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Reviewed: 09/26/24

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Subject: Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Gene expression profile (GEP) and circulating tumor DNA (ctDNA) tests have been developed for use as prognostic markers of stage II or III colon cancer to help identify patients who are at high risk for recurrent disease and could be candidates for adjuvant chemotherapy. 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). Multigene expression assay testing and ctDNA testing for predicting recurrent colon cancer are available under the auspices of CLIA.

Summary and Analysis of Evidence: GEP testing for individuals who have stage II or III colon cancer, the evidence includes development and validation studies and decision-impact studies. The available evidence has shown that GEP testing for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage II or III colon cancer. However, the degree of difference in risk conferred by the test is small. Evidence to date does not permit conclusions on whether GEP classification is sufficient to modify treatment decisions in stage II or III patients. Studies showing management changes as a consequence of testing have not demonstrated whether such changes improve outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Circulating tumor DNA (ctDNA) testing for individuals who have stage II or III colon cancer, the evidence includes cohort studies. Several cohort studies have reported an association between positive ctDNA results and risk of recurrence of colon cancer. However, while these studies showed an association between ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients. Management decisions were not based on ctDNA test results. One randomized trial studied management changes

made in response to ctDNA test results compared to other risk factors, but progression-free survival was similar between groups. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. The National Comprehensive Cancer Network (NCCN) guidelines for Colon Cancer (v4.2024) states, "In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy."

POSITION STATEMENT:

Note: Coverage may be governed by state or federal mandates.

Gene expression assays and circulating tumor DNA assays for determining the prognosis of stage ll or stage lll colon cancer following surgery are considered **experimental or investigational.** The evidence is insufficient to permit conclusions on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding

81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score (**Investigational**) [Oncotype DX Colon Cancer Assay]
0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis (**Investigational**) [Colvera]

Unlisted codes 81599, 84999, & 88299 may be used to report other gene expression or circulating tumor DNA assays.

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following were reviewed on the last guideline reviewed date: Local Coverage Determination (LCD) Genetic Testing for Oncology (L39367) and Billing and Coding: Genetic Testing for Oncology (A59123) located at fcso.com.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

None applicable.

OTHER:

Other names used to report gene expression and ctDNA tests:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Colvera® ctDNA
GeneFx® Colon (also known as ColDx)
OncoDefender-CRC™
Oncotype DX® Colon Recurrence Score.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 09/26/24.

GUIDELINE UPDATE INFORMATION:

05/15/10	New Medical Coverage Guideline.
03/15/11	Annual review; position statement maintained and references updated.
03/15/12	Annual review; position statement maintained, Program Exceptions section and references updated.
03/15/13	Annual review; investigational status maintained, position statement, description section, and references updated.
03/15/14	Annual review; position statement maintained, Medicare program exception and references updated.
05/15/14	Revision; references updated.
06/15/15	Annual review; position statement and references updated.
01/01/16	Annual HCPCS/CPT update; code 81525 added.
10/15/16	Revision; description, position statement, program exception, and references updated.
10/15/17	Review; investigational position maintained, description, program exception, and references updated.
10/15/18	Review; investigational position maintained, description, coding, and references updated.
11/15/19	Review; position statement maintained and references updated.
11/15/20	Review; Position statement, title, description, and references updated.
01/01/21	Annual CPT/HCPCS update. Code 0229U added.
10/15/21	Review: Position statement maintained and references updated.
09/15/22	Revision: Program exception section and references updated.
06/15/23	Revision: Note added to the position statement section.
11/15/23	Review: Position statement maintained; program exception and references updated.

10/15/24	Review: Position statement maintained description and references updated.