MEDICAL POLICY

POLICY TITLE	INVESTIGATIONAL MISCELLANEOUS GENETIC AND MOLECULAR DIAGNOSTIC TESTS
POLICY NUMBER	MP 2.277

Effective Date:	4/1/2024

I. POLICY

All of the tests listed in this policy are considered **investigational**, and are grouped according to the categories of genetic testing as outlined in MP 2.326, General Approach to Genetic Testing:

- Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
- Diagnostic testing
- Prognostic testing
- Therapeutic testing
- Testing an asymptomatic individual to determine future risk of disease.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these tests.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

POLICY GUIDELINES

Genetic testing is considered **investigational** when criteria are not met, including when there is insufficient evidence to determine whether the technology improves health outcomes.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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Cross-reference:

MP 2.326 General Approach to Genetic Testing

II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND TOP

There are numerous commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with certain diseases or asymptomatic individuals with future risk. This evidence review evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on the clinical validity for the test. As a result, these tests do not have clinical utility, and the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Tests Addressed in This Medical Policy

Tests assessed in this medical policy are listed in Table 1. All coding information is also found in this Table. Three types of tests are related to testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing): diagnostic testing, prognostic testing, and therapeutic testing. The fourth type of test reviewed is testing of an asymptomatic individual to determine future risk of disease. More information regarding each test, and how they are categorized is provided in detail, after Table 1.

Table 1. Genetic and Molecular Diagnostic Tests in This Medical Policy

All tests listed in this table are considered **investigational** therefore **not covered.**

Test Name	Manufacturer	Coding Information
Avantect Pancreatic Cancer Test	ClearNote Health	0410U
Aventa FusionPlus	Aventa Genomics	0444U
BeScreened-CRC	Beacon Biomedical	0163U
BluePrint	Agendia	81479

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Test Name	Manufacturer	Coding Information
BTG Early Detection of Pancreatic Cancer	Breakthrough Genomics	0405U
Celiac PLUS	Prometheus	81382, 81554, 82784, 83520, 86255, 88346, 88350
ColonSentry®	Stage Zero Life Sciences	81479
Crohn's Prognostic	Prometheus	81401, 81479, 83520, 86021, 86036, 86255, 88346, 88350
Cxbladder Detect	Pacific Edge Diagnostics	0420U
Decipher Bladder TURBT	Veracyte	0016M
DH Optical Genome Mapping Assay	Dartmouth Health/Bionano Genomics	0413U
DNA Methylation Pathway Profile	Great Plains Laboratory	81479
GI Effects® (Stool)	Genova Diagnostics	87045, 87046, 87075, 87102, 87177, 87209, 87328, 87329, 87336, 87798
Guardant360 Response	Guardant Health	0422U
IBScheck®	Commonwealth Diagnostics International	0176U
ibs-smart®	Gemelli Biotech	0164U
Kelch-Like Protein 11 Antibody	Mayo Clinic	0432U
ImmunoGenomic® Profile	Genova Diagnostics	81479
Insight TNBCtype™	Insight Genetics	0153U
Know Error™	Strand Diagnostics	84999
LungLB®, LungLife®	LungLife AI	0317U
LungOI	Imagene AI	0414U
OncoSignal 7 Pathway Signal	Protean Bio-diagnostics	0262U
Oncuria® Predict	DiaCarta Clinical Lab	0365U, 0366U, 0367U
PredictSURE IBD™ Test	KSL Diagnostics	0203U
PreciseType™ HEA	Immucor	0001U
ResponseDX®: Colon	Cancer Genetics	81479
SEPT9 methylated DNA	Several*	81327

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Test Name	Manufacturer	Coding Information
(example ColoVantage and Epi proColon)		

* ARUP, Quest, Clinical Genomics and Epigenomics.

Note: Some genetic tests identified above do not have specific codes; therefore, identification of a code in this section does not denote coverage. When several or all of the codes listed are used to identify these tests they are considered investigational. The list of codes may not be all-inclusive, and are subject to change at any time. Eligibility is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

DIAGNOSTIC TESTS

Multiple Conditions

Single-nucleotide variants (SNVs) are the most common type of genetic variation, and each SNV represents a difference in a single nucleotide in the DNA sequence. Most commonly, SNVs are found in the DNA between genes and can act as biologic markers of genes and disease association. When SNVs occur within a gene or a gene regulatory region, they can play a more direct role in disease by affecting the gene's function. SNVs may predict an individual's response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases.

DNA specimen provenance assays can be used to confirm that tissue specimens are correctly matched to the patient of origin. Specimen provenance errors may occur in up to 1% to 2% of pathology tissue specimens and have serious negative implications for patient care if the error is not corrected. Analysis of DNA microsatellites from tissue specimens can be performed by analyzing long tandem repeats (LTR) and comparing the LTRs of the tissue specimen with LTRs from a patient sample.

Test Description: DNA Methylation Pathway Profile

The DNA Methylation Pathway Profile (Great Plains Laboratory) analyzes SNVs associated with certain biochemical processes, including methionine metabolism, detoxification, hormone imbalances, and vitamin D function. Intended uses for the test include clarification of a diagnosis suggested by other testing and as an indication for supplements and diet modifications.

Test Description: Know Error DNA Specimen Provenance Assay

The Know Error test (Strand Diagnostics) compares the LTRs of tissue samples with LTRs from a buccal swab of the patient. The intended use of the test is to confirm tissue of origin and avoid specimen provenance errors due to switching of patient samples, mislabeling, or sample contamination.

Breast Cancer

Breast cancer is the most common noncutaneous cancer in U.S. women, with an estimated 51,400 cases of female breast ductal carcinoma *in situ* and 287,850 cases of invasive disease in 2022. Breast cancer also affects men and children and may occur during pregnancy, although it is rare in these populations**.** Classification of breast cancer into molecular subtypes may be important for the proper selection of therapy, as tumors with seemingly similar histopathological features can have strikingly different clinical outcomes.

Test Description: BluePrint

BluePrint, a molecular subtyping test, analyzes 80 genes that distinguish between three tumor subtypes; Luminal-type, HER2-type and Basal-Type. Blueprint may enable rationalization in patient selection for either chemotherapy or endocrine therapy prescription.

Test Description: Insight TNBCtype™

Uses next-generation sequencing of 101 genes to generate 5 molecular subtypes, as well as a complementary immunomodulatory classifier to help predict response to immuno-oncology therapies. This may include directing selection and combination of chemotherapies, as well as to support development of novel TNBC targeted therapeutics and diagnostics.

Celiac Disease

Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in patients who carry at least 1 human leukocyte antigen DQ2 or DQ8 allele; the negative predictive value of having neither allele exceeds 98%. Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide (DGP) support a diagnosis of celiac disease, but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.

Test Description: Celiac PLUS

Celiac PLUS (Prometheus Therapeutics & Diagnostics) is a panel of 2 genetic and 5 serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies future risk of celiac disease. Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease, serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-deamidated gliadin peptide antibodies, IgG anti-deamidated gliadin peptide, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for disease (e.g., with an affected first-degree relative) or with symptoms suggestive of disease.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the United States and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal

inflammation and disturbances in GI flora. Recommended treatments include dietary restriction and pharmacologic symptom control. As living microorganisms that promote health when administered to a host in therapeutic doses, probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials (RCTs) have found evidence to support efficacy, but results from recent RCTs have been mixed. This discrepancy may be due in part to the differential effects of different probiotic strains and doses.

Test Descriptions: IBScheck® and ibs-smart

The IBScheck® is designed to assist with diagnosis of diarrhea-predominant or mixed-symptom irritable bowel syndrome. This based blood test designed to detect the presence of two antibodies: anti-vinculin and anti-CdtB. The ibs-smart tests a patient's blood to assist in the diagnosis of diarrhea-predominant and mixed-type irritable bowel syndrome. Blood is tested for anti-CdtB and anti-vinculin.

Inflammatory Bowel Disease

Inflammatory bowel disease is comprised of two major disorders: ulcerative colitis and Crohn disease. Ulcerative colitis affects the colon, whereas Crohn disease can involve any component of the gastrointestinal tract[77]. Ulcerative colitis is characterized by recurring episodes of inflammation to the mucosal layer of the colon. Patients usually present with diarrhea which may be associated with blood.[78] Crohn disease may have a similar presentation to ulcerative colitis, patients typically have abdominal pain, diarrhea, fatigue and weight loss.

Test Description: GI Effects Comprehensive Stool Profile

The GI Effects Comprehensive Stool Profile (Genova Diagnostics) is a multianalyte stool assay. The test uses polymerase chain reaction (PCR) to quantify 26 commensal gut bacteria and standard biochemical and culture methods to measure levels of other stool components (e.g., lipids, fecal occult blood) and potential pathogens (ova and parasites, opportunistic bacteria, yeast). The test is purported to optimize management of gut health and to differentiate IBS from inflammatory bowel disease (IBD).

Test Description: PredictSURE IBD™

This blood test is a RT-qPCR test that extracts RNA to generate gene expression data which, combined with proprietary software algorithm, is used to stratify patients with Crohn disease or ulcerative colitis into high- and low-risk sub-groups.

Colon Cancer

Early detection of colorectal cancer (CRC) reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy. A simpler screening blood test may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (*SEPT9*). The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of *SEPT9* is reduced.

A cofounder of the biotechnology firm GeneNews developed a patented platform technology based on the sentinel principle. The sentinel principle posits that because blood interacts with all bodily tissues, "subtle changes occurring in association with injury or disease, within the cells and tissues of the body, may trigger specific changes in gene expression in blood cells reflective of the initiating stimulus." In this way, blood cells (specifically, leukocytes) may act as sentinels of disease. In studies that led to the formulation of this principle, investigators compared gene expression (total RNA levels) in blood samples with cataloged genes from 9 different organs (brain, colon, heart, kidney, liver, lung, prostate, spleen, stomach) and estimated that 66% to 82% of genes encoded in the human genome are expressed in human leukocytes.

***Test Descriptions: SEPT9* Methylated DNA**

ColoVantage tests serum for *SEPT9* methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration (FDA) approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp.

ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers, probes).

Gene Expression Profiling

Test Description: ColonSentry

ColonSentry (Stage Zero Life Sciences) is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with controls: *ANXA3*, *CLEC4D*, *TNFAIP6*, *LMNB1*, *PRRG4*, *VNN1*, and *IL2RB*. The test is intended to stratify average-risk adults who are non-compliant with colonoscopy and/or fecal occult blood testing. "Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules."

Test Description: BeScreened

BeScreened-CRC (Beacon Biomedical) is a PCR assay that uses a blood sample to detect the expression of 3 protein biomarkers: teratocarcinoma derived growth factor-1 (TDGF-1, Cripto-1); carcinoembryonic antigen, a well-established biomarker associated with CRC; and an extracellular matrix protein involved in early stage tumor stroma changes.

Lung Nodules

Test Description: LungLB®

LungLB® is an AI-enhanced, blood-based test to stratify cancerous and benign lung nodules identified by CT scan and is designed to support a physician's decision to biopsy or to monitor non-invasively using additional imaging. The test utilizes well-established FISH (Fluorescence in situ hybridization) techniques to identify rare target cells isolated from whole blood.

PROGNOSTIC TESTS

Crohn Disease

Recent studies have identified serologic- and genetic correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

Test Description: Crohn's Prognostic

Crohn's Prognostic (Prometheus Therapeutics & Diagnostics) is a panel of 6 serologic (n=3) and genetic (n=3) biomarkers. Limited information about the test is available on the manufacturer's website.

THERAPEUTIC TESTS

Test Description: ResponseDX: Colon

Response Genetics currently markets 2 colon cancer genetic panels to guide treatment selection, as well as separate tests for 11 genes associated with colon cancer prognosis and/or treatment response. The Driver Profile panel comprises PCR variant testing in *KRAS*, *BRAF*, and mismatch repair genes (microsatellite instability), plus *NRAS* exon 2 and 3 sequencing. These gene tests are reviewed elsewhere (see evidence reviews 5.013and 2.316), and this panel is not considered here. The ResponseDX: Colon test comprises the 4 tests in the Driver Profile plus: EGFR expression; PI3K exon 1, 9, and 20 sequencing; TS expression; ERCC1 expression; UGT1A1 SNV testing (rs8175347, rs4148323); VEGFR2 expression; and MET amplification by fluorescence in situ hybridization.

Test Description: Decipher Bladder

Decipher Bladder is indicated for individuals considering neoadjuvant chemotherapy (NAC) prior to a radical cystectomy. The test uses mRNA bladder oncology microarray gene expression profiling of 209 genes reported as an algorithm for molecular subtyping. Bladder tumors are classified into four molecular subtypes.

Test Description: OncoSignal 7 Pathways Signal

OncoSignal utilizes mRNA transcriptional measurements to accurately calculate the pathway activity of seven key oncogenic signaling pathways. The tissue testing method could be used to better analyze breast and other cancers to improve therapy selection for cancer patients.

Tests for Future Risk of Disease

Immunologic Disorders

Test Description: ImmunoGenomic Profile

The ImmunoGenomic Profile (Genova Diagnostics) is a buccal swab test that evaluates SNVs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1b, IL-4, IL-6, and tumor necrosis factor α. According to the company website, variations in these genes "can affect balance between cell (Th-1) and humoral (Th-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive

inflammatory responses." "The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and *Helicobacter pylori* infection (cause of ulcers)."

Other

Test Description: PreciseType™ HEA

PreciseType™ HEA test is a multiplexed molecular assay that generates detailed molecular information from patient and donor samples, rapidly detecting genotypes for accurate prediction of phenotypes which can assist in determining donor-patient compatibility. This test screens blood donors and recipients to prevent a mismatch via molecular typing of red blood cell antigens.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic tests evaluated in this evidence review are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed under the CLIA for high-complexity testing. To date, the Food and Drug Administration has chosen not to require any regulatory review of these tests.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. If it is determined that enough evidence has accumulated to reevaluate its potential clinical utility, the test will be removed from this evidence review and addressed separately. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test.

Diagnostic Testing

For individuals with symptoms of various conditions thought to be hereditary or with a known genetic component who receive diagnostic testing with a miscellaneous genetic or molecular test (e.g., DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects [Stool], BluePrint, LungLB®), the evidence is limited. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Prognostic Testing

For individuals who are diagnosed with various conditions who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., Crohn's Prognostic), there are no published studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Therapeutic Testing

For individuals who are diagnosed with various conditions (e.g., colorectal cancer) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., ResponseDX: Colon), no evidence was identified. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Testing for Future Risk of Disease

For individuals with a family history of various conditions thought to be hereditary or with a known genetic component who receive testing for future risk of disease with a miscellaneous genetic or molecular test (e.g., ImmunoGenomic Profile), no evidence was identified. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a

specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.277	**12/30/21 Major review.** Policy title updated (added "Investigational")_ Removed: DecisionDx-Thymoma and TransPredict FC gamma 3A (no longer marketed). Removed G6PD testing from coding section (see MP 2.326) Added: BeScreened, ibs-smart (moved from MP 4.002 policy) and insight TNBC. Added tests listed in coding section to table 1: Decipher Bladder, IBSChek, Oncosignal 7 and PreductSURE IBC. Added coding for Crohns Prognostic to align with company website. Removed 5 columns from table 1 (date added, diagnostic, therapeutic, prognostic and future risk) and added one column (coding information). Coding information from the bottom of the policy was moved to coding information column in Table 1.

POLICY TITLE	INVESTIGATIONAL MISCELLANEOUS GENETIC AND MOLECULAR DIAGNOSTIC TESTS
POLICY NUMBER	MP 2.277

	Description/background updated. Updated references. Added NCCN statement.
	3/13/22 Administrative update. New code added 0317U; effective 4-1-22.
	12/29/22 Consensus review. No change to policy statement, all tests on policy remain. Reformatted and updated background to include OncoSignal 7 and LungLB®. Updated references.
	3/16/23 Administrative update. New codes added 0365U, 0366U & 0367U; effective 4-1-23.
	9/7/23 Administrative update. New codes added 0405U, 0410U, 0413U, 0414U. Effective 10/1/2023.
	12/12/23 Administrative update. Added 0420U, 0422U, and 0432U. Effective 1/1/2024.
	3/15/24 Administrative update. Added 0444U. Effective 4/1/24.

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