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Clinical Appropriateness Guidelines

# Genetic Testing

# Appropriate Use Criteria: Predictive and Prognostic Polygenic Testing

**Proprietary**

# Table of Contents

# 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. 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

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.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

## Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

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

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

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 ongoing 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 an asymptomatic individual or 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, RNA, RNA fusion products, proteins, methylation, etc.) into an algorithmic risk score. The risk score offers to predict if an asymptomatic or 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 for Genetic Testing (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 scores (PRS) evaluate multiple inherited DNA single nucleotide polymorphisms (SNP) in the human genome. PRS reflect the cumulative weighted risk of individual genetic variation for a set of traits. These individual genetic variants confer an incrementally small disease risk, but summated, they may improve prediction of certain common chronic diseases.[1] Common conditions can include diabetes mellitus type II, Alzheimer's disease, cancer types 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). Genome-wide association studies (GWAS) conducted over the past decade have been the technique used to examine 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.[1,2] PGS

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.[3] 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.[1,4,5] 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.[6] The American College of Medical Genetics and Genomics (ACMG) and National Comprehensive Cancer Network (NCCN) do not support the use of PRS to inform medical management due to limited evidence of clinical utility. ACMG has summarized key points to consider with PRS. Summarized below are six of those points that help illustrate the limitations of PRS[4,7]:

1. PRS test results do not provide a diagnosis, instead they provide a statistical prediction of increased clinical risk
2. A low PRS does not rule out significant risk for the disease in question
3. If the risk prediction of a PRS is derived from a population that is different from the patient being tested, then the results may have a poor predictive value for the patient
4. Isolated PRS testing is not the appropriate test for clinical scenarios in which monogenic etiology is known or suspected
5. Before testing, a patient and provider should discuss the indications for the PRS test, and the patient should be informed how the PRS results will be used to guide medical management
6. PRS-based medical management should be evidence-based; however, there is currently limited evidence to support the use of PRS to guide medical management

Future research in this realm is focused on addressing the lack of diversity in these data by enrolling non-European participants in newer biobanks and including rare variants in the scores. Efforts are ongoing to base polygenic risk prediction using methods other than genome-wide association studies such as using machine learning, Bayesian regression, neural networks and other methods. Most importantly, use of PRS for specific aspects of medical management need to be investigated in prospective clinical trials to demonstrate not only that PRS can improve predictions, but that providers and patients can use PRS to improve medical care and outcomes (i.e. to demonstrate clinical utility). Although PGS is not ready for clinical implementation currently, large clinical trials are in progress seeking to further evaluate various polygenic risk scores.[3,8]

## Polygenic expression prognostic testing (RNA)

Polygenic expression prognostic testing evaluates RNA 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). The scientific literature is teeming with speculative and exploratory studies investigating the diagnostic potential and clinical validity of various RNA biomarkers. Laboratories are developing and marketing tests based on this preliminary data; however, the clinical utility of polygenic expression prognostic testing with few exceptions has not been proven.[9-14] This includes polygenic gene expression tests screening for or evaluating suspicion for autoimmune diseases, cardiac diseases, pain, psychiatric conditions and some cancers, etc. While clinical research has been performed for a few of these conditions, large prospective studies are still needed to determine clinical utility.[5, 15-17]

### Hematuria/Bladder Cancer

Hematuria is common and raises concerns for underlying malignancy.[18] About 2-5% of individuals with microscopic hematuria have urothelial cancer, and thus the standard of care is that many patients undergo cystoscopy although low risk patients may be offered surveillance per guideline of the American Urological Association. There has been exploration in search of a urinary biomarker testing strategy with high enough negative predictive value to safely reduce the burden of cystoscopy in this population. One small prospective study involved a comparison of 81 patients in the biomarker test arm to 54 patients in the control arm.[19] The authors cite several major limitations due to missing data. Too many patients who did not have cystoscopy were lost to follow-up. Also, the study's risk stratification did not align with American Urological Association 2020 guidelines on the evaluation of patients with hematuria using a risk-based approach whereby low-risk patients may be offered the option of surveillance rather than immediate cystoscopy. Currently, the American Urological Association and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction jointly recommend against the use of urine-based tumor markers in the initial evaluation of patients with microhematuria.[18]

### Melanoma

Commercially available gene expression classifiers have been developed and clinically validated to distinguish benign lesions from malignant neoplasms. For example, a 23-gene classifier (MyPath Melanoma) was shown to have up to 92% sensitivity and 93% specificity at distinguishing benign from malignant lesions.[20-22] The clinical utility related to use of this kind of testing has not been demonstrated. Prospective studies controlling the risk of bias and including clinically meaningful outcomes are

needed to better understand the role of techniques used to clarify the diagnosis of the target subset of difficult to diagnose melanocytic lesions.

### Lung Cancer

The diagnosis of lung cancer is based on the microscopic exam of tissue or liquid. Various studies have explored the role of micro-RNA and metabolites for their potential as diagnostic biomarkers for lung cancer. A meta-analysis of 79 studies demonstrated that although there are a vast number of biomarkers, techniques and non-tissue sample types being evaluated for diagnostic value in lung cancer,[23] the test properties and predictive value of such tests is inadequate at this point. Prospective studies need to be performed to inform the clinical utility of any specific approach.

### Prostate Cancer

Several proprietary screening and diagnostic marker assays (e.g., EpiSwitch® Prostate Screening Test, ExoDx, miR SentinelTM Prostate Cancer Test, MyProstateScore 2.0, SelectMDx, and Progensa, among others) exist, and vary in testing methodology, some of which are FDA-approved. The use of such assays include assistance in evaluating general/early diagnosis, identifying clinically significant disease, and deciding whether to repeat biopsy. Although there is interest in further exploration of these assays, impactful prospective studies, standardized cut-off scores (when applicable), and routine-testing recommendations from national guidelines are lacking.[24]

For discussion of polygenic expression prognostic testing of cancer tissue samples (tumor biomarker tests), please see the Carelon Guidelines for Somatic Tumor Testing. For discussion of polygenic expression testing of liquid biopsy, see Cell-free DNA Testing (Liquid Biopsy) for the Management of Cancer. 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, RNA, RNA fusion products, proteins, methylation, etc.). Multivariable prognostic genetic testing is typically marketed to asymptomatic individuals, 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.[9-14]

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# 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



### 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) |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 81402 | Molecular pathology procedure, Level 3 (eg, > 10 SNP's 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) |
| 81403 | Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) |
| 81404 | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) |
| 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 81406 | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) |
| 81407 | Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) |
| 81408 | Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) |
| 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 |
| 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 |

| Code | Not Medically Necessary |
|---|---|
| 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 |
| 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 |
| 0005U | Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score |
| 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 |
| 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) |
| 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 |
| 0114U | Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus |
| 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 |
| 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) |
| 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) |
| 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 |
| 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 |

| Code | Not Medically Necessary |
|---|---|
| 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 urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer |
| 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) of 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], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD |
| 0466U | Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease |
| 0500U | Auto-inflammatory disease (VEXAS syndrome), DNA, UBA1 gene mutations, targeted variant analysis (M41T, M41V, M41L, c.118-2A>C, c.118-1G>C, c.118- 9_118-2del, S56F, S621C) |
| 0506U | Gastroenterology (Barrett's esophagus), esophageal cells, DNA methylation analysis by next-generation sequencing of at least 89 differentially methylated genomic regions, algorithm reported as likelihood for Barrett's esophagus |
| 0529U | Hematology (venous thromboembolism [VTE]), genome-wide single-nucleotide polymorphism variants, including F2 and F5 gene analysis, and Leiden variant, by microarray analysis, saliva, report as risk score for VTE |

### ICD-10 Diagnosis

Refer to the ICD-10 CM manual

# History

| Status | Review Date | Effective Date | Action |
|---|---|---|---|
| Updated codes 01/01/2025 | n/a | Unchanged | CPT code update: added 0529U (NMN); removed termed 0456U (NMN). |
| Reaffirmed | 10/28/2024 | Unchanged | Independent Multispecialty Physician Panel (IMPP) review. Guideline reaffirmed. Edited the Description/Scope, Rationale, and References. |
| Revised | 01/23/2024 | 10/20/2024 | 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 81401, 81599, in addition to 81313, 81504, 81551, 0019U, 0069U, 0089U, and 0114U (moved from Somatic Tumor Testing guidelines). |

| Status | Review Date | Effective Date | Action |
|---|---|---|---|
| Updated codes 10/01/2024 | n/a | Unchanged | Added CPT codes 81402, 81403, 81404, 81405, 81406, 81407, 81408, 0500U, 0506U (NMN). Removed/Moved to Cell-free DNA Testing (Liquid Biopsy) for Cancer guideline: 81327, 0011M, 0356U, 0368U. Removed/Moved to Somatic Tumor Testing guideline: 81525, 81529, 81540, 81541, 81542, 81552, 0006M, 0013M, 0016M, 0017M, 0020M, 0045U, 0047U, 0120U, 0287U, 0288U, 0315U, 0343U, 0362U. Updated descriptions for 0006M, 0012M, 0090U, 0113U, 0287U, 0288U, 0315U, 0343U, 0362U, 0368U, and 0403U. |
| Updated codes 07/01/2024 | n/a | Unchanged | Added new CPT codes 0020M, 0456U, 0466U (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 to General Clinical Guideline 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. |