Introduction

A thyroid nodule is a clump of unusual cells in the thyroid gland. Most thyroid nodules are not cancerous. Obtaining a sample of a thyroid nodule to see if it contains cancerous cells requires a test called a fine needle aspiration. A thin needle is inserted through the skin and into the nodule, a sample is drawn into the needle, and the needle is then removed. Several samples may be taken at one appointment, with a new needle used for each sample. Reviewing the samples under a microscope is usually enough to determine if cancer is present. In those cases where the results are uncertain, additional tests, known as a gene expression classifier or gene variant analysis, may be done. This medical policy describes when these types of tests may be medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Afirma Gene Expression Classifier (GEC) | The use of Afirma Gene Expression Classifier (GEC) to assess fine needle aspirates (FNA) of thyroid nodules may be considered medically necessary when ALL of the following criteria are met:  
  - Thyroid nodule \( \geq 1 \) cm on ultrasound
  
  **AND**
  - Presence of indeterminate thyroid FNA cytopathology described as:
    - Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (ie, Bethesda category III)
    - OR
      - Follicular neoplasm or suspicious for a follicular neoplasm (ie, Bethesda category IV)
  
  **AND**
  - Surgical decision making would be affected by test results

  Afirma Gene Expression Classifier (GEC) testing may be considered NOT medically necessary, including but not limited to any of the following:
  - Evaluation of fine needle aspirates (FNA) cytology with any of the following Bethesda cytologic classifications:
    - Non-diagnostic or unsatisfactory (insufficient) samples (ie, Bethesda category I)
    - Benign (ie, Bethesda category II)
    - Suspicious for malignancy (ie, Bethesda category V)
    - Malignant (ie, Bethesda category VI)
    - OR
  - Evaluation of specimen other than fine needle aspirate (FNA) of thyroid nodules
    - OR
  - Evaluation of thyroid nodule less than 1 cm
    - OR
  - Evaluation of thyroid nodule with high suspicion of malignancy based on clinical or ultrasonographic features

<p>| Afirma Malignancy Classifiers-Afirma | The use of an Afirma Malignancy Classifier: Afirma Medullary Thyroid Cancer (MTC) and/or Afirma BRAF may be considered |</p>
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Medullary Thyroid Cancer (MTC) and Afirma BRAF**                     | *medically necessary when the Afirma Gene Expression Classifier (GEC) result suggests the patient should be considered for surgery:*  
  * The Afirma BRAF test is performed after the Afirma Gene Expression Classifier (GEC) result is noted as suspicious (see Table 3 below)  
  * The Afirma MTC test is performed after the Afirma Gene Expression Classifier result is noted as suspicious or malignant (see Table 3 below)  
  Suspicious findings are defined as Bethesda diagnostic category V (suspicious for malignancy)                                                                                                                                 |
| **ThyroSeq v2, ThyraMIR, ThyGenX**                                    | *The use of ThyroSeq v2, ThyraMIR microRNA and ThyGenX* to assess fine needle aspirates (FNA) of thyroid nodules may be considered medically necessary when ALL of the following criteria are met:*  
  * Presence of indeterminate thyroid FNA cytopathology described as:  
    o Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (ie, Bethesda category III);  
    **OR**  
    o Follicular neoplasm or suspicious for a follicular neoplasm (ie, Bethesda category IV)  
    **OR**  
    o Suspicious findings (ie, Bethesda category V suspicious for malignancy)  
  **AND**  
  * Thyroid nodule(s) without a strong clinical or radiological findings suggestive of malignancy  
  **AND**  
  * Surgical decision making would be affected by test results:  
    o Guide surgical planning for initial resection (hemi vs a total thyroidectomy or performance of a central neck dissection), rather than a two-stage surgical biopsy followed by definitive surgery. |
Testing | Medical Necessity
--- | ---
**Thyroid cancer targeted mutational analysis** | Thyroid cancer targeted mutational analysis to detect the following individual genes is considered medically necessary:
- PAX8/PPARgamma
- PIK3CA
- RAS (HRAS, KRAS, NRAS)
- RET/PTC

Testing | Investigational
--- | ---
- Gene expression classifiers
- Genetic variant analysis
- Molecular marker testing in fine needle aspirates of the thyroid | Gene expression classifiers, genetic variant analysis, and molecular marker testing on fine needle aspirates of the thyroid not meeting the criteria outlined above, including but not limited to use of RosettaGX Reveal and single-gene TERT testing, are considered investigational.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>0018U</td>
<td>Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy (new code effective 10/1/17) (ThyraMir)</td>
</tr>
<tr>
<td>0026U</td>
<td>Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result (&quot;Positive, high probability of malignancy&quot; or &quot;Negative, low probability of malignancy&quot;) (new code effective 1/1/18) (ThyroSeq v.2)</td>
</tr>
<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81545</td>
<td>Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) (Afirma GEC)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>
In patients who do not undergo surgical biopsy or thyroidectomy on the basis of gene expression classifier or molecular marker results, regular active surveillance is indicated.

Using molecular marker testing on fine needle aspirates of thyroid nodules may be used to rule in malignancy prior to surgical biopsy. It may also be used to guide surgical planning, including such things as choosing an appropriate surgical facility that has the capability of doing a pathological examination of a frozen section during the biopsy. In this way, the surgeon’s approach may be appropriately adjusted so that only one surgery is needed.

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.
Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing; including possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Description

To determine which patients need thyroid resection, many physicians will perform a cytologic examination of fine needle aspirate (FNA) samples from a thyroid lesion; however, this method has diagnostic limitations. As a result, assays using molecular markers have been developed to improve the accuracy of thyroid FNA biopsies.

Background

**Thyroid Nodules**

Thyroid nodules are common, present in 5-7% of the U.S. adult population; however, most are benign, and most cases of thyroid cancer are curable by surgery when detected early.

**Diagnosis**

Sampling thyroid cells by fine needle aspirate (FNA) is currently the most accurate procedure to distinguish benign thyroid lesions from malignant ones, reducing the rate of unnecessary thyroid surgery for patients with benign nodules and triaging patients with thyroid cancer to appropriate surgery.

About 60% to 70% of thyroid nodules are classified cytologically as benign, and 4% to 10% of nodules are cytologically deemed malignant. However, the remaining 20% to 30% have equivocal findings, usually due to overlapping cytologic features between benign and malignant nodules; these nodules usually require surgery for a final diagnosis. Thyroid FNA cytology is classified by Bethesda System criteria into the following groups: nondiagnostic; benign; follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS); follicular neoplasm (or suspicious for follicular neoplasm); suspicious for malignancy; and malignant. Lesions with FNA cytology in the atypia of undetermined significance or follicular neoplasm of undetermined significance or follicular neoplasm categories are often considered indeterminate.

**Management**

There is some individualization of management for patients with FNA-indeterminate nodules, but many patients will require a surgical biopsy, typically thyroid lobectomy, with intraoperative
pathology. Consultation would typically be the next step in diagnosis. Approximately 80% of patients with indeterminate cytology undergo surgical resection; postoperative evaluation has revealed a malignancy rate ranging from 6% to 30%, making this a clinical process with very low specificity.² Thus, if analysis of FNA samples could reliably identify the risk of malignancy as low, there is potential for patients to avoid surgical biopsy.

Preoperative planning of optimal surgical management of patients with equivocal cytological results is challenging because different thyroid malignancies require different surgical procedures (e.g., unilateral lobectomy vs total or subtotal thyroidectomy with or without lymph node dissection), depending on several factors, including histologic subtype and risk-stratification strategies (tumor size, patient age). If a diagnosis cannot be made intraoperatively, a lobectomy is typically performed, and if on postoperative histology the lesion is malignant, a second surgical intervention may be necessary for completion thyroidectomy.

**Thyroid Cancer**

Most thyroid cancers originate from thyroid follicular cells and include well-differentiated papillary thyroid carcinoma (PTC; 80% of all thyroid cancers) and follicular carcinoma (15%). Poorly differentiated and anaplastic thyroid carcinomas are uncommon and can arise de novo or from preexisting well-differentiated papillary or follicular carcinomas. Medullary thyroid carcinoma originates from parafollicular or C cells and accounts for about 3% of all thyroid cancers.

The diagnosis of malignancy in the case of PTC is primarily based on cytologic features. If FNA in a case of PTC is indeterminate, surgical biopsy with intraoperative pathology is most often diagnostic, although its efficacy and therefore its use will vary across institutions, surgeons, and pathologists. In 2016, reclassification of encapsulated follicular-variant PTC as a noninvasive follicular tumor with papillary-like nuclei was proposed and largely adopted; this classification removes the word carcinoma from the diagnosis to acknowledge the indolent behavior of these tumors.³

For follicular carcinoma, the presence of invasion of the tumor capsule or blood vessels is diagnostic, and cannot be determined by cytology, because tissue sampling is necessary to observe these histologic characteristics. Intraoperative diagnosis of follicular carcinoma is challenging and often not feasible because extensive sampling of the tumor and capsule is usually necessary and performed on postoperative, permanent sections.

New approaches for improving the diagnostic accuracy of thyroid FNA include variant analysis for somatic genetic alterations, to more accurately classify which patients need to proceed to
surgery (and may include the extent of surgery necessary), and a gene expression classifier to identify patients who do not need surgery and can be safely followed.

**Genetic Variants Associated with Thyroid Cancer**

A number of genetic variants have been discovered in thyroid cancer. The most common 4 gene variants are BRAF and RAS single nucleotide variants (SNVs), and RET/PTC and PAX8/PPARγ rearrangements.

Papillary carcinomas carry SNVs of the BRAF and RAS genes, as well as RET/PTC and TRK rearrangements, all of which are able to activate the mitogen-activated protein kinase pathway. These mutually exclusive variants are found in more than 70% of papillary carcinomas. BRAF SNVs are highly specific for PTC. Follicular carcinomas harbor either RAS SNVs or PAX8/PPARγ rearrangements. These variants have been identified in 70% to 75% of follicular carcinomas. Genetic alterations involving the PI3K/AKT signaling pathway also occur in thyroid tumors, although they are rare in well-differentiated thyroid cancers and have higher prevalence in less differentiated thyroid carcinomas. Additional variants known to occur in poorly differentiated and anaplastic carcinomas involve the TP53 and CTNNB1 genes. Medullary carcinomas, which can be familial or sporadic, frequently possess SNVs located in the RET gene.

Studies have evaluated the association between various genes and cancer phenotype in individuals with diagnosed thyroid cancer.

Telomerase reverse transcriptase (TERT) promoter variants occur with varying frequency in different thyroid cancer subtypes. Overall, TERT C228T or C250T variants have been reported in approximately 15% of thyroid cancers, with higher rates in the undifferentiated and anaplastic subtypes compared with the well-differentiated subtypes. TERT variants are associated with several demographic and histopathologic features such as older age and advanced TNM stage. TERT promoter variants have been reported to be independent predictors of disease recurrence and cancer-related mortality in well-differentiated thyroid cancer. Also, the co-occurrence of BRAF or RAS variants with TERT or TP53 variants may identify a subset of thyroid cancers with unfavorable outcomes.
**Molecular Diagnostic Testing**

**Variant Detection and Rearrangement Testing**

SNVs in specific genes, including BRAF, RAS, and RET, and evaluation for rearrangements associated with thyroid cancers can be accomplished with Sanger sequencing or pyrosequencing or with real-time polymerase chain reaction (PCR) of single or multiple genes or by next-generation sequencing (NGS) panels. Panel tests for genes associated with thyroid cancer, with varying compositions, are also available. For example, Quest Diagnostics offers a Thyroid Cancer Mutation Panel, which includes BRAF and RAS variant analysis and testing for RET/PTC and PAX8/PPARγ rearrangements.

The ThyroSeq v.2 Next-Generation Sequencing panel (CBLPath) is an NGS panel of more than 60 genes. According to the CBLPath’s website, the test is indicated when FNA cytology indicates atypia of uncertain significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, or suspicious for malignancy. In particular, it has been evaluated in patients with follicular neoplasm and/or suspicious for follicular neoplasm on FNA as a test to increase both sensitivity and specificity for cancer diagnosis.

ThyGenX is an NGS panel that sequences 8 genes and identifies specific gene variants and translocations associated with thyroid cancer. ThyGenX is intended to be used in conjunction with the ThyraMIR microRNA expression test when the initial ThyGenX test is negative.

**Gene Expression Profiling**

Genetic alterations associated with thyroid cancer can be assessed using gene expression profiling, which refers to the analysis of messenger RNA (mRNA) expression levels of many genes simultaneously. Several gene expression profiling tests are now available to stratify tissue from thyroid nodules biologically.

The Afirma Gene Expression Classifier (Afirma GEC; Veracyte) analyzes the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. It is designed to evaluate thyroid nodules that have an “indeterminate” classification on FNA as a method to select patients (“rule out”) who are at low risk for cancer.

Other gene expression profiles have been reported in investigational settings, but have not been widely validated or used commercially (eg, Barros-Filho et al [2015], Zheng et al [2015]); they are not addressed in this review.
ThyraMIR is a micro-RNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.

**Algorithmic Testing**

Algorithmic testing involves the use of 2 or more tests in a prespecified sequence, with a subsequent test automatically obtained depending on results of an earlier test.

**Algorithmic Testing Using Afirma GEC With Afirma MTC and Afirma BRAF**

In addition to Afirma GEC, Veracyte also markets 2 “malignancy classifiers” that use mRNA expression-based classification to evaluate for BRAF variants (Afirma BRAF) or variants associated with medullary thyroid carcinoma (Afirma MTC). Table 3 outlines the testing algorithms for Afirma MTC and Afirma BRAF.

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 1 Result</th>
<th>Reflex to Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid nodule on fine needle aspirate</td>
<td>“Indeterminate”</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>“Malignant” or “suspicious”</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>“Suspicious”</td>
<td>Afirma BRAF</td>
</tr>
</tbody>
</table>

In a description of the Afirma BRAF test, the following have been proposed as benefits of the mRNA-based expression test for BRAF variants: (1) PCR-based methods may have low sensitivity, requiring that a large proportion of the nodule have a relevant variant; (2) testing for only 1 variant may not detect patients with low-frequency variants that result in the same pattern of pathway activation; and (3) PCR-based approaches with high analytic sensitivity may require a large of amount of DNA that is difficult to isolate from small FNA samples.\(^{18}\)

The testing strategy for both Afirma MTC and Afirma BRAF is to predict malignancy from a FNA sample with increased pretest probability for malignancy. A positive result with Afirma MTC or Afirma BRAF would inform preoperative planning such as planning for a hemi- vs a total thyroidectomy or performance of a central neck dissection.
Algorithmic Testing Using ThyGenX and ThyraMIR

The ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics; testing done at Asuragen Clinical Laboratory) is an NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of 8 genes associated with papillary thyroid carcinoma and follicular carcinomas. ThyGenX has replaced the predicate miRInform Thyroid test that assesses for 17 validated gene alterations.

ThyraMIR (Interpace Diagnostics) is a microRNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.

The testing strategy for combined ThyGenX and ThyraMIR testing is first to predict malignancy. A positive result on ThyGenX would “rule in” patients for surgical resection. The specific testing results from a ThyGenX positive test would be used to inform preoperative planning when positive. For a ThyGenX negative result, the reflex testing involves the ThyraMIR microRNA expression test to “rule out” for a surgical biopsy procedure given the high negative predictive value of the second test. Patients with a negative result from the ThyraMIR test would be followed with active surveillance and avoid a surgical biopsy.

Summary of Evidence

For individuals with thyroid nodule(s) and indeterminate findings on fine needle aspirate (FNA) who receive FNA sample testing with molecular markers to rule out malignancy and to avoid surgical biopsy or resection, the evidence includes a prospective clinical validity study with the Afirma GEC and a chain of evidence to support clinical utility. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In a multicenter validation study, the Afirma GEC was reported to have a high negative predictive value (NPV); (range, 90%-95%). These results are supported by an earlier development and clinical validation study (Chudova et al [2010]), but the classifiers used in both studies do not appear to be identical. In other multicenter and multiple single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma patients who are benign, but the exact NPV is unknown. The available evidence suggests that the decisions a physician makes regarding surgery are altered by GEC results; however, it should be noted that long-term follow-up of patients with thyroid nodules who avoided surgery based on GEC results is limited. A chain of evidence can be constructed to establish the potential for clinical utility with GEC testing in cytologically indeterminate lesions, but with only a single study of the marketed test reporting a
true NPV, the clinical validity is uncertain. For the RosettaGX Reveal test, no prospective clinical studies were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular markers to rule in malignancy and to guide surgical planning, the evidence includes prospective and retrospective studies of clinical validity. Relevant outcomes are disease-specific survival, test accuracy and validity, morbidity events, and resource utilization. Variant analysis has the potential to improve the accuracy of an equivocal FNA of the thyroid and may play a role in preoperative risk stratification and surgical planning. Single-center studies have suggested that testing for a panel of genetic variants associated with thyroid cancer may allow for the appropriate selection of patients for surgical management with an initial complete thyroidectomy. Prospective studies in additional populations are needed to validate these results. The variant analysis does not achieve an NPV sufficiently high enough to identify which patients can undergo active surveillance over thyroid surgery. Although the presence of certain variants may predict more aggressive malignancies, the management changes that would occur as a result of identifying higher risk tumors, are not well-established. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular markers to rule out malignancy and to avoid surgical biopsy or to rule in malignancy for surgical planning, the evidence includes multiple retrospective and prospective clinical validation studies for the ThyroSeq v2 or v3 test and 2 retrospective clinical validation studies that utilized a predicate test 17-variant panel (miRInform) test to the current ThyGenX and ThyraMIR. Relevant outcomes are disease-specific survival, test accuracy and validity, morbidity events, and resource utilization. In a retrospective validation study on FNA samples, the 17-variant panel (miRInform) test and ThyraMIR had a sensitivity of 89%, and a NPV of 94%. Pooled retrospective and prospective clinical validation studies of ThyroSeq v2 have reported a combined NPV of 96% and a PPV of 83% in studies conducted at the institution developing the test but poorer performance at external institutions. No studies were identified demonstrating the diagnostic characteristics of the marketed ThyGenX. No studies were identified demonstrating evidence of direct outcome improvements. A chain of evidence for the ThyroSeq v2 test and the combined ThyGenX and ThyraMIR testing would rely on establishing clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02352766</td>
<td>Role of NGS-based ThyroSeq Panel in Cancer Diagnosis in Thyroid Nodules</td>
<td>300</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT03170804</td>
<td>Genomic Profiling of Nodular Thyroid Disease and Thyroid Cancer</td>
<td>200</td>
<td>Jan 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

In response to requests, clinical input on 7 tests for molecular markers was received from 9 respondents, including 1 specialty society-level response, 1 physician from an academic center, and 7 physicians from 2 health systems while this policy was under review in 2017.

Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of the following types of molecular marker testing in fine needle aspirate (FNA) of thyroid nodules with indeterminate cytologic findings (ie, Bethesda diagnostic category III
[atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) to rule out malignancy and to avoid surgical biopsy:

- Afirma Gene Expression Classifier; or
- ThyroSeq v2

• Use of the following type of molecular marker testing in FNA of thyroid nodules with indeterminate cytologic findings or Bethesda diagnostic category V (suspicious for malignancy) to rule in the presence of malignancy to guide surgical planning for the initial resection rather than a 2-stage surgical biopsy followed by definitive surgery:

  - ThyroSeq v2;
  - ThyraMIR microRNA/ThyGenX;
  - Afirma BRAF after Afirma Gene Expression Classifier; or
  - Afirma MTC after Afirma Gene Expression Classifier.

Based on the evidence and independent clinical input, the clinical input does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

- Use of the following types of molecular marker testing in FNA of thyroid nodules:
  - RosettaGX Reveal.

**2016 Input**

In response to requests, input was received from 2 physician specialty societies (one of which provided 3 responses) and 1 academic medical center while this policy was under review in 2016. Input focused on the use of gene expression classifiers with a high negative predictive value in nodules indeterminate on FNA. Although individual uses of a gene expression classifier with negative predictive value in these situations varied, there was general agreement that the tests are considered standard in the evaluation of some indeterminate cases of FNA.
Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists et al

In 2016, the American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi updated their joint guidelines for cytologically indeterminate thyroid nodules, stating:

- “Cytopathology expertise, patient characteristics, and prevalence of malignancy within the population being tested impact the negative predictive values (NPVs) and positive predictive values (PPVs) for molecular testing.”
- “Consider the detection of BRAF and RET/PTC and, possibly, PAX8/PPARG and RAS mutations if such detection is available.”
- “TERT mutational analysis on FNA, when available, may improve the diagnostic sensitivity of molecular testing on cytologic samples.”
- “Because of the insufficient evidence and the limited follow-up, we do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate nodules.”

For the role of molecular testing for deciding extent of surgery, the following recommendations were made:

- “Currently, with the exception of mutations such as BRAFV600E that have a PPV approaching 100% for papillary thyroid carcinoma (PTC), evidence is insufficient to recommend in favor of or against the use of mutation testing as a guide to determine the extent of surgery.”

American Thyroid Association

In 2016, the American Thyroid Association updated its guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults. These guidelines made the following statements on molecular diagnostics in thyroid nodules that are atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) on cytology and follicular neoplasm (FN) or suspicious for follicular neoplasm (SFN) on cytology (see Table 5).
Table 5. Molecular Diagnostics in Thyroid Nodules That Are AUS or FLUS or FN or SFN on Cytology

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUS or FLUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA [fine needle aspirate] or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making.”</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>“If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference.”</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td><strong>FN or SFN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making.”</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasm; FNA: fine needle aspirate; QOE: quality of evidence; SFN: suspicious for follicular neoplasm; SOR: strength of evidence.

The guidelines also stated, “there is currently no single optimal molecular test that can definitively rule in or rule out malignancy in all cases of indeterminate cytology, and long-term outcome data proving clinical utility are needed.”

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network guidelines on the treatment of thyroid cancer (v.1.2018) comment on the use of molecular diagnostics in thyroid cancer. For thyroid nodules evaluated with FNA, molecular diagnostics may be employed when lesions are suspicious for (category 2B recommendation):

- Follicular or Hürthle cell neoplasms
- AUS or FLUS
The guidelines also state: “Molecular testing (both the Gene Expression Classifier and individual variant analysis) was available in the majority of NCCN Member Institutions (>75%). About 70% of the panelists would recommend using a gene expression classifier in the evaluation of follicular lesions.”

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

MoLDX Program contractors Palmetto GBA, Wisconsin Physicians Service Insurance Corp., and CGS Administrators determined that the Afirma Gene Expression Classifier test meets criteria for analytical and clinical validity and clinical utility as a reasonable and necessary Medicare benefit. Effective 2012, the MoLDX Program contractors began to reimburse Afirma Gene Expression Classifier services for patients with the following conditions:

- Patients with one or more thyroid nodules with a history or characteristics suggesting malignancy such as:
  - Nodule growth over time
  - Family history of thyroid cancer
  - Hoarseness, difficulty swallowing or breathing
  - History of exposure to ionizing radiation
  - Hard nodule compared with rest of gland consistency
  - Presence of cervical adenopathy
- Have an indeterminate follicular pathology on fine needle aspiration

**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. Thyroid variant testing and gene expression classifiers are available under the auspices 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 this test.

In 2013, the THxID™-BRAF kit (bioMérieux), an in vitro diagnostic device, was approved by the Food and Drug Administration through the premarket approval process to assess specific BRAF variants in melanoma tissue via real-time PCR. However, there are currently no diagnostic tests for thyroid cancer mutation analysis with approval from the Food and Drug Administration.

Table 6 provides a summary of commercially available molecular diagnostic tests for indeterminate thyroid pathology.

### Table 6. Summary of Molecular Tests for Indeterminate Thyroid Cytopathology FNA Specimens

<table>
<thead>
<tr>
<th>Test</th>
<th>Methodology</th>
<th>Analyte(s)</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afirma® GEC</td>
<td>mRNA gene expression</td>
<td>167 genes</td>
<td>Benign/suspicious</td>
</tr>
<tr>
<td>Afirma® BRAF</td>
<td>mRNA gene expression</td>
<td>1 gene</td>
<td>Negative/positive</td>
</tr>
<tr>
<td>Afirma® MTC</td>
<td>mRNA gene expression</td>
<td></td>
<td>Negative/positive</td>
</tr>
<tr>
<td>ThyroSeq v2, v3</td>
<td>Next-generation sequencing</td>
<td>60+ genes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>ThyGenX&lt;sup&gt;tm&lt;/sup&gt;</td>
<td>Next-generation sequencing</td>
<td>8 genes</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>TERT single-gene test</td>
<td>Unclear for commercially available test&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 gene</td>
<td>Specific gene variants</td>
</tr>
<tr>
<td>miRInform®&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multiplex PCR by sequence-specific probes</td>
<td>14 DNA variants, 3 RNA fusions</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>ThyraMIR™</td>
<td>microRNA expression</td>
<td>10 microRNAs</td>
<td>Negative/positive</td>
</tr>
<tr>
<td>RosettaGX™ Reveal</td>
<td>microRNA expression</td>
<td>24 microRNAs</td>
<td>Benign Suspicious for malignancy High risk for medullary carcinoma</td>
</tr>
</tbody>
</table>

FNA: fine needle aspirate; NGS: next-generation sequencing; PCR: polymerase chain reaction
<sup>a</sup> The miRInform® test is the predicate test to ThyGenX™ and is not commercially available
<sup>b</sup> Includes TERT
<sup>c</sup> Available literature on TERT testing used PCR


13. Song YS, Lim JA, Choi H, et al. Prognostic effects of TERT promoter mutations are enhanced by coexistence with BRAF or RAS mutations and strengthen the risk prediction by the ATA or TNM staging system in differentiated thyroid cancer patients. Cancer. May 1 2016;122(9):1370-1379. PMID 26969876


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<thead>
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<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>04/14/14</td>
<td>New PR policy; replaces 12.04.78. Literature review performed through February 27, 2014. Policy statement revised from that of 12.04.78: The use of a gene expression classifier may be considered medically necessary (previously investigational). References 9, 15, 17, 18, 20, 21, 23, 24 and 25 added.</td>
</tr>
<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
</tr>
<tr>
<td>06/17/15</td>
<td>Annual Review. Policy updated to state mutation analysis in fine-needle aspirates of the thyroid including BRAF is considered to be investigational. Policy updated with literature review through March 2, 2015. References 5-9, 15, 18, 20-24, 28, 29 added. Policy statements changed as noted.</td>
</tr>
<tr>
<td>02/04/16</td>
<td>Coding update. Added 81545, effective 1/1/16.</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. Added reference 27. No change to policy statements.</td>
</tr>
<tr>
<td>02/01/17</td>
<td>Annual Review, approved January 10, 2017. Policy updated with literature review and results of clinical input; references 10-11, 18-20, 24, 28, 34, 43-45, and 48-49 added. Removed Appendix table. No change to policy statements.</td>
</tr>
<tr>
<td>07/28/17</td>
<td>Policy moved into new format, no changes to policy statement.</td>
</tr>
<tr>
<td>11/21/17</td>
<td>Coding update, added CPT code 0018U (new code effective 10/01/17).</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Interim Review, approved April 17, 2018. Modified medical necessity statements for greater clarity. Added statements for when Afirma GEC is considered not medically necessary to reinforce intent of medically necessary policy statement. Added Thyroid cancer targeted mutational analysis (PAX8/PPARgamma, PIK3CA, RA [HRAS, KRAS, NRAS], RET/PTC) as not medically necessary.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Annual Review, approved August 14, 2018. Policy updated with literature review through April 2018; references 4-10, 20, 26-30, 45-47, 65, and 69 added. Policy statements revised to add investigational statement for TERT single-gene testing. Thyroid cancer targeted mutational analysis to detect the following individual genes is considered medically necessary: PAX8/PPARgamma, PIK3CA, RAS (HRAS, KRAS, NRAS), RET/PTC (previously these were considered not medically necessary). Added</td>
</tr>
</tbody>
</table>
### Disclaimer

This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

### Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>CPT code 0026U.</td>
</tr>
</tbody>
</table>

Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
- Civil Rights Coordinator - Complaints and Appeals
  PO Box 91102, Seattle, WA 98111
  Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
- U.S. Department of Health and Human Services
  200 Independence Avenue SW, Room S09F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本文通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本文通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健保保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Итальянский (Italian):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Empòtan ladan. Avi sila a kapab genyen enfòmasyon empòtan konsènan aplikasyon w lan osawa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan av si a. Ou ka gen pou princ kék akson av an senten dat limit pou ka kente kouvèti asirans sante w lan osawa pou yo ka ede w avèk depans yo. Se dwa w pou resewwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):
Tsab ntaaw tshaj xo no muaj cov ntsib lus tseem ceeb. Tej zaum tsab ntaaw tshaj xo no muaj cov ntsib lus tseem ceeb bokj koj dainw tshov kov pab los yoj kog qhov kov pab cuam los ntaaw Premera Blue Cross. Tej zaum muaj cov hnb tseem ceeb uas rau hauv daim ntaaw nbo. Tej zaum koj kuj yuav tau ua qee yam uas peb koj uas tsep pub dhuav cov caij nyog uas teev bokj rau hauv daim ntaaw no mas koj traih yuav tau baais kov pab cuam kum kho mob los yoj kog qhov pab them tej nqi kho mob ntaaw. Koj muaj cai kom lawv muab cov ntsib lus no uas tau muab sau uaj koj hom lus pub daww rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Illoko (Illoko):
Daytoy a Pakdaak ket naglaon iti Napateg nga Impormasjon. Daytoy a pakdaak mabalini nga adda ket naglaon iti napateg nga impormasjon maianggep iti aplikasyoonu yowo coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaak. Mabalini nga adda rumbag nga aramidenyo nga addang sakbay dagiti particular a naituding nga aldaw tapno mapagtalinedyo ti coverage ti salun-aywo yowo tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasjon ken tulong ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawg iti numero nga 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):
Premera Blue Cross has sent you a notice that may contain important information. This notice contains information about dates that may be important to you. It is advisable to provide help and support to customers who need assistance in the area of day-to-day living.

If you have any questions, please call 800-722-1471 (TTY: 800-842-5357) for more information.

Польский (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie prawa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub sztuki podatkowej.

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso.

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