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 at least 1 cm on ultrasound; **AND**  
  - 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); **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:  
    o Non-diagnostic or unsatisfactory (insufficient) samples (ie, Bethesda category I)  
    o Benign (ie, Bethesda category II)  
    o Suspicious for malignancy (ie, Bethesda category V)  
    o 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  |
| **Afirma Malignancy Classifiers-Afirma Medullary Thyroid Cancer (MTC) and Afirma BRAF** | The use of an Afirma Malignancy Classifier, Afirma Medullary Thyroid Cancer (MTC) and/or Afirma BRAF may be considered medically necessary when the Afirma Gene Expression Classifier (GEC) result suggests the patient should be |
### Testing

<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **considered for surgery:**  
- The Afirma BRAF test is performed after the Afirma Gene Expression Classifier (GEC) result is noted as suspicious (see Table 1 below)  
- The Afirma MTC test is performed after the Afirma Gene Expression Classifier result is noted as suspicious or malignant (see Table 1 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:
    - 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)  
    **OR**
    - 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:
    - 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. | |
| Thyroid cancer targeted mutational analysis | Thyroid cancer targeted mutational analysis to detect individual genes is considered not medically necessary, |
Testing | Medical Necessity
---|---
| **including but not limited to:**
- 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, are considered investigational.**

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</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)</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)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Related Information

Regular active surveillance would be indicated in patients who do not undergo surgical biopsy or thyroidectomy on the basis of gene expression classifier results.

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 to do 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.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

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 and 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 AUS or FLUS 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. 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. Different thyroid malignancies require different surgical procedures (eg, unilateral lobectomy vs total or subtotal thyroidectomy with or without lymph node dissection).
Selecting the appropriate surgical procedure depends on several factors, including histologic subtype and risk-stratification strategies such as tumor size and patient age. If a diagnosis cannot be made intraoperatively, a lobectomy is typically performed. If postoperative histology shows the lesion is malignant, a second surgery for complete thyroidectomy may be necessary.

**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.

For follicular carcinoma, the presence of invasion of the tumor capsule or blood vessels is diagnostic. It 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**

Various genetic variants have been discovered in thyroid cancer. The most common 4 gene variants that carry the highest impact on tumor diagnosis and prognosis are BRAF and RAS single nucleotide variants (SNVs), and RET/PTC and PAX8/PPARγ rearrangements.
Papillary carcinomas may 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.

**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, Ocala, FL) 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, South San Francisco, CA) analyzes the expression of 142 different genes for 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™ (Interpace Diagnostics, Parsippany, NJ) 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 two 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 1 describes the testing algorithms for Afirma MTC and Afirma BRAF.

**Table 1. Afirma MTC and Afirma BRAF Testing Algorithms**

<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 “suspicous”</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.10

The testing strategy for both Afirma MTC and Afirma BRAF is to predict malignancy from an 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, Parsippany, NJ; 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, Parsippany, NJ) 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, 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), 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 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, morbid 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. 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 and to rule in surgical planning, the evidence includes multiple retrospective and prospective clinical validation studies for the ThyroSeq v2 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, morbid 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 positive predictive value of 83%. 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**

A search of ClinicalTrials.gov in November 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

**Clinical Input Received from Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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 (NPV) in nodules shown to be indeterminate on fine needle aspirate (FNA). Although individual uses of a gene expression classifier with NPV 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 Associazione Medici Endocrinologi updated their joint guidelines and made the following statements on molecular testing for cytologically indeterminate thyroid nodules:

- “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.”
- “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 (ATA)**

In 2016, the American Thyroid Association (ATA) 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 2).
Table 2. 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 (NCCN)**

National Comprehensive Cancer Network (NCCN) guidelines on the treatment of thyroid cancer (v.2.2017) 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
- Atypia of undetermined significance or follicular lesion of undetermined significance
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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Palmetto GBA**

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare.

Palmetto GBA completed an assessment of the Afirma GEC and determined that the test meets criteria for analytical and clinical validity and clinical utility as a reasonable and necessary Medicare benefit.62 Effective 2012, Palmetto GBA will reimburse Afirma GEC 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Thyroid variant testing and gene expression classifiers are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In 2013, the THxID™-BRAF kit (bioMérieux, Marcy l'Etoile, France), an in vitro diagnostic device, was approved by the FDA through the premarket approval process to assess specific BRAF variants in melanoma tissue via real-time polymerase chain reaction (PCR). However, there are currently no diagnostic tests for thyroid cancer mutation analysis with approval from the FDA.

Table 3 provides a summary of commercially available molecular diagnostic tests for indeterminate thyroid pathology.

Table 3. 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</td>
<td>Next-generation sequencing</td>
<td>60+ genes</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>ThyGenX™a</td>
<td>Next-generation sequencing</td>
<td>8 genes</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>miRInform®a</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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk for medullary carcinoma</td>
</tr>
</tbody>
</table>
FNA: fine needle aspirate; NGS: next-generation sequencing; PCR: polymerase chain reaction.

The miRInform® test is the predicate test to ThyGenX™ and is not commercially available.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</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>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</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>
</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.
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 425-918-5952, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can 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 OCR Portal 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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

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).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan lidann. Avi sila a kapab genyen enfòmasyon enpòtan konsènplik aviplaksyon w la osa konèsan kwenti kouverti amsir an travay Premera Blue Cross. Kapab genyen dat ki enpòtan nan av sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kens kwenti kouverti amsir anante w la osa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye ou pa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):
Tsaab ntawv tshaj xoo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xoo no muaj cov ntshiab lus tseem ceeb boex kong dain tawv thov kev pab los yoy kog kev qhov kev pab cuam los ntawv Premera Blue Cross. Tej zaum muaj cov hrub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koy kev yuuq tai uau gee yam uas peb kom koy uas tsip pub dhaa cov caij nyong uas teev tseg rau hauv daim ntawv no mas koy thaj yuuq tai basis kev pab cuam khowmob los yoy kev pab them tej nqi kho mob ntawv. Koy muaj cai kom laww mbab cov ntshiab lus no uas taw muab sau uak yom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket nagloan iti Napateg nga Impomarsion. Daytoy a pakdaar mabalin nga adda ket nagloan iti napateg nga impomarsion maipanggip iti aksiyonowo nyo coverge babaen iti Premera Blue Cross. Daytoy ket mabalim dagiti importante a pelsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidens na nga addang sakbay dagiti partikular a na lituding nga adlaw tapo napagtalainado ni coverge ti salun-ayo nga tungol kadagiti gastos. Adda karbengowo a mangala iti daytoy nga impomarsion ken tungol iti bukodyo a pagasasao nga awan ti bayadanoy. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

This notification may contain important information. This notification may contain important information. This notification may contain important information.

To obtain a copy of this notification in another language, call 800-722-1471 (TTY: 800-842-5357).