Hereditary Cancer Syndrome Multigene Panels Using Messenger RNA (mRNA)

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DESCRIPTION

When a mutation in a single gene causes a significantly increased risk for certain cancers, it is called a hereditary cancer syndrome. Hereditary cancer syndromes are usually characterized by a pattern of a specific cancer types occurring together in the same family, younger cancer diagnosis ages than usual, and/or other co-existing non-cancer conditions.

Most cancer is sporadic and believed to be caused by a mix of behavioral or lifestyle, environmental, and inherited risk factors. However, about 5-10% of cancers are believed to have a major inherited component.

Per Hampel et. al. (2015) there are more than 50 hereditary cancer syndromes. Some of the most common are listed below with associated cancers:

- Hereditary breast and ovarian cancer syndromes (HBOC): breast, ovarian/fallopian tube/primary peritoneal cancer, pancreatic, prostate cancers.
- Lynch syndrome: colorectal endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors.
- Familial adenomatous polyposis: colorectal and other gastrointestinal cancers, gastrointestinal tract polyps (adenomas, fundic gland), osteomas, desmoids, thyroid cancer and hepatoblastoma.
- MUTYH-associated polyposis: colorectal and other gastrointestinal cancers, adenomas, hyperplastic polyps.
- Cowden syndrome: benign and malignant tumors of the breast, endometrium, and thyroid; cancer and polyps (hamartomas) in the colon and rectum.
- Li-Fraumeni syndrome: soft tissue sarcoma, osteosarcoma, leukemia, melanoma and cancer of the breast, uterine and ovarian cancer.

Many hereditary cancer syndromes can include the same types of cancer and therefore have overlapping clinical findings. For example, breast cancer is feature of HBOC, Li-Fraumeni syndrome, Cowden syndrome, and other hereditary syndromes. The pattern of cancers in the family and pathognomonic features may help determine the underlying syndrome. However, in many cases it can be difficult to reliably diagnose hereditary cancer syndromes based on clinical and family history alone.

Testing for hereditary cancer syndrome may include multigene panel testing using messenger RNA (mRNA). Messenger RNA (mRNA) genetic testing primary function 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. Because of the limitations of current DNA genetic testing, including but not limited to the identification of variants of uncertain significance (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 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 time to identify VUS that may result in an increased risk for hereditary cancer.

Clinical Context and Test Purpose

The purpose of predictive testing for cancer susceptibility is to predict cancer risk from a gene variant associated with a cancer syndrome in an affected member or in a family member of an affected person. The criteria under which predictive testing may be considered clinically useful are as follows:

- An association of the marker with the natural history of the disease has been established; and

- The clinical utility of identifying the variant has been established (eg, by demonstrating that testing will lead to changes in the clinical management of the condition or changes in surveillance).

Populations
The relevant population of interest are patients with a personal and/or family history suggesting an inherited cancer syndrome.

Intervention
The test being considered is an expanded gene testing panel using messenger RNA (mRNA).

Comparator
The following tests are currently being used to make decisions about managing cancer susceptibility: individual gene variant testing and limited DNA panel testing for genes with high clinical validity.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, and test validity. Specific outcomes of interest include sensitivity and specificity, positive and negative predictive value, and reductions in morbidity and mortality.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

For genetic susceptibility to cancer, clinical validity can be considered at the following levels:

- Does a positive test identify a person as having an increased risk of developing cancer?
- If so, how high is the risk of cancer associated with a positive test?

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The following criteria can be used to evaluate the clinical utility of cancer susceptibility panel testing:

- Is decision-making based on potential results of panel testing well-defined?
    - Do positive results on panel testing result in changes in cancer susceptibility that are clinically important?
    - Does this change in cancer susceptibility lead to changes in management that result in health outcome benefits for the patient being tested?

- Is the impact of ancillary information provided by panel testing well-defined?
    - What is the probability that ancillary information leads to further testing or management changes that may have either a positive or a negative impact on the patient being tested?

Identifying a person with a genetic variant that confers a high risk of developing cancer could lead to changes in clinical management and improve health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (eg, prophylactic surgery), and treatment guidance (eg, avoidance of certain exposures). Also, other at-risk family members could be identified.

On the other hand, identifying variants that have intermediate or low penetrance is of limited clinical utility. Clinical management guidelines for patients found to have one of these variants are not well-defined. Also, there is a potential for harm, in that the diagnosis of an intermediate- or low-risk variant may lead to undue psychological stress and unnecessary prophylactic surgical intervention.

Paired DNA and Messenger RNA (mRNA) Genetic Testing in Hereditary Cancer Predisposition

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 (VUS).

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 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.

In another industry sponsored study that was conducted in collaboration with 19 clinical institutions, Landrith and colleagues (2020) reported the results of a prospective study that explored whether RNA genetic testing conducted at the same time as DNA testing identifies additional pathologic mutations in individuals with suspected hereditary cancer syndromes. In order to develop splicing profiles, the researchers evaluated 18 tumor suppressor genes in 345 samples collected from healthy donors. The researchers then evaluated the utility of this splicing profile on 1000 individuals believed to have hereditary cancer syndromes. The authors reported that when RNA testing was paired with DNA testing, RNA testing identified an additional 7 individuals with pathogenic mutations that would have been negative or inconclusive using DNA testing alone. Of the 7 individuals in which the pathogenic mutation was identified, changes in medical management might have been recommended for 6 individuals.

Summary of Evidence

Currently, there is very limited data available to assess how messenger RNA (mRNA) testing operates outside a collaborative research setting, or how decision-making based on the results of such testing impacts health outcomes. Larger, well-designed prospective studies are needed which demonstrate the clinical utility of 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. Use of mRNA testing may be appropriate in the research setting, or to aid publicly available repositories of variant classifications; however, clinical application of the technology in the real world remains unclear.

Professional Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Multi-Gene Testing
Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to multi-gene testing. Multi-gene testing can detect pathogenic or likely pathogenic variants not found in single-gene testing. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. In these cases, phenotype-directed testing based on personal and family history through a multi-gene panel test may be more efficient and/or cost effective. Multi-gene testing may also be considered for those who tested negative for one particular syndrome, but who's personal and family history is suggested of an inherited susceptibility. It has become routine practice at many institutions to now order phenotypically directed multi-gene panel tests to assess for pathogenic changes in multiple relevant genes simultaneously. There are several issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, insurance coverage, laboratory expertise, variant reclassification protocol, methods of DNA/RNA analysis, and availability of financial assistance for cascade testing of relatives, among others. Therefore, the specific laboratory and multi-gene test should be chosen carefully. In addition, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations. A management plan based on genetic test results should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

PRIOR APPROVAL

Not applicable.

POLICY

Messenger RNA (mRNA) Genetic Testing in Hereditary Cancer Predisposition
Messenger RNA (mRNA) sequence analysis alone or in conjunction with DNA sequence analysis to aid in the classification of variations of uncertain significance (VUS) or to otherwise to determine hereditary cancer predisposition is considered **investigational, i**ncluding but not limited to the following testing, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- +RNAinsight for ColoNext (0130U)
- +RNAinsight for BreastNext (0131U)
- +RNAinsight OvaNext (0132U)
- +RNAinsight for ProstateNext (0133U)
- +RNAinsight for CancerNext (0134U)
- +RNAinsight for GYNPlus (0135U)
- +RNAinsight for ATM (0136U)
- +RNAinsight for PALB2 (0137U)
- +RNAinsight for BRCA 1/2 (0138U)
- CustomNext + RNA: APC (0157U)
- CustomNext +RNA: MLH1 (0158U)
- CustomeNext +RNA: MSH2 (0159U)
- CustomeNext +RNA MHS6 (0160U)
- CustomNext +RNA PMS2 (0161U)
- CustomNext +RNA: Lynch (MLH1, MLH2, MSh6, PMS2) (0162U)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0130U Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) ,(Use 0130U in conjunction with 81435, 0101U)
- 0131U Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)
- 0132U Hereditary ovarian cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)
- 0133U Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) (Use 0133U in conjunction with 81162)
- 0134U Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure) (Use 0134U in conjunction with 81162, 81432, 81435)

- 0135U Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure) (Use 0135U in conjunction with 81162)
- 0136U ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0136U in conjunction with 81408)
- 0137U PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0138U BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0157U APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0158U MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0159U MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0160U MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0161U PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0162U Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)

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POLICY HISTORY

Date	Reason	Action
November 2022	Annual Review	Policy Renewed
November 2021	Annual Review	Policy Revised
May 2021	Interim Review	Policy Revised
November 2020	Annual Review	Policy Revised
January 2020	Interim Review	Policy Revised
November 2019	Annual Review	Policy Revised
October 2019	New Coding Update	Policy Revised
November 2018	Annual Review	Policy Revised
November 2017	Annual Review	Policy Revised
November 2016	New Policy	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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