BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.121 Miscellaneous Genetic and Molecular Diagnostic Tests

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Related Policies:

2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.10 - Identification of Microorganisms Using Nucleic Acid Probes
2.04.120 - Gene Expression Profiling for Uveal Melanoma
2.04.146 - Gene Expression Profiling for Cutaneous Melanoma
2.04.150 - Serologic Genetic and Molecular Screening for Colorectal Cancer
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)
2.04.68 - Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer
2.04.91 - General Approach to Genetic Testing
2.04.92 - General Approach to Evaluating the Utility of Genetic Panels

Miscellaneous Genetic and Molecular Diagnostic Tests

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether diagnostic, prognostic, or therapeutic, or future risk assessment testing using one of several miscellaneous genetic or molecular diagnostic tests improves the net health outcome in individuals with, or with risk of, one of the various genetic conditions.

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POLICY STATEMENT

All tests listed in this policy are considered **investigational** and grouped according to the categories of genetic testing outlined in evidence review 2.04.91:

- 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.

POLICY GUIDELINES

Genetic testing is considered **investigational** when BCBSA criteria are not met, including when there is insufficient evidence to determine that the technology results in an improvement in the net health outcome.

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

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The ImmunoGenomic Profile (Genova Diagnostics) was a buccal swab test that evaluated 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.][26,] The test was intended to uncover 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. Due to low testing volume, this test was discontinued in February 2022.

RATIONALE

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 (eg, DNA Methylation Pathway Profile, know error , Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic), the evidence is limited. Relevant outcomes are overall survival (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.

Prognostic Testing

For individuals who are diagnosed with various conditions who receive prognostic testing with a miscellaneous genetic or molecular test (eg, Crohn's Prognostic), there are no published studies. 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The NCCN (v.2.2023) guidelines for colon cancer state that it has "not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis."[39,]

American College of Gastroenterology

Celiac Disease

In 2023 , the American College of Gastroenterology published a clinical practice update for the diagnosis and management of celiac disease.[40,] A recommendation for genetic testing using a multigene panel test (eg, Celiac PLUS) was not included.

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Inflammatory Bowel Disease

In 2018, the American College of Gastroenterology practice guidelines on Crohn disease [41], state that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.

Medicare National Coverage

There is no national coverage determination for the tests in this review. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Pfeifer JD, Zehnbauer B, Payton J. The changing spectrum of DNA-based specimen provenance testing in surgical pathology. Am J Clin Pathol. Jan 2011; 135(1): 132-8. PMID 21173135
2. Beauvais W, Fourni G, Jones BA, et al. Modelling the expected rate of laboratory biosafety breakdowns involving rinderpest virus in the post-eradication era. Prev Vet Med. Nov 01 2013; 112(3-4): 248-56. PMID 24029703
3. Pallav K, Kabbani T, Tariq S, et al. Clinical utility of celiac disease-associated HLA testing. Dig Dis Sci. Sep 2014; 59(9): 2199-206. PMID 24705698
4. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut. Jan 2013; 62(1): 43-52. PMID 22345659
5. Prometheus Laboratories. Celiac PLUS. https://www.prometheuslabs.com/disease-tests/celiac-plus/#:~:text=PROMETHEUS%20%C2%AE%20Celiac%20PLUS%20is%20the%20only%20celiac,disease%20to%20be%20ruled%20out%20for%20life%201. Accessed June 2, 2023.
6. Pietzak MM, Schofield TC, McGinniss MJ, et al. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. Clin Gastroenterol Hepatol. Sep 2009; 7(9): 966-71. PMID 19500688
7. Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol. Oct 2014; 109(10): 1547-61; quiz 1546, 1562. PMID 25070051
8. National Institute for Health and Care Excellence (NICE). Irritable bowel syndrome in adults: diagnosis and management [CG61]. 2017; https://www.nice.org.uk/guidance/cg61. Accessed June 2, 2023.
9. McKenzie YA, Alder A, Anderson W, et al. British Dietetic Association evidence-based guidelines for the dietary management of irritable bowel syndrome in adults. J Hum Nutr Diet. Jun 2012; 25(3): 260-74. PMID 22489905
10. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. Nov 2014; 147(5): 1146-8. PMID 25224526
11. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. Aug 2014; 11(8): 506-14. PMID 24912386
12. Trinkley KE, Nahata MC. Treatment of irritable bowel syndrome. J Clin Pharm Ther. Jun 2011; 36(3): 275-82. PMID 21545610
13. Hungin AP, Mulligan C, Pot B, et al. Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice -- an evidence-based international guide. Aliment Pharmacol Ther. Oct 2013; 38(8): 864-86. PMID 23981066
14. Ortiz-Lucas M, Tobas A, Saz P, et al. Effect of probiotic species on irritable bowel syndrome symptoms: A bring up to date meta-analysis. Rev Esp Enferm Dig. Jan 2013; 105(1): 19-36. PMID 23548007
15. Whelan K. Probiotics and prebiotics in the management of irritable bowel syndrome: a review of recent clinical trials and systematic reviews. Curr Opin Clin Nutr Metab Care. Nov 2011; 14(6): 581-7. PMID 21892075
16. Stevenson C, Blaauw R, Fredericks E, et al. Randomized clinical trial: effect of Lactobacillus plantarum 299 v on symptoms of irritable bowel syndrome. Nutrition. Oct 2014; 30(10): 1151-7. PMID 25194614
17. Shavakhi A, Minakari M, Farzamnia S, et al. The effects of multi-strain probiotic compound on symptoms and quality-of-life in patients with irritable bowel syndrome: A randomized placebo-controlled trial. Adv Biomed Res. 2014; 3: 140. PMID 25161987
18. Ludidi S, Jonkers DM, Koning CJ, et al. Randomized clinical trial on the effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients. Neurogastroenterol Motil. May 2014; 26(5): 705-14. PMID 24588932
19. Rogha M, Esfahani MZ, Zargarzadeh AH. The efficacy of a synbiotic containing Bacillus Coagulans in treatment of irritable bowel syndrome: a randomized placebo-controlled trial. Gastroenterol Hepatol Bed Bench. 2014; 7(3): 156-63. PMID 25120896
20. Urgesi R, Casale C, Pistelli R, et al. A randomized double-blind placebo-controlled clinical trial on efficacy and safety of association of simethicone and Bacillus coagulans (Colinox) in patients with irritable bowel syndrome. Eur Rev Med Pharmacol Sci. 2014; 18(9): 1344-53. PMID 24867512
21. Sisson G, Ayis S, Sherwood RA, et al. Randomised clinical trial: A liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome--a 12 week double-blind study. Aliment Pharmacol Ther. Jul 2014; 40(1): 51-62. PMID 24815298
22. Genova Diagnostics. GI Effects Comprehensive Profile - Stool. n.d.; https://www.gdx.net/product/gi-effects- comprehensive-stool-test. Accessed June 2, 2023.
23. Targan SR, Landers CJ, Yang H, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. Gastroenterology. Jun 2005; 128(7): 2020-8. PMID 15940634

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24. Ippoliti A, Devlin S, Mei L, et al. Combination of innate and adaptive immune alterations increased the likelihood of fibrostenosis in Crohn's disease. Inflamm Bowel Dis. Aug 2010; 16(8): 1279-85. PMID 20027650
25. Abreu MT, Taylor KD, Lin YC, et al. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. Gastroenterology. Sep 2002; 123(3): 679-88. PMID 12198692
26. Genova Diagnostics. Immunogenomic Profile. n.d.; https://www.gdx.net/product/immunogenomic-profile-saliva. Accessed June 1, 2023.
27. Pfeifer JD, Singleton MN, Gregory MH, et al. Development of a decision-analytic model for the application of STR-based provenance testing of transrectal prostate biopsy specimens. Value Health. 2012; 15(6): 860-7. PMID 22999136
28. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. May 2013; 108(5): 656-76; quiz 677. PMID 23609613
29. Hanaway P. Ask the experts. Explore (NY). May 2006; 2(3): 284. PMID 16781657
30. Prometheus Laboratories. IBD sgi Diagnostic. https://www.prometheusbiosciences.com/ibd-sgi/ Accessed June 1, 2023.
31. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. Am J Gastroenterol. Nov 2012; 107(11): 1760-1. PMID 23160303
32. Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. Autoimmun Rev. 2014; 13(4-5): 463-6. PMID 24424198
33. Laass MW, Roggenbuck D, Conrad K. Diagnosis and classification of Crohn's disease. Autoimmun Rev. 2014; 13(4-5): 467-71. PMID 24424189
34. Ords I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. Nov 03 2012; 380(9853): 1606-19. PMID 22914296
35. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. Mar 2010; 105(3): 501-23; quiz 524. PMID 20068560
36. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. Nov 03 2012; 380(9853): 1590-605. PMID 22914295
37. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. Management of Crohn's disease in adults. Am J Gastroenterol. Feb 2009; 104(2): 465-83; quiz 464, 484. PMID 19174807
38. Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. Am J Gastroenterol. Oct 2006; 101(10): 2410-22. PMID 16952282
39. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: colon cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 2, 2023.
40. Singh S, Ananthakrishnan AN, Nguyen NH, et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis. Gastroenterology. Mar 2023; 164(3): 344-372. PMID 36822736
41. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. Apr 2018; 113(4): 481-517. PMID 29610508

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through June 1, 2023; no references added. Policy statements unchanged. FEP 2024 Benefit updates. New FEP Policy

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