GUIDELINES
This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION
Gene expression profiling (GEP) is a method of laboratory testing that measures the activity (or expression) of many genes at one time to determine prognosis, refine risk stratification and/or optimize treatment regimens primarily for cancer. Over a dozen different gene expression profile (GEP) tests have been developed and reported for use as prognostic markers in stage II or stage III colon cancer. These assays are intended to help identify patients with stage 2 or stage 3 colon cancer who are at high risk for recurrent disease and would be good candidates for adjuvant chemotherapy. The gene signatures range from as small as 5 to as many as 634 genes. Independent validation studies ranging in size from 33 to 1,436 patients have been reported on these assays.

Four assays are currently being marketed for clinical use in the United States:

Oncotype DX® Colon Cancer Assay is a reverse transcription PCR (RT-PCR)-based profiling test that measures the RNA gene expression pattern of 12 genes (7 associated with recurrence and 5 reference genes) from FFPE tumor tissue from a patient with stage II or stage III colon cancer. A proprietary algorithm is used to calculate a Recurrence Score (RS) that quantifies patient risk for colon cancer recurrence.

ColoPrint® is a microarray-based, 18 GEP designed to predict the risk of distant recurrence of the disease in individuals with stage II and III colon cancer. The ColoPrint test determines the risk of recurrence independent of other risk factors such as T stage, perforation, and tumor grade. Higher recurrence scores are associated with shorter time to progression and shorter overall survival.

GeneFx Colon® is a 634-transcript DNA microarray-based gene signature developed for stage II colon cancer using formalin-fixed and paraffin-embedded (FFPE) specimens. Following surgery, GeneFx Colon assesses the individual's risk of recurrence within 5 years.

OncoDefender-CRC® is a 5-gene assay used to assess the risk of recurrence of cancer in individuals previously treated with surgical resection of stage I or II colon cancer or stage I rectal cancer. Lenehan and colleagues (2012) reported on the development of the OncoDefender. The archived FFPE primary adenocarcinoma tissues of 74 individuals with CRC were used for training/test sets. Of this group, 15 individuals had stage I CRC; 59 had stage II CRC; 60 had colon cancer and 14 had rectal cancer. For external validation, FFPE tissues were obtained from 264 individuals (49 with stage I CRC and 215 with stage II colon cancer) from 18 hospitals in four countries. None of the individuals had received neoadjuvant/adjuvant therapy. A proprietary genetic programming which analyzed the expression profiles for 225 prespecified tumor genes was used to create a 36-month recurrence risk signature. The test appeared to differentiate participants at high- versus low-risk of recurrence with a hazard ratio of 1.63, p=0.031. Sensitivity and specificity of the assay was compared to National Cancer Consortium Network guidelines and demonstrated similar sensitivity (69% vs. 73%) with improved specificity (48% vs. 26%). However, several findings considered to be high-risk by the National Cancer Consortium Network (lymphovascular invasion and bowel obstruction/perforation) demonstrated higher hazard ratios than observed using the molecular signature. Also, isolated performance of the test in individuals with stage II colon cancer was not reported.

In summary, much of the scientific literature for this topic primarily addresses the diagnostic validity and clinical validity of these tests, that is, the ability of the test to detect specific gene variants and the possible association of those variants with development or recurrence of colon cancer. Thus far, there is no information in the published peer-reviewed medical literature demonstrating the clinical utility of GEP assays to improve outcomes in individuals at risk for or with a history of colon cancer.

POLICY
Oncotype DX® Colon is non-covered for HMO, PPO, Individual Marketplace, & Advantage.
Oncotype DX® Colon does not require prior authorization for Elite.

ColoPrint®, GeneFx Colon®, OncoDefender-CRC® are non-covered for all product lines.

HMO, PPO, Individual Marketplace, Advantage
Paramount has determined that multigene expression assays for predicting recurrence in colon cancer (eg, ColoPrint®, GeneFx Colon®, OncoDefender-CRC®, Oncotype DX® Colon) are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of this procedure.

Elite
While there is insufficient evidence in the published medical literature to demonstrate the safety, efficacy and long-term outcomes of Oncotype DX® Colon, CMS requires this test be covered for Elite members.

To report a Oncotype DX® Colon service, submit the following claim information:
- For services prior to 01/01/2016 use CPT code 84999
- For services after 01/01/2016 use CPT code 81525

Paramount has determined that ColoPrint®, GeneFx Colon®, OncoDefender-CRC® are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of this procedure.

CODING/BILLING INFORMATION
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

CPT CODES

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>81525</td>
<td>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 (Effective 01/01/16)</td>
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TAWG REVIEW DATES: 04/22/2016

REVISION HISTORY EXPLANATION
04/22/16: Policy created to reflect most current clinical evidence per TAWG.

REFERENCES/RESOURCES
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid http://jfs.ohio.gov/
American Medical Association, Current Procedural Terminology (CPT®) and associated publications and services
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets
Industry Standard Review
Hayes, Inc.