Conflict of interest

• No conflict of interest

Thyroid nodules

Basic Facts
Myth 1

**Solitary Nodule vs. Multiple Nodules**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Ultrasound/Autopsy</th>
<th>Palpation</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall/USA</td>
<td>scan/histo</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Belfiore/Italy</td>
<td>scan</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Cochand/France</td>
<td>scan/US</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Sachamedchi/USA</td>
<td>scan</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Marques/USA</td>
<td>US</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Papini/Italy</td>
<td>US</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Barroeta/USA</td>
<td>US</td>
<td>52%</td>
<td>47%</td>
</tr>
</tbody>
</table>
**Too Many Thyroid FNA’s**

Is it Over-detection?

**Nodule Biopsy Guidelines & Operators**

**ATA Thyroid Biopsy Guidelines 2009**

<table>
<thead>
<tr>
<th>Module sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk history</td>
<td>Recommendation A</td>
</tr>
<tr>
<td>Nodule WITH suspicious sonographic features</td>
<td>&gt;5mm</td>
</tr>
<tr>
<td>Nodule WITHOUT suspicious sonographic features</td>
<td>&gt;5mm</td>
</tr>
<tr>
<td>Abnormal cervical lymph nodes</td>
<td>All</td>
</tr>
<tr>
<td>Microcalcifications present in nodule</td>
<td>1 cm</td>
</tr>
<tr>
<td>Solid nodule</td>
<td></td>
</tr>
<tr>
<td>AND hypoechogenic</td>
<td>&gt;1 cm</td>
</tr>
<tr>
<td>AND iso- or hyperechogenic</td>
<td>1–1.5 cm</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td>1.5–2.0 cm</td>
</tr>
<tr>
<td>WITH any suspicious ultrasound features</td>
<td>Recommendation B</td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>2.0 cm</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>2.0–3.0 cm</td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated</td>
</tr>
</tbody>
</table>

**SRU Guidelines 2005**

**Solitary nodule**

- Microcalcification: Strongly consider US-guided FNA if 1 cm
- Solid (or almost entirely solid) or coarse calcifications: Strongly consider US-guided FNA if 1.5 cm
- Mixed solid and cystic or almost entirely cystic with solid mural component: Consider US-guided FNA if 2 cm
- None of the above but substantial growth since prior US examination: Consider US-guided FNA
- Almost entirely cystic and none of the above and no substantial growth (or no prior US): US-guided FNA probably unnecessary

**Multiple nodules**

- Consider US-guided FNA of one or more nodules, with selection prioritized on basis of criteria (or order listed) for solitary nodule

Note: — FNA is likely unnecessary in diffusely enlarged gland with multiple nodules of similar US appearance without intervening parenchyma. Presence of abnormal lymph nodes overrides US features of thyroid nodule(s) and should prompt US-guided FNA or biopsy of lymph node and/or palatine nodule.

*Panel had two opinions regarding selection of nodules for FNA. The majority opinion is stated here.
Biopsy Recommendations Correlated With Final Diagnosis of Thyroid Nodules

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BX Recommended (n = 511)</th>
<th>BX Not Recommended (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant or follicular neoplasm</td>
<td>343</td>
<td>14</td>
</tr>
<tr>
<td>Benign</td>
<td>168</td>
<td>182</td>
</tr>
</tbody>
</table>

Note—Data are no. of thyroid nodules. Positive predictive value was 67%, negative predictive value was 92.9%, sensitivity was 96.1%, and specificity was 52%.

Final Diagnosis of Thyroid Nodules Compared for Each Malignancy Rating

<table>
<thead>
<tr>
<th>Malignancy Rating</th>
<th>Final Diagnosis</th>
<th>1 (n = 46)</th>
<th>2 (n = 150)</th>
<th>3 (n = 258)</th>
<th>4 (n = 162)</th>
<th>5 (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant or follicular neoplasm</td>
<td>2 (4.3)</td>
<td>12 (8.0)</td>
<td>128 (49.6)</td>
<td>130 (80.2)</td>
<td>85 (93.4)</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>44 (95.7)</td>
<td>138 (92.0)</td>
<td>130 (50.4)</td>
<td>32 (19.8)</td>
<td>6 (6.6)</td>
<td></td>
</tr>
</tbody>
</table>

Note—Data are no. (%) of thyroid nodules.

Sensitivity, Specificity, and Accuracy of Biopsy Recommendation for Each Reader Correlated With Years of Experience

<table>
<thead>
<tr>
<th>Years of Reader Experience</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
<td>40</td>
<td>70.3</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>38</td>
<td>69.3</td>
</tr>
<tr>
<td>10</td>
<td>94.1</td>
<td>50</td>
<td>72.3</td>
</tr>
<tr>
<td>11</td>
<td>90.2</td>
<td>64</td>
<td>77.2</td>
</tr>
<tr>
<td>13</td>
<td>98.1</td>
<td>48</td>
<td>73.3</td>
</tr>
<tr>
<td>16</td>
<td>98.1</td>
<td>56</td>
<td>77.2</td>
</tr>
<tr>
<td>33</td>
<td>92.2</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>
HISTOLOGY
ALL CASES (n=621)

NG, FA/HA, PTC, FCA/HCCA, MED-CA, OTHER MALIGNANCY, OTHER BENIGN

F/M 499/122 168/32 136/26 177/48 29/12 3/1 2/2 2/2

Age Ave.: 50.7

NODULE SIZES (n=663)

Measurement Type
0.1-1.0 cm
US (n=14)
Thyroidectomy (n=105)

1.1-1.5 cm
US (n=129)
Thyroidectomy (n=153)

1.6-3.0 cm
US (n=322)
Thyroidectomy (n=274)

3.1-5.0 cm
US (n=158)
Thyroidectomy (n=96)

5.1-10 cm
US (n=40)
Thyroidectomy (n=35)

Abreviations: NG; Nodular Goitre, FA/HA; Follicular Adenoma/Hurthle cell Adenoma, PTC; Papillary Thyroid Carcinoma, FCA/HCCA; Follicular Carcinoma/Hurthle Cell Carcinoma, MED-CA; Medullary Carcinoma, n; the number of nodules or cases, Ave.; Average, §; There are 41 cases with multiple (39 cases with 2 nodules, and 2 cases with 3 nodules) and, the diagnoses in 21 cases are different, OTHER MALIGNANCY*: Follicular Derived Carcinoma (2), Mucoepidermoid Carcinoma, Metastatic Renal Cell Carcinoma, OTHER BENIGN**: Adenolipoma, Parathyroid Adenoma, Neurofibroma, Parathyroid cyst, Thymic cyst, Normal thyroid tissue.

Deveci et al Diag Cytpathol 2006

Key Thyroid Cancer Stats

• Estimated cases in USA – 2010:
  – New cases: 44,670
  – Deaths: 1,690
• 2 of 3 cases are found in people between the ages of 20 and 55.
• Increase in thyroid cancer cases may be the result of the increased use of thyroid ultrasound. Still, at least part of the increase is from finding more larger tumors, as well.

The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years.

Hughes et.al Thyroid 2011

• SEER database 1974-2006
  – Diagnosis of PTC shifted 30yrs – 40-50 yrs
  – Until 1999 < 45 yrs
  – After 1999 >45 yrs
  – Largest increase in <1.0 cm PTC
  – Morris et.al Am J Surg: Increase in small tumor detection but presentation at higher stage has doubled.
“Ultrasound has high sensitivity but low specificity”

FNA Cytology
92% Sensitivity
85% Specificity

Objectives of Thyroid FNA

- Recognize specific diagnostic entities
- Provide meaningful, management oriented diagnosis
- Potential utilization of ancillary techniques

Thyroid FNA Bethesda Classification Scheme

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or Unsatisfactory</td>
<td></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 (AUS/FLUS)</td>
<td>~ 5-15%</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Specify - Hurtle type or Oncocytic)</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 Battle of 5 vs. 6 Category Scheme

Across Atlantic

Deandrea et al. – Thyroid 2010

<table>
<thead>
<tr>
<th># Cases</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>THY 1</td>
<td>51</td>
</tr>
<tr>
<td>THY 2</td>
<td>319</td>
</tr>
<tr>
<td>THY 3</td>
<td>294</td>
</tr>
<tr>
<td>THY 4</td>
<td>91</td>
</tr>
<tr>
<td>THY 5</td>
<td>172</td>
</tr>
</tbody>
</table>

Splitting THY 3

- **SA** – FLUS/AUS – 101 (34.3)
  - 5/101 = 5%

- **SB** – Follicular neoplasm – 92 (31.2)
  - 25/92 = 25%

- **SC** – Hurthle cell neoplasm – 101 (34.3)
  - 23/101 = 22.8%

The Atypical Category

Something in between benign and malignant
The Grayest Zone
What can lead to an Atypical Thyroid FNA?

- Inadequate history
- Inadequate specimen
  - Quantity and quality of representative cells
- Suboptimal preparation
- Sampling
- Lesional heterogeneity
- Cytomorphology vs. Cytopreps
- Interpretative and diagnostic errors

Clinical History is as Important as your diagnosis

Thyroid FNA without history

Is this a test?

- 52-year-old woman
- Ultrasound – Left thyroid lobe occupied by a predominantly ill-defined hypoechoic structure – suspicious for anaplastic carcinoma
Cytologic Diagnoses

Case 1:
• Original Diagnosis Suspicious for Anaplastic Carcinoma
  – More History
    • Transient symptomatic hyperthyroidism (TSH – 0.03) followed by hypothyroidism.
    • Current medication: Synthroid
  – Second opinion Dx: Suspect sub-acute thyroiditis
  – Surgical excision of left lobe
Lesson Learned

- History is as important as your diagnosis
  - Nodule characteristics
  - TFT’s
  - Prior FNA – Dx
Sampling and Lesional Heterogeneity

Fact well-known to surgical pathologist

US-Guided FNA
43 year old with multiple hypo-functioning thyroid nodules

- 2.3 x 2.1 x 3.5 cm – Left Inferior
- 1.5 x 1.7 x 2.2 cm – Right lower pole
FNA Diagnosis

- Atypical cells of undetermined significance
  - Majority of the specimen appears benign except one focus of atypical cells with nuclear features suspicious for papillary thyroid carcinoma.
- Left lobe
  - Hemorrhagic 2.2 x 3.0 x 1.5 cm nodule
  - Adjacent 1.4 cm cystic nodule with papillary growth pattern.
Lesional Heterogeneity
Cytomorphology vs. Cytopreps

The Dreaded Atypical Thyroid FNA Specimen?

Clinicians: What Atypia? YOU are just an Atypical Cytopathologist
Pathologist: I never classify my cases as atypical; lets get rid of this diagnosis
Making Sense of AUS/FLUS

1. ATYPIA OF UNDETERMINED SIGNIFICANCE - AUS
   (nuclear atypia)
   or

2. FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE - FLUS
   (architectural atypia)

Nuclear Atypia in Thyroid

• Nuclear pleomorphism
  – Nuclear enlargement
  – Hyperchromasia
  – Prominent nucleoli

• Nuclear Anaplasia

• Changes in Nuclear Chromatin
  – Reactive
  – Neoplastic

Nuclear Atypia in Benign Thyroid Lesions

• Nuclear Pleomorphism
  – Chronic Lymphocytic thyroiditis (CLT)
  – Long Standing Goiter
  – Post FNA Change
  – Graves’ Disease
    • Post Radioactive Iodine Treatment
    • Post Tapazole Treatment
  – Dyshormonogenetic Goiter
43-year-old with history of breast carcinoma underwent ultrasound guided FNA of a suspicious poorly circumscribed vascular area in right thyroid.

Surgical Excision

Chronic lymphocytic thyroiditis (CLT) with random nuclear atypia

43-year-old female with long standing history of Hashimoto’s Thyroiditis-FNA

Suspicious for Papillary Thyroid Carcinoma
Total Thyroidectomy

Nuclear Atypia in Benign Thyroid Lesions

1. Chronic Lymphocytic Thyroiditis
2. Graves’ Disease
   • Additional history
     – TFF’s, Treatment, Previous FNA

Architectural “Atypia”

1. Papillary Formations
2. Microfollicles
20-year-old woman underwent biopsy of a 3.0 cm left thyroid hypoechoic vascular nodule with possible intra-nodular micro-calcifications.

**DX:** Papillary Hyperplastic Nodule

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Neoplasm/Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td></td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>Clinical follow-up</td>
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<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)</td>
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<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
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<td>Surgical lobectomy</td>
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<tr>
<td>Suspicious for Malignancy</td>
<td>60-75%</td>
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</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>

**Follow-up Studies**

The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cases/patients</th>
<th>No. of patients/cases with S/P-F/U</th>
<th>Malignancy in excised nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. (2007)</td>
<td>152 (3.2)</td>
<td>52 (34)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Yassa et al. (2007)</td>
<td>144 (4)</td>
<td>84 (58)</td>
<td>20 (24)</td>
</tr>
<tr>
<td>Nayyar et al. (2009)</td>
<td>924 (18)</td>
<td>430 (46)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Layfield et al. (2009)</td>
<td>673 (9.7)</td>
<td>127 (18.9)</td>
<td>36 (28)</td>
</tr>
<tr>
<td>Constantine et al. (2009)</td>
<td>95 (3)</td>
<td>27 (28)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Ohori et al. (2010)</td>
<td>517 (20.6)</td>
<td>121 (23.4)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Faquin et al. (2010)</td>
<td>509 (NA)</td>
<td>273 (54)</td>
<td>52 (19%)</td>
</tr>
<tr>
<td>Jo et al. (2010)</td>
<td>104 (3.4)</td>
<td>53 (51%)</td>
<td>17 (9%)</td>
</tr>
<tr>
<td>Renshaw (2010)</td>
<td>548 (14)</td>
<td>204 (37)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>Nga et al. (2010)</td>
<td>341 (17.2%)</td>
<td>131 (38.45)</td>
<td>17 (13%)</td>
</tr>
</tbody>
</table>

**Beyond Bethesda Classification**

<table>
<thead>
<tr>
<th>Cytological Diagnosis</th>
<th>N (%)</th>
<th>N (%) of all FNA</th>
<th>N (%)</th>
<th>N (%) of all cases with histological follow-up</th>
<th>Benign histology</th>
<th>Malignant histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic</td>
<td>3215</td>
<td>13.1%</td>
<td>511</td>
<td>8.6%</td>
<td>427</td>
<td>83.6%</td>
</tr>
<tr>
<td>Benign</td>
<td>14433</td>
<td>59.0%</td>
<td>1390</td>
<td>23.5%</td>
<td>1344</td>
<td>100%</td>
</tr>
<tr>
<td>FLUS/AUS</td>
<td>2433</td>
<td>10.0%</td>
<td>949</td>
<td>16.1%</td>
<td>798</td>
<td>84.1%</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>2399</td>
<td>9.8%</td>
<td>1631</td>
<td>27.6%</td>
<td>1196</td>
<td>73.3%</td>
</tr>
<tr>
<td>Suspicious for Malignant</td>
<td>656</td>
<td>2.7%</td>
<td>477</td>
<td>8.1%</td>
<td>76</td>
<td>98%</td>
</tr>
<tr>
<td>Malignant</td>
<td>1309</td>
<td>5.4%</td>
<td>953</td>
<td>16.1%</td>
<td>12</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Total**

|                  | 24445 | (100%)          | 5911  | (100%)                                       | 3891             | (65.8%)            |

**How helpful it is to sub-classify AUS/FLUS cases?**

Relay what you see in a note...
Renshaw, A. Cancer Cytopathology June 2010

Risk of Malignancy for Sub-classified Atypical Follicular Cells

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (% ) of Cases</th>
<th>No. (% ) of Cases With Histologic Follow-Up</th>
<th>No. (% ) Benign Histology</th>
<th>No. (% ) Malignant Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypia, NOS</td>
<td>55 (1)</td>
<td>15 (27)</td>
<td>11 (73)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Atypia, rule out follicular neoplasm</td>
<td>184 (3)</td>
<td>73 (40)</td>
<td>57 (78)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Atypia, rule out Hurthle cell neoplasm</td>
<td>144 (2)</td>
<td>44 (31)</td>
<td>41 (93)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Atypia, rule out papillary carcinoma</td>
<td>165 (2)</td>
<td>72 (44)</td>
<td>45 (62)</td>
<td>27 (38)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>548 (14)</strong></td>
<td><strong>204 (37)</strong></td>
<td><strong>154 (75)</strong></td>
<td><strong>50 (25)</strong></td>
</tr>
</tbody>
</table>

HUP Sub-Classifiers for FLUS/AUS

- Few microfollicles with nuclear overlapping and crowding
- Few microfollicles with nuclear elongation and crowding
- Few cells with nuclear elongation and grooves
- Few cells with nuclear elongation and grooves
- Favor Hyperplastic nodular but cellular specimen

Have we created an ASCUS of Thyroid FNA?

- Take control of AUS/FLUS diagnosis?
  - QA - % of total thyroid FNA diagnosis / year
- AUS/FLUS ratio to various diagnosis
  - AUS/FLUS : Neoplasm
  - AUS/FLUS : Malignant
  - AUS/FLUS : Benign
Management of AUS / FLUS

- Second opinion
- Repeat FNA
- Molecular testing
  - Reflex
  - Regardless

Can Molecular Analysis be Helpful in Further Classification of Thyroid FNA Cases?

Can Molecular Analysis of Thyroid FNA Specimens be Helpful in Further Classification of Atypical Cases?
Cost Effectiveness of a Molecular Test

**The key drivers of cost effectiveness are:**
- Cost of the test
- Cancer prevalence in cytologically indeterminate nodules
- The likelihood of surgery being performed on patients with such nodules
- Specificity of the novel molecular test.

Molecular Testing of Thyroid-FNA Specimens

<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
<th>Molecular Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Diagnostic/Unsatisfactory</td>
<td>26% mutation positive. Reduce second FNA</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;FN?</td>
</tr>
<tr>
<td>AUS/FLUS</td>
<td>Increase sensitivity 86-97% &amp; specificity 97-100%</td>
</tr>
<tr>
<td>Follicular neoplasm /Suspicious for follicular neoplasm</td>
<td>Malignancy risk from 20% to 87.5%</td>
</tr>
<tr>
<td>Suspicous for PTC</td>
<td>Decrease the rate of second surgery</td>
</tr>
<tr>
<td>PTC</td>
<td>Define the extent of surgery? LN dissection – usually level VI</td>
</tr>
</tbody>
</table>

Making Sense of Available Molecular Tests Based on Type of Thyroid FNA Case

1. Test with High Positive Predictive Value
2. Test with High Negative Predictive Value
High Positive Predictive Value

- The use of molecular markers (e.g., BRAF, RAS, RET/PTC, Pax8-PPARγ) may be considered for patients with indeterminate cytology on FNA to help guide management.

- How good is this test for nodules which are?
  - Smaller, <2.0 cm
  - Less suspicious on ultrasound – spongiform
  - Diagnosed as AUS/FLUS and Follicular neoplasm / suspicious for follicular neoplasm.

Lets Ask the Question Differently?

Query – Benign vs. Malignant
Test with a high negative predictive value

Molecular Classifier Utilizes 167 Genes in Multiple Biological Pathways

- Signaling
- Development
- Cell Cycle
- Adhesion
- Immune Response
- Transcription
- Apoptosis
- Migration
- Inflammation
Prospective, multicenter, double blind study design

Performance:
- Risk of malignancy < 6% for cytopathology indeterminate (defined as atypia/FLUS + follicular/Hürthle cell neoplasm)
- Sensitivity 92% across all three indeterminate sub-types
- Specificity 52% (over half of benign nodules identified)
- Benign cytology (6% were malignant) - 100% sensitivity (to detect 3/3 malignancies)
- Malignant cytology - 100% sensitivity

False negative cases
- Independent marker analysis suggests insufficient sampling of follicular cells occurred in 6/7 cases
- Close clinical and sonographic follow-up of cytology atypia/FLUS and follicular neoplasm but molecularly (GEC) benign FNAs is recommended

Gene expression classifier utilizes 167 genes
- Expression of 142 mRNAs in the “main classifier”
- 25 additional genes are used raise suspicion of rare thyroid neoplasms like medullary thyroid cancer, parathyroid cells, or metastases to the thyroid

Validation of Final Molecular Classifier

Negative Predictive Value (NPV) 96%

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<table>
<thead>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>95%</td>
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<tr>
<td>Specificity</td>
<td>63%</td>
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<tr>
<td>Positive Predictive Value (PPV)</td>
<td>57%</td>
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Few Questions & More

- How good is your diagnosis
  - Clinical history and nodule features
  - Consistent and management based
- Molecular analysis
  - Case selection
  - All or few
  - Economic effects
  - Test with high positive vs. high negative predictive value.
1. Relying on Cytomorphology
2. Learning (certification) or at least acquire basic knowledge of Ultrasound
3. Molecular test – which one to use?