Policy Name: Gene Expression Profiling for Assessing Cancers of Unknown Origin
Effective Date: 11/18/2019

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

Coverage Policy
Gene expression profiling for assessing cancers of unknown origin is investigative and unproven, and therefore NOT COVERED. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

Description
Cancers of an unknown primary (CUP) origin represent 3% to 4% of cancers diagnosed U.S. With advances in targeted chemotherapy regimens and advances in tumor gene-expression profiling techniques (such as real-time reverse transcriptase-polymerase chain reaction and microarray analysis), work has proceeded in developing assays to identify the primary site of CUPs. It has been purported that identification of a likely primary source using gene expression profiling will improve health outcomes by more accurately directing treatment.

Genetic profiles for various types of CUPs have been compiled into gene expression databases spanning multiple tumor types and many others are under development. Thus, in theory, tissue from a patient with a CUP (either at a primary or a metastatic tumor site) can undergo gene expression profiling and then be compared with known profiles from CUPs. These tests are referred to as molecular cancer classifier assays (MCCAs) and are based on the premise that, even with different degrees of loss of differentiation, CUP tumors retain sufficient gene expression ‘signatures’ to indicate their tissue of origin, even following metastasis, with a high degree of accuracy. Assay results are then compared with the CUP database to aid in identification of the tumor type/organ of origin and assist with targeted pharmacotherapy selection. However, studies are needed to determine whether knowing the tissue of origin in patients with CUP will result in interventions leading to improved long-term treatment outcomes.

In addition to DNA and messenger RNA (mRNA)-based profiles, microRNA (miRNA)-based profiles have been researched for their potential to identify tissue of origin. These miRNAs are noncoding RNAs that regulated gene expression and purport to demonstrate high tissue specificity. Most recently, research has begun using next generation sequencing as a potential means to characterize the genome of occult primary tumors.
FDA Approval
Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations and the test is not marketed for general distribution.

Several tests for gene expression profiling for assessing primary sites of CUPs are commercially available or in development. These include, but are not limited to:
1. Rosetta Cancer Origin Test™
2. CancerTYPE ID®
3. ProOnc Tumor Source Dx™
4. Response DX
5. SourceDX
6. Pathfinder TG

Prior Authorization
Prior authorization is not applicable. Claims for this service are subject to retrospective review and denial of coverage, as investigative services are not eligible for reimbursement.

Coding Considerations
Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT Codes:
- 81479 - Unlisted molecular pathology procedure
- 81504 - Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
- 81540 – Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype
- 81599 – Unlisted multianalyte assay with algorithmic analysis

Original Effective Date: 2/1/2011

Re-Review Date(s):
- 9/24/2013
- 1/4/2016 – administrative update; code 81540 added
- 10/19/2016
- 9/18/2019
- 2/10/2020 – administrative update; format