2.04.78  Molecular Markers in Fine Needle Aspirates of the Thyroid

Section 2.0 Medicine  Effective Date  November 26, 2014
Subsection 2.04  Pathology/Laboratory  Original Policy Date  November 26, 2014  Next Review Date  November 2015

Description
Fine needle aspiration (FNA) of a thyroid lesion to identify which patients need to undergo surgery has diagnostic limitations and has led to the development of molecular markers in an attempt to improve the accuracy.

Related Policies
- N/A

Policy
Thyroid nodule gene expression testing (e.g., Afirma Thyroid FNA Analysis) may be considered medically necessary for assessing fine needle aspiration samples from thyroid nodules that have indeterminate cytology on fine needle aspirate, as indicated by one or more of the following conditions:
- Atypical (atypia) cells of undetermined significance
- Follicular (Hurthle cell) neoplasm, known or suspected
- Follicular lesion of undetermined significance
- Malignancy, suspected

The use of a gene expression classifier in fine-needle aspirates from thyroid nodules is considered to be investigational for all other indications not listed above.

Mutation analysis in fine-needle aspirates of the thyroid (e.g. miRInform) is considered to be investigational.

Policy Guidelines
There is no specific CPT code for this testing. The following CPT codes would likely be used:
- 81599: Unlisted multianalyte assay with algorithmic analysis
- 88199: Unlisted cytopathology procedure

According to the Asuragen website, the following CPT codes would be used to report miRInform™ Thyroid: “83913, 83907, 83891, 83902, 83896, 83898, 83909, 83912.” These codes are no longer valid codes after 12/31/12.
Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

Fine Needle Aspiration (FNA) of the Thyroid

Thyroid nodules are common, present in 5% to 7% of the U.S. adult population. Most are benign, and most cases of thyroid cancer are curable by surgery when detected early. Fine needle aspiration (FNA) of the thyroid 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 (inclusive, indeterminate, atypical, suspicious), usually due to overlapping cytologic features between benign and malignant nodules; these nodules usually require surgery for a final diagnosis.

The current guidelines recommend repeat FNA for patients with a diagnosis of “atypia of undetermined significance” and lobectomy with or without intraoperative pathology consultation for those with a suspicious diagnosis.

Approximately 80% of patients with indeterminate cytology undergo surgical resection; postoperative evaluation reveals a malignancy rate ranging from 6% to 30%, making this a clinical process with very low specificity.

Preoperative planning of optimal surgical management in patients with equivocal cytologic results is challenging, as different thyroid malignancies may require different surgical procedures (e.g., unilateral lobectomy versus 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 ~3% of all thyroid cancers.

The diagnosis of malignancy in the case of PTC is primarily based on cytologic features. If an FNA in a case of PTC is indeterminate, intraoperative consultation is most often diagnostic, although its efficacy and therefore use will vary between institutions, surgeons, and pathologists.

For follicular carcinoma, the presence of invasion of the tumor capsule or of blood vessels is diagnostic and cannot be determined by cytology, as 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 mutation 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.

**Mutations Associated with Thyroid Cancer**

Various mutations have been discovered in thyroid cancer. The 4 gene mutations that are the most common and carry the highest impact on tumor diagnosis and prognosis are BRAF and RAS point mutations and RET/PTC and PAX8/PPARγ rearrangements.

Papillary carcinomas carry point mutations 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 (MAPK) pathway. These mutually exclusive mutations are found in more than 70% of papillary carcinomas. BRAF mutations are highly specific for PTC. Follicular carcinomas harbor either RAS mutations or PAX8/PPARγ rearrangement. These mutations are also mutually exclusive and 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 cancer and have higher prevalence in less differentiated thyroid carcinomas. Additional mutations 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 point mutations located in the RET gene.

**Regulatory Status**

Commercially available panels of molecular markers utilizing FNA specimens from the thyroid include miRInform™ (Asuragen) and Veracyte® (Afirma).

**miRInform** is a panel of 7 analytically validated molecular markers [mutations] (KRAS, BRAF, HRAS, NRAS, RET/PTC 1, RET/PTC 3, and PAX8/PPARγ).

The Afirma “gene expression classifier” (GEC) is a proprietary diagnostic test offered by Veracyte, which claims to classify a thyroid nodule with indeterminate cytology as benign (with >95% negative predictive value) or as suspicious for malignancy (>50% risk of malignancy). The GEC measures the gene expression of 142 genes and applies a multidimensional algorithm to classify whether a nodule with an indeterminate cytologic diagnosis is benign or suspicious.

These commercially available, laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the
United States Food and Drug Administration is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Literature Review

The literature on the use of molecular markers for thyroid nodules diagnosed by fine needle aspiration (FNA) as indeterminate, atypical, or suspicious consists of approximately 20 publications. These studies have analyzed either panels of mutations or a single mutation in these fine needle aspirates and compared the preoperative cytologic diagnosis and mutation status with postoperative final histologic diagnosis to determine diagnostic accuracy of the presence of a mutation, to predict the presence of malignancy. Some authors have also reported that the presence of certain mutations may predict more aggressive behavior in a malignant thyroid lesion. A gene expression classifier has been developed to predict the likelihood that a thyroid lesion with indeterminate cytology is benign, allowing a patient to avoid surgical excision if that action is deemed to be clinically appropriate. However, neither prospective nor comparative studies to determine how the preoperative result of the presence of a mutation in a thyroid nodule with equivocal cytology results would impact patient management have been performed.

Molecular Markers to Predict Malignancy (Mutation Analysis)

Ferraz et al evaluated 20 publications that reported on the type and number of mutations in cases of FNA of the thyroid diagnosed as indeterminate and compared the results with final histology after surgical resection. Sixteen studies analyzed 1 mutation (e.g., \textit{BRAF} or \textit{RET/PTC}) and 4 studies analyzed a panel of several mutations (\textit{BRAF}, \textit{RAS}, \textit{RET/PTC}, \textit{PAX8/PPARγ}). The detection of a mutation in a histologically (surgically resected) benign thyroid lesion was categorized as a false positive case, detecting no mutation in an FNA sample from a histologically benign surgical sample was considered a true negative, and finding no mutation in a histologically malignant lesion was categorized as a false negative. Based on 4 studies that examined a panel of mutations, there was a broad sensitivity range of 38% to 85.7% (mean, 63.7%), a mean specificity of 98% (range, 95%-100%), mean false positive rate of 1.25% (0%-4%) and mean false negative rate of 9% (1%-21%). Based on 2 studies that examined \textit{RET/PTC} rearrangements, mean sensitivity was 55% (50%-60%), specificity 100%, false positive rate of 0% and mean false negative rate 3.5% (91%-6%). Based on 3 studies that examined \textit{BRAF} mutations, mean sensitivity was 13% (0%-37.5%), mean specificity, 92.3% (75%-100%), mean false positive rate, 0.5% (0%-1%) and mean false negative rate of 6% (3%-12%). The authors concluded that testing for a panel of mutations leads to an improvement in the sensitivity and specificity for indeterminate FNA of the thyroid but that further standardizations and further molecular markers are needed before broad application of molecular FNA cytology for the diagnosis of thyroid nodules.

Nikiforov et al prospectively tested a panel of mutations (\textit{BRAF}, \textit{RAS}, \textit{RET/PTC}, \textit{PAX8/PPARγ}) in 470 FNA samples of thyroid nodules from 328 consecutive patients. Mutational status was correlated with cytology and either surgical pathology diagnosis or follow-up (mean, 34 months). A total of 40 patients were excluded for poor quality of specimen or loss to follow-up. Sixty-nine patients (with 86 thyroid FNA samples) underwent surgery soon after completion of the cytologic evaluation; preoperative cytologic diagnosis was: positive for malignancy in 22 samples, indeterminate (including atypical and suspicious for malignancy) in 52 samples, and negative for malignancy in 12 samples. By FNA, 32 mutations were found (18 \textit{BRAF}, 8 \textit{RAS}, 5 \textit{RET/PTC}, and 1 \textit{PAX8/PPARγ}); after surgery, 31 mutation-positive nodules (97%) were diagnosed as malignant on pathologic examination, and 1 was a benign tumor (3%). Thirteen of the 32
mutation-positive FNA samples had a definitive cytologic diagnosis of malignancy, whereas the rest were either indeterminate or negative for malignancy.

Of the remaining 219 patients, 147 (229 FNAs) who did not undergo surgery were followed by serial ultrasound with no change in the nodule status (124 patients) or by repeated FNA with cytology negative for malignancy (23 patients) and no mutation found in the FNA material. These nodules were considered as negative for malignancy. The remaining 72 patients who were initially in the follow-up group underwent subsequent surgery. Combining all 3 groups, the specificity for malignancy was high (99.7%), but the sensitivity of the molecular test alone was 62%.

Moses et al prospectively tested FNA samples from 417 patients with 455 thyroid nodules for BRAF, NRAS, KRAS, and RET/PTC 1 and 3 TRK1 mutations.(7) Overall, 50 mutations (23 BRAF V600E, 21 NRAS, 4 RET/PTC 1, and 2 RET/PTC 3 rearrangements) were detected. There were significantly more mutations detected in malignant nodules than in benign (p<0.001). For thyroid FNA biopsies that were indeterminate or suspicious (n=137), genetic testing had a sensitivity of 12%, specificity of 98%, positive predictive value of 38% and negative predictive value (NPV) of 65%.

Ohori et al performed mutation screening in 117 FNA samples classified as a follicular lesion of indeterminate significance/atypia of indeterminate significance.(8) BRAF, RAS, RET/PTC, or PAX8/PPARγ mutations were detected in 10% of this category. They demonstrated that the probability of having a malignancy in this cytology category together with a detection of one of the somatic mutations investigated was 100%, whereas the probability of having a thyroid malignancy without a mutation detected was 7.6%.

In 2011, Nikiforov et al reported results of a prospective study to assess the clinical utility of a panel of mutations to predict the likelihood of malignancy in thyroid nodules that were indeterminate on FNA.(9) The authors included 1056 consecutive FNA samples with indeterminate cytology on FNA that underwent mutation testing, with 967 of those adequate for molecular analysis (653 follicular lesion of undetermined significance/atypia of undetermined significance; 247 follicular or Hürthle cell neoplasm or suspicious for follicular neoplasm; 67 suspicious for malignant cells). One hundred seventeen of the samples were included in the Ohori et al analysis previously described. Eighty-seven BRAF, RAS, RET/PTC, or PAX8/PPARγ mutations were detected. At the time of analysis, 479 patients had undergone thyroidectomy for further evaluation, providing a histopathologic diagnosis for 513 samples. The presence of a mutation had low sensitivity for predicting malignant histology (63%, 57%, 68% for samples with follicular lesion of undetermined significance/atypia of undetermined significance, follicular or Hürthle cell neoplasm/suspicious for follicular neoplasm, and suspicious for malignant cells on cytology, respectively), but high specificity (99%, 97%, 96%, respectively). The NPV for the mutation analysis results was 94%, 86%, and 72% for samples with follicular lesion of undetermined significance/atypia of undetermined significance, follicular or Hürthle cell neoplasm/suspicious for follicular neoplasm, and suspicious for malignant cells on cytology, respectively. The authors conclude that mutation analysis may be useful in surgical planning, such as determining whether patients should undergo a thyroid lobectomy or a total thyroidectomy as a first surgery.

Cantara et al analyzed a panel of mutations in samples of 174 patients undergoing thyroid surgery for indeterminate/inadequate/benign FNA results.(10) The most prevalent mutation was BRAF (49.3% of the positive samples), followed by RAS (34.3%) and RET/PTC (16.4%). The combination of cytology and mutation analysis improved the accuracy for diagnosing cancer from 83% to 93.2% when compared with cytologic analysis alone. Molecular analysis detected 8 thyroid cancers that were missed on cytology from a total
of 32 cancers that were diagnosed as indeterminate/inadequate/benign. When the FNA mutation analysis was compared with the mutation analysis of the corresponding histologic material from the surgical sample, in 88.2% of cases, the mutation found in the FNA material was also detected in the histologic samples. The 11.8% discrepant results were due to the presence of a mutation in the tissue sample that was not found in the cytology sample.

Mathur et al collected thyroid FNA samples, thyroid tissue, clinical and histopathology data, and tumor genotyping for mutations BRAF V600E, NRAS, KRAS, RET/PTC 1, RET/PTC 3, and NTRK1 for 341 patients with 423 dominant thyroid nodules. (11) A cytologic examination of the samples showed that 51% were benign (one quarter of these were surgically resected), 21% were malignant, 11% were atypical lesions, 12% were follicular or Hürthle cell neoplasms, and 4% were suspicious for malignancy. On final analysis, 165 nodules were benign and 123 were malignant. Of the 423 FNA samples, 24 BRAF V600E mutations, 7 KRAS, 21 NRAS, 4 PAX8-PPARY rearrangements, 3 RET/PTC 1, and 2 RET/PTC 3 rearrangements were detected. In all, 17 of 165 (10.3%) benign thyroid nodules had a mutation compared with 26% (32/123) malignant tumors (p<0.05).

BRAF

Adeniran et al conducted a study of 157 cases with equivocal thyroid FNA readings (indeterminate and suspicious for papillary thyroid carcinoma [PTC]) or a positive diagnosis for PTC and concomitant BRAF mutation analysis. (1) The results of histopathologic follow-up were correlated with the cytologic interpretations and BRAF status. Based on the follow-up diagnosis after surgical resection, the sensitivity for diagnosing PTC was 63.3% with cytology alone and 80.0% with the combination of cytology and BRAF testing. No false positives were noted with either cytology or BRAF mutation analysis. All PTCs with extrathyroidal extension or aggressive histologic features were positive for BRAF mutation. The authors concluded that patients with an equivocal cytologic diagnosis and BRAF V600E mutation could be candidates for total thyroidectomy and central lymph node dissection.

Xing et al investigated the utility of BRAF mutation testing of thyroid FNA specimens for preoperative risk stratification of PTC in 190 patients. (12) A BRAF mutation in preoperative FNA specimens was associated with poorer clinicopathologic outcomes of PTC. In comparison with the wild-type allele, a BRAF mutation strongly predicted extrathyroidal extension (23% vs. 11%; p=0.039), thyroid capsular invasion (29% vs. 16%; p=0.045), and lymph node metastasis (38% vs. 18%; p=0.002). During a median follow-up of 3 years (range, 0.6-10 years), PTC persistence/recurrence was seen in 36% of BRAF mutation-positive patients versus 12% of BRAF mutation-negative patients, with an odds ratio of 4.16 (95% confidence interval [CI], 1.70 to 10.17; p=0.002). The positive and NPVs for preoperative FNA detected BRAF mutation to predict PTC persistence/recurrence were 36% and 88%, respectively, for all histologic subtypes of PTC. The authors concluded that preoperative BRAF mutation testing of FNA specimens may provide a novel tool to preoperatively identify PTC patients at higher risk for extensive disease (extrathyroidal extension and lymph node metastases) and those who are more likely to manifest disease persistence/recurrence.

**Molecular Markers to Predict Benignity (Gene Expression Classifier)**

**Analytic Validity**

Walsh et al verified the analytic performance of the Afirma gene expression classifier (GEC) in the classification of cytologically indeterminate (FNAs from thyroid nodules). (13) The analytic performance studies were designed to characterize the stability of the RNA in the aspirates during collection and shipment, analytical sensitivity and specificity, and
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assay performance studies including intranodule, intraassay, interassay, and interlaboratory reproducibility. The authors concluded that the analytic sensitivity and specificity, robustness and quality control of the GEC were successfully verified.

Chudova et al developed a molecular test to distinguish between benign and malignant thyroid nodules using FNAs. (3) The authors used mRNA analysis to measure more than 247,000 transcripts in 315 thyroid nodules. The data set consisted of 178 retrospective surgical specimens, representing the most common benign and malignant histologic subtypes, and 137 prospectively collected aspirate specimens. Two classifiers were trained separately on surgical samples and aspirates. The performance was evaluated using an independent test set of 48 prospective FNA samples, which had known surgical pathology diagnoses, and included 50% with indeterminate cytopathology. The performance of the classifier was markedly lower in the FNAs than in tissue, likely due to differences in cellular heterogeneity between the 2 types of specimens. On the test set, NPV and specificity were estimated to be 96% and 84%, respectively.

Clinical Validity

Alexander et al reported on a 19-month, prospective, multicenter validation study of the Afirma GEC, which involved 49 clinical sites (both academic and community centers), 3789 patients and 4812 FNAs from thyroid nodules that were at least 1 cm in size. (14) Local pathology reports of the cytologic diagnosis were collected for all patients, and reports without a definitive benign or malignant diagnosis at the local site were reviewed by 3 expert cytopathologists, who reclassified them as atypical, follicular neoplasm or suspicious for a follicular neoplasm, or suspicious for malignancy. Corresponding histopathologic diagnoses from excised specimens were available (excisions were performed without knowledge of the results of the GEC). After inclusion criteria were met, 265 FNA samples deemed to be cytologically indeterminate were successfully tested with the GEC assay at Veracyte Laboratory. Of the 265 samples, 85 were malignant; the GEC correctly identified 78 of the 85 as suspicious (92% sensitivity; 95% CI: 84% to 97%), with a specificity of 52% (95% CI: 44% to 59%). NPV ranged from 85% for “suspicious cytologic findings” to 95% for “atypia of undetermined clinical significance.” There were 7 FNAs with false negative results, 6 of which were thought to be due to hypocellular aspirate specimens.

Harrell and Bimston reported a single center’s results for the diagnostic accuracy of the Afirma GEC. (15) Of a total sample of 645 FNA results, 58 were classified as indeterminate on cytology (either follicular lesion of undetermined significance/atypia of undetermined significance or follicular neoplasm). Of these, 36 (62%) were classified as suspicious on the Afirma GEC, 20 (34%) were classified as benign, and 2 were inadequate due to low mRNA content. Thirty patients with suspicious GEC findings underwent thyroidectomy, 21 of whom had malignancy on pathology. Five patients with benign GEC findings underwent thyroidectomy, 2 of whom had malignancy on pathology. Based on an assumption about the cancer prevalence in the patient population, the authors report an NPV of 89.6%. Given that a significant proportion of the samples were not assessed with the criterion standard for diagnosis, this study does not provide meaningful information about the validity of the Afirma GEC.

Clinical Utility

Duick et al reported on the impact of Afirma GEC test results on physician and patient decision making to operate on thyroid nodules with indeterminate cytology. (16) This retrospective, multicenter study included patients who were 21 years or older, had 1 or more thyroid nodules 1 cm or greater by ultrasound, and had an indeterminate diagnosis by cytology and a GEC from the same nodule that was reported as benign. A total of 51
endocrinologists at 21 endocrinology practices in 11 states participated. Data were collected on 368 patients with 395 nodules. The data collection period was September 2011 through March 2012. Surgery was performed in 7.6% of the patients with indeterminate cytology and a benign GEC. (Surgery was primarily performed on those patients with indeterminate cytology and a benign GEC because of large or symptomatic nodules, rapidly growing nodules or a second suspicious or malignant nodule in the same patient, the same reasons typically given for operation on cytologically benign nodules). The authors compared this surgical excision rate of the study population (7.6%) with a historical rate of surgical excision of 74% previously reported for patients with an indeterminate cytologic diagnosis (but no GEC test).

In 2014, Alexander et al reported results from a retrospective analysis of 339 thyroid nodules which underwent Afirma GEC testing for indeterminate cytology on FNA (follicular lesion of undetermined significance/atypia of undetermined significance, follicular neoplasm, or suspicious for malignancy) at 5 academic medical centers. Most of the nodules sent for GEC testing were follicular lesions of undetermined significance/atypia of undetermined significance or follicular neoplasm. The distribution of GEC testing results for each cytologic classification is shown in Table 1.

<table>
<thead>
<tr>
<th>Cytologic Classification</th>
<th>Total</th>
<th>GEC Testing Results, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Benign</td>
</tr>
<tr>
<td>Follicular lesion of undetermined significance</td>
<td>165</td>
<td>91 (55)</td>
</tr>
<tr>
<td>atypia of undetermined significance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>161</td>
<td>79 (49)</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>13</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>339</td>
<td>174</td>
</tr>
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</table>

A subset of patients whose nodules underwent GEC testing underwent a subsequent thyroid resection. Among 148 cases with suspicious Afirma GEC findings, surgery (thyroid resection) was recommended for 141 (95%). For the 174 cases with benign Afirma GEC findings, surgery was recommended for 4 (2%; p<0.01). Using the assumption that, in the absence of the GEC results, thyroid surgery would be recommended for patients with cytologically indeterminate FNA results, the authors report that the GEC results altered management in 50% of patients. Table 2 shows thyroidectomy biopsy results for the subset of patients shown in Table 1 who underwent surgery.

<table>
<thead>
<tr>
<th>GEC Testing Results</th>
<th>Total, n</th>
<th>Surgery Recommended, n</th>
<th>Surgery Completed, n</th>
<th>Pathology Malignant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious</td>
<td>148</td>
<td>141</td>
<td>121</td>
<td>53 (44% of those with completed surgery)</td>
</tr>
<tr>
<td>Benign</td>
<td>174</td>
<td>4</td>
<td>11</td>
<td>1 (9% of those with completed surgery)</td>
</tr>
</tbody>
</table>

Seventeen patients who had indeterminate cytology, benign Afirma GEC results, and did not undergo surgery had follow-up beyond 1 year. Of those, 3 patients underwent surgical removal of the nodule because of compressive symptoms (n=2) or nodule growth (n=1); all nodules were benign on final histology. The remaining 14 patients had ongoing follow up with ultrasound with no ongoing evidence of malignancy. The study demonstrated site-to-site variation in the proportion of samples that were GEC benign.
This study suggests that the Afirma GEC may alter clinical management of patients with indeterminate thyroid nodules. While the treating physicians presumably elected to obtain the GEC testing with the intent of altering management recommendations, the magnitude of the difference in surgical recommendations for patients with GEC suspicious or benign results was large. A limitation of this study is its retrospective, unblinded nature; thus, factors other than GEC testing may have contributed to either the recommendation for surgery or patients' decisions to undergo surgery. A benign GEC result did not completely rule out malignant pathology. Long-term follow up was available for only a small proportion of patients with benign GEC findings who did not undergo surgery.

In a single-center study, Aragon Han et al reported surgical management decision making outcomes among 114 patients with thyroid nodules who underwent molecular testing. Of 114 patients, 87 underwent thyroid surgery. Testing included a combination of the Afirma gene-expression classifier (n=37), a DNA-based somatic mutation panel (n=21), and testing for BRAF mutations (n=29), BRAF/NRAS (n=1), and BRAF/RET/PTC (n=1). A surgical decision-making algorithm that did not include mutation testing was developed by consensus among 4 thyroid surgeons. If the surgeon performed the same surgery as anticipated by the management algorithm, then the molecular test was considered to have no impact. If the surgeon performed a different surgery than anticipated by the management algorithm, the molecular test was considered to effect a change in management. The authors report that surgical management was not changed by molecular testing in 89.7% of cases. This study is limited by its use of multiple types of molecular testing, along with a nonstandardized incorporation of molecular genetic testing results into the surgical decision making. As such, the study has limited implications for the clinical utility of molecular diagnostics for thyroid cancer.

Ongoing and Unpublished Clinical Trials

A search of online database ClinicalTrials.gov identified 1 study currently enrolling patients that is investigating the role of gene expression and thyroid cancer:

- Genetic Analysis in Diagnosing Thyroid Cancer in Patients With Thyroid Nodules (NCT00316823). This is an observational study to evaluate the diagnostic accuracy of biomarkers and mRNA expression analysis using FNA biopsy samples from patients with thyroid nodules and correlate the level of gene expression with the aggressiveness of differentiated thyroid cancer in FNA biopsy samples. Enrollment is planned for 400 subjects; the planned study completion date was December 2009. The study was verified on February 21, 2014, but no publications were identified.

A search of the National Cancer Institute clinical trials database identified no phase 3 trials analyzing mutation analysis in FNAs of the thyroid.

Summary

Mutation Analysis

Mutation analysis of fine needle aspirates (FNA) of the thyroid that are cytologically indeterminate has a high positive predictive value for malignancy. However, patients with an equivocal FNA result would likely proceed to surgery regardless of mutation status, with intraoperative consultation to guide the necessity and extent of surgery. Mutation analysis does not achieve a high enough negative predictive value to identify which patients can undergo watchful waiting over thyroid surgery. Although the presence of certain mutations may predict more aggressive malignancies, the clinical utility of identifying these mutations preoperatively has not been established.
The incremental added value of mutation analysis to an equivocal FNA result is not known, and although mutation 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, at this time, it is not clear how it will impact patient management or surgical decision making and is considered investigational.

Gene Expression Classifier

The evidence supporting the validity and utility of the Afirma Thyroid FNA Analysis is used to help exclude malignancy in thyroid nodules with indeterminate FNA cytology. The evidence supporting the validity and utility of the Afirma Thyroid FNA Analysis is somewhat limited, but consistently supports the assertion that the assay may be useful as a “rule out” test. Given its relatively high NPV (i.e., approximately 95%), the likelihood of a thyroid malignancy may be significantly decreased in many patients with indeterminate FNA biopsies. Evidence supporting the clinical utility indicates that GEC results may influence medical management decisions in patients with indeterminate thyroid nodules and can lead to a significant decrease in diagnostic thyroid surgeries. Therefore, based on the overall summary of evidence, the use of a GEC to predict which thyroid nodules with indeterminate cytology are benign may be considered medically necessary.

Practice Guidelines and Position Statements

The American Thyroid Association (ATA) states that the currently available mutation analysis panel and gene expression classifier have promising roles but that at this time, experience with them remains limited. ATA feels that until an expert consensus review of existing data (currently underway) can be completed, no evidence-based recommendation for or against the use of these methods can be made. (19) The most recent ATA guidelines on the management of thyroid nodules is from 2009, before the widespread clinical availability of mutation analysis or gene expression profiles for thyroid cancer. (20)

National Comprehensive Cancer Network (NCCN) Guidelines on the treatment of thyroid cancer state, “Molecular diagnostics to detect individual mutations (e.g., BRAF, RET/PTC, RAS, PAX8/PPAR [peroxisome proliferator-activated receptors] gamma) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate. “(21) In the guidelines’ 2013 update, the NCCN added the guidelines to consider molecular diagnostics in cases where FNA results were (1) follicular or Hürthle cell neoplasm or (2) follicular lesion of undetermined significance (category 2A recommendation).

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 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 has completed an assessment of the Afirma GEC and determined that the test meets criteria for analytic and clinical validity, and clinical utility as a reasonable and necessary Medicare benefit. (22) Effective January 1, 2012, Palmetto GBA will reimburse Afirma services for patients with the following conditions:

1. Patients with 1 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

2. Have an indeterminate follicular pathology on fine needle aspiration

References


**Documentation Required for Clinical Review**

- Laboratory invoice/order indicating specific test(s)/panel(s) and associated procedure codes
- Referring physician’s history and physical and/or consultation report(s) including:
  - Preliminary diagnosis and prognosis
  - Operative reports
  - Specific test(s) requested and clinical reason/justification for testing
  - How test result will impact clinical decision making
  - Treatment plan
- Laboratory and/or Pathology report(s) (e.g., Fine Needle Aspiration (FNA) of the thyroid cytology reports)
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Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services are considered investigational and therefore not covered for any indication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>See Policy Guidelines</td>
<td></td>
</tr>
<tr>
<td>HCPC</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>For dates of service on or after 10/01/2015</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>For dates of service on or after 10/01/2015</td>
<td></td>
</tr>
</tbody>
</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/26/2014</td>
<td>BCBSA medical policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or
conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements**

This service (or procedure) is considered *medically necessary* in certain instances and *investigational* in others (refer to policy for details).

For instances when the indication is *medically necessary*, clinical evidence is required to determine *medical necessity*.

For instances when the indication is *investigational*, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.