Molecular Markers in Fine Needle Aspirates of the Thyroid

Description

Fine needle aspiration 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.

Thyroid nodules are common, present in 5-7% of the U.S. adult population. The vast majority are benign and most cases of thyroid cancer are curable by surgery if detected early. Fine needle aspiration 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 60-70% of thyroid nodules are classified cytologically as benign, and 4-10% of nodules are cytologically deemed malignant. However, the remaining 20-30% have equivocal findings (inclusive, indeterminate, atypical or 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 6-30%, making this clinical process one 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 sub-total thyroidectomy with or without lymph node dissection) depending on several factors, including histologic subtype and risk-stratification strategies (tumor size, patient age, etc.) 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 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 a fine-needle aspiration 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 as 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 molecular analysis for somatic genetic alterations, in order to more accurately classify which patients need to proceed to surgery (and may include the extent of surgery necessary) versus those patients who do not need surgery and can be safely followed.

**Molecular markers associated with thyroid cancer**

Various molecular markers have been discovered in thyroid cancer. The four gene mutations that are the most common and carry the highest impact on tumor diagnosis and prognosis and 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 70-75% 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.

There are no specific markers for benign thyroid lesions.

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 (KRAS, BRAF, HRAS, NRAS, RET/PTC 1, RET/PTC3 and PAX8/PPARγ).
Veracyte offers a proprietary “gene expression classifier” which claims to classify a thyroid nodule with indeterminate cytology as benign with >95% negative predictive value or as suspicious.

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

Policy

Mutation analysis in fine-needle aspirates of the thyroid is considered to be investigational.

The use of a gene expression classifier in fine-needle aspirates of the thyroid that are cytologically considered to be indeterminate, atypical or suspicious for malignancy, is considered to be investigational.

Policy Guidelines

Investigative service is defined as the use of any treatment procedure, facility, equipment, drug, device, or supply not yet recognized by certifying boards and/or approving or licensing agencies or published peer review criteria as standard, effective medical practice for the treatment of the condition being treated and as such therefore is not considered medically necessary.

The coverage guidelines outlined in the Medical Policy Manual should not be used in lieu of the Member's specific benefit plan language.

Medicare National Coverage: None

Investigational Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Description</th>
</tr>
</thead>
</table>

42 Memorial Drive • Suite 1 • Pinehurst, N.C. 28374 • Phone (910) 715-8100 • Fax (910) 715-8101

FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of
<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

**ICD-9 Procedure**

**ICD-9 Diagnosis**

**HCPCS**

**References**


Index
miRInform™ (Asuragen)
Veracyte® (Afirma)