

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

## Clinical Appropriateness Guidelines

# Genetic Testing

# Appropriate Use Criteria: Predictive and Prognostic Polygenic Testing

**Proprietary**

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## Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

# General Clinical Guideline

## Clinical Appropriateness Framework

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Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

## Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

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Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

## Repeat Diagnostic Intervention

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In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns

- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

## **Repeat Therapeutic Intervention**

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In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered. Requests for on-going services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

# Predictive and Prognostic Polygenic Testing

## Description and Scope

Predictive and prognostic polygenic testing includes DNA-based polygenic risk scores, mRNA-based polygenic expression prognostic testing and multivariable prognostic genetic testing.

Polygenic testing using germline DNA involves the aggregation of common, low penetrance variants determined by genome-wide association studies (GWAS) into a weighted risk score to calculate the inherited component of an individual's lifetime risk to develop certain common diseases.

Polygenic expression prognostic testing using mRNA involves the aggregation of gene expression levels of several genes (in blood, tissues or bodily fluids) into an algorithmic prognostic risk score. The risk score is used to predict if a symptomatic individual has a specific diagnosis or if an affected individual is at risk for worsening disease or disease recurrence. Some polygenic expression prognostic tests also offer medication suggestions for affected individuals.

Multivariable prognostic genetic testing involves the aggregation of data from multiple biomarkers (i.e., germline DNA, cell-free DNA, mRNA, RNA fusion products, proteins, methylation, etc.) into an algorithmic risk score. The risk score offers to predict if a symptomatic individual has a specific diagnosis or if an affected individual is at risk for worsening disease or disease recurrence.

This guideline addresses the use of genetic testing for application to polygenic risk scores, polygenic expression prognostic testing, and multivariable prognostic genetic testing.

## Exclusions

### Polygenic risk scores

The use of polygenic risk scores is considered **not medically necessary** for all indications.

### Polygenic expression prognostic testing

Unless otherwise indicated in other [Carelon Guidelines](#) (i.e., Somatic Tumor Testing and Genetic Testing for Inherited Conditions), the use of polygenic expression prognostic testing is considered **not medically necessary** for all indications.

### Multivariable prognostic genetic testing

The use of multivariable prognostic genetic testing is considered **not medically necessary** for all indications.

## Rationale

### Polygenic risk score testing

Polygenic risk score testing (PGS) evaluates multiple inherited DNA single nucleotide polymorphisms (SNPs) in the human genome to predict the risk for an individual to develop a common condition. Common conditions can include diabetes mellitus type II, Alzheimer's disease, and coronary artery disease. These conditions have multifactorial etiology, caused by a combination of heritable (germline) and non-heritable factors (lifestyle, behavioral factors, and environmental exposures). Individually, the heritable SNPs each have small effects on risk.<sup>1</sup> GWAS conducted over the past decade have examined the role of common, low penetrance genetic variants in disease risk, identifying associations of these individual common, variants, or single-nucleotide polymorphisms (SNP), with a small increased risk in disease. More than 70,000 associations between SNPs and human traits are now documented.<sup>2,3</sup> PGSs involve the aggregation of these common, low penetrance variants into a weighted risk score to calculate the inherited component of an individual's lifetime risk of a disease.<sup>4</sup> Important caveats thus far are that most of the data have been derived from individuals of European ancestry, and the clinical utility of a PGS depends

not only on its accuracy, but also on the existence of interventions that individuals can and would act upon to reduce disease risk.<sup>2, 5, 6</sup> Another caveat is that it is incorrect to assume that odds ratios derived from PGS, important etiologically, are also directly useful in risk prediction and population screening.<sup>7</sup> PGS is not ready for clinical implementation currently, but large clinical trials are in progress seeking to further evaluate various polygenic risk scores.<sup>4, 8</sup>

#### Polygenic expression prognostic testing (mRNA)

Polygenic expression prognostic testing evaluates mRNA expression levels of multiple genes and can be performed on tissue, bodily fluid or blood samples. Gene expression is not inherited and represents the function of genes in an individual or tissue at a specific time. Polygenic expression prognostic testing is typically marketed to symptomatic or affected individuals and provides prognostic information for a specific diagnosis including likelihood of a diagnosis, worsening of disease or disease recurrence (e.g., inflammatory bowel disease). While this technology holds promise, the clinical utility of polygenic expression prognostic testing for prognosis of diseases other than cancer of the breast and thyroid has not been proven.<sup>9-14</sup>

For discussion of polygenic expression prognostic testing of breast and thyroid cancer please see Somatic Tumor Testing. For discussion of polygenic expression prognostic testing to evaluate transplant tissue rejection, see Genetic Testing for Inherited Conditions.

#### Multivariable prognostic genetic testing

Multivariable prognostic genetic testing evaluates a combination of biomarkers (germline DNA, cell-free DNA, mRNA, RNA fusion products, proteins, methylation, etc.). Multivariable prognostic genetic testing is typically marketed to symptomatic or affected individuals and provides prognostic information for a specific diagnosis. While this technology holds promise, the clinical utility of multivariable prognostic genetic testing for prognosis of diseases has not been proven.<sup>9-14</sup>

## References

1. Sugrue LP, Desikan RS. What Are Polygenic Scores and Why Are They Important? *JAMA*. 2019;321(18):1820-1.
2. Hunter DJ, Drazen JM. Has the Genome Granted Our Wish Yet? *N Engl J Med*. 2019;380(25):2391-3.
3. European Molecular Biology Laboratory. GWAS Catalog [April 11, 2024]. Available from: <https://www.ebi.ac.uk/gwas/>.
4. Zeinomar N, Chung WK. Cases in Precision Medicine: The Role of Polygenic Risk Scores in Breast Cancer Risk Assessment. *Ann Intern Med*. 2021;174(3):408-12.
5. Abu-El-Hajja A, Reddi HV, Wand H, et al. The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(5):100803.
6. O'Sullivan JW, Raghavan S, Marquez-Luna C, et al. Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2022;146(8):e93-e118.
7. Wald NJ, Old R. The illusion of polygenic disease risk prediction. *Genet Med*. 2019;21(8):1705-7.
8. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med*. 2020;12(1):44.
9. Byron SA, Van Keuren-Jensen KR, Engelthaler DM, et al. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. *Nat Rev Genet*. 2016;17(5):257-71.
10. Kouter K, Paska AV. Biomarkers for suicidal behavior: miRNAs and their potential for diagnostics through liquid biopsy - a systematic review. *Epigenomics*. 2020;12(24):2219-35.
11. Li W, Li X, Li Y, et al. Diagnostic value of MicroRNAs for depression: A systematic review and meta-analysis. *J Psychiatr Res*. 2023;157:132-40.
12. Miles AE, Dos Santos FC, Byrne EM, et al. Transcriptome-based polygenic score links depression-related corticolimbic gene expression changes to sex-specific brain morphology and depression risk. *Neuropsychopharmacology*. 2021;46(13):2304-11.
13. Polli A, Godderis L, Ghosh M, et al. Epigenetic and miRNA Expression Changes in People with Pain: A Systematic Review. *J Pain*. 2020;21(7-8):763-80.
14. Szalat R, Avet-Loiseau H, Munshi NC. Gene Expression Profiles in Myeloma: Ready for the Real World? *Clin Cancer Res*. 2016;22(22):5434-42.

## Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

## CPT/HCPCS

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### Not Medically Necessary

Code	Not Medically Necessary
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis; lab test to detect, in free circulating DNA in the blood, methylation of gene promoter regions that affect expression of suppressor gene Septin9 (SEPT9), which serves as a marker for conditions such as colorectal cancer.
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score (Decipher)
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP])
81599	Unlisted multianalyte assay with algorithmic analysis
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier. Lab tests for alpha-fetoprotein and for mRNA gene expression profiling for 161 genes using fresh tumor tissue from hepatocellular carcinoma. The test also includes an algorithmic analysis using patient data and the lab test results to report a risk classification score.
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma. Lab tests for mRNA gene expression profiling for five genes listed in the code and carries out an algorithmic analysis using patient data and the lab test results to report a risk score for urothelial carcinoma, such as bladder cancer.
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)



Code	Not Medically Necessary
0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score.
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant) - myPath Melanoma
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score. Uses RNA amplification and fluorescence labeling to detect two genes (TMPRSS2-ERG and PCA3) specific for prostate cancer, which are entered into a proprietary algorithm along with serum PSA level to develop a risk score for prostate cancer.
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)
0258U	Autoimmune (psoriasis), mRNA, next-generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high) - ThyroSeq® CRC. Using a thyroid specimen such as fine needle aspiration (FNA) or formalin-fixed paraffin-embedded (FFPE) tissue, the test examines 112 genes using next-generation sequencing (NGS) and performs an algorithmic analysis to report a risk for cancer recurrence of low, intermediate, or high.
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score - DetermaRx™. Using a non-small cell lung cancer (NSCLC) formalin-fixed paraffin-embedded (FFPE) tissue specimen, the test examines messenger RNA (mRNA) gene expression of the 11 genes listed in the code descriptor using polymerase chain reaction (PCR). The test includes an algorithmic analysis of findings to report a recurrence risk score for NSCLC.
0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score - MindX Blood Test™ - Memory/Alzheimer's
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0294U	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score - MindX Blood Test™ - Longevity
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing of at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)

Code	Not Medically Necessary
0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B). Castle Biosciences, Inc. Using formalin-fixed paraffin-embedded (FFPE) tissue from a skin lesion diagnosed as squamous cell carcinoma (SCC), the test uses reverse-transcription polymerase chain reaction (RT-PCR) gene expression profiling to analyze the specimen for the activity of 40 genes (34 content and 6 housekeeping). An algorithmic analysis of the findings categorizes the risk of metastasis as Class 1 (low risk), Class 2A (moderate risk), and Class 2B (high risk).
0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm-generated evaluation reported as decreased or increased risk for lung cancer
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer. The test extracts and analyzes relevant small RNA segments from a urine specimen and performs an algorithmic analysis to classify and monitor prostate cancer risk without invasive procedures such as biopsy.
0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence. NavDx®, Naveris, Inc, Naveris, Inc
0362U	Oncology (papillary thyroid cancer), gene expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes. The test evaluates a formalin-fixed paraffin-embedded (FFPE) tissue specimen from a patient with papillary thyroid cancer for expression of 82 genes and uses an algorithmic analysis to classify the molecular subtype as it relates to risk of recurrence.
0363U	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer. A proprietary laboratory analysis that evaluates a plasma specimen for eight gene mutations and seven gene methylation markers from circulating cell-free DNA (cfDNA) using quantitative polymerase chain reaction (qPCR) methodology.
0389U	KawasakiDx, OncoOmicsDx Laboratory from mProbe. The test evaluates a patient blood specimen for RNA expression of two genes listed in the code and reports a risk score for Kawasaki disease (KD), a fever of unknown origin in children.
0401U	CARDIO inCodeScore (CICSCORE) from GENinCode U.S. Inc. Using a blood, saliva, or buccal (cheek) swab specimen, the test evaluates 12 variants of nine genes associated with risk of coronary heart disease (CHD)
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer
0414U	Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker
0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma
0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer
0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
0437U	Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT],

<b>Code</b>	<b>Not Medically Necessary</b>
	cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD

## ICD-10 Diagnosis

Refer to the ICD-10 CM manual

## History

Status	Review Date	Effective Date	Action
Revised	01/23/2024	10/20/2024	Independent Multispecialty Physician Panel (IMPP) review. Broadened guideline scope to include polygenic expression prognostic testing and multivariable prognostic genetic testing, both considered not medically necessary (unless indicated in another CMBM guideline). Retitled guideline to Predictive and Prognostic Polygenic Testing to address this change in scope. Added references. Added CPT codes 81313, 81401, 81504, 81551, 81599, 0019U, 0069U, 0089U, 0414U (NMN).
Updated codes 03/17/2024	n/a	Unchanged	Added CPT codes 81525, 81540, 0016M, 0017M, 0045U, 0090U, 0120U, 0253U, 0314U, 0339U, 0403U, 0439U, 0440U. Removed 0004M, 0205U. Updated 0368U code description. Added required language per new Medicare regulations.
Updated	n/a	01/01/2024	Annual CPT update: Added 81327, 81529, 81541, 81542, 81552, 81554, 0004M, 0005U, 0006M, 0011M, 0012M, 0013M, 0047U, 0113U, 0170U, 0203U, 0205U, 0258U, 0287U, 0288U, 0290U, 0291U, 0292U, 0293U, 0296U, 0313U, 0315U, 0317U, 0343U, 0356U, 0362U, 0363U, 0368U, 0389U, 0401U, 0420U, 0424U, 0433U, 0437U.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.