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Medical Policy

Subject:	**Paired DNA and Messenger RNA (mRNA) Genetic Testing to Detect, Diagnose and Manage Cancer**		
Document#:	**GENE.00054**	**Publish Date:**	**04/15/2020**
Status:	**New**	**Last Review Date:**	**02/20/2020**

Description/Scope

Messenger RNA (mRNA) is the product of RNA transcription, the firsts step in protein synthesis. Testing for DNA in combination with mRNA has been proposed as a method of detecting, diagnosing and managing cancer; in particular, when DNA genetic testing identifies variants of uncertain significance.

Position Statement

Investigational and Not Medically Necessary:

Messenger RNA (mRNA) sequence analysis alone or in conjunction with DNA sequence analysis to aid in the classification of variations of uncertain significance or to otherwise detect, diagnose or manage cancer is considered investigational and not medically necessary.

Rationale

Oncology clinicians use diagnostic genetic testing (DGT) to inform clinical decisions surrounding cancer treatment and surveillance. The clinical utility of germline DGT is dependent upon the ability of the test to identify and characterize inherited disease-causing variants; however, genetic testing is not without limitations. DNA testing alone can identify variants of uncertain significance (VUS), resulting in inconclusive test results with regards to whether a genetic variant increases the risk of an individual developing cancer. Moreover, standard DNA testing for cancer excludes large portions of DNA, thereby omitting some variants that increase an individual's risk of cancer. Similarly, multigene panel testing may identify VUS. Additionally, a substantial proportion of inconclusive results arise from the identification of variants that are associated with abnormal mRNA transcripts but lack functional evidence. Based on the belief that mRNA

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provides considerably more evidence than DNA alone about whether these VUS result in an increased risk for cancer, researchers are exploring the use of combining mRNA with DNA testing to overcome these limitations. It has been hypothesized that clinicians can then use this information to try to prevent cancer from developing or to detect cancer sooner.

In 2019 Ambry Genetics® (Aliso Viejo, CA), announced the launch of +RNAinsight™, an mRNA sequence analysis that can be paired with DNA testing at the same time. It has been hypothesized that this type of paired testing will identify whether an individual has a sequence variant that either may have contributed to their existing cancer or increases their risk for developing cancer in the future. At the time of the writing of this document, Ambry Genetics is the first and only lab to offer paired DNA and mRNA genetic testing to detect, diagnose and mange individuals with an inherited malignant condition. The +RNAinsight™ test is performed in the Amby Genetics CLIA (Clinical Laboratory Improvement Amendments) approved laboratory and as such, does not require approval by the U.S. Food and Drug Administration (FDA). Information on the Ambry Genetics web site also indicates that an mRNA sequence analysis may be ordered in conjunction with the Custom Next (single gene or panel) test.

In the Karam (2019) study, investigators from Ambry Genetics and four collaborating institutions (Dana-Farber Cancer Institute, Cedars-Sinai Medical Center, Rutgers Cancer Institute, and University of Kansas Cancer Center) evaluated the ability of mRNA genetic testing to help determine whether specific VUSs (as identified by DNA testing) could be reclassified according to likely pathogenicity (that is: pathogenic variant; variant, likely pathogenic [VLP]; VUS; variant, likely benign [VLB]; or benign variant); or in other words, whether the variant actually increased an individual's risk of cancer and whether the management of individuals with suspected hereditary cancer predisposition was altered based on those determinations. In this diagnostic study, participants and/or families with inconclusive variants detected by DGT in genes associated with hereditary breast and ovarian cancer, Lynch syndrome, and hereditary diffuse gastric cancer, submitted blood samples for RNA genetic testing (RGT) from March 2016 to April 2018. Clinicians who ordered genetic testing and received a reclassification report for these variants were queried to determine whether RGT-related variant reclassifications changed the clinical management of these individuals. To estimate the potential number of tested individuals who could possibly benefit from RGT, a cohort of 307,812 participants who underwent DGT for hereditary cancer were separately surveyed to identify variants of uncertain significance potentially affecting splicing. Data analysis was conducted during March 2016 through September 2018.

In total, 93 of 909 eligible families (10.2%) submitted samples for RGT, with 64 unique alterations studied; 56 (88%) had been classified as VUS and 8 (13%) as VLP prior to RGT. RGT provided evidence to reclassify the interpretation of 86% of 55 variants analyzed in the study. Of VUS examined, 49 VUS were upgraded to VLP or downgraded to VLB, and 7 VUS were not reclassified because of insufficient evidence or because RGT identified transcripts of unknown significance. Of the VLP examined, 4 were upgraded to pathogenic, 2 were downgraded to VUS, and 2 remained VLP. Additionally, all of the participants who had been previously tested and who had these same VUS, received updated reports. As a result, an additional 322 participants had their inconclusive results clarified as negative, and 88 participants had their inconclusive results clarified as positive (i.e., increased risk for cancer). Of the clinicians who received clarified results and responded to a study survey, 44% modified their care for the patients and 78% changed their care for the patient's relatives based on the RGT results. The study was limited to a small sample of participants tested, and a lack of outcome data (only clinician survey results on possible management was evaluated); the possible benefits and harms of variant reclassification was not evaluated. Given that updated variant classifications were made publicly available at ClinVar, the variants identified in this study will no longer benefit from RGT reclassification (because these variants will continue to be seen in future individuals, these reclassifications have a downstream impact).

While the investigators conclude that RGT could possibly impact the medical management of at least 1 in 50 individuals who have first undergone DNA genetic testing via reclassification of uncertain genetic variants to either benign or disease-causing based on RNA evidence (thus enabling improved application of risk-reducing surgeries and pre-symptomatic screening measures), this claim has not been substantiated by other published studies in the peer-reviewed medical literature. Furthermore, as noted above, as part of routine data sharing with ClinVar, RGT results found in this study would be expected to also affect individuals with the same variants identified through other clinical laboratories. Currently, there is no data available to assess how mRNA testing operates outside a collaborative research setting, or how decision-making based on the results of such testing impacts health outcomes. Use of mRNA testing may be appropriate in the research setting, or to aid publically available repositories of variant classifications; however, clinical application of the technology in the real world remains unclear.

Background/Overview

The primary function of mRNA is to act as an intermediary between the genetic information contained in DNA and the amino acid sequence of proteins. mRNA contains codons that match the sequence of nucleotides on the template DNA and provide instruction for the formation of amino acids.

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Because of the limitations of current DNA genetic testing, including but not limited to the identification of VUS, researchers are exploring the use of DNA paired with mRNA genetic testing as a means to detect, diagnose and managing cancers. RNA genetic testing aims to provide functional evidence to help interpret the whether a DNA variant produces an abnormal (disease) causing protein. Currently, at least one laboratory test, the +RNAinsight™ (Ambry Genetics) has been developed which pairs both DNA and mRNA genetic testing at the same in order to identify VUS that may result in an increased risk for hereditary cancer.

Definitions

Genetic variant: An error in an individual's DNA.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) +RNAinsight™ for ProstateNext®, Ambry Genetics
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis +RNAinsight™ for ATM, Ambry Genetics
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis +RNAinsight™ for PALB2, Ambry Genetics

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0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis +RNAinsight™ for BRCA1/2, Ambry Genetics
0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis CustomNext + RNA: APC, Ambry Genetics®, Ambry Genetics®
0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis CustomNext + RNA: MLH1, Ambry Genetics®, Ambry Genetics®
0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis CustomNext + RNA: MSH2, Ambry Genetics®, Ambry Genetics®
0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis CustomNext + RNA: MSH6, Ambry Genetics®, Ambry Genetics®
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis CustomNext + RNA: PMS2, Ambry Genetics®, Ambry Genetics®
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2), Ambry Genetics®, Ambry Genetics®

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Karam R, Conner B, LaDuca H, et al. Assessment of Diagnostic Outcomes of RNA Genetic Testing for Hereditary Cancer. JAMA Netw Open. 2019; 2(10):e1913900.

Websites for Additional Information

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1. **Ambry Genetics. +RNAinsight™. Beyond DNA for Unparalled Clarity. Available at: https://www.ambrygen.com/clinician/genetic-testing/rna. Accessed on December 14, 2019.**

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Custom Next
+RNAinsight
Paired DNA and Messenger RNA (mRNA) Genetic Testing

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.

Document History

Status	Date	Action
New	02/20/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.