Evaluation and Management of Thyroid Nodules

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Objectives

• Understand the appropriate diagnostic evaluation of thyroid nodules

• Recognize nodules which merit further evaluation with ultrasound guided fine needle aspiration (FNA)

• Understand utility of ancillary testing for nodules which are indeterminate on cytology
Thyroid Nodules

• Prevalence depends on population and method of detection
  – U.S. population ages 30-60 yrs, 6.4% of women and 1.5% of men possess palpable thyroid nodules
  – Finnish population ages 19-60 yrs, 27% possess thyroid nodules via neck ultrasound
  – 60% of the elderly (>70 yrs) possess nonpalpable thyroid nodules on autopsy
Thyroid Nodule Prevalence

Mazzaferri E, NEJM. 1993; 328:553-559.
Diagnostic Evaluation

- Physical Examination
- Laboratory Testing
- Thyroid Imaging
  - Neck ultrasound
  - $I^{123}$ Uptake and scan
- Fine Needle Aspiration
Diagnostic Evaluation

Physical Examination

• Helpful in differentiating non-thyroidal from thyroidal lesions

• Limited value in differentiating benign from malignant thyroid nodules
  – Firm, fixation to adjacent structures and concomitant cervical lymphadenopathy

• Thyroid “nodules” may **NOT** be true nodules
• What is the thyroid function?
  – TSH and free T4
“Huge Nodule”
“Rapidly Enlarging Painful Nodule”

Left Transverse

Left Longitudinal
Diagnostic Evaluation

- **Low TSH**
  - $^{123}$I Thyroid Uptake/Scan
  - Hyperfunctioning “Hot” Nodule
  - Treat Hyperthyroidism

- **Normal TSH**
  - Nonfunctioning “Cold” Nodule
  - Ultrasound and Fine Needle Aspiration (*if clinically indicated)

- **High TSH**
  - Nodule Initially Detected via Ultrasound?
    - Yes
      - Evaluate/Treat Hypothyroidism
    - No
      - Nodule Still Present w/Palpation?
        - Yes
          - Continue to Treat Hypothyroidism
        - No
          - Continue to Treat Hypothyroidism
CASE #1: 62 yo M presents to establish care with a new physician. He has no acute complaints, but reports mild fatigue and occasional insomnia on review of systems.

PMHx: colitis, “thyroid problem many years ago”

PSHx/FmHx/SoHx: Noncontributory.

Medications: Asacol

Physical Examination: 160/80 120
anxious w/pressured speech
slight stare, but no exophthalmous, lid lag, conjunctival injection, or periorbital edema
no diffuse thyromegaly, bruit, or thrill; + 3.5 cm right sided nodule lateral to larynx which moved with swallowing
tachycardic with regular rhythm, no JVD or edema
warm/moist skin, no dermopathy or onycholysis
+peripheral tremor; hyperreflexic DTRs
Case #1

Laboratory Evaluation:
TSH - <0.01 uIU/mL (0.3 – 5.0)
Free T4 - 4.2 ng/dL (0.73 – 1.84)
Total T3 - 570 ng/dL (60 -180)

What’s the next diagnostic step?
Normal TSH

123I Thyroid Uptake/Scan

Hyperfunctioning “Hot” Nodule

Treat Hyperthyroidism

Nonfunctioning “Cold” Nodule

Ultrasound and Fine Needle Aspiration (*if clinically indicated)

Evaluate/Treat Hypothyroidism

No

Yes

Nodule Initially Detected via Ultrasound?

High TSH

Continue to Treat Hypothyroidism

Low TSH

Yes

Nodule Still Present w/Palpation?

No

Evaluate/Treat Hypothyroidism

Evaluate/Treat Hypothyroidism

Yes

Hyperfunctioning “Hot” Nodule

Nodule Initially Detected via Ultrasound?
Case #1

Laboratory Evaluation:
TSH - <0.01 uIU/mL (0.3 – 5.0)
Free T4 - 4.2 ng/dL (0.73 – 1.84)
Total T3 - 570 ng/dL (60 -180)

$^{123}$I – 24 hour uptake = 57%
Case #1: Thyroid/neck Ultrasound

Does this nodule need to be FNA’d?
Case #1: Thyroid/neck Ultrasound
Diagnostic Evaluation
Fine Needle Aspiration (FNA)

• Safe, inexpensive, and accurate
• Results dependent on adequacy of specimen and interpretation (expertise of those performing FNA and interpreting cytology)
• Significantly impacts management of thyroid nodular disease
## FNA Cytology

**"the statistics"**

<table>
<thead>
<tr>
<th>Series</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
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<tbody>
<tr>
<td>Schnürer &amp; Widström, 1978</td>
<td>96</td>
<td>76</td>
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<td>99.5</td>
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<td>Löwhagen et al., 1979</td>
<td>91</td>
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<td>100</td>
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<td>Gardiner et al., 1986</td>
<td>65</td>
<td>91</td>
<td>100</td>
<td>88.5</td>
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<tr>
<td>Abu-Nema et al., 1987</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>98.9</td>
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<tr>
<td>Hawkins et al., 1987</td>
<td>86</td>
<td>95</td>
<td>95.4</td>
<td>97.6</td>
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<tr>
<td>Hall et al., 1989</td>
<td>84</td>
<td>90</td>
<td>98.7</td>
<td>97</td>
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<tr>
<td>La Rosa et al., 1991</td>
<td>98</td>
<td>98</td>
<td>98.3</td>
<td>97.3</td>
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<tr>
<td>Gharib &amp; Goellner, 1993</td>
<td>98</td>
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<td>98</td>
<td>99.3</td>
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<tr>
<td>Holleman et al., 1995</td>
<td>84</td>
<td>52</td>
<td>53</td>
<td>83</td>
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<tr>
<td>Leonard &amp; Melcher, 1997</td>
<td>88</td>
<td>78</td>
<td>46</td>
<td>97</td>
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<tr>
<td>Hamming et al., 1998</td>
<td>67</td>
<td>99</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Baloch et al., 1998</td>
<td>92</td>
<td>84</td>
<td>73.3</td>
<td>98.7</td>
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</table>

## FNA Cytology
### Diagnostic Accuracy

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Pathology</td>
<td>516</td>
<td>86</td>
<td>74</td>
<td>34</td>
<td>97</td>
</tr>
<tr>
<td>Surgical Path + U/S follow-up</td>
<td>1289</td>
<td>86</td>
<td>89</td>
<td>31</td>
<td>99</td>
</tr>
</tbody>
</table>

*7.5% of FNA’s were non-diagnostic*

Thyroid nodules are extremely common, affecting nearly 50% by age 60.

Thyroid nodules are rarely cancerous (5-10%).

The incidence of thyroid cancer appears to be increasing, particularly small cancers, which may not be significant in the long run.

Do we evaluate all thyroid nodules with FNA?

How do we select or exclude nodules for evaluation?
## Sonographic Features of Malignancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Malignant Nodules (n=360)</th>
<th>Benign Nodules (n=489)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly solid</td>
<td>354 (98.3%)</td>
<td>426 (87.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked Hypoechogenicity</td>
<td>149 (41.4%)</td>
<td>38 (7.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spiculated margin</td>
<td>174 (48.3%)</td>
<td>40 (8.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>159 (44.2%)</td>
<td>45 (9.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taller than wide</td>
<td>144 (40.0%)</td>
<td>42 (8.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Nodule Composition: Solid versus Cystic

<table>
<thead>
<tr>
<th>Composition</th>
<th>Benign</th>
<th>Malignant</th>
<th>Percent Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely Solid</td>
<td>330</td>
<td>55</td>
<td>14.3</td>
</tr>
<tr>
<td>Predominantly Solid</td>
<td>209</td>
<td>24</td>
<td>10.3</td>
</tr>
<tr>
<td>Mixed Solid and Cystic</td>
<td>129</td>
<td>8</td>
<td>5.8</td>
</tr>
<tr>
<td>Predominantly Cystic</td>
<td>85</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Completely Cystic</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ p < 0.01 \]
## Sonographic Features of Malignancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio for Malignancy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly solid</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marked Hypoechochogenicity</td>
<td>8.499</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spiculated margin</td>
<td>2.749</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>4.599</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taller than wide</td>
<td>2.787</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Suspicious Ultrasound Features

Right Transverse

Right Longitudinal
### Ultrasound Characteristics of *Benign* Nodules

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>10.4</td>
<td>99.7</td>
<td>45.0</td>
<td>98.1</td>
</tr>
<tr>
<td>Isoechoic</td>
<td>56.6</td>
<td>88.1</td>
<td>59.9</td>
<td>86.6</td>
</tr>
<tr>
<td>Spongiform and isoechoic</td>
<td>6.1</td>
<td>100</td>
<td>44.0</td>
<td>100</td>
</tr>
</tbody>
</table>

### Ultrasound Characteristics of Benign Nodules

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Total Nodules</th>
<th>Benign</th>
<th>Surgical Intervention Necessary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform</td>
<td>210</td>
<td>210</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyst w/colloid clot</td>
<td>53</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Giraffe</td>
<td>23</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“White knight”</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>197</td>
<td>157</td>
<td>17</td>
<td>23</td>
</tr>
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</table>

**Negative Predictive Value 100%**

- Spongiform
- Cyst w/colloid clot
- Giraffe
- “White knight”

Spongiform and Cystic Thyroid Nodules

Spongiform

Cystic w/colloid clot
Which nodules should be biopsied?

<table>
<thead>
<tr>
<th>Sonographic Pattern</th>
<th>Estimated Risk of Malignancy, %</th>
<th>FNA Size Cutoff</th>
<th>Sonographic Features</th>
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<tr>
<td>High suspicion</td>
<td>&gt;70-90</td>
<td>≥ 1 cm</td>
<td>• Solid hypoechoic nodule with one or more of the following: irregular margins, microcalcifications, taller than wide shape, rim calcification with extrusive soft tissue, evidence of extrathyroidal extension (ETE)</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>10-20</td>
<td>≥ 1 cm</td>
<td>• Solid hypoechoic nodule with smooth margins without microcalcifications, taller than wide shape, or ETE</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>5-10</td>
<td>≥ 1.5 cm</td>
<td>• Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area without microcalcification, irregular margin, taller than wide shape, or ETE</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>&lt;3</td>
<td>≥ 2 cm or observation without FNA</td>
<td>• Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion nodules</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;1</td>
<td>No FNA</td>
<td>• Purely cystic nodules (no solid component)</td>
</tr>
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2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Which nodules should be biopsied?

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2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Which nodules should be biopsied?

Diagnostic Categories

Thyroid Nodule Cytology

- Benign (60-70%)
- Indeterminate (15-20%)
- Malignant (5%)
  - Primary Thyroid Cancer
  - Metastatic Cancer
  - Lymphoma
- Nondiagnostic (10%)
# The Bethesda System

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0-3</td>
<td>Clinical Follow-up</td>
</tr>
<tr>
<td>AUS/(F)LUS</td>
<td>5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
</tr>
<tr>
<td>Non-diagnostic/Unsat.</td>
<td>1-4</td>
<td>Repeat FNA with u/s guidance</td>
</tr>
<tr>
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<td>Risk of Malignancy (%)</td>
<td>Recommended Management</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------</td>
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</tr>
</tbody>
</table>
"Historical" Cytology Management Algorithm

- **Benign**
  - Surveillance

- **Indeterminate**
  - Follicular lesion of undetermined significance (F)LUS
  - Follicular or oncocytic neoplasm
  - Suspicious for malignancy
  - Repeat FNA versus Surgery?

- **Malignant**
  - Total Thyroidectomy

- **Non-diagnostic**
  - Repeat FNA w/Ultrasound
  - Diagnostic?
    - No
    - See Above
    - Yes
      - See Above
“Historical” Cytology Management Algorithm

**Indeterminate Lesions**

Follicular Lesion of Undetermined Significance (F)LUS

Follicular or Oncocytic Neoplasm

Suspicious for Papillary Thyroid Carcinoma

**Risk of Thyroid Cancer**

- 5-15%
- 15-30%
- 60-75%

**Treatment Approach**

- Repeat FNA
- Hemithyroidectomy
- Total Thyroidectomy
MAPK Signaling Pathway

### “Early” Mutations Recognized in DTC

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papillary Carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>45</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>20</td>
</tr>
<tr>
<td>RAS</td>
<td>10</td>
</tr>
<tr>
<td><strong>Follicular Carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>RAS</td>
<td>45</td>
</tr>
<tr>
<td>PAX8-PPARγ</td>
<td>35</td>
</tr>
</tbody>
</table>

### +BRAF Specificity in Indeterminate Cytology

<table>
<thead>
<tr>
<th></th>
<th>BRAF</th>
<th>Thyroid CA</th>
<th>Adenoma</th>
<th>Goiter</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xing M, 2004</td>
<td>2/25</td>
<td>2/13</td>
<td>0/4</td>
<td>0/7</td>
<td>0/1</td>
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<tr>
<td>Cohen Y, 2004</td>
<td>23/91</td>
<td>23/59</td>
<td>-/-</td>
<td>-/-</td>
<td>0/32</td>
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<tr>
<td>Salvatore G, 2004</td>
<td>4/11</td>
<td>4/11</td>
<td>0</td>
<td>0</td>
<td>-/-</td>
</tr>
<tr>
<td>Rowe LR, 2006</td>
<td>3/19</td>
<td>3/19</td>
<td>0</td>
<td>0</td>
<td>-/-</td>
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<tr>
<td>Sapio MR, 2007</td>
<td>4/36</td>
<td>4/8</td>
<td>-/-</td>
<td>-/-</td>
<td>0/28</td>
</tr>
<tr>
<td>Marchetti I, 2009</td>
<td>18/52</td>
<td>18/33</td>
<td>-/-</td>
<td>0/19</td>
<td>-/-</td>
</tr>
<tr>
<td>Jo YS, 2009</td>
<td>7/24</td>
<td>7/9</td>
<td>-/-</td>
<td>-/-</td>
<td>0/15</td>
</tr>
<tr>
<td>Zatelli, MC, 2009</td>
<td>11/107</td>
<td>11/31</td>
<td>0/74</td>
<td>-/-</td>
<td>0/2</td>
</tr>
<tr>
<td><strong>Totals (2004-09)</strong></td>
<td><strong>72/365</strong></td>
<td><strong>72/183</strong></td>
<td><strong>0/78</strong></td>
<td><strong>0/26</strong></td>
<td><strong>0/78</strong></td>
</tr>
</tbody>
</table>

Positive Predictive Value of +BRAF = 100% (72/72)
+BRAF in Indeterminate Nodules

Follicular Lesion of Undetermined Significance (F)LUS

Follicular or Oncocytic Neoplasm

Suspicious for Papillary Thyroid Carcinoma

Molecular Marker Testing +BRAF

Risk of Thyroid Cancer

- 5-15%
  - 100%
  + 15-30%
  - 100%
  + 60-75%
  - 100%

Treatment Approach

Repeat FNA

Hemithyroidectomy

Total Thyroidectomy

Total Thyroidectomy
Cytology Management Algorithm

*Indeterminate Lesions*

- Follicular Lesion of Undetermined Significance (F)LUS
- Follicular or Oncocytic Neoplasm
- Suspicious for Papillary Thyroid Carcinoma

**Risk of Thyroid Cancer**

*Molecular Testing Results (+/-)*

- ?
- ?
- ?

**Treatment Approach**
What is Molecular Testing?

• Afirma – Gene Expression Classifier (GEC)
  • Commercially available gene expression “chip”
  • Uses proprietary algorithm to differentiate “benign” and “suspicious” expression patterns of mRNA of 167 gene transcripts

• ThyroSeq
  • Tests for genetic mutations and gene fusions known to occur in thyroid cancer
RECOMMENDATION 16:
(A) 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.
## GEC in Follicular Neoplasm Cytology

**Prospective, Double-blind, Multicenter Study**

<table>
<thead>
<tr>
<th>GEC Result</th>
<th>Malignant (n = 20)</th>
<th>Benign (n = 61)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicious</td>
<td>18</td>
<td>31</td>
<td>PPV = 37% (23-52)</td>
</tr>
<tr>
<td>Benign</td>
<td>2</td>
<td>30</td>
<td>NPV = 94% (79-99)</td>
</tr>
</tbody>
</table>

+Prevalence of malignancy = 25%

*20/81 (40%) “benign” on GEC

ThyroSeq v2 in Follicular Neoplasm Cytology

## ThyroSeq v2 in Follicular Neoplasm Cytology

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) Negative Mutation</td>
<td>101</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>(+) Positive Mutation</td>
<td>42</td>
<td>35</td>
<td>7</td>
</tr>
</tbody>
</table>

Prevalence of malignancy = 27%
Accuracy 92% (CI 88-97%)
PPV 83% (CI: 72-95%)
NPV 96% (CI: 92-95%)
101/143 (71%) tested negative on ThyroSeq v2

Indeterminate Lesions

- Follicular Lesion of Undetermined Significance F(LUS)
- Follicular or Oncocytic Lesion
- Suspicious for Papillary Thyroid Carcinoma

Risk of Thyroid Cancer
- 5-15%
- 20-30%
- 50-75%

Negative Molecular Marker Testing
- 4-6%

Treatment Approach
- Ultrasound Follow-up
Utility of Molecular Testing


- Molecular Markers