Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Polymetabolite Urine Testing for Adenomatous Polyps

Description/Background

PolypDx™ is a non-invasive urine-based diagnostic test developed by Atlantic Diagnostic laboratories (ADL) for the detection of adenomatous polyps, which can be the precursor to colorectal cancer. The assay uses triple-quad mass spectrometry to measure the levels of three metabolites in patient's urine: ascorbic acid, succinic acid, and carnitine.

PolypDx is intended for use in healthy patients who should, according to standard guidelines, receive regular colonoscopies to check for tumors or precancerous polyps. That includes patients between ages 50 and 74 who have no family history of the disease, and patients between 40 and 74 who do have a family history.

PolypDx is the flagship product of Metabolomic Technologies Inc. (MTI), a privately held Canadian company based in Edmonton, Alberta. MTI has signed a multi-million dollar agreement with ADL giving them the exclusive licensing and distribution rights to bring PolypDx into the US market. Metabolomics refers to the study of metabolite biomarkers ('metabolites'), which are tiny molecules produced by human cells at the end of cellular activities (i.e. energy consumption). Since metabolites are produced as an end product of cell activities, there is a unique opportunity to see what has already occurred in the cells. Metabolomics is also defined as the quantification of low molecular weight compounds (metabolites) generated by metabolism.

A non-exclusive licensing and distribution agreement signed between MTI and Evolution Laboratories in association with Lab Express, LLC, provides additional entry points into five western U.S. states including Nevada, California, Arizona, Utah and Texas. An exclusive, multi-million dollar licensing and distribution agreement signed back in May, 2016, between MTI and Atlantic Diagnostic Laboratories, LLC, facilitated the initial introduction of PolypDx™ across twelve eastern states.

Regulatory Status

PolypDx™ is not currently FDA approved. PolypDx™ is currently available as a laboratory developed test (LDT) through Clinical Laboratory Improvement Amendments (CLIA) certified laboratories.

Medical Policy Statement

The peer reviewed medical literature has not demonstrated the clinical utility of triple-quad mass spectrometry to measure the levels of three metabolites in patient's urine: ascorbic acid, succinic acid, and carnitine, for the detection of adenomatous polyps. Therefore, this service is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0002U

Rationale

Version 1.0 of the nuclear magnetic resonance (NMR)-based PolypDx™ test for colonic polyps was developed and validated using 1,200 samples collected in a clinical trial attached to the Edmonton (Canada) colon cancer screening program (SCOPE) in conjunction with Alberta Health Services (formerly, Capital Health). This clinical trial compared the sensitivity and specificity of the urine metabolomics test (PolypDx™) and fecal-based tests (fecal-guaiac and fecal-immune) relative to the gold standard of full colonoscopy by expert gastroenterologists. Based on results of the 1,200 patient clinical trial, the manufacturers found that the urine-based test could detect polyps with a sensitivity of 71 per cent. In contrast, standard of care fecal-based tests are designed to detect colorectal cancer, not colonic polyps. When used to detect polyps, fecal-based tests have sensitivities of 1 to 15 per cent. Therefore, in their opinion, the PolypDx™ test represents a significant advance in polyp detection.

Apart from the trials and tribulations associated with running a large scale clinical trial, a main hurdle in the development of this test has been identifying key collaborators who are experts in this cutting edge field of research.

There are no peer-reviewed published data or pertinent directions from professional/clinical guidelines for this test.

In a Canadian-based clinical trial study looking at roughly 1,000 Canadian patients, the test detected adenomatous polyps with sensitivity of 82 percent and specificity in the 40 percent range. The sensitivity and specificity of the test may not be as significant a concern given that all tested patients should be undergoing colonoscopies, regardless.

A 2014 article by Wang et al reported on a study wherein prospective urine and stool samples were collected from 876 participants undergoing colonoscopy examination in a colon cancer screening program, from April 2008 to October 2009 at the University of Alberta.[1] Of the 963 participants sequentially enrolled in the colon cancer screening program and completing colonoscopy, results from 876 were used to determine the urine-based metabolomic diagnostic test for colonic adenomatous polyps. The remaining 87 were excluded because of incomplete colonoscopy, corrupted urine samples, or other diagnoses found at the time of colonoscopy. Colonoscopy reference standard identified 633 participants with no colonic polyps and 243 with colonic adenomatous polyps. One-dimensional nuclear magnetic resonance spectra of urine metabolites were analyzed to define a diagnostic metabolomic profile for colonic adenomas. A urine metabolomic diagnostic test for colonic adenomatous polyps was established using 67% of the samples (un-blinded training set) and validated using the other 33% of the samples (blinded testing set). The urine metabolomic diagnostic test's specificity and sensitivity were compared with those of fecal-based tests. The results of the study showed that using a two-component, orthogonal, partial least-squares model of the metabolomic profile, the un-blinded training set identified patients with colonic adenomatous polyps with 88.9% sensitivity and 50.2%specificity. Validation using the blinded testing set confirmed sensitivity and specificity values of 82.7% and 51.2%, respectively. Sensitivities of fecal-based tests to identify colonic adenomas ranged from 2.5 to 11.9%. The authors concluded that a this was a proof-of-concept spot urine-based metabolomic diagnostic test that properly identifies patients with colonic adenomatous polyps with a greater level of sensitivity (83%) than fecal-based tests.

In 2017, Deng et al published a report on a study done on urine samples that were collected from 1,000 participants undergoing colonoscopy examination from March 2013 to July 2014 at Minhang District, Shanghai Centre for Disease Control and Prevention.[2] One-dimensional nuclear magnetic resonance spectra of wine metabolites were analyzed to determine the concentrations of three key metabolites used in PolypDx™. The predicted results were then compared to the gold standard for colorectal cancer diagnosis, colonoscopy. Area under curve (AUC) was calculated specifically for the Chinese population and compared with the Canadian dataset. Sensitivity and specificity of this urine-based metabolomic diagnostic test were also compared with three commercially available fecal-based tests. The results showed that an AUC of 0.717 for PolypDx™ was calculated on Chinese dataset which is slightly lower than the AUC on the Canadian dataset. A sensitivity of 82.6% and a specificity of 42.4% were achieved on Chinese dataset. The authors concluded that a novel urine-based metabolomic diagnostic test for the detection of adenomatous polyps, PolypDx™, on Chinese population through a sample size of 1000 participants had a greater level of sensitivity than fecal-based tests.

Deng et al (2019) reported on a multicenter study assessing the potential clinical utility of urine-based testing for detection of colorectal cancer. There were 342 participants (171 colorectal cancer; 171 healthy controls) from two study sites in Canada and the U.S. Targeted liquid chromatography-mass spectrometry (LC-MS) was performed to quantify 140 highly valuable metabolites in each urine sample. Potential biomarkers for colorectal cancer were identified by comparing the metabolomic profiles from colorectal cancer versus controls. A panel of 17 metabolites was identified as possible biomarkers for colorectal cancer. Using only two of the selected metabolites, namely diacetylspermine and kynurenine, a predictor for detecting colorectal cancer was developed with an AUC of 0.864, a specificity of 80.0%, and a sensitivity of 80.0%. Additional research is needed to confirm the clinical utility of the metabolic biomarker panel for colorectal cancer screening.

Additional randomized, controlled clinical trials are needed to confirm this test's sensitivity and specificity and effect and patient's clinical outcomes.

SUPPLEMENTAL INFORMATION

Ongoing and Unpublished Clinical Trials

One unpublished study was identified that may influence the outcome of this evaluation, see Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT03173729	Point of Care Test to Diagnose Colorectal Cancer and Polyps in Low Middle Income Countries	926	Dec 2023

NCT: national clinical trial

PRACTICE GUIDELINES AND POSITION STATEMENTS

There are no professional guidelines for colorectal cancer screening that include recommendations for urine-based testing for detection of colon polyps.

U.S. Multi-Society Task Force on Colorectal Cancer

- First-tier tests
  Colonoscopy every 10 years and annual fecal immunochemical test (FIT) are recommended as the cornerstones of screening regardless of how screening is offered. Patients should first be offered colonoscopy, followed by FIT for patients who decline colonoscopy. Colonoscopy and FIT should be recommended as tests of choice when multiple options are presented as alternatives. It is appropriate to use colonoscopy screening in high prevalence populations and FIT screening in populations with an estimated low prevalence of advanced neoplasia, as well as in organized screening programs.
- Second-tier tests
  These tests are appropriate screening tests, but each has disadvantages relative to the tier one tests:
  - CT colonography every five years.

- FIT–fecal DNA test every three years.
- Flexible sigmoidoscopy every five to 10 years.

- Third-tier test
  - Capsule colonoscopy every five years is recommended as a third-tier test due to limited evidence and current obstacles to use.

The task force suggests that the Septin9 serum assay (Epigenomics, Seattle, Wash) not be used for screening. The Task Force does not mention the Polymetabolite urine testing in any of its recommendations.

National Comprehensive Cancer Network (NCCN)
NCCN Guidelines for Colon Cancer, V.3.2024: Urine-based testing for detection of colon polyps is not mentioned in the NCCN guidelines.

Government Regulations
National/Local:

There is no national or local coverage determination addressing urine-based testing for detection of colon polyps.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer (e.g., Coloprint, Colon PRS, GeneFx, OncoDefender, Oncotype Dx® Colon Cancer Test)
- Genetic Testing - Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS,BRAF, MMR/MSI, HER2, and TMB)
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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References

1. Chang, David. PolypDx™-Diagnosis for Prevention. Canada-Taiwan Cancer Prevention, Diagnosis and Treatment Forum. Presentation available at http://www.albertacanada.com/taiwan/documents/03-MTI-Canada-Taiwan-Cancer-Forum.pdf (6/27/17).
2. Deng L, Chang D, Foshaug RR, Eisner R, Tso VK, Wishart DS and Fedorak RK. Development and Validation of a High-Throughput Mass Spectrometry Based Urine Metabolomic Test for the Detection of Colonic Adenomatous Polyps. Metabolites 2017, 7, 32. Available at https://pubmed.ncbi.nlm.nih.gov/28640228/ (Accessed 6/29/23)

3. Deng L, Fang H, Tso V, Sun Y, et al. Clinical validation of a novel urine-based metabolomic test for the detection of colonic polyps on Chinese population. International Journal of Colorectal Disease; v:32 i:5 p:741-743; 5/2017. doi: 10.1038/ajg.2017.174
4. Deng L, Ismond K, Liu Z et al. Urinary Metabolomics to Identify a Unique Biomarker Panel for Detecting Colorectal Cancer: A Multicenter Study. Cancer Epidemiology, Biomarkers & Prevention, Vol 28, Issue 9, August 1, 2019.
5. Rex D, Boland R, Dominitz J et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. American Journal of Gastroenterology: July 2017 - Volume 112 - Issue 7 - p 1016-1030
6. Wang H, Wong C, Sadowski D and Fedorak RN. Development and Validation of a Highly Sensitive Urine-Based Test to Identify Patients with Colonic Adenomatous Polyps. Clinical and Translational Gastroenterology (2014) 5, e54; doi:10.1038/ctg.2014.2 Published online 20 March 2014.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 31, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/17	8/15/17	8/15/17	Joint policy established
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine policy maintenance, no change in policy status.
11/1/20	8/18/20		Routine policy maintenance, no change in policy status.
11/1/21	8/17/21		Routine policy maintenance, no change in policy status.
11/1/22	8/16/22		Routine policy maintenance, no change in policy status.
11/1/23	8/15/23		Routine policy maintenance, no change in policy status. Vendor: N/A. (ky)
11/1/24	8/20/24		Routine policy maintenance, no change in policy status. Vendor: N/A. (ky)

Next Review Date: 3rd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: POLYMETABOLITE URINE TESTING FOR ADENOMATOUS POLYPS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A