Innovations in the Management of Thyroid Nodules and Thyroid Cancer

Mira Milas MD, FACS
Professor of Surgery

Objectives

1. “Molecular Cytology” and the Thyroid
2. Hereditary Thyroid Cancer Syndromes
3. Resources for Thyroid Surgery & Cancer Care

No conflicts of interest or financial relationships to disclose.
New Markers for Thyroid Cancer Management

- Molecular markers for cancer diagnosis
- Molecular markers for cancer prognosis
- Molecular markers for targeted therapies

“Learn more how personalized genetic testing at Cancer Treatment Centers of America...reveals the genomic profile of the patient’s individual cancer to help guide more precise cancer treatment options”

“Rapidly evolving area.....the promise of precision cancer treatment”

“Genomic testing is the future of cancer....... in every possible way”

TV Commercial July 27, 2013

Clinical Evaluation of your Patient
Relevant, thorough, and thoughtful history and examination

http://www.lerner.ccf.org/gmi/ccscore/
Risk Calculator for Estimating a Patient's Risk for PTEN Mutation

Clinical Evaluation of your Patient
Relevant, thorough, and thoughtful history and examination

The Context

Discovery of thyroid nodule → History and Exam
TSH → US → FNA

“Code words” in US reports that suggest high suspicion of malignancy

- Microcalcifications
- Coarse/peripheral calcifications (eggshell gaps)
- Indistinct borders/local invasion/infiltrating or irregular margins
- Lymphadenopathy
- Taller than wide
- Markedly hypoechoic
- Intranodular hypervascularity
Nodule Features Size Threshold for FNA *

- **HIGH RISK PATIENTS**
  - suspicious sonographic features
    - iso/hyper echoic solid
    - partially cystic with eccentric solid areas
  - no suspicious features
    - hypoechoic solid, regular border
    - taller-than-wide shape
  - > 5 mm
  - > 5 mm

- **ABNORMAL LYMPH NODES**
  - all
  - A

- **MICROCALCIFICATIONS**
  - ≥ 1 cm
  - B

- **SOLID NODULE**
  - hypoechoic
  - iso- or hyperechoic
  - ≥ 1 cm
  - ≥ 1 – 1.5 cm
  - B
  - C

- **MIXED CYSTIC/SOLID NODULE**
  - suspicious sonographic features
  - no suspicious features
  - ≥ 1.5 – 2.0 cm
  - ≥ 2 cm
  - B
  - C

- **SPONGIOFORM NODULE**
  - ≥ 2 cm
  - C

- **PURELY CYSTIC NODULE**
  - no FNA indicated
  - E

* 2009 ATA Guidelines

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2.5 cm right thyroid nodule
“spongiform” or “honeycomb”

>50% nodule is aggregation of multiple microcystic components: honeycomb of internal cystic spaces

<1% risk of malignancy

The Context

Discovery of thyroid nodule → History and Exam
  TSH → US → FNA

Bethesda cytopathology with % risk for thyroid cancer

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Diagnostic</td>
<td>Benign</td>
<td>AUS or FLUS</td>
<td>Follicular neoplasm</td>
<td>Suspicious for Cancer</td>
<td>Cancer</td>
</tr>
<tr>
<td>rare</td>
<td>&lt;5%</td>
<td>10-15%</td>
<td>30%</td>
<td>75%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Repeat FNA
Monitor
Repeat FNA
Lobectomy
Lobe vs Total
Total

Molecular Markers

Diagnosis of Cytopathology Indeterminate Subtype Not Reproducible on Expert Re-review

Using subtype diagnoses to drive clinical recommendations may not be reliable.
The Solutions in 2014:
1. DETECTING MUTATIONS in FNA TISSUE
2. DETECTING BENIGN GENETIC SIGNATURES in FNA TISSUE
3. DETECTING CIRCULATING THYROID CANCER CELLS

The wrong question:
“Which one of the molecular tests is the best?”

The right question:
“What is the best treatment path for my patient?”

even before any thought of FNA
even if it is your initial assessment.....
because without a context or a goal, you cannot judge what test is best

The better question:
“Which one of the molecular tests is the best for this patient?”
Your Patient

A 38 year old woman with history of radiation exposure for Hodgkin’s disease has a visible goiter, mild symptoms, normal TSH and undergoes US-guided FNA of 3 nodules. Cytology: 2 benign, 1 follicular neoplasm.

The right questions:

“What is the best treatment path for my patient?”

*total thyroidectomy*

“What one of the molecular tests is the best for this goal?”

*none*

Surgical Options for Follicular Neoplasms:

“Common Sense” Consideration

- Total thyroidectomy
- XRT exposure
- Anticoagulation
- Bilateral nodules
- Elderly patients
- Co-morbidities
- Already on LT4
- Nodule>3cm?
Your Patient
A 58 year old woman undergoes carotid US that detects 2.0 cm right thyroid nodule. Cytology indicates follicular neoplasm. She has no family cancer history, no risk factors, no symptoms, and she is euthyroid.

The right questions:
“What is the best treatment path for my patient?”
*If FNA had been “benign”: observation*  
*If FNA had been “cancer”: total thyroidectomy*

“Which one of the molecular tests is the best for this goal?”
*Define your goal based on what you think is most likely category*
Thyroid Ultrasound

*Features Suspecting Thyroid Cancer are not Independently Diagnostic*

- Irregular margins
- Hypervascularity
- Indistinct borders
- Microcalcifications


Thyroid Ultrasound

*Risk Stratification by Sonographic Patterns is Possible*

<table>
<thead>
<tr>
<th>Pure cyst</th>
<th>Mixed cystic/solid</th>
<th>Spongioform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iso/ Hyper echoic solid</td>
<td>Partially cystic with eccentric solid areas</td>
<td>Microcalcifications, Irregular border, Taller&gt;wide shape</td>
</tr>
<tr>
<td>Hypoechoic solid, regular border</td>
<td>Metastatic LN, Extra-thyroidal invasion</td>
<td></td>
</tr>
</tbody>
</table>

Pattern Recognition is Important

Mandel WCTC 2013
Milas Surgery 2007

The Context

Bethesda cytopathology with % risk for thyroid cancer

<table>
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<th>I NOT Adequate</th>
<th>II Benign</th>
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<th>IV Follicular neoplasm</th>
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Repeat FNA

Monitor

Repeat FNA

Lobectomy

Lobe vs Total

Total

Molecular Markers

VERACYTE®

http://www.veracyte.com/afirma/
DETECTING BENIGN GENETIC SIGNATURES in FNA TISSUE SAMPLES

Approach: Gene Expression Test to Identify Benign Signature in Cytopathology Indeterminate Nodules

Approach: Gene Expression Test to Identify Benign Signature in Cytopathology Indeterminate Nodules

Identify genes and measure their expression using microarray technology

Develop optimal multidimensional algorithm

142 genes

Identify benign nodules

Chudova et al 2010 JCEM

Molecular Cytology
Setting a New Standard in Diagnosis

The NEW ENGLAND JOURNAL OF MEDICINE

This article is available to subscribers.
Sign in now if you’re a subscriber.


1st prospective, randomized, double-blind study
Afirma® Gene Expression Classifier

Molecular marker panel used to confirm benign thyroid nodule. Prospectively validated on indeterminate cytology FNA specimens. Multi-institutional study.

<table>
<thead>
<tr>
<th>Cytologic Diagnosis (n=265)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS/FLUS</td>
<td>90%</td>
<td>53%</td>
<td>95%</td>
<td>36%</td>
</tr>
<tr>
<td>FN/SFN</td>
<td>90%</td>
<td>49%</td>
<td>94%</td>
<td>37%</td>
</tr>
<tr>
<td>SUSP</td>
<td>94%</td>
<td>52%</td>
<td>85%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Alexander et al NEJM 2012

GEC Benign Results Identify Histologically Benign Nodules with Few False Negatives

NCCN Guideline Version 1.2013
Thyroid Carcinoma - Nodule Evaluation

- Indeterminate Cytology (Bethesda 3 and 4):
  - “If molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less) consider observation”.

APPROPRIATE USAGE

- “rule-out” test
- If “affirmed” benign, supports option to observe thyroid nodule and avoid surgery
- If “suspicious”, back to standard approach, no further quantification of cancer risk.
- Veracyte uses own panel of cytologists
- Needs education and consent: physicians and patients both

Version 1.2013, 12/21/12 © National Comprehensive Cancer Network
Avoiding Diagnostic Lobectomy

How will this change what I do?
Your Patient

A 28 year old man without thyroid cancer risk factors loses weight, revealing a large left thyroid nodule that deviates the trachea. He was treated for testicular seminoma 10 years ago. TSH is normal.

The Context

| Bethesda cytopathology with % risk for thyroid cancer |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| I NOT Adequate  | II Benign        | III AUS or FLUS | IV Follicular neoplasm | V Suspicious for Cancer | VI Cancer |
| rare            | <5%              | 10-15%          | 30%                      | 75%                      | 99%        |

Repeat FNA Monitor

Repeating FNA Lobectomy Lobe vs Total Molecular Markers "BRAF and beyond" panels Asuragen®

http://www.asuragen.com/ClinicalLab/
DETECTING MUTATIONS in FNA TISSUE SAMPLES: BRAF & Co., “Asuragen”

Courtesy Dan Duick MD

Mutational Panel for Cancer Detection in Thyroid Nodules

- BRAF: 71%
- PAX8/PPARγ
- RET/PTC1
- RET/PTC3
- NRAS
- HRAS
- KRAS

Nikiforov WCTC July 2013

Specificity in Thyroid FNAs

<table>
<thead>
<tr>
<th>Prospective FNA Studies</th>
<th>BRAF (n=123)</th>
<th>RAS (n=79)</th>
<th>RET/PTC (n=20)</th>
<th>PAX8/PPARγ (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikiforov et al JCEM 2009</td>
<td>100%</td>
<td>87%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Cantara et al JCEM 2010</td>
<td>100%</td>
<td>74%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Nikiforov et al JCEM 2011</td>
<td>100%</td>
<td>85%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>83%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Nikiforov WCTC 2013

16% Frequency of Gene Mutation in Thyroid FNAs with Indeterminate Cytology (Follicular Neoplasm)
Low NPV Tests Cannot Avoid Diagnostic Surgery

Gene mutations have high PPV, but low sensitivity/NPV

Low NPV Tests Cannot Avoid Diagnostic Surgery

Final Histopathology Diagnosis

- Benign
- Malignant

- Non Diagnostic
- Indeterminate
- Suspicious for Malignancy

- 12% Benign
- 6% Malignant
- 23% Indeterminate
- 52% Suspicious for Malignancy
- 97% Malignant

41% False Negatives

59% Sensitivity

Cancer Risk Stratification in Thyroid Nodules Based on Mutational Analysis

Seven-gene mutational panel

<table>
<thead>
<tr>
<th>Cancer Risk by Indeterminate Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology only</td>
</tr>
<tr>
<td>Mutational Status</td>
</tr>
<tr>
<td>Cancer Risk</td>
</tr>
<tr>
<td>Clinical Management</td>
</tr>
</tbody>
</table>

Nikiforov et al. J Clin Endocrinol Metab 2011; 96: 3390
(adapted from NIH conference syllabus Nov 2014)

How will this change what I do?

**APPROPRIATE USAGE**

- “rule-in” test
- If “positive”, support to perform total thyroidectomy as initial surgery
- If “negative”, back to standard approach or consider other markers
- Needs a *panel* of genes
- Needs education and consent: physicians and patients *both*

---

**Molecular Markers for Thyroid Cancer Diagnosis**

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Follicular Neoplasm</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-gene panel of mutations &amp; Asuragen (other investigators)</td>
<td>SENS “rule out”</td>
<td>SPEC “rule in”</td>
</tr>
<tr>
<td></td>
<td>57% (49-81%)</td>
<td>96% (95-100%)</td>
</tr>
<tr>
<td>Afirm gene expression classifier</td>
<td>90%</td>
<td>49%</td>
</tr>
</tbody>
</table>

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The Take-Home

- **74% of patients avoid surgery for benign disease**
- **5-year overall treatment cost estimates:**
  - Current practice: $12,172
  - With the molecular test: $10,719
- **Slight improvement in quality of life years:**
  - Current practice: 4.50 QALY
  - With the molecular test: 4.57 QALY

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Genetic Alterations in Thyroid Cancer

- 11% Targeted NGS
- 10% Novel
- BRAF
- RET/PTC1
- RET/PTC3
- NRAS, HRAS, KRAS

ThyroSeq (Targeted NGS for Thyroid Cancer) Nikiforova et al JCEM 2013 Nov; 98(11):E1852-60

Multi-gene panels: ThyroSeq v.1

- 12 genes, >280 mutation hotspots
- Next generation sequencing

<table>
<thead>
<tr>
<th>Gene Mutations</th>
<th>Gene Fusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF RET</td>
<td>RET/PTC1 1</td>
</tr>
<tr>
<td>NRAS TSHR</td>
<td>RET/PTC3 1</td>
</tr>
<tr>
<td>HRAS AKT1</td>
<td>PAX8/PPARγ 3</td>
</tr>
<tr>
<td>KRAS TP53</td>
<td></td>
</tr>
<tr>
<td>PIK3CA GNAS</td>
<td></td>
</tr>
<tr>
<td>PTEN CTNNB1</td>
<td></td>
</tr>
</tbody>
</table>

(adopted from NIH conference syllabus Nov 2014)

Detection of Mutations Using ThyroSeq v.1

- Papillary Carcinomas
- Follicular Carcinomas
- Dedifferentiated Carcinomas
- Medullary Carcinomas

(adopted from NIH conference syllabus Nov 2014)

ThyroSeq v.1 Testing of FN/FNL Cytology Nodules

- Prospective analysis of 61 consecutive nodules with FN/FNL cytology (03/2013-09/2013)

<table>
<thead>
<tr>
<th>ThyroSeq “Malignant”</th>
<th>Surgery Malignant</th>
<th>Surgery Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BRAF (PTC)</td>
<td>1 NRAS codon 61 (FA)</td>
<td></td>
</tr>
<tr>
<td>3 KRAS codon 12 (PTC)</td>
<td>1 PTEN del (FA)</td>
<td></td>
</tr>
<tr>
<td>3 KRAS codon 61 (PTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 NRAS codon 13 (PTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 NRAS codon 61 (PTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ThyroSeq “Benign”</td>
<td>2 PTC, FV</td>
<td>3 GNAS (HN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 NEGATIVE (HN)</td>
</tr>
</tbody>
</table>

Cancer probability in ThyroSeq NEGATIVE cases - 4.3%

(adopted from NIH conference syllabus Nov 2014)
TSHR mRNA Detects Circulating Thyroid Cancer

**HOW**
- Blood sample (3 tubes)
- Separate mononuclear cells
- Extract total RNA
- Quantitative RT-PCR
- TSHR mRNA >1 ng/ug

**Proposed Clinical Pathway**

Routine Cytopathology

- Non Diagnostic
  - Repeat FNA
- Indeterminate
  - Follow with Ultrasound
  - Molecular markers?
- Cancer
  - Thyroid Surgery

**Will this change what I do?**

NO….

**Proposed Clinical Pathway**

Routine Cytopathology

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- Cancer

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**Proposed Clinical Pathway**

Routine Cytopathology

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  - Follow with Ultrasound
  - Molecular markers?
- Indeterminate
  - Thyroid Surgery
- Cancer

**Will this change what I do?**

YES….

**Proposed Clinical Pathway**

Routine Cytopathology

- Non Diagnostic
  - Repeat FNA
- Benign
  - Follow with Ultrasound
  - Molecular markers?
- Indeterminate
  - Thyroid Surgery
- Cancer

**Wish to confirm BENIGN?**

YES….

**Redo FNA**
**Proposed Clinical Pathway**

Routine Cytopathology

- Non Diagnostic
- Benign
- Indeterminate
- Cancer

- Repeat FNA
- Follow with Ultrasound
- Molecular markers?
- Thyroid Surgery

**BRAF and Beyond**

Wish to confirm CANCER?

**Proposed Clinical Pathway**

Routine Cytopathology

- Non Diagnostic
- Benign
- Indeterminate
- Cancer

- Repeat FNA
- Follow with Ultrasound
- Molecular markers?
- Thyroid Surgery

The referring doc already obtained markers? How often will this change what I do?

---

**“How Often Will This Change What I Do?”**

- Physician performing 240 FNA’s annually will identify 24 patients who might avoid surgery (www.afirma.com)
- Alexander et al *JCEM* 2014: cancer in <2% Afirma benign nodules followed for 8 months
- Zeiger et al *Ann Surg Oncol* 2014: molecular testing altered surgical management in 10%
- Duick et al *Thyroid* 2012: diagnostic surgery fell from 74% to 7%
- Asuragen study (Beaudenon-Huibregtse et al) in *Thyroid*, May 2014

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**Molecular Markers and Thyroid Cancer**

- *Real*, good performance, and here to stay

- Usage requires
  - Be thoughtful: “right test for right goal”
  - Know your patient
  - Know your ultrasound
  - Know your endocrinologist
  - Inform yourself and prepare *logistics*
  - Counsel and consent your patients

- Ongoing validation in *your* patients
Your Patient: 59 year old woman referred for primary hyperparathyroidism

- Incidental hypercalcemia on labs
- Fatigue and kidney stones
- No known thyroid disease
- History: uterine cancer
- Family history: hypothyroidism
- Physical examination without palpable neck mass or thyromegaly
Cowden Syndrome (CS)

- Characterized by benign hamartomas
- Increases risk of malignant transformation
- Dominantly inherited germline mutation
  - tumor suppressor PTEN
  - PTEN mut+ is ultimate diagnostic confirmation
PTEN hamartoma tumor syndrome

International Cowden Consortium (ICC)
Operational Criteria for Diagnosis

Pathognomonic Major Minor
Mucocutaneous lesions Breast cancer Fibrocystic breast disease
Trichilemmomas Endometrial cancer Mental retardation
Acral keratoses Thyroid cancer Benign thyroid lesions
Papillomas Macrogenphy GI hamartomas
Mucosal lesions Lipomas
Adult Lhermitte-Duclos disease Fibromas
GU tumors or malformation
Renal cell carcinoma
Uterine fibroids

• 2 Major but one must be macrocephaly or LDD
• 1 Major + 3 Minor
• 4 Minor

Trichilemmoma
Papillomas

Macrocephaly

Men: 58.0 cm
Women: 57.3 cm

occipitofrontal circumference
>2 standard deviations over the population mean
97.5\(^{th}\) percentile

“The Eye Cannot See What The Mind Does Not Know”
Phillip Zaret, M.D.
Risk Calculator for Estimating a Patient’s Risk for PTEN Mutation

Welcome to the Cleveland Clinic risk assessment tool for estimation of a person’s risk of having a PTEN mutation. Clinical syndromes often associated with this gene mutation include Cowden Syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS). This tool was designed for use by healthcare professionals. If you are not a healthcare professional, you are encouraged to discuss the results with your doctor or a genetic healthcare provider. Detailed information on the Cleveland Clinic adult score and pediatric criteria is available.

Tan et al Am J Hum Gen 2011

Should patients with Cowden syndrome undergo prophylactic thyroidectomy?

Mira Milea, MD,1 Jessica Mester, MS, CGC,1,2 Rosemarie Metzger, MD, MPH,3 Joyce Shin, MD,4 Jamie Mitchell, MD,1 Eren Berber, MD,1 Allan E. Siperstein, MD,4 and Charis Eng, MD, PhD5,6,7,8
Portland, OR, and Cleveland, OH
(Surgery 2012;152:1201-10)

DIAGNOSES

Age range 4-51 yrs (median 16 yrs)

- 56% Goiter
- 31% Thyroiditis or Both
- 13% Normal
- In all patients ≥ 13 yrs old

Likelihood to Encounter Patients with Cowden Syndrome

- Hereditary cancer syndromes
  - BRCA 1/300
  - Lynch 1/600
  - FAP 1/10,000
  - MEN2 1/35,000
  - Cowden 1/250,000

- 200 consecutive DTC patients
  - 17 had clinical CS diagnosis (8.5%)
  - 2 found to be PTEN mut+ (1%)

Nagy R et al Thyroid 2011;21:505-10
Of 18 patients (28%) overall eligible for referral to genetics:

- 9 accepted this recommendation
- 5 completed formal genetics consultation

PTEN (n=3)
BRCA (n=1)
Fragile X/array CGH/ Sotos Syndrome (n=1)
Rose: “Dr. Milas, I’ve invented a new screening tool for you!”
Mira: “I’m very interested to hear about it, Dr. Metzger”
Rose: “We just ask the patient…….were you born?….and if they say, yes….we advise referral to genetics!”

Cowden Syndrome: Summary

- Higher than anticipated prevalence
- Screening for Cowden Syndrome is not difficult or invasive (“dot phrase” in Epic and measure head circumference)
- Pattern recognition is key
- Implications of Screening
  - Thoughtful patient counseling
  - Early genetics referral
  - Cancer preventative care
  - Ongoing surveillance

More efficient, more comprehensive and personalized management of thyroid cancer patients

Generous gift of a donor who wanted to make a difference in the care of patients with thyroid cancer
(Mark L Urken MD and Robert M Tuttle MD)

TCCC is an independent application completely owned by the Foundation and is not affiliated with any individual medical institution or practice
Information Flow (TCCC)

Creation of enhanced connectivity between Clinicians involved in the care of a particular patient

Endocrinologist
Surgeon
Nuclear Medicine
Radiologist
Medical Oncologist

TCCC

Patient

1. Portability of clinical information
2. HIPAA compliant
3. De-identified patients

Patient Education Modules

Dr. Cynara Coomer
Fox News Medical consultant
Thyroid cancer survivor
Narrator for patient modules

Highly illustrated modules written by experts in thyroid cancer care

Imaging Module
Summary

1. “Molecular Cytology” and molecular markers complement traditional surgical management of thyroid nodules
2. Awareness to screen for Cowden’s Syndrome may lead to meaningful cancer prevention care
3. Upcoming guidelines: new insights
Thank You