available at: https://www.genome.gov/. Accessed on October 21, 2021.

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Ion Torrent Next Generation Sequencing Ion AmpliSeq
MatePair
Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)
Multi-Omic Molecular Profiling (MMP)
MyAML
myRisk Hereditary Cancer test
OmniSeq Advance
OncInsights
Oncotype MAP™ PanCancer Tissue Test
OvaNext Test
SmartGenomics
Target Now Molecular Profiling Service

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	11/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Added MN criteria for breast cancer susceptibility using gene panels. Added MN criteria for advanced non-small cell lung cancer using gene panels. Added MN criteria for whole exome sequencing. Updated Description/Scope, Rationale, References, and Websites for Additional Information sections. Updated Coding section to include 01/01/2022 CPT changes, added 0297U, 0298U, 0299U, 0300U.
	10/01/2021	Updated Coding section with 10/01/2021 CPT changes; added 0260U, 0264U-0274U, 0276U-0278U.
	07/01/2021	Updated Coding section with 07/01/2021 CPT changes; added 0250U.
Reviewed	02/11/2021	MPTAC review. Updated Description/Scope, Rationale, References, and Index sections. Updated Coding section with 04/01/2021 CPT changes; added 0244U.
Revised	11/05/2020	MPTAC review. Added MN criteria for prostate cancer using gene panels when the panel evaluates HRR repair gene alterations and an individual is a candidate for treatment with Lynparza (olaparib). Updated Rationale and Reference sections. Updated Coding section to include 01/01/2021 CPT changes to add 81419, 0237U, 0238U.
Revised	08/13/2020	MPTAC review. Removed MN indication for molecular profiling for NSCLC. Added MN 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 0211U-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	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.