Negative ThyroSeq® Genomic Testing for Indeterminate Thyroid Nodules:
The Memorial Sloan Kettering Cancer Center Experience

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Darren Buonocore
Assistant Attending
www.MSKCC.org
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Dr. Darren Buonocore declares he has no conflict(s) of interest to disclose.
<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy(%)</th>
<th>Usual management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td>b</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0–3</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>~5–15c</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>15–30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60–75</td>
<td>Near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97–99</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>
The Solution to Our Problems?

Afirma
GENOMIC SEQUENCING CLASSIFIER

ThyroSeq
Thyroid Genomic Classifier

Precision
Assurance
Guidance
A noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or Niftp, a type of tumor that was previously considered a kind of cancer, but has been downgraded by a panel of doctors. Yuri Nikiforov
What does this mean for the Bethesda System?
The 2017 Bethesda System for Reporting Thyroid Cytopathology

Edmund S. Cibas and Syed Z. Ali

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy if NIFTP ≠ CA (%)</th>
<th>Risk of malignancy if NIFTP = CA (%)</th>
<th>Usual management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td>5–10</td>
<td>5–10</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0–3</td>
<td>0–3</td>
<td>Clinical and sonographic follow-up</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>6–18</td>
<td>~10–30</td>
<td>Repeat FNA, molecular testing, or lobectomy</td>
</tr>
<tr>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>10–40</td>
<td>25–40</td>
<td>Molecular testing, lobectomy</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>45–60</td>
<td>50–75</td>
<td>Near-total thyroidectomy or lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>94–96</td>
<td>97–99</td>
<td>Near-total thyroidectomy or lobectomy</td>
</tr>
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</table>
American Thyroid Association guidelines

• Suggest the use of molecular studies in the management of patients with an indeterminate cytology diagnosis
ThyroSeq®
ThyroSeq® Performance in Bethesda III/IV

- Sensitivity: 94%
- Specificity: 82%
- NPV: 97%
- PPV: 66%
The Memorial Sloan Kettering Experience

• We propose to evaluate the NPV of ThyroSeq® at MSKCC, a major cancer center in the U.S. in which the prevalence of malignancy is high.
Methods

- Cytology material from 252 thyroid nodules diagnosed as indeterminate which were submitted for ThyroSeq® analysis

- The results were reported as negative in 151 cases.

- Twenty-one of these 151 cases were surgically resected.
Methods

• Gross description of the surgical resection specimen was compared to the radiologic findings at the time of biopsy to ensure the diagnosis correlated with the biopsied nodule
  – i.e. excluded any other carcinomas detected elsewhere in the specimen

• The ThyroSeq® results were correlated with the surgical diagnosis
Results

• Surgical resection was performed with intent to remove the tested nodule was performed in 18 of the 21 nodules. They were commonly removed due large size, growth or patient’s preference.

• Three nodules were resected due to the presence of a concurrent suspicious nodule.
Results

- 16 of 21 cases were confirmed to be benign or diagnosed as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NFTIP)
  - Malignant potential of this lesion is unclear
- 5 were malignant
  - 2 classical papillary carcinoma
  - 3 follicular carcinoma

THYROSEQ NEGATIVE NODULES

- Benign 62%
- NIFTP 14%
- Malignant 24%
Results

- Negative Predictive Value based on surgically resected nodules

  61.9 (if NIFTP = CA)

  76.2 (if NIFTP ≠ CA)
Results

- Negative Predictive Value assuming unresected nodules are benign
  
  89.4 (if NIFTP = CA)

  91.3 (if NIFTP ≠ CA)
Breakdown of Benign lesions & NIFTP

- Hyperplastic nodule/Nodular goiter: 44%
- Oncocytoma: 25%
- Follicular Adenoma: 12%
- NIFTP: 19%
Reasons for Surgery on Malignant Nodules

- Size (>4.0 cm): 40%
- Pt requested: 20%
- Other Nodule: 40%
**Conclusion**

- The NPV of ThyroSeq® is lower than reported and a negative result should be correlated with other clinico-radiological findings, particularly, in institutions with a high cancer prevalence.