Investor Day
October 9, 2014

Forward-Looking Statements

Various remarks that we make in this presentation that are not historical, including those about our business strategy and goals, future plans and prospects, growth opportunities, drivers of our business, the size of potential addressable markets, international expansion plans, our pending acquisition of Allegro, and future products and product pipeline, constitute forward-looking statements within the meaning of the Safe Harbor provisions of the Private Securities Litigation Reform Act of 1995.

Forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from our expectations. These risks and uncertainties include, but are not limited to: our limited operating history; our ability to increase usage of and reimbursement for Afirma and any future products we may develop or sell, including the lung cancer test acquired from Allegro Diagnostics; our dependence on a few payers for a significant portion of our revenue; risks associated with new laws and regulations, including regulation of our tests by the FDA; our ability to develop and commercialize new products and the timing of commercialization; the timing, results and applicability of clinical study results to actual outcomes; our ability to conserve cash and leverage existing infrastructure to develop additional products; our ability to commercialize the Allegro lung cancer test or our ability to launch other pulmonology products and the other risks set forth under the heading “Risk Factors” in our filings with the Securities and Exchange Commission. These forward-looking statements speak only as of the date hereof. We disclaim any obligation to update these forward-looking statements.

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Introductions

Bonnie Anderson	President & Chief Executive Officer
Shelly Guyer	Chief Financial Officer
Chris Hall	Chief Operating Officer
Giulia C. Kennedy, PhD	Chief Scientific Officer
Andy Thorson	EVP, Corporate Strategy and BD
Richard Kloos, MD	Senior Medical Director, Endocrinology

Erik K. Alexander, MD	Brigham & Women's Hospital and Harvard Medical School
Anil Vachani, MD, MS	Perelman School of Medicine, University of Pennsylvania
Fernando J. Martinez, MD, MS	Weill Cornell Medical College

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Agenda

Presenter	Topic
Bonnie Anderson	Overview of Veracyte
Giulia C. Kennedy, PhD	Veracyte Research & Development
Erik K. Alexander, MD	State of the Art Care for Managing Patients with Thyroid Nodules
Anil Vachani, MD, MS	Clinical Unmet Need in Lung Cancer Detection
Fernando J. Martinez, MD, MS	The Current Approach to the Diagnosis of Interstitial Lung Disease
	Q&A (All speakers)

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Accomplishments Since October 2013 IPO

- **Recent News: Two Commercial Payer Contracts** Executed and Effective by End of 2014
  - UnitedHealthcare
  - Cigna
- **>70% Revenue Growth** 1H 2014 over 1H 2013
- **Acceleration** into institutions and integrated delivery networks
- **Pathway to Profitability** provided with agreement to amend Genzyme agreement
- **Positive Recommendations in Practice Guidelines**
  - Preliminary American Thyroid Association (ATA) guidelines presented in June 2014
  - NCCN Guidelines updated in August 2014
- **Over 135 Million Lives** under positive medical coverage decisions
- **Launch of Afirma Malignancy Classifiers** in May 2014
- **Early Interstitial Lung Disease Data** Presented at American Thoracic Society International Conference in May 2014
- Acquisition of **Allegro Diagnostics** in September 2014 **Accelerate Entry into Pulmonology**

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Molecular Cytology

Improving Patient Outcomes and
Reducing the Cost of Care

Improving Outcomes and Reducing the Cost of Care

Too many patients undergo unnecessary and invasive procedures to resolve ambiguous diagnosis– costing the healthcare system billions of dollars

Our mission is to change that.

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Veracyte's Differentiated Approach

1. Formulate a relevant clinical question
2. Apply whole-genome biomarker discovery to cytology samples
3. Plan and execute publication strategy in advance of commercial launch

Answer the clinical question that improves care and reduces costs

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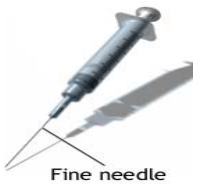
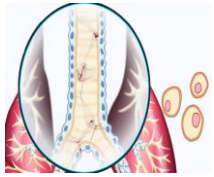
Molecular Cytology = Genomics at the Front End of Patient Care

Molecular Cytology Paradigm





Minimally invasive cytology biopsy

High rate of ambiguity

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Molecular Dx informs treatment decision pre-operatively

Surgery

Watchful waiting/ Monitoring

Ongoing treatment

Challenge: High Diagnostic Ambiguity

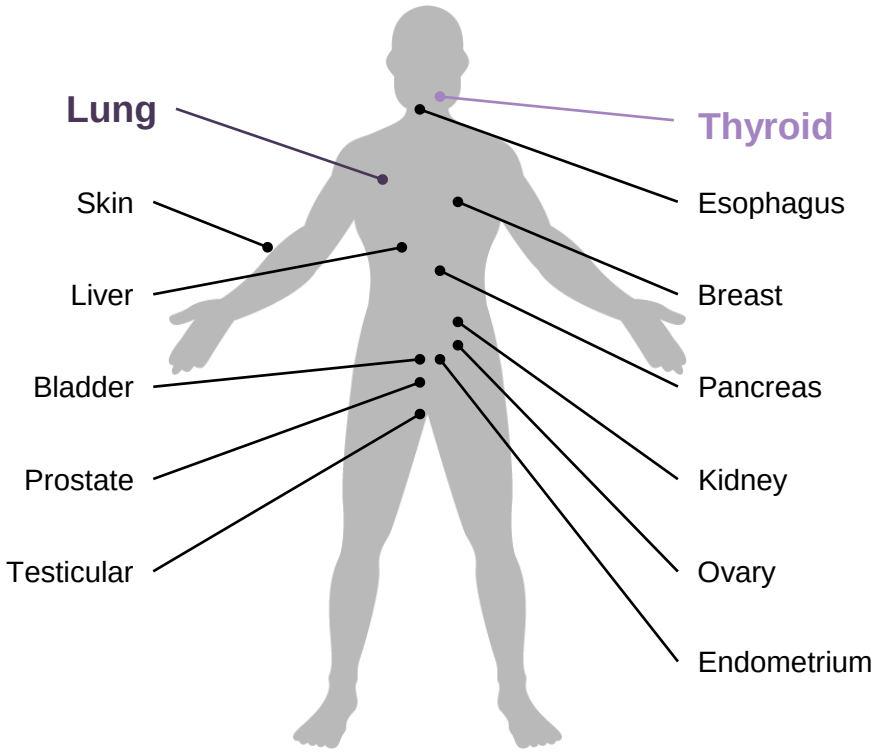
- ✘ Low yield of nucleic acids
- ✘ Cellular heterogeneity
- ✘ Variable sampling techniques

Opportunity: More Efficient Care

- ✓ Minimally invasive, outpatient procedure
- ✓ Reduce unnecessary surgeries
- ✓ Efficient validation using surgical “truth”

Building a Molecular Cytology Franchise

Diagnostic Opportunities



Prioritization Criteria

- Large addressable market
- Substantial unmet clinical need
- Efficient development, validation and commercialization
- Attractive competitive landscape

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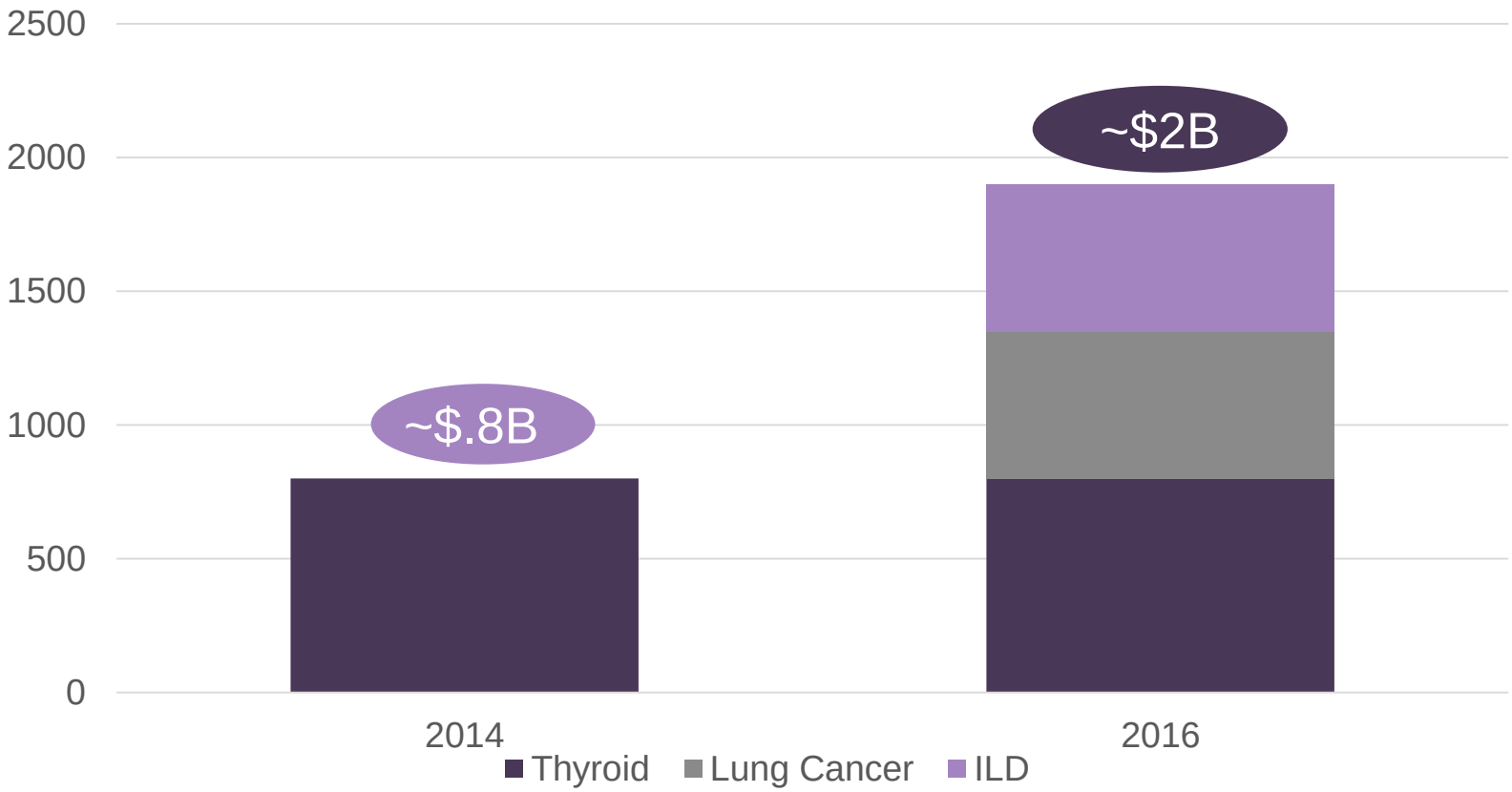
Large, Expanding Addressable Genomic Testing Markets

More than Doubling with New Product Launches Over Next Two Years



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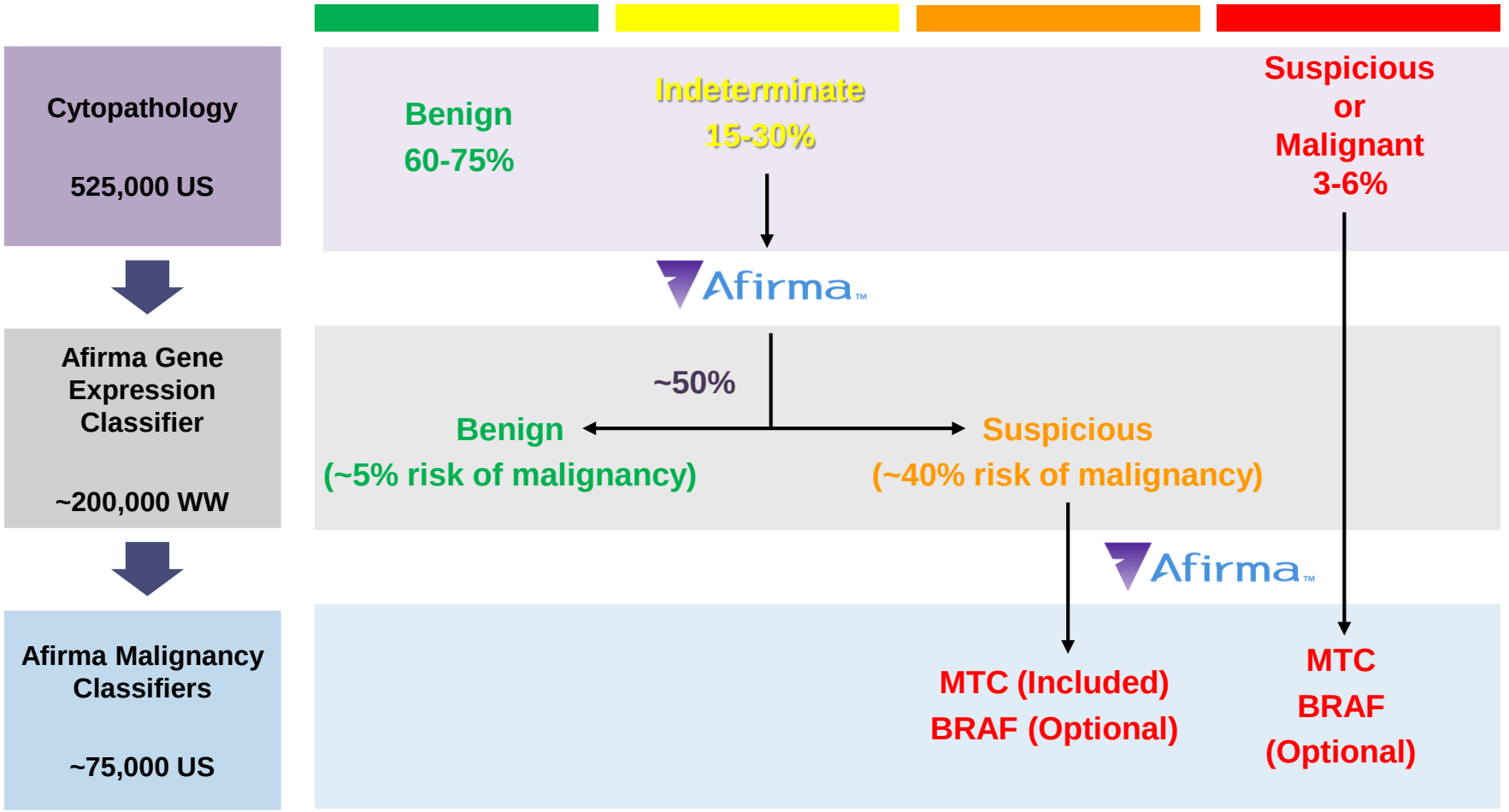
The Afirma Solution

A Comprehensive Assessment for Patients with Thyroid Nodules



Clinical utility that changes the standard of care

MTC = Medullary Thyroid Cancer

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Published Evidence Drives Guidelines and Positive Coverage

Published Evidence	Guidelines	135+ Million Covered Lives

Clinical Validation
Chudova D, et al. *JCEM* 2010
Alexander E, et al. *NEJM* 2012

Analytic Validation
Walsh PS, et al. *JCEM* 2012

Clinical Utility
Monroe R, et al. abstract *ATA* 2011
Duick D, et al. *Thyroid* 2012
Alexander E, et al. *JCEM* 2014

Cost-effectiveness and Quality of Life
Li H, et al. *JCEM* 2011
Duick D, et al. *Thyroid* 2012

Recent Reviews
Ali S, et al. *PLoS Currents* 2013
Xing M, et al. *Lancet* 2013
Ward L, Kloos R. *Arq Bras Endo Metab*. 2013

National Comprehensive Cancer Network (NCCN) – published 2013, updated 2014

UpToDate – evidence-based clinical decision support resource of physicians – 2013

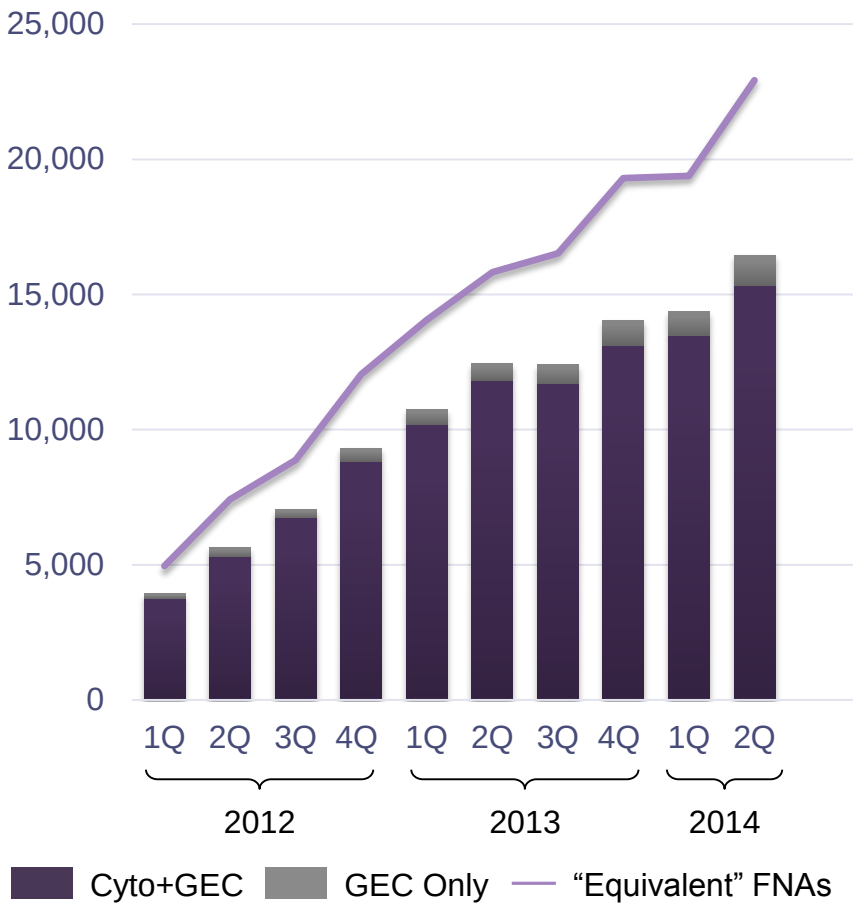
American Thyroid Association (ATA) – preliminary guidelines issued

American Association of Clinical Endocrinology (AACE) – guideline update in process

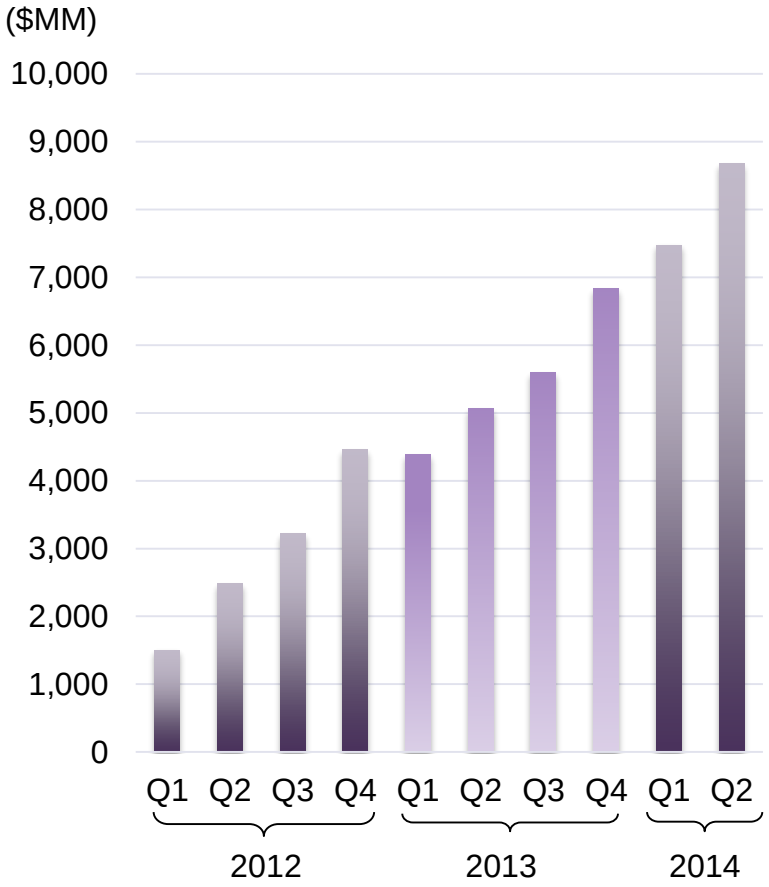
Medicare
UnitedHealthcare® A UnitedHealth Group Company
aetna℠
Humana.
Cigna.
PREMERA BLUE CROSS
Wellmark BlueCross BlueShield
Horizon Horizon Blue Cross Blue Shield of New Jersey
HIGHMARK. An Independent Licensee of the Blue Cross and Blue Shield Association

Strong Afirma Volume and Revenue Growth

FNA Trends



Revenue



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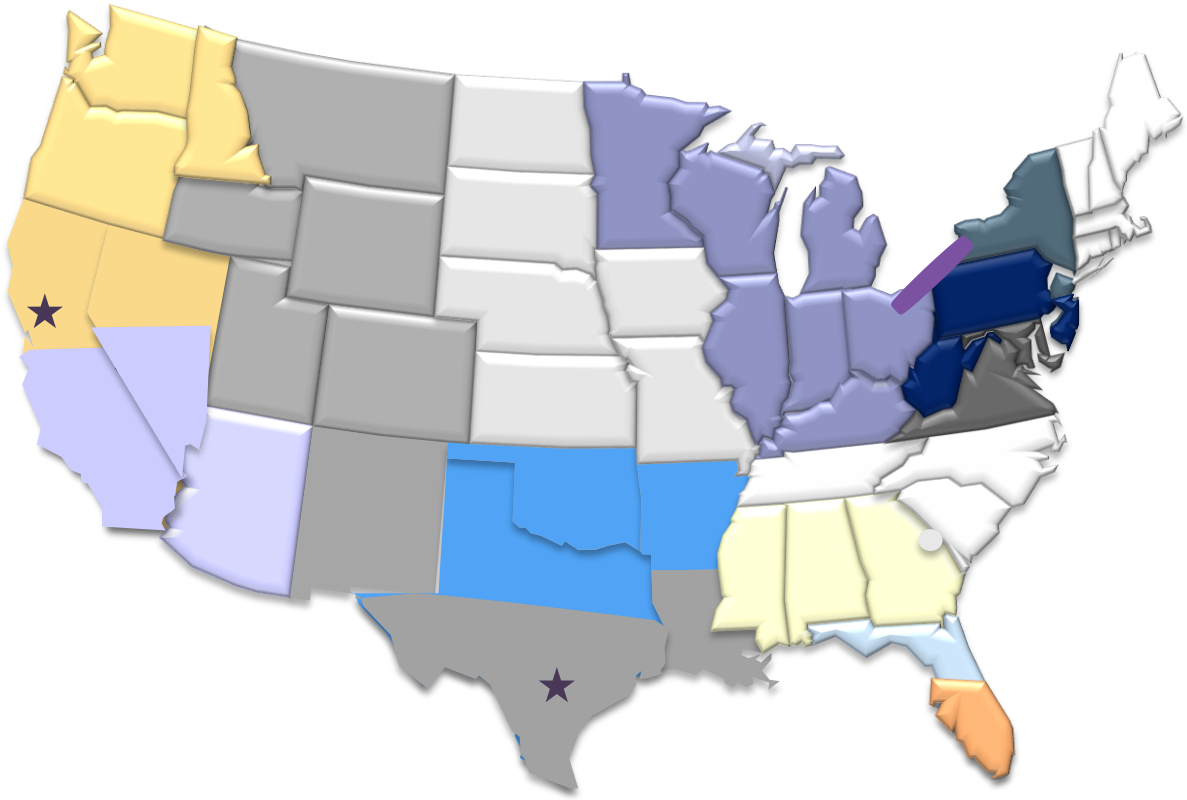
Commercial Footprint Expanded to Drive Growth



- U.S. expanded to 16 territories from 8, with 3 regional managers and a VP Sales
- Each region augmented by Genzyme Sales Reps
- Leverages Genzyme's established endocrinology effort
- Strengthens both community practice and institutional channels
- Intention to add 10 additional sales and marketing hires in 2H14

★ **South San Francisco, CA**
Headquarters
- GEC CLIA Laboratory Operations
- Client Services
- Billing & Reimbursement

★ **Austin, TX**
- Cytopathology CLIA Laboratory Operations
- Billing & Reimbursement

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Genzyme Co-Promotion Agreement: Agreement to Amend

- Genzyme sales force selling Thyrogen® in U.S. and 42 countries
- Synergistic partnership
- Reps re-positioned in U.S. to leverage strength
  - Lead generation
  - Maintenance calls
- Close coordination between sales and marketing teams
- Selected international launches targeted for 2014
  - Launched in Brazil in partnership with Fleury Medicine and Health
  - Country-by-country go forward plan with Genzyme announced by year end

Subject to signing the final amendment, effective January 1, 2015, Veracyte's co-promotion fees paid to Genzyme will decrease from 32% to 15% of Afirma revenue in the United States.

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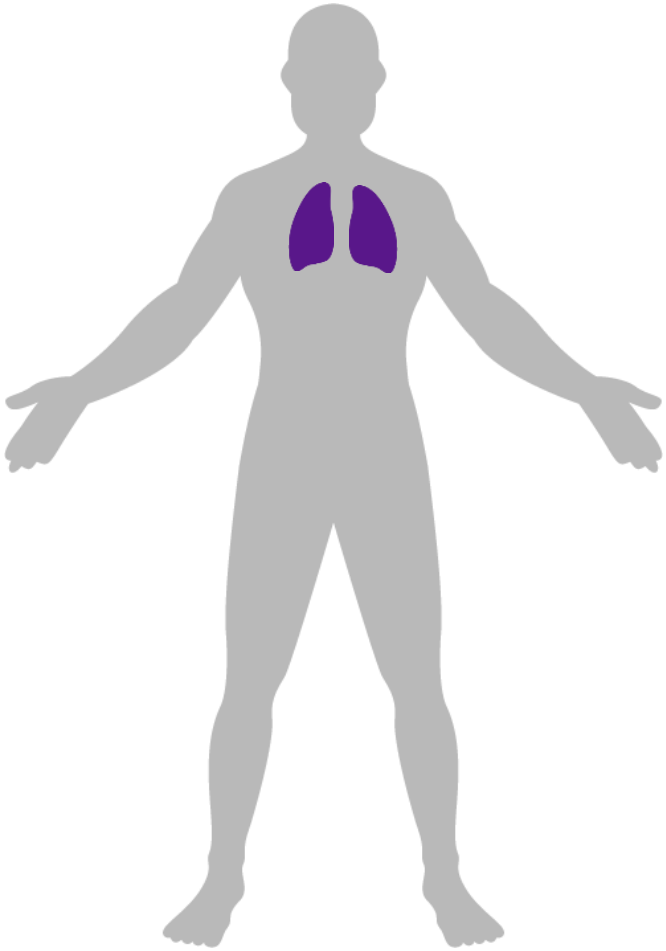
Lung Disease and Cancer

Significant Unmet Needs



The Opportunity

- Lung diseases are difficult to diagnose without surgery
- Significant opportunity to reduce unnecessary surgeries and lower costs
- Inconsistent practice guidelines ripe for emerging standard approaches to care
- Pulmonologist is underserved but secures sample
- Two programs advance
  - Clinical development stage for lung cancer diagnostic
  - Early product development for Interstitial Lung Disease (ILD) diagnostic

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Acquisition of Allegro Diagnostics, Inc.

Clinical Development Stage Lung Cancer Diagnostic

Business	• Molecular diagnostics company focused on developing genomic tests to improve the preoperative diagnosis of lung cancer
Diagnostic Solution	• Lead test helps physicians assess which lung nodule patients can safely be monitored with CT scans in lieu of invasive procedures following a non-diagnostic bronchoscopy
Stage	• Pre-commercial • Two prospective multi-center clinical validation studies completed
Company	• Founded in 2006 • Spun out of Boston University by Avrum Spira MD and Jerome Brody MD, Pulmonology thought leaders • Venture-backed and privately held
Transaction Terms	• $21 million, ~$8 million cash and ~$13 million VCYT stock

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Deal Rationale

- Accelerates Entry into Pulmonology
- Clinically-Validated Test That Addresses a Significant Unmet Need
- Further Establishes Our Leadership in Molecular Cytology
- Assets Provide Substantial Value and Future Growth Opportunities
- Uniquely Poised to Drive Commercialization and Reimbursement

Lung Cancer : A Significant Diagnostic Challenge

- Lung cancer is responsible for more deaths than the next three most common cancers combined
- Push to diagnose lung cancer earlier to decrease mortality

CT screening for over 8M high risk individuals recommended

~250,000 bronchoscopy procedures annually in US for suspicious lung cancers

Up to 40% are non-diagnostic

Physicians left to decide whether to advance to a more invasive procedure

40% of diagnostic surgeries result in a benign diagnosis

Lead Lung Cancer Test:

Improves preoperative diagnosis of lung cancer to reduce unnecessary surgeries

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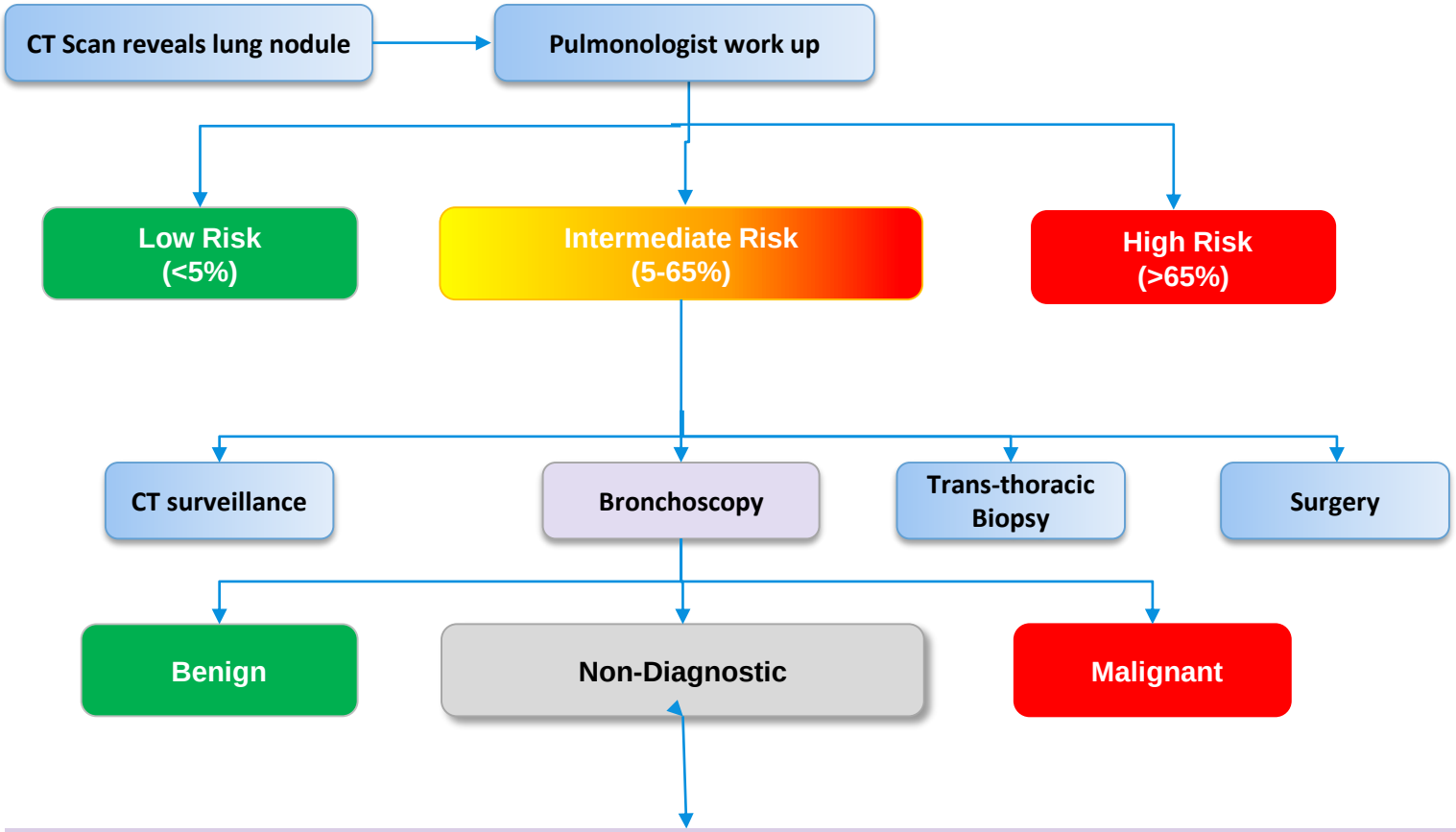
Current Flow for Pulmonary Nodule Diagnosis



Clinical Dilemma Today:
How do you manage patients with a non-diagnostic bronchial biopsy?

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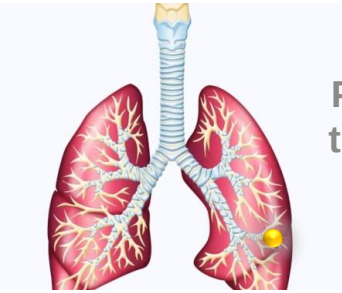
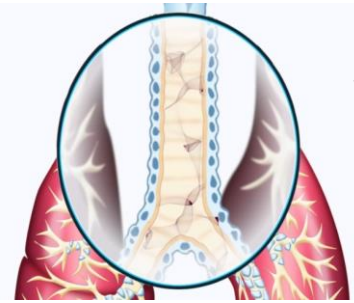
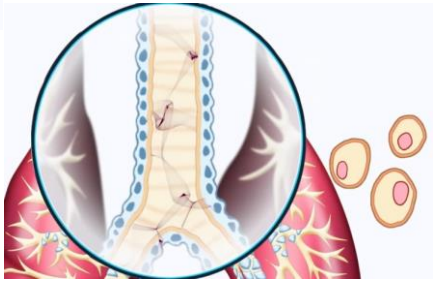
Innovative, Proprietary "Field of Injury" Genomic Technology



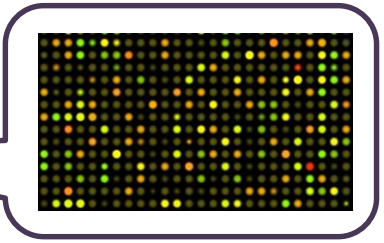
Peripheral lung nodules are difficult to biopsy yielding high rates of non-diagnostic bronchoscopies



Smoking alters the epithelial cell gene expression throughout the airway



A gene signature of a cytology sample collected from the airway can predict the risk of cancer of a peripheral lung nodule



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Patients Suspicious for ILD Receive Suboptimal, Harmful Treatment

175-200,000 Patients*

HRCT for ILD

Current

Confident for IPF

- High False Positive Rate
- Incorrect Therapy
- Delayed Therapy

OR

Inconsistent/ Possible IPF

- Consider Diagnostic Surgery
- High Rate of Complications
- Costly, Invasive Procedure

Surgery best informs diagnosis

Future

Genomic Results Replace Surgical Pathology

Inform Clinical Decisions Without Surgery

*Company estimate including United States and 5 major European Countries (annual number of patients)

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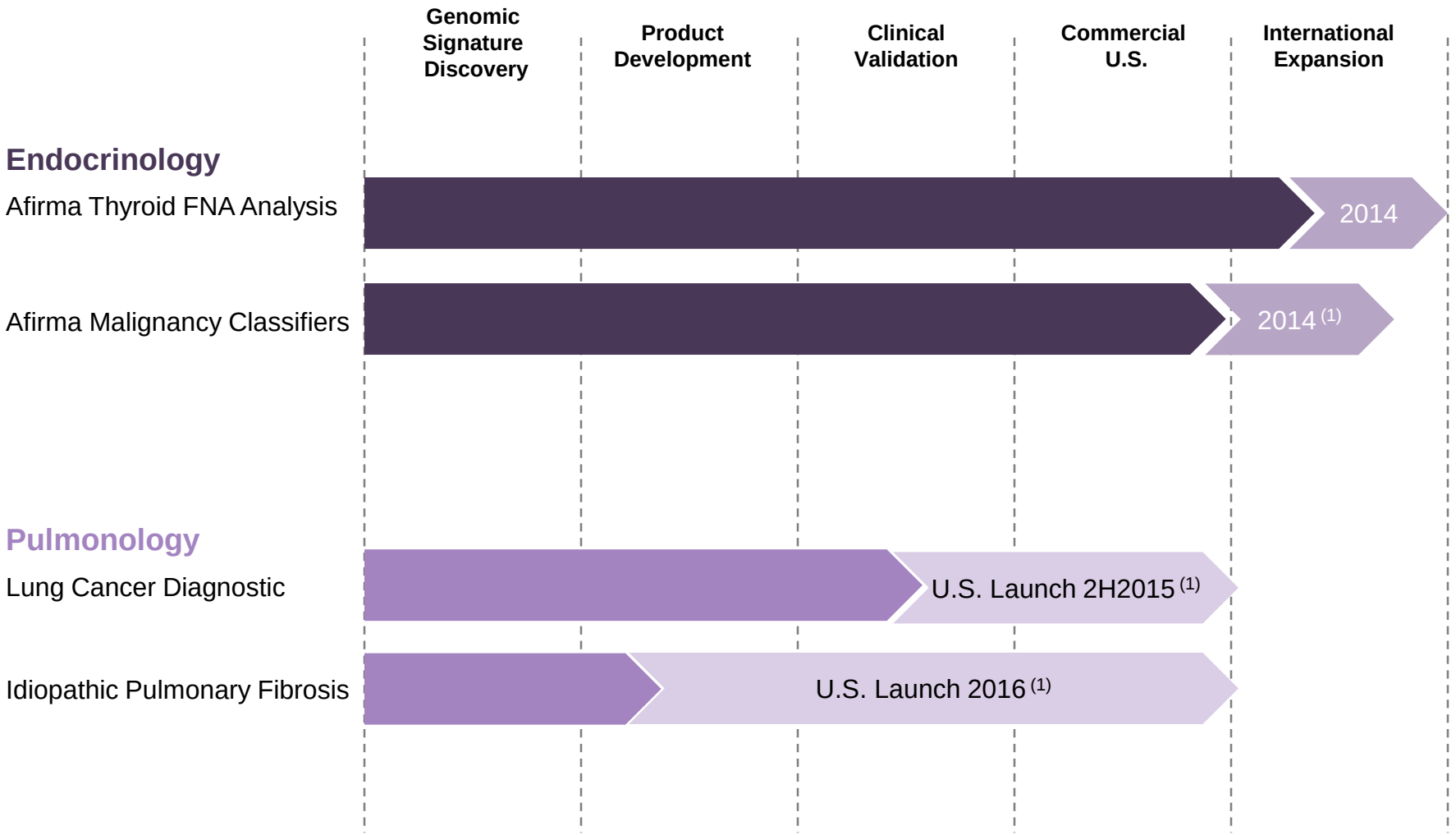
Deep Pipeline With Multiple Near-Term Milestones



1 Estimated

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Acknowledgements

Clinical and Scientific Luminaries Advising the Company

Paul W. Ladenson, MD	*Johns Hopkins University School of Medicine* Prof. of Medicine, Pathology, Oncology, Radiology,
Edison Liu, MD	*The Jackson Laboratory* President and CEO
Fernando J. Martinez, MD	*Weill Cornell Medical College/New York Presbyterian Hospital* Executive Vice Chair of Medicine
Ganesh Raghu, MD	*University of Washington Medical Center* Prof. Medicine, Pulmonology
Steven I. Sherman, MD	*MD Anderson School of Medicine* Prof., Dept. Chair, Endocrinology & Metabolism,
Terry Speed, PhD	*UC Berkeley, Bioinformatics and Statistics* Prof. Emeritus
Avrum Spira, MD, MSc	*Boston University School of Medicine* Chief of Medicine, Division of Computational Biomedicine
R. Michael Tuttle, MD	*Memorial Sloan Kettering Cancer Center* Prof. Medicine
Lewis T. “Rusty” Williams, MD, PhD	*Five Prime Therapeutics* President and CEO

Conclusion

Pioneering molecular cytology solutions for Endocrinology and Pulmonology

Clinically validated solution that reduces unnecessary thyroid surgeries by 50%

Proven roadmap for developing clinical evidence to drive guidelines and reimbursement

Focused on large, underserved specialty markets

Building a molecular cytology franchise with a pipeline of high-value opportunities

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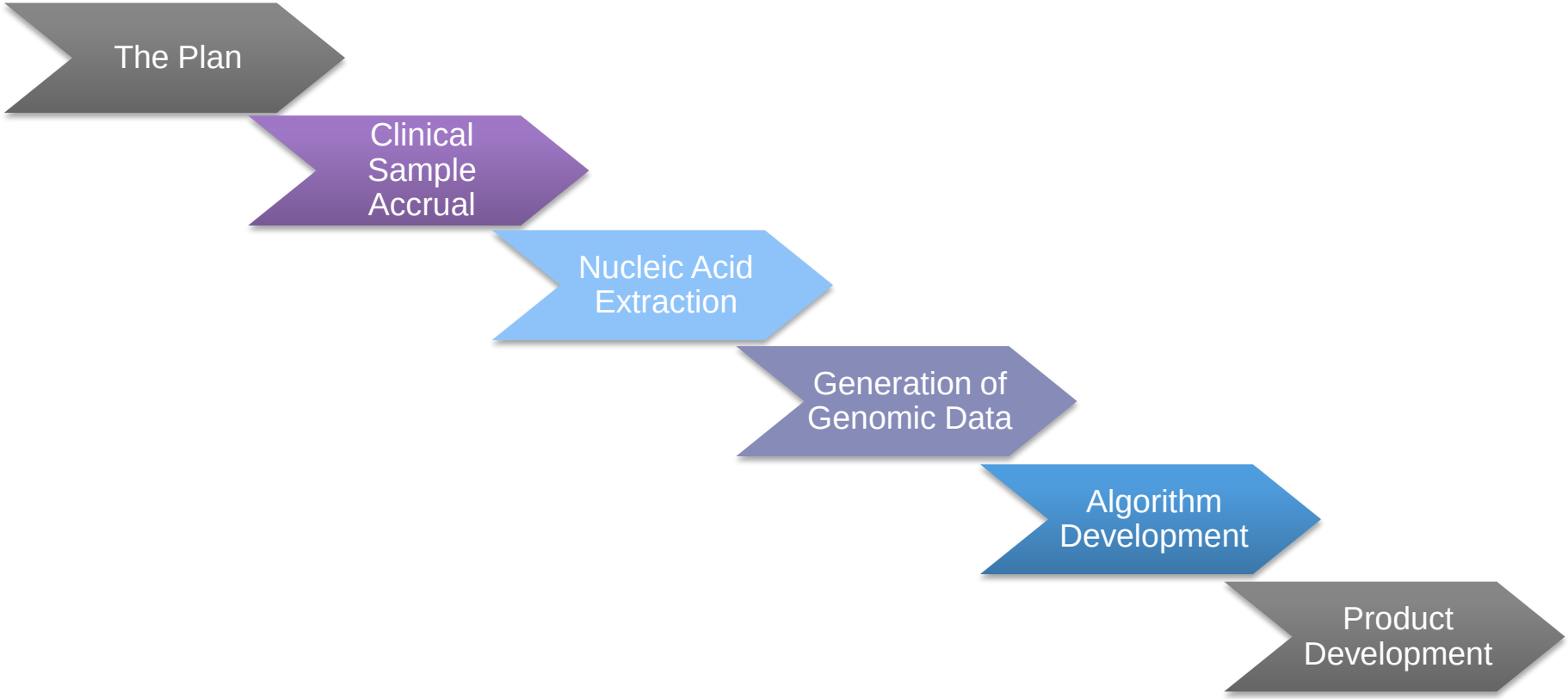
Research & Development

Giulia C. Kennedy, PhD
Chief Scientific Officer

R&D Pipeline: Discrete Steps



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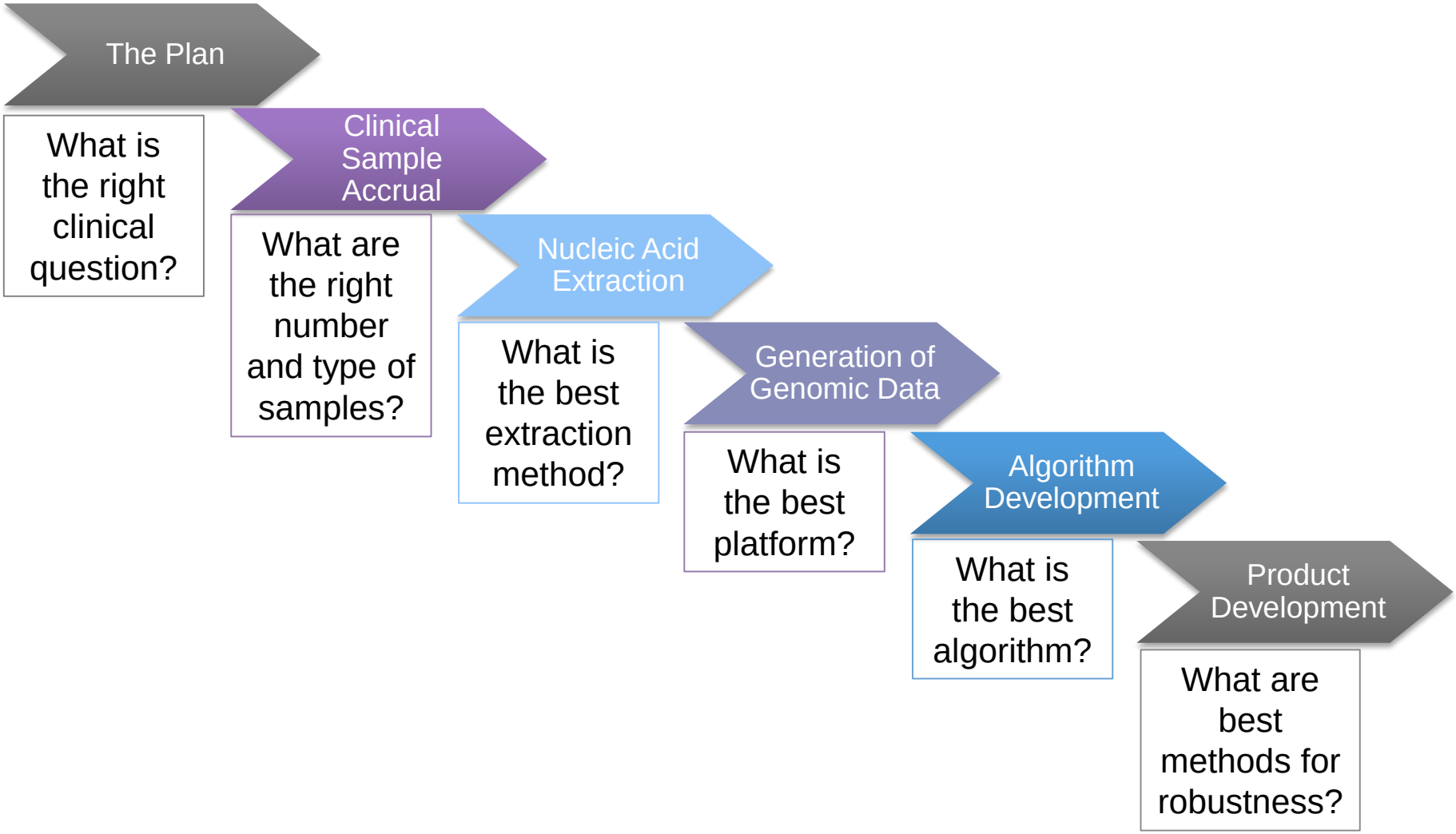
R&D Pipeline: Discrete Steps



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Four R&D Engines Make This Possible

Clinical Sample Accrual	Genomic Discovery	Algorithm Development	Product Development
• Write clinical protocols • Plan and execute clinical trials • Receive samples • Collect and record clinical annotations • Develop and execute rubric for obtaining “truth”	• Develop extraction, amplification and assay methods • Exploit multiple platforms – Microarrays – Copy Number – Next-Generation RNASeq – DNASeq	• Normalization • Alignment • Feature extraction • Classification • “Lock and Roll”	• Reproducibility • Reagent effects • Interfering substances • Limit of detection

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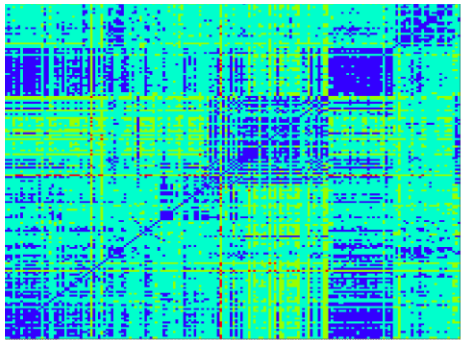
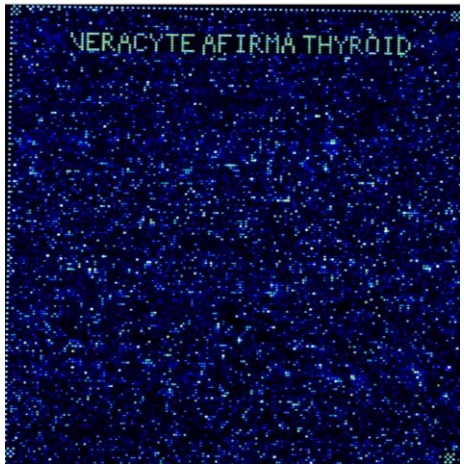
Afirma Thyroid Products

Development of Afirma Thyroid GEC

Whole Genome Discovery on Clinical Samples





- Collected both surgical tissue and FNAs through clinical protocols
- Truth = Expert Surgical Pathology
- Developed assays to work on 15 ng RNA
- Extracted genomic data on >240,000 unique RNA transcripts using Exon microarrays
- Designed a custom microarray with 3,000 genes
- Extra content allowed us to develop the follow-on product, **Malignancy Classifier**

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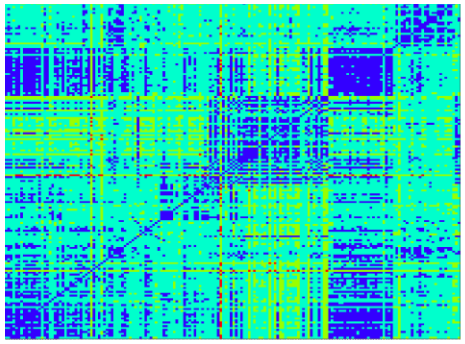
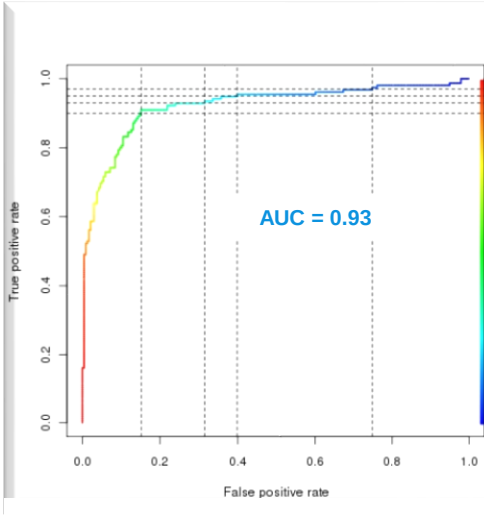
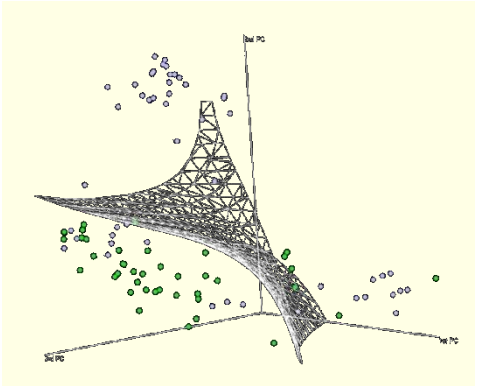
Development of Afirma Thyroid GEC

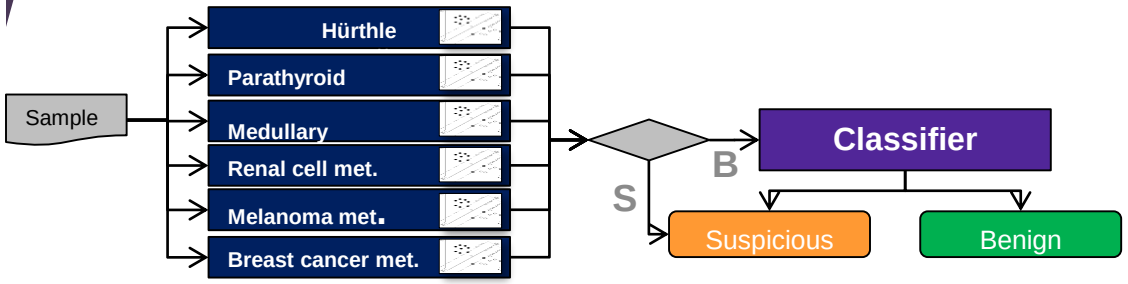
Whole Genome Discovery on Clinical Samples





Assay and Algorithm Development





- Tested a suite of classification algorithms, ultimately choosing Support Vector Machine
- Developed diagnostic methods to assess level of over fitting
- Developed a cassette filtering system to score rare neoplasms

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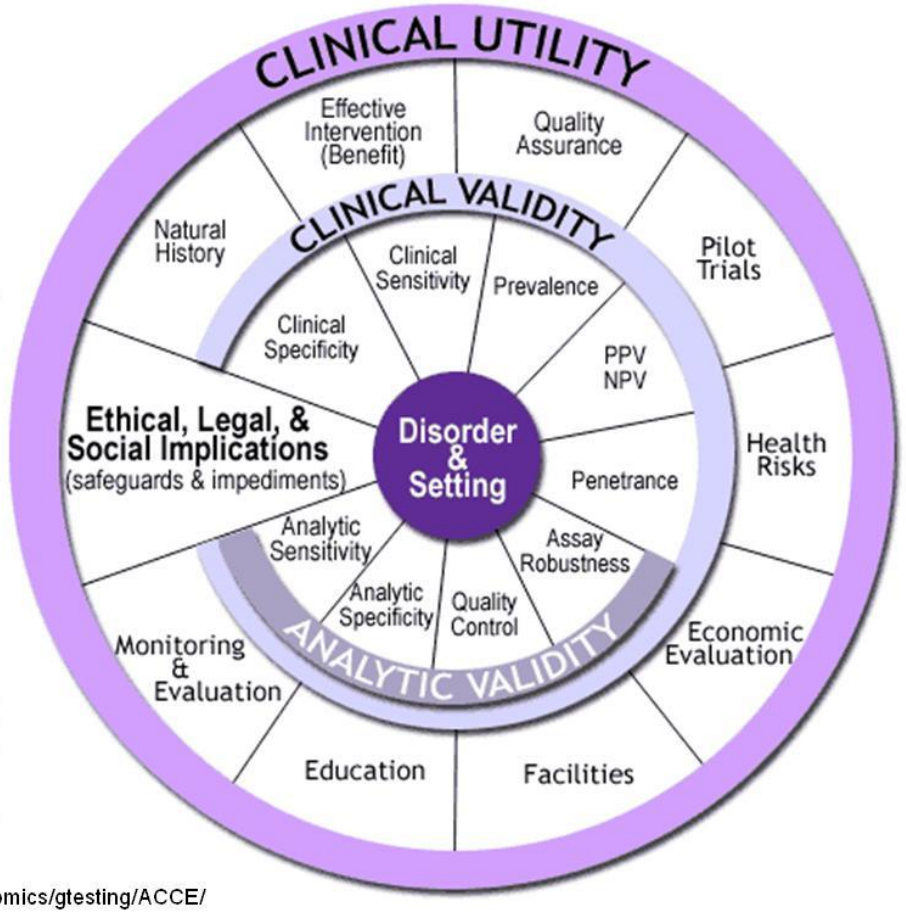
Triple Pillars of Validation



http://www.cdc.gov/genomics/gtesting/ACCE/

Best Practice:
Fully characterize and de-risk test performance, prior to un-blinding Clinical Validation

Meets EGAPP/CDC guidelines for evidence-based insurance coverage decisions (CMS)
- Analytic Validity
- Clinical Validity
- Clinical Utility

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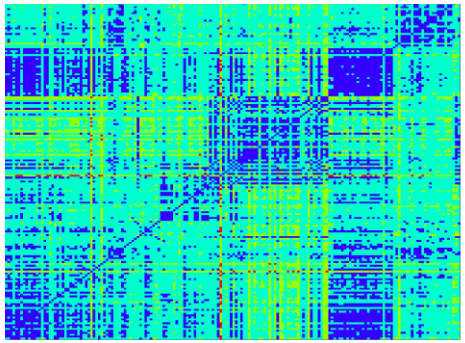
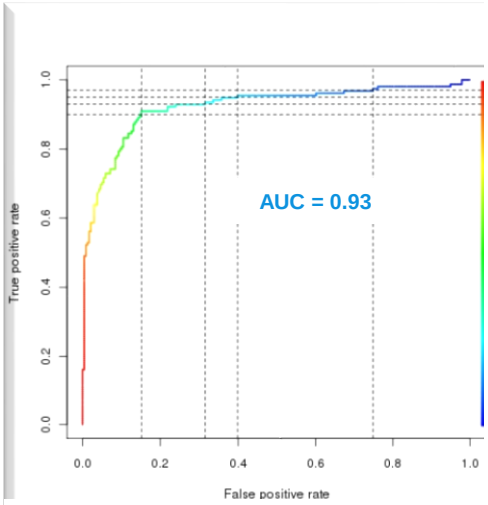
Development of Afirma Thyroid GEC

Whole Genome Discovery on Clinical Samples





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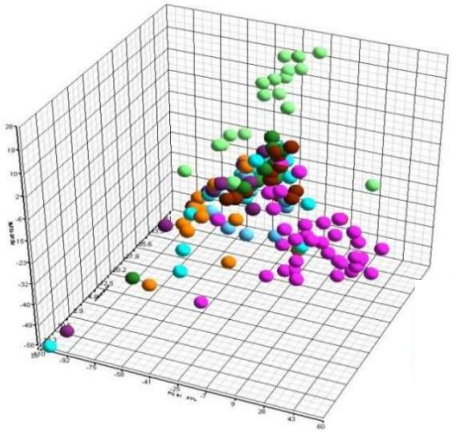
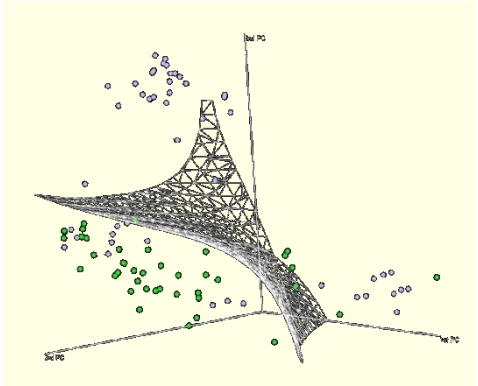
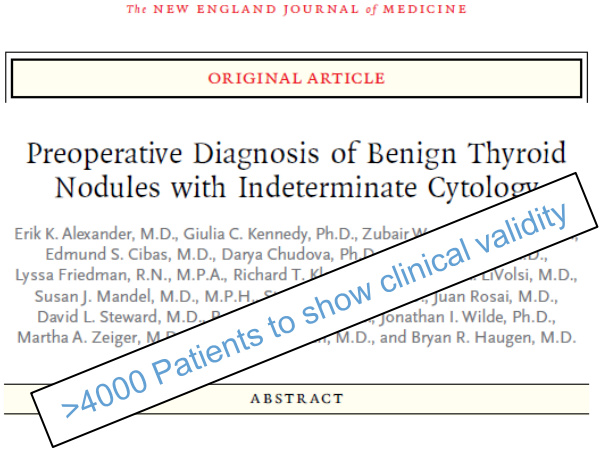




Verification and Validation


The NEW ENGLAND JOURNAL of MEDICINE

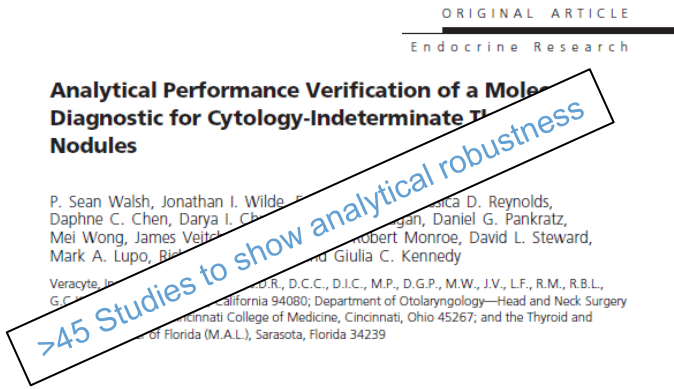
ORIGINAL ARTICLE

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

Erik K. Alexander, M.D., Giulia C. Kennedy, Ph.D., Zubair W. ... Edmund S. Cibas, M.D., Darya Chudova, Ph.D. ... Lyssa Friedman, R.N., M.P.A., Richard T. Kloos, M.D., ... LiVolsi, M.D., Susan J. Mandel, M.D., M.P.H., ... Juan Rosai, M.D., David L. Steward, M.D., ... Jonathan I. Wilde, Ph.D., Martha A. Zeiger, M.D., ... M.D., and Bryan R. Haugen, M.D.

ABSTRACT

>4000 Patients to show clinical validity


ORIGINAL ARTICLE

Endocrine Research

Analytical Performance Verification of a Molecular Diagnostic for Cytology-Indeterminate Thyroid Nodules

P. Sean Walsh, Jonathan I. Wilde, ... Jessica D. Reynolds, Daphne C. Chen, Darya I. Chudova, ... Daniel G. Pankratz, Mei Wong, James Veitch, ... Robert Monroe, David L. Steward, Mark A. Lupo, Richard ... and Giulia C. Kennedy

Veracyte, Inc., ... D.R., D.C.C., D.I.C., M.P., D.G.P., M.W., J.V., L.F., R.M., R.B.L., G.C. ... California 94080; Department of Otolaryngology—Head and Neck Surgery ... Cincinnati College of Medicine, Cincinnati, Ohio 45267; and the Thyroid and ... of Florida (M.A.L.), Sarasota, Florida 34239

>45 Studies to show analytical robustness

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Afirma Malignancy Classifier

Medullary Thyroid Cancer Cassette

- Five genes using a linear classifier
- Truth was obtained by surgical pathology
- Validated in over 7,000 patient FNAs to have extraordinary sensitivity and specificity
  - Two MTCs were misclassified (96% sensitivity)
  - One very, very rare tumor called a paraganglioma was misclassified as an MTC (>99% specificity)

BRAF RNA Classifier

- SVM algorithm that uses 128 RNA transcripts already measured on the custom microarray
- Truth was obtained by running a BRAF PCR assay on DNA from the same FNA
- High negative percent agreement (99%) and high positive percent agreement (90%)

Four Issued Patents

(12) **United States Patent**
Kennedy et al.

(10) **Patent No.: US 8,541,170 B2**
(45) **Date of Patent: *Sep. 24, 2013**

(54) **METHODS AND COMPOSITIONS OF MOLECULAR PROFILING FOR DISEASE DIAGNOSTICS**

(75) Inventors: **Giulia C. Kennedy**, San Francisco, CA (US); **Bonnie H. Anderson**, Half Moon Bay, CA (US); **Darya I. Chudova**, San Jose, CA (US); **Eric T. Wang**, Milpitas, CA (US); **Hui Wang**, San Bruno, CA (US); **Moraima Pagan**, San Francisco, CA (US); **Nusrat Rabbee**, South San Francisco, CA (US); **Jonathan I. Wilde**, Burlingame, CA (US)

(73) Assignee: **Veracyte, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 413 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/592,065**

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(12) **United States Patent**
Kennedy et al.

(10) **Patent No.: US 8,669,057 B2**
(45) **Date of Patent: Mar. 11, 2014**

(54) **METHODS AND COMPOSITIONS FOR DIAGNOSIS OF THYROID CONDITIONS**

(75) Inventors: **Giulia C. Kennedy**, San Francisco, CA (US); **Bonnie H. Anderson**, Half Moon Bay, CA (US); **Darya I. Chudova**, San Jose, CA (US); **Eric T. Wang**, Milpitas, CA (US); **Hui Wang**, San Bruno, CA (US); **Moraima Pagan**, San Francisco, CA (US); **Nusrat Rabbee**, San Francisco, CA (US); **Jonathan I. Wilde**, Burlingame, CA (US)

(73) Assignee: **Veracyte, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/318,751**

(22) PCT Filed: **May 7, 2010**

(86) PCT No.: **PCT/US2010/034140**

(52) **U.S. Cl.**
USPC **435/6.1**

(58) **Field of Classification Search**
USPC 506/7; 435/6.1
See application file for complete search history.

(56) **References Cited**

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(12) **UK Patent** (19) **GB** (11) **2507680** (13) **B**
(45) Date of B Publication **18.06.2014**

(54) Title of the Invention: **Methods and compositions of molecular profiling for disease diagnostics**

(51) INT CL: ***C12Q 1/68*** (2006.01) ***G01N 33/574*** (2006.01) ***G06F 19/20*** (2011.01)

(21) Application No: **1401364.3**

(22) Date of Filing: **17.11.2009**

Date Lodged: **27.01.2014**

(30) Priority Data:
(31) **61199585** (32) **17.11.2008** (33) **US**
(31) **61270812** (32) **13.07.2009** (33) **US**

(62) Divided from Application No
1315760.7 under section 15(9) of the Patents Act 1977

(43) Date of A Publication **07.05.2014**

(72) Inventor(s):
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United States of America

(12) **UK Patent** (19) **GB** (11) **2477705** (13) **B**
(45) Date of B Publication **23.04.2014**

(54) Title of the Invention: **Methods and compositions of molecular profiling for disease diagnostics**

(51) INT CL: ***C12Q 1/68*** (2006.01) ***C12N 15/12*** (2006.01) ***G01N 33/574*** (2006.01) ***G06F 19/00*** (2011.01)

(21) Application No: **1110195.3**

(22) Date of Filing: **17.11.2009**

Date Lodged: **16.06.2011**

(30) Priority Data:
(31) **61199585** (32) **17.11.2008** (33) **US**
(31) **61270812** (32) **13.07.2009** (33) **US**

(60) Parent of Application No(s)
1315760.7 under section 15(9) of the Patents Act 1977

(86) International Application Data:
PCT/US2009/006162 En 17.11.2009

(72) Inventor(s):
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Bonnie Anderson
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United States of America

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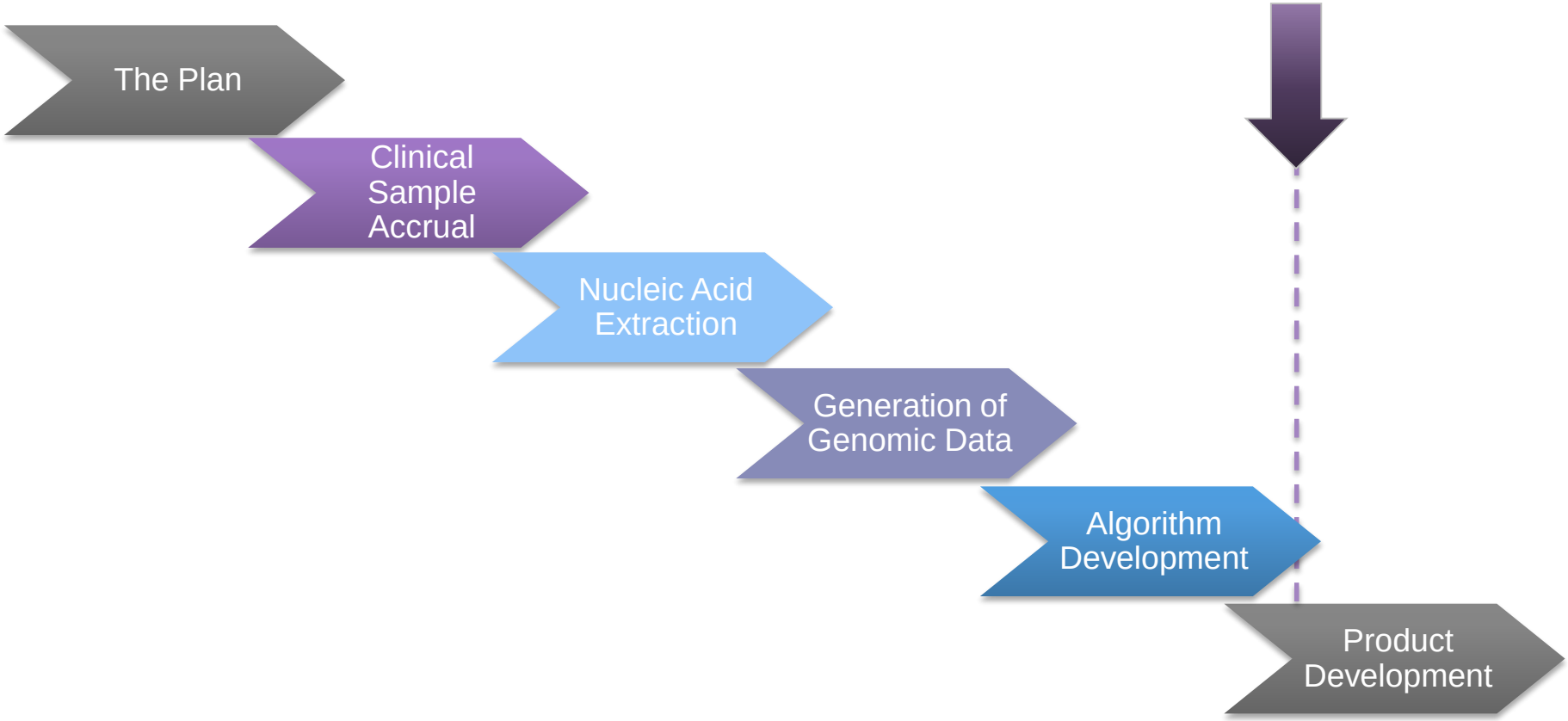
Lung Cancer Test

Lung Cancer Diagnostic: Late Stage Development



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Commercialization of Veracyte Lung Cancer Test

Whole Genome Discovery and Algorithm Development

Bronchial Brushings

- Training set n=299
- Affymetrix GeneST array
- Supervised Learning Exploiting the *"Field of Injury"*
- 22 genes
- Logistic Regression Classification Algorithm

Two Clinical Validation Studies

Prospective Bronchial Brushing Samples

- Aegis I (n=298)
- Aegis II (n=341)

Performance shows high >90% NPV

Support with Robust Clinical Evidence

- Publish AEGIS I and II **Clinical Validation Studies**
- Perform **Analytical Verification** Studies to transfer test to CLIA lab
- Initiate **Clinical Utility** and **Cost-effectiveness Studies**
- Extra content on the microarray will help us develop follow-on products

We Are Here

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Lung Cancer Test Performance is Highly Consistent Across Studies

AEGIS II: Prospective, Multi-center, Blinded Study

- 22 sites: 15 academic, 7 community with enrollment from 2010-2012
- 341 patients in validation set
- Performance highly consistent with AEGIS I

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Interstitial Lung Diseases

Interstitial Lung Diseases Pose Difficult Challenges

- Diverse group of disorders
- Can have similar symptoms, physiology, pathology radiology
- Inconsistent nomenclature
- Limited, often toxic, treatments
- Difficult to diagnose

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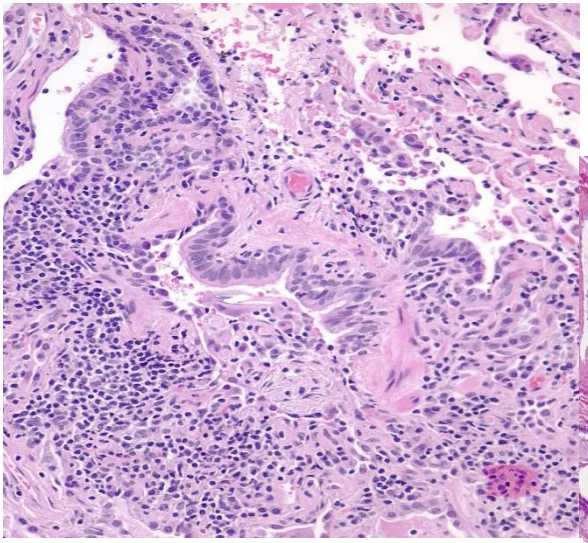
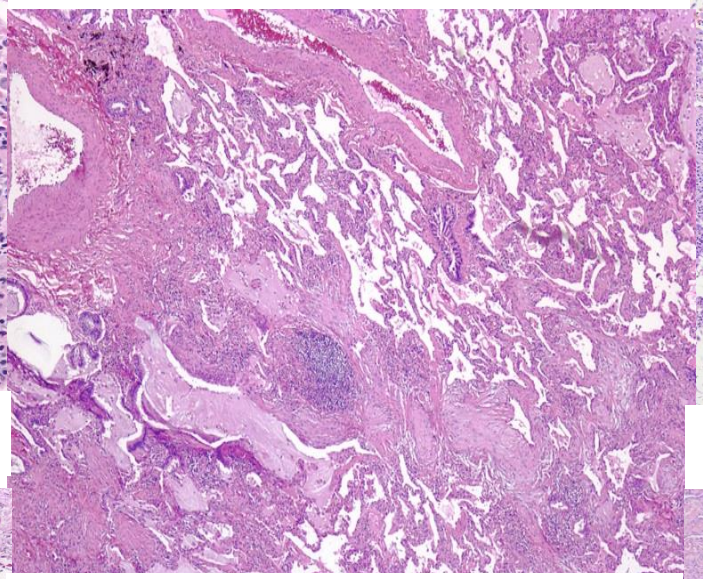
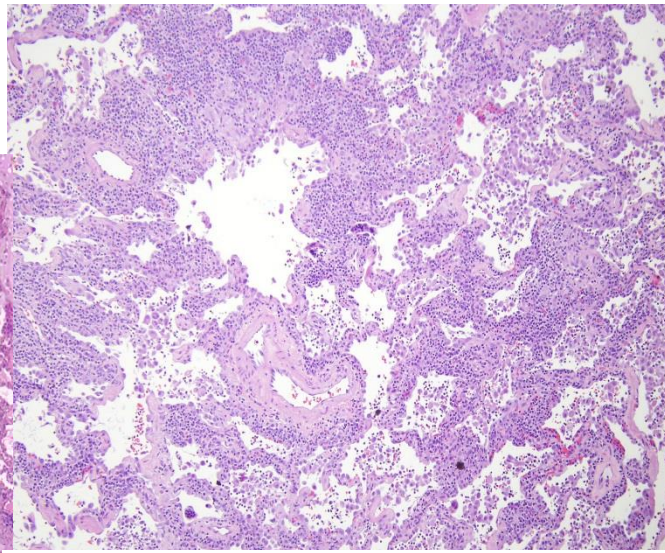
Interstitial Lung Diseases: Heterogeneous Pathology Patterns



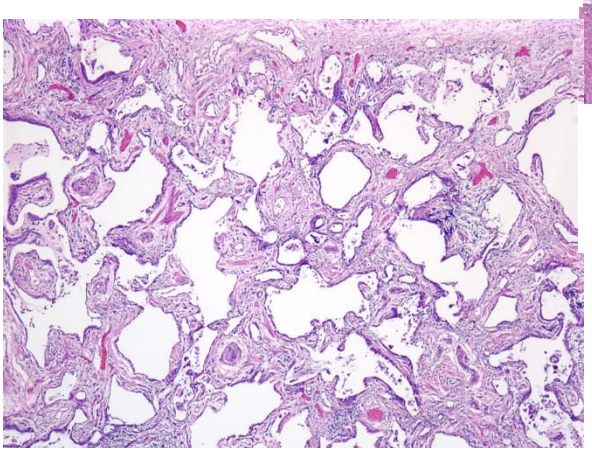
Organizing Pneumonia



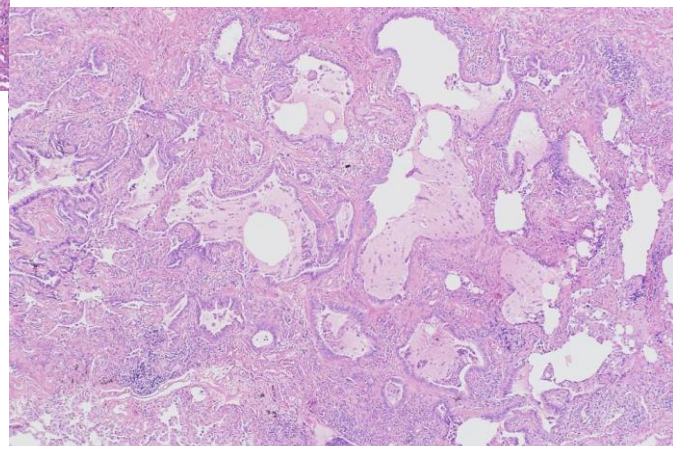
Idiopathic Pulmonary Fibrosis



Chronic Bronchiolitis



Nonspecific Interstitial Pneumonia



Hypersensitivity Pneumonitis

Thyroid Development Process Replicated for ILD

Whole Genome Discovery and Algorithm Development in Surgical Tissue

Surgical tissue

- Banked ILD Surgical Tissues (n = 309)
- Local clinical diagnosis and some with expert surgical pathology review

Machine Learning Algorithms

- Microarray and Deep RNA sequencing
- Support Vector Machines

Bridge to Clinically Relevant Biopsy Samples

- **Prospective** bronchoscopy sample collection
- ~20 sites in US and EU
- Diagnoses by expert pathologist and **multi-disciplinary team (MDT)**
- Further assay and algorithm development
- Lock test and algorithm

We Are Here

Publish Robust Evidence

- **Analytical** validation
- Prospective, multi-center **clinical validation**
- Clinical utility and cost-effectiveness studies

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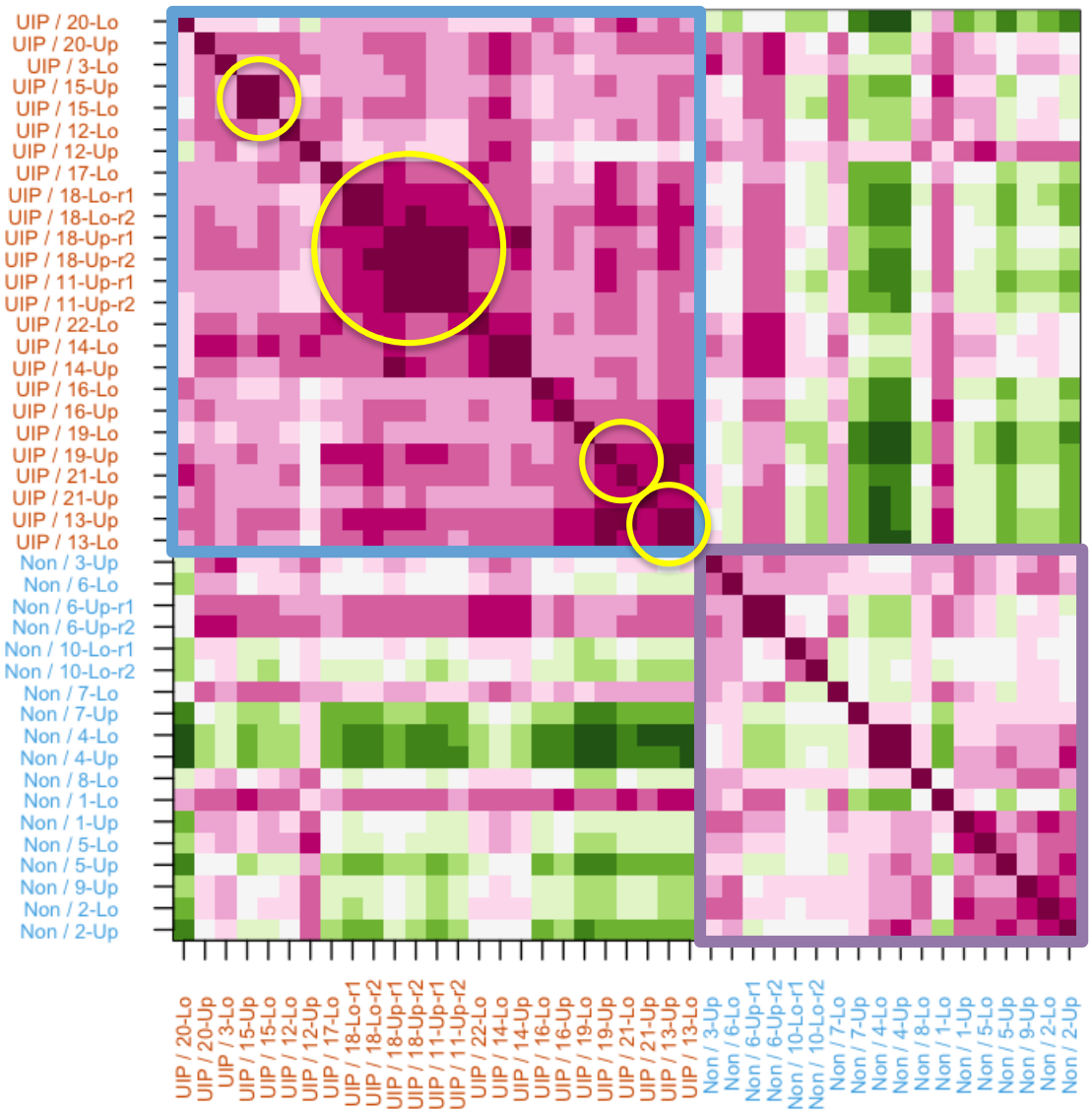
Top 200 Genes Reveals Structure in Tissue Data



- Clustering within UIP and non-UIP groups
- Multiple samples from same patient cluster together

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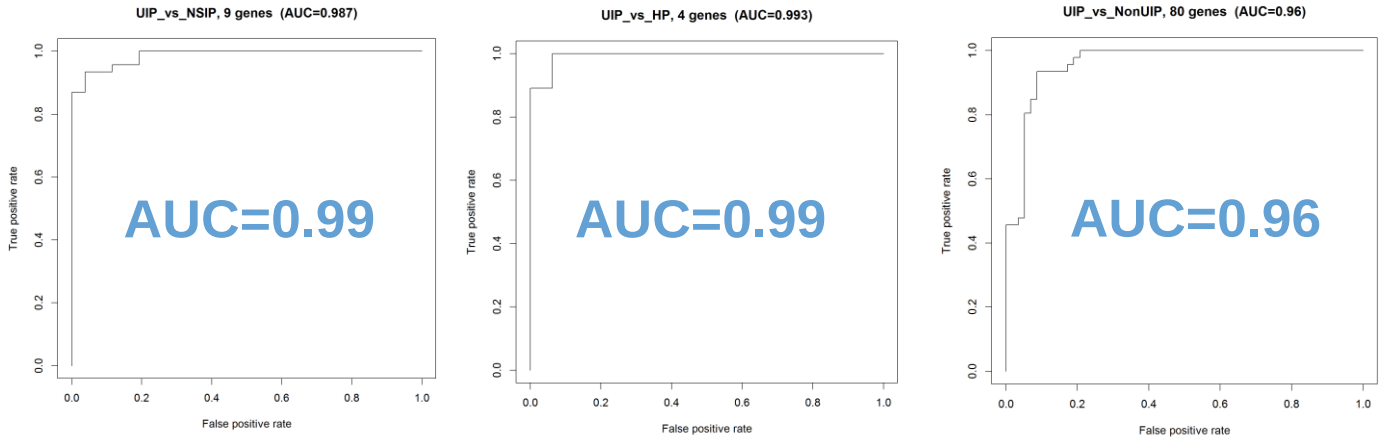
Classification Performance* to Pathology Pattern

	Pathology Pattern (UIP vs Other)		
	Non-specific Idiopathic Pneumonia (NSIP)	Hypersensitivity Pneumonitis (HP)	Non-UIP
Whole-genome Array	0.99	0.99	0.96
Patients n=	29 vs 14	29 vs 15	29 vs 40
RNA-Seq	1.0	0.96	0.90
Patients n=	14 vs 6	14 vs 2	14 vs 15



*leave-one-patient-out cross-validation on surgical tissue

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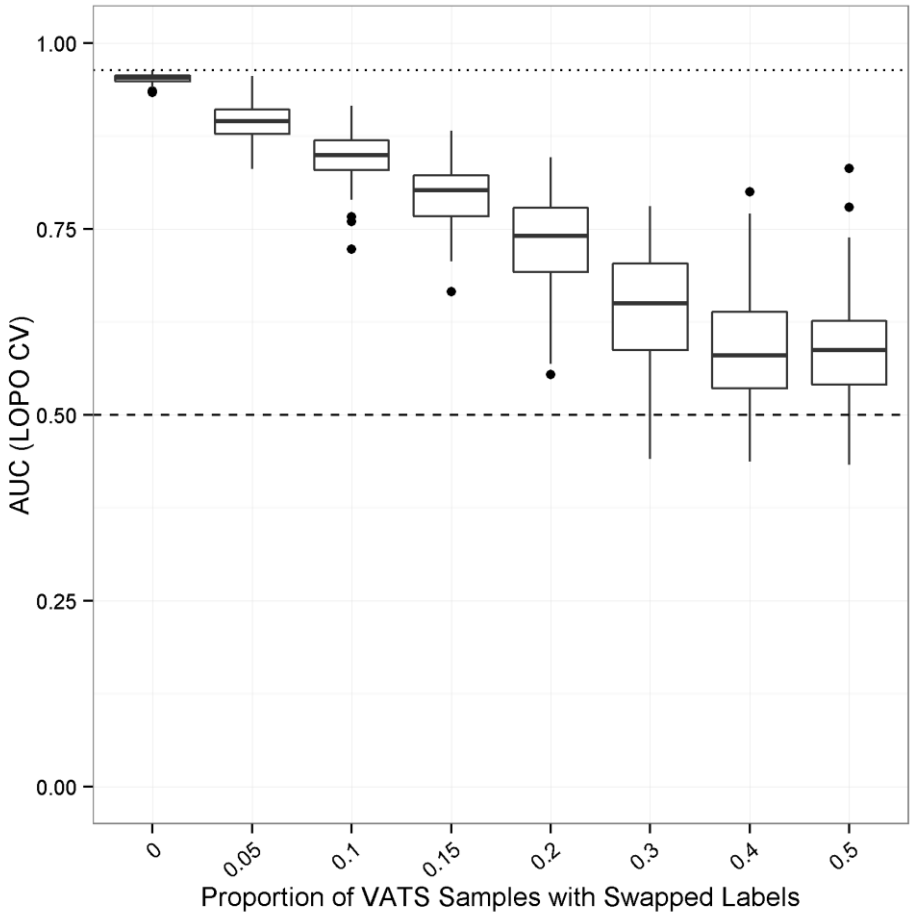
Getting Pathology Labels Right Is Important…

…and This Is What Happens When You Get It Wrong



If we do a simulation where we randomly introduce pathology label errors, the performance of the ILD classifier steadily drops

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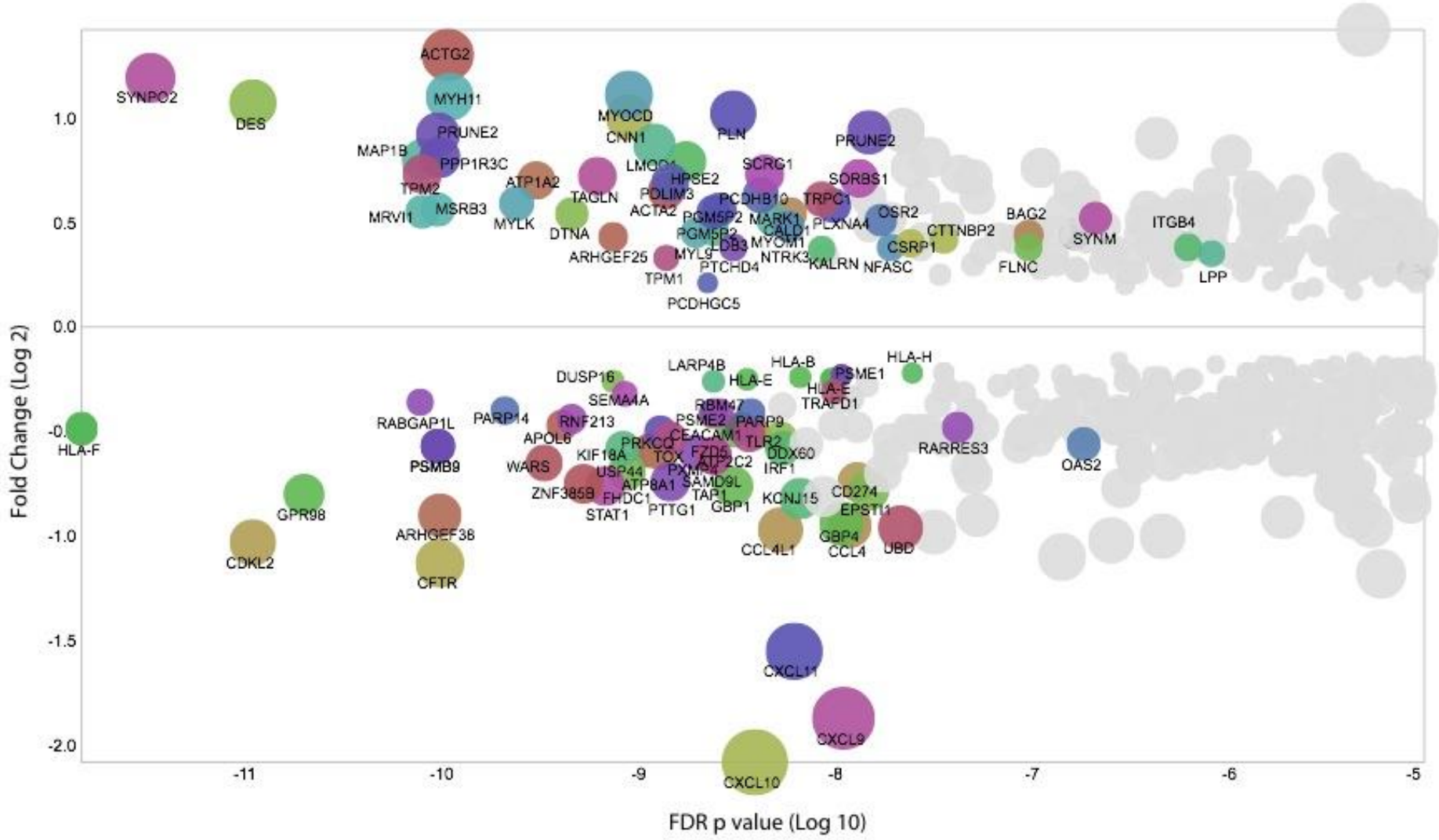
Top 500 UIP vs. Non-UIP Genes



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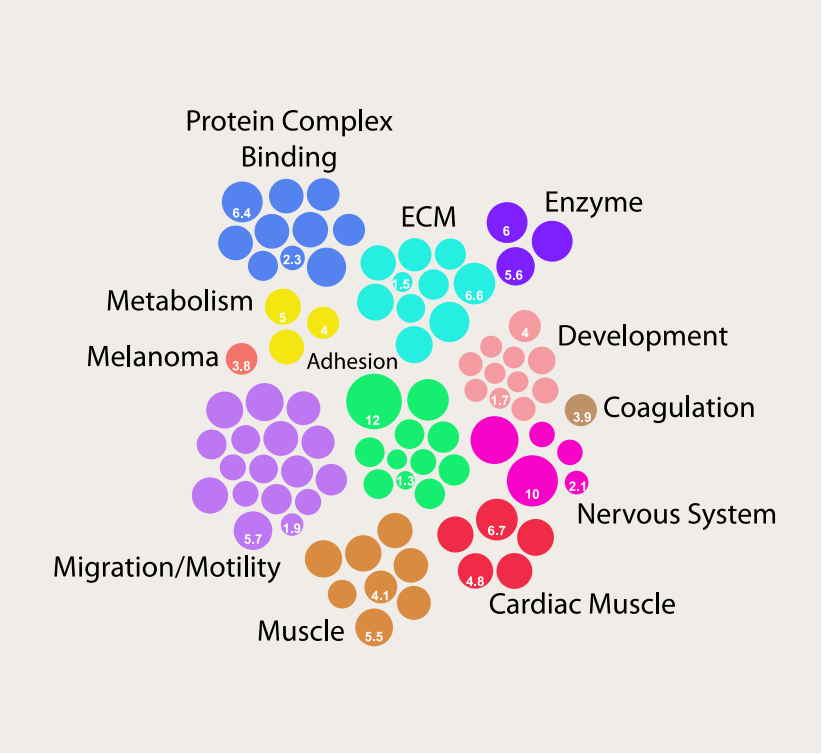
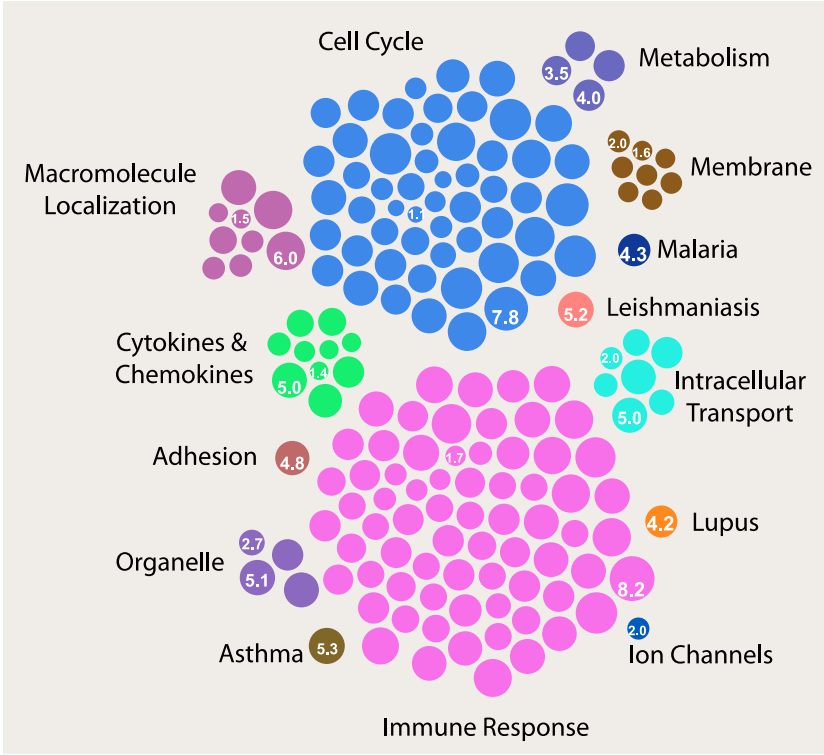
UIP and Non-UIP Samples Characterized by Distinct Pathway and Gene Ontology Groups

Over-represented in UIP



Over-represented in non-UIP



GeneTrail Software http://genetrail.bioinf.uni-sb.de/enrichment_analysis

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R&D Summary

- **Four major engines drive R&D**
  - Clinical Studies
  - Genomic Marker Discovery
  - Algorithm Development
  - Product Development
- Clinical site selection **yields right samples** with a truth label
- Assay and platform **optimized to fit** the indication
- High-density genomic data **collected on every patient** using the latest technology
- A **toolbox of sophisticated algorithms** are tested on all classification problems
- **Blinded clinical validation** studies foster confidence in the performance of our products
- **Unused genomic data** can be used to develop new products
- Publications drive **adoption, inclusion in guidelines and payer coverage**

State of the Art Care for Managing Patients with Thyroid Nodules

Erik K. Alexander, MD

Division of Endocrinology, Diabetes, & Hypertension

Brigham & Women's Hospital

Harvard Medical School

Outline:

1. Thyroid Nodule Evaluation - 2014:
   - Our current standard
   - Why we need better
2. Afirma GEC Analysis– 2014:
3. The Importance of High-Quality Clinical Validation

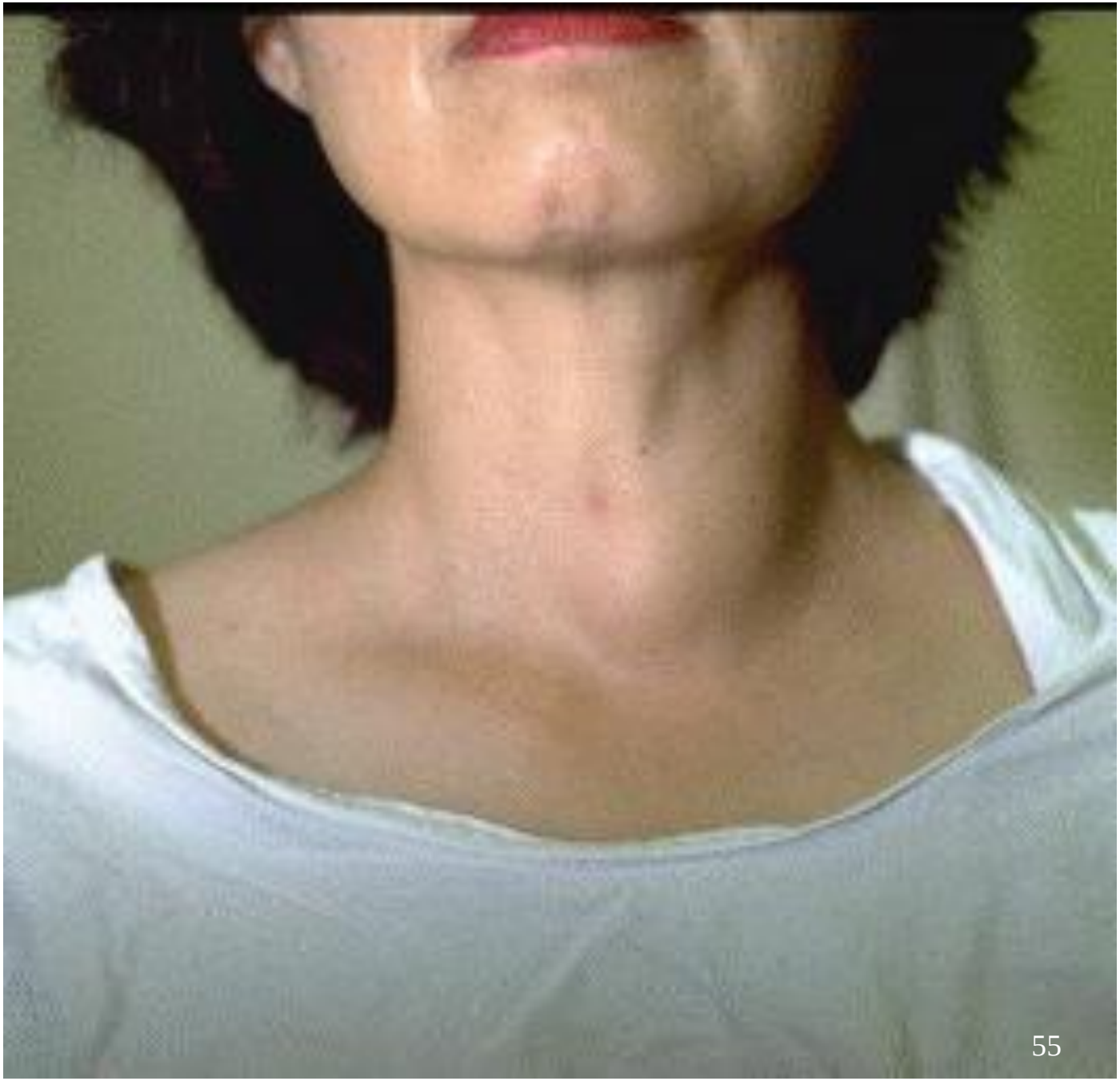
A Typical Patient:

48yo female is found to have an incidental thyroid mass during a CT scan. The mass is asymptomatic. She has no history of any thyroid problems, and fells 'well'. On examination, a 3.5cm left sided thyroid mass is identified, in an otherwise healthy individual.

The patient has been told that the importance of further evaluation is to exclude thyroid cancer.

She is worried…

Fine Needle Aspiration (FNA) is recommended



Traditional Approach to Thyroid Nodules >1-1.5cm:

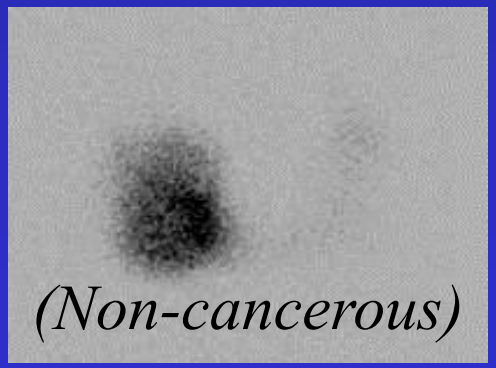
Initial Assessment:

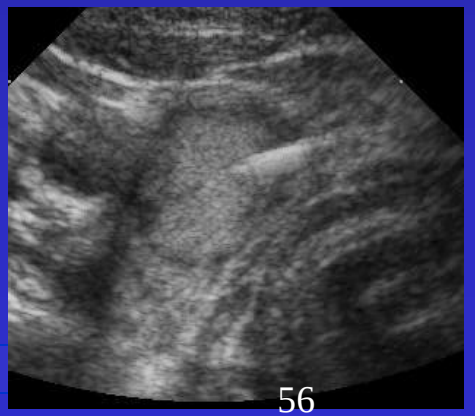
I. Ultrasound

II. Check TSH

suppressed (< 5%) → Thyroid Scan

normal or elevated (~95%) → Fine Needle Aspiration





Cooper, et al. *Thyroid* 2009

Limitations of Thyroid Nodule FNA:

A high rate of Indeterminate cytology

~ 65-70% - No Malignant Cells

~ 5% - Malignant (Papillary Carcinoma)

~ 15-30% - Indeterminate:

- "Suspicious for Malignancy"
- "Suspicious for a Follicular Neoplasm"
- "Atypical (follicular) lesion of Uncertain Significance"

~ 5% - Non Diagnostic

The Low Specificity of Indeterminate Cytology

~9,350 consecutive thyroid nodules at Brigham & Women's Hospital evaluated with fine needle aspiration over a 13-year period

FNA Cytology:	*Proportion Cancer on Histopathology:*
Suspicious for Papillary Carcinoma:	70 %
Suggestive of a Follicular Neoplasm:	27 %
Atypical of an undetermined significance:	24 %

Despite recommendations for surgery, >50% of patients with 'abnormal' cytology prove to have benign disease

Yassa, et al. *Cancer Cytopath*. 2007;

Incidence of Complications from Thyroidectomy

Complication:	*Rate:*
I. Perioperative risk of death from thyroid surgery[1,2,4]:	0.1-0.2% (0.8% if >80yo)
II. Permanent Complications[3]:	
Hypocalcemia >6mo:	4.4%
RLN damage >6mo:	1.0%
III. Other:	
Significant rebleeding[3]:	2.1%
Infection:	1.6%

1. Shrime MG, et al. *Arch Otolaryngol Head Neck Surg* 2007.
2. Hundahl SA, et al. *Cancer* 2000.
3. Bergenfelz A, et al. *Langenbecks Arch Surg* 2008.
4. Mekel M, et al. *Surgery* 2009.

Can we do better - 2014?

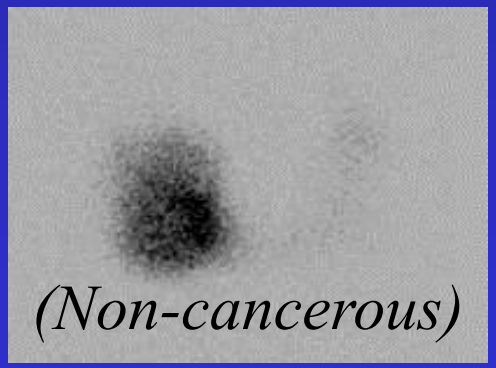
Initial Assessment:

I. Ultrasound

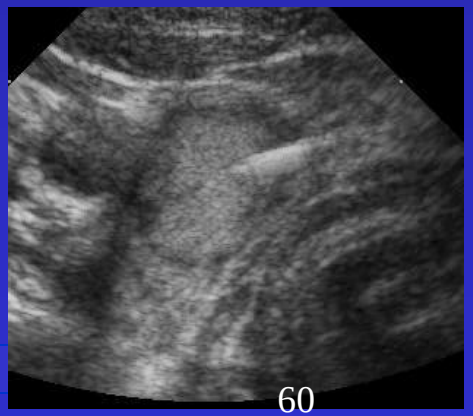
II. Check TSH

suppressed (< 5%) → Thyroid Scan

normal or elevated (~95%) → Fine Needle Aspiration



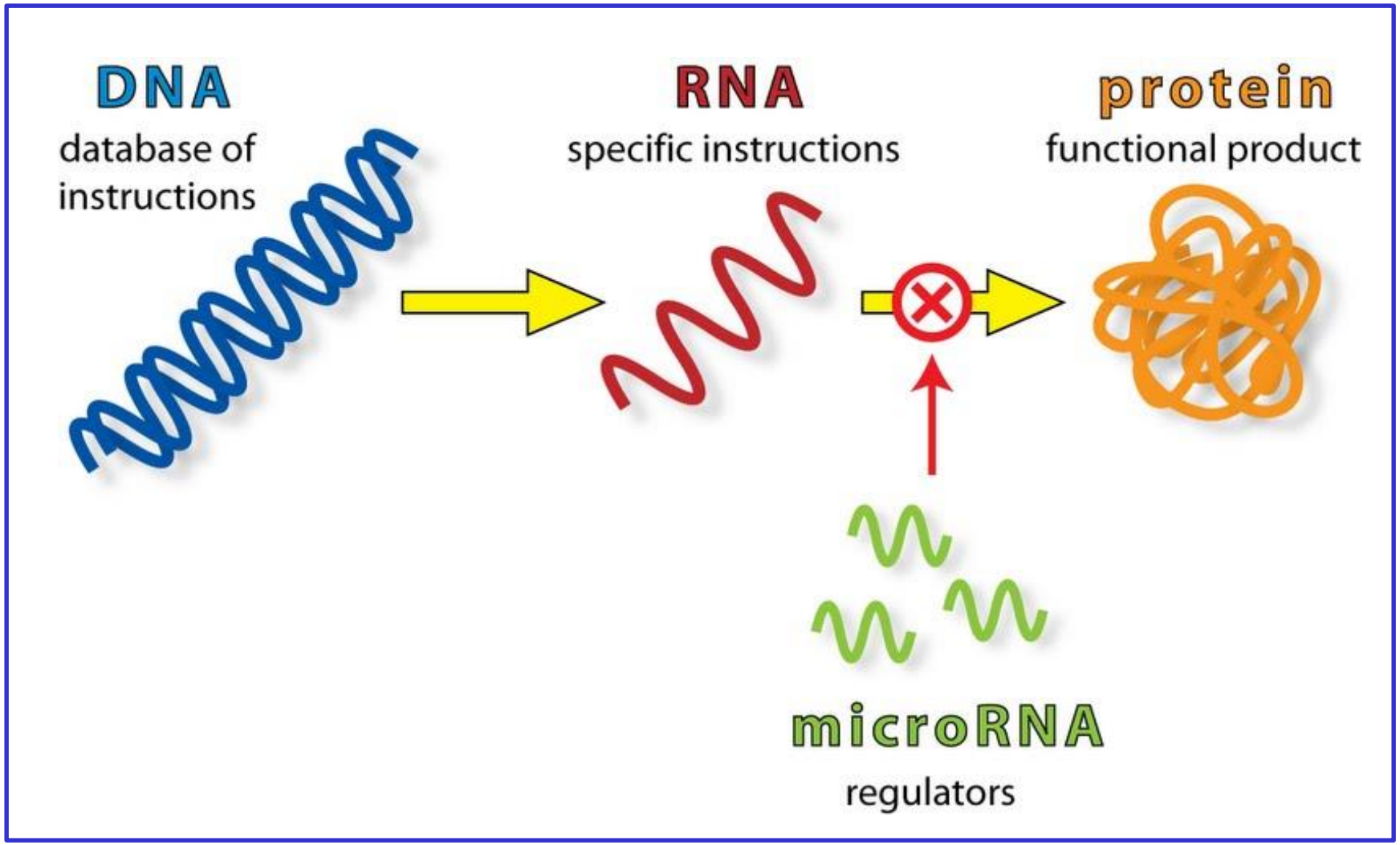
(Non-cancerous)



Cooper, et al. *Thyroid* 2009

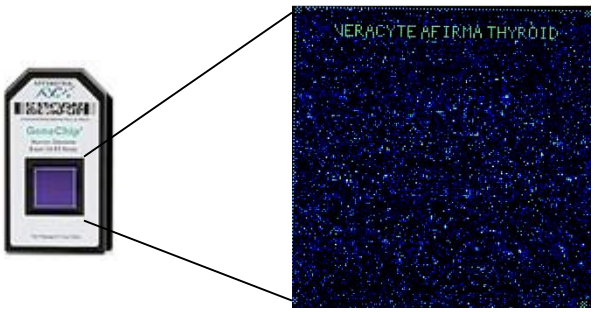
Addressing the clinical need:

Synergistic Molecular Diagnostic Testing

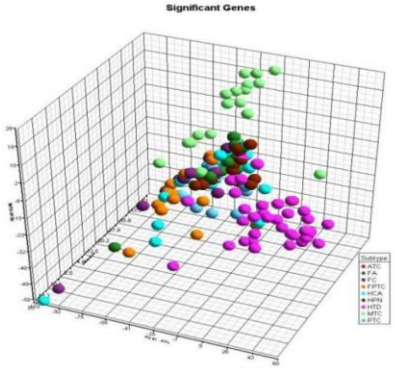


Afirma Gene Expression Classifier:

Measure expression of 22,000 genes (mRNA) from nodule biopsy



Calculations via a multidimensional algorithm



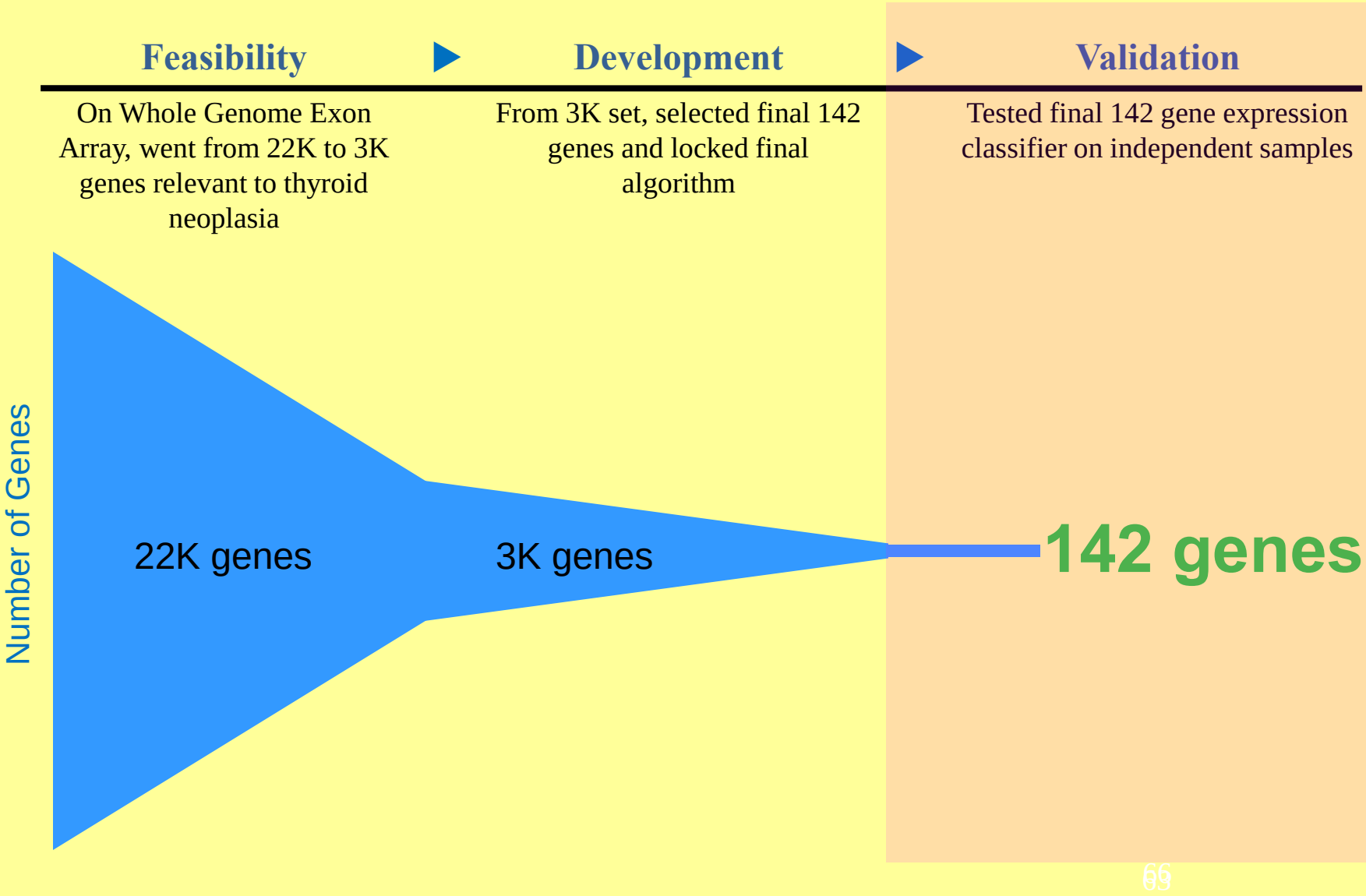
Pattern (Signature)

- Resulting from ~160 mRNA transcripts
- Binary Result (Benign vs. Suspicious)

Key Feature: Maximized Sensitivity (NEG predictive value) → BENIGN Afirma similar to that of a BENIGN Cytology result

Alexander, et al NEJM 2012; 367:705. Wiseman JCEM 2013; 98:4072

Afirma GEC Design & Development:



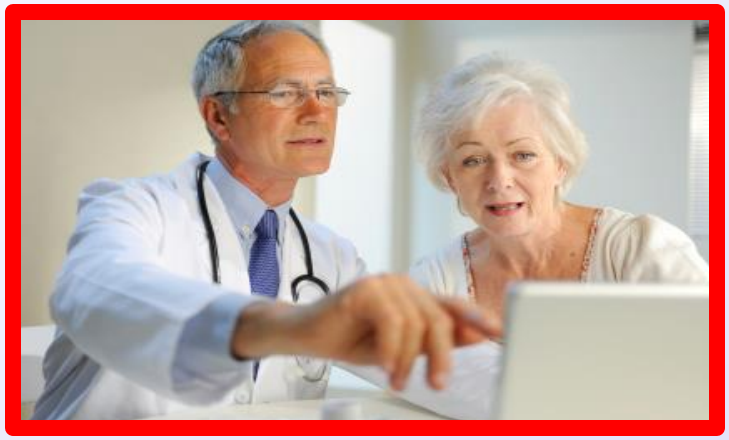
Chudova D, et al. *J Clin Endocrinol Metab* 2010.

2014 Focus – High Quality Validation

Discovery:

Development & Analytic Testing:

Clinical Validation & Clinical Utility

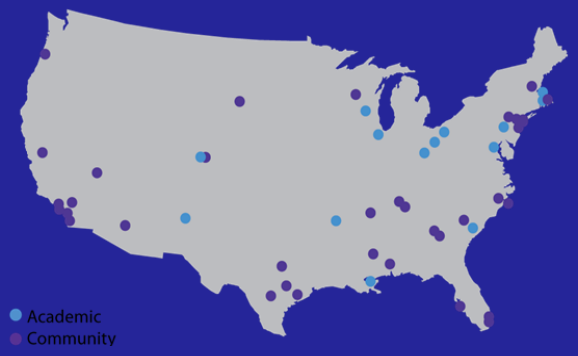


For Effective, Safe, & Accurate translation:

- Large, prospective, multi-center validation trial
- Double Blinded (molecular lab, pathologist, & clinician)
- Diverse & Representative of 'standard' population
- Pre-specified &Transparent – Led by Academic PI(s)

Afirma Validation: Study Design

- Prospective:
  - *19 month enrollment of 3,789 pts (4,812 nodules)*
  - *Followup from time of sampling: 301 days*
- Multi-center:
  - 49 clinical sites
  - Academic & Community
- Double-blinded:
  - *Patient & Physicians unaware of GEC results*
  - *Molecular Lab blind to surgical pathology diagnosis.*



Afirma GEC Validation:

When applied to patient with indeterminate thyroid nodules, in which diagnostic surgery would typically be recommended:

a 'benign' Afirma GEC means…

Performance on all Indeterminate: n=265	*Cytology Atypical (AUS):* n=129	*Cytology Foll. Neoplasm* n=81
NPV:93%	NPV:95%	NPV:94%

High NPV prevents unnecessary surgery –
False Negative rate similar to benign cytology

Alexander, NEJM 2012;367

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

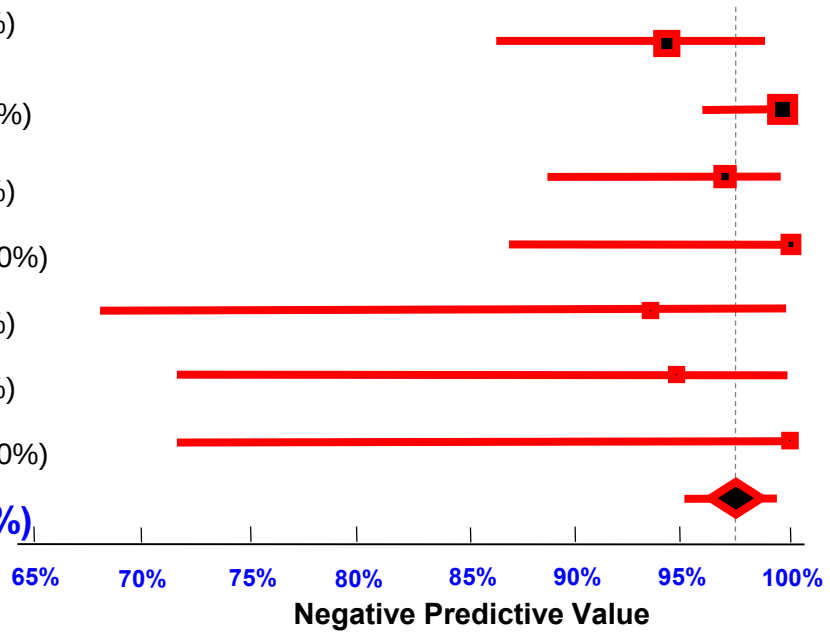
Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

Erik K. Alexander, M.D., Giulia C. Kennedy, Ph.D., Zubair W. Baloch, M.D., Ph.D., Edmund S. Cibas, M.D., Darya Chudova, Ph.D., James Diggans, Ph.D., Lyssa Friedman, R.N., M.P.A., Richard T. Kloos, M.D., Virginia A. LiVolsi, M.D., Susan J. Mandel, M.D., M.P.H., Stephen S. Raab, M.D., Juan Rosai, M.D., David L. Steward, M.D., P. Sean Walsh, M.P.H., Jonathan I. Wilde, Ph.D., Martha A. Zeiger, M.D., Richard B. Lanman, M.D., and Bryan R. Haugen, M.D.

Online First Release: June 25, 2012.

Consistency - Multiple Real-World Studies:

Study:	N*	Malignancy Prevalence	NPV (95% CI)
Alexander 2012	210	24.3%	94.3% (86.5% to 97.9%)
Alexander 2014	309	15.5%	99.4% (96.3% to 100.0%)
Michael 2013	133	26.3%	96.9% (88.2% to 99.5%)
Arce 2013	80	25.0%	100.0% (87.0% to 100.0%)
McIver 2014	60	10.0%	93.8% (67.7% to 99.7%)
Harrell 2013	55	32.7%	94.7% (71.9% to 99.7%)
Patel 2013	39	23.1%	100.0% (71.7% to 100.0%)
Total	**886**	**21.1%**	**97.5% (95%to 99%)**



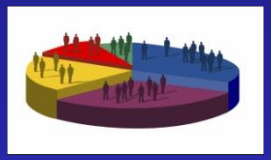
NPV calculated as true negatives (GEC benign and either unoperated or operated and histopathologically benign) divided by all GEC benign results
*Includes Bethesda III (atypia/follicular lesion of undetermined significance) and IV (follicular/Hürthle cell neoplasm)
NPV: Negative Predictive Value; CI: confidence intervals

Alexander EK et al. N Eng J Med 2012
Alexander EK et al. J Clin Endocrinol Metab 2014
Michael B et al. AACE Annual Meeting Abstract #1038, 2013
Michael B. Personal communication, December 1, 2013
Arce KM et al. ATA Annual Meeting Abstract #115, 2013
Harrell RM & Bimston DN. Endocr Pract 2013
Patel LN & Heller KS. ATA Annual Meeting Abstract #78, 2013
McIver B et al. JCEM 2014

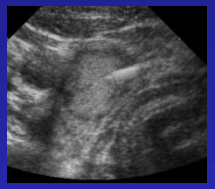
The Current Approach – 2014

Improves: The Traditional Standard: through: Synergy:

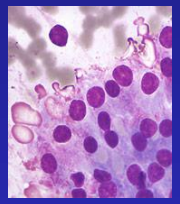
Clinical Risk Assessment:



Sonographic Risk Assessment:



Cytologic Risk Assessment:



Afirma Risk Assessment:

For any patient with a thyroid nodule:

Surgery only when Needed.

A Better Understanding of Individual Cancer RISK

In just 2 years…
The Profound Impact of Afirma GEC

322 Nodules with Indeterminate Biopsy
(Traditionally: Surgery recommended in >90%)

174 Afirma GEC
"Benign"

↓

4 of 174 (2%)
surgery recommended

148 Afirma GEC
"Suspicious"

↓

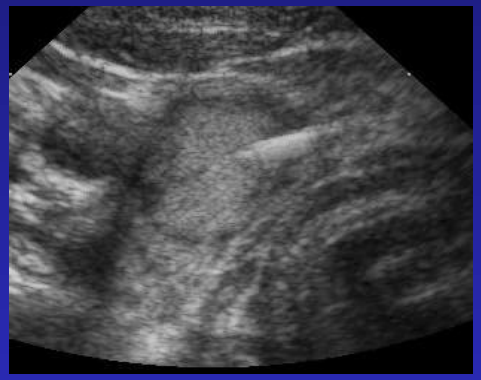
141 of 148 (95%)
surgery recommended

Alexander EK, et al. JCEM 2014

The New Standard:

Initial Assessment:

Fine Needle Aspiration



FNA Cytology:

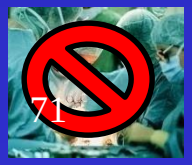
Benign: No Intervention

Abnormal: Likely Surgical Removal:
(hemi vs. near-total?)

Afirma GEC:

Suspicious → Surgical Removal

Benign → No Surgery Needed



Use of the Afirma GEC Today:

- Used routinely on my patients with indeterminate thyroid nodule FNA cytology:
  - Prospectively Validated in blinded fashion
  - Addresses an important unmet need in my population

- Increasingly used at throughout the U.S.
- An emerging standard of care in U.S.
  - NCCN guidelines
  - ATA guidelines

Afirma GEC provides significant opportunity to reduce unnecessary surgeries and save costs

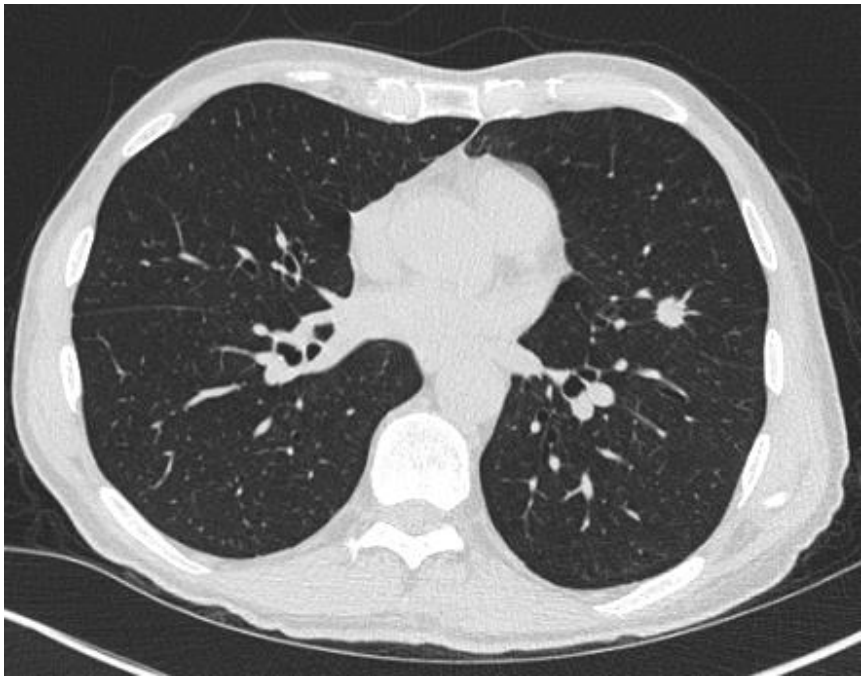
Clinical Unmet Need in Lung Cancer Detection

Anil Vachani, MD, MS
Assistant Professor of Medicine
Department of Medicine
University of Pennsylvania

Penn Medicine

Clinical Case

- 55 y/o woman
- 20 pack year smoking history
- Early stage breast cancer 2 years ago
- Chest CT done for evaluation for shortness of breath
- 11mm LUL nodule



Clinical Challenges

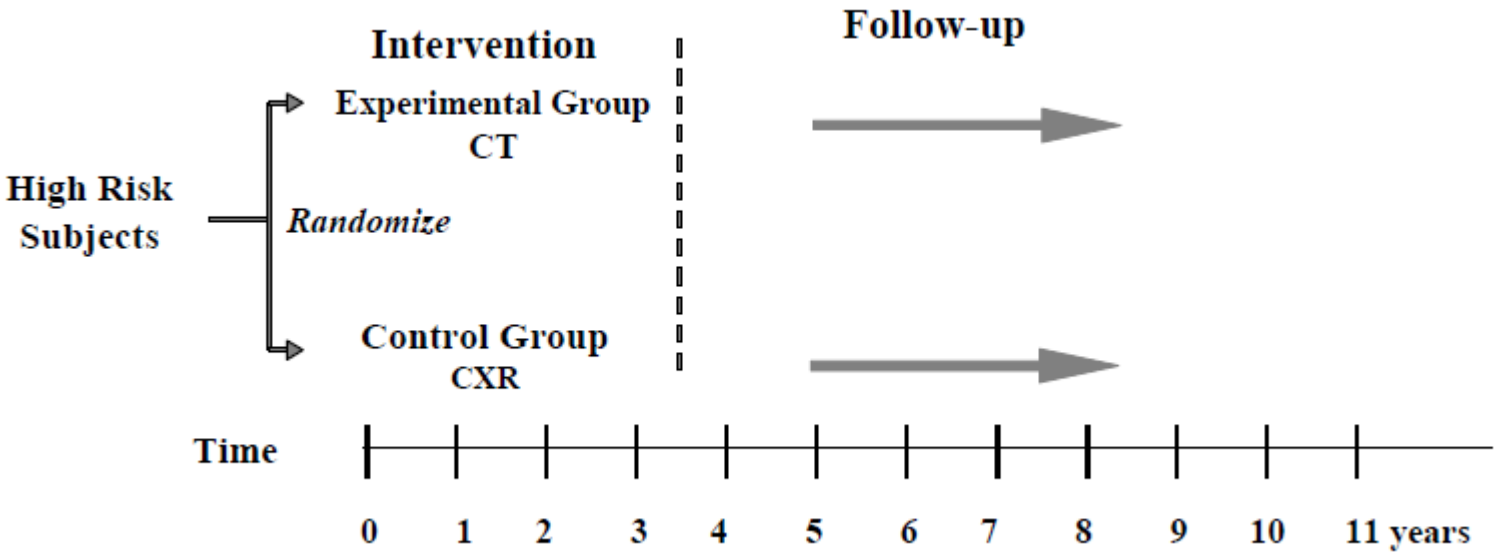
- Effective treatment for early stage disease but most lung cancers present at advanced stage
- Limited therapeutic advances for patients with advanced disease
  - Chemotherapy and Radiation
- The Lung is a difficult organ to biopsy
  - Bronchoscopy
  - CT guided needle biopsy (TTNA)
  - Surgery

Potential Solutions

- Diagnose patients at an earlier stage of disease
  - Screening
- Improve the diagnostic yield of current biopsy techniques
- Improve therapeutic strategies for patients with late stage disease

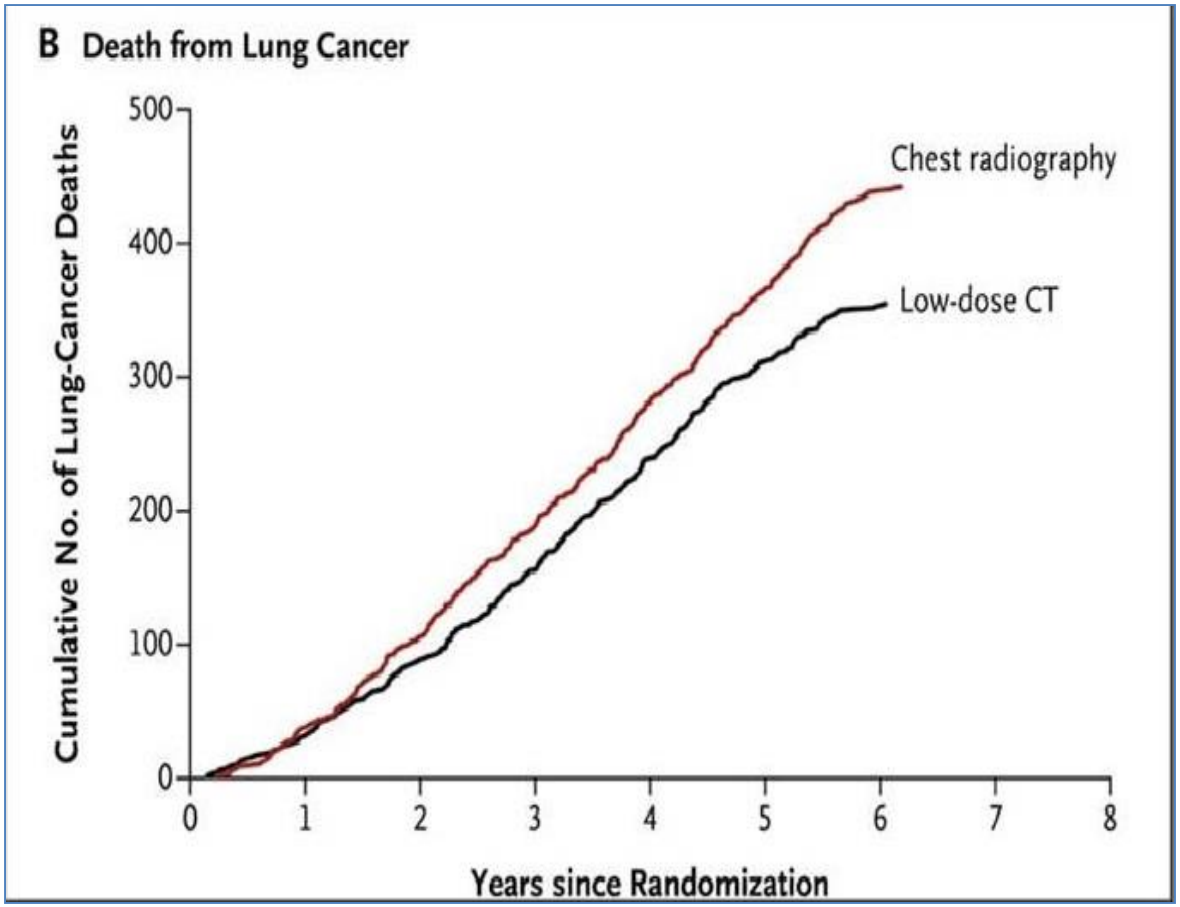
NLST – Study Design

Prospective randomized controlled trial
Screening for 3 consecutive years with either CXR or low-dose chest CT

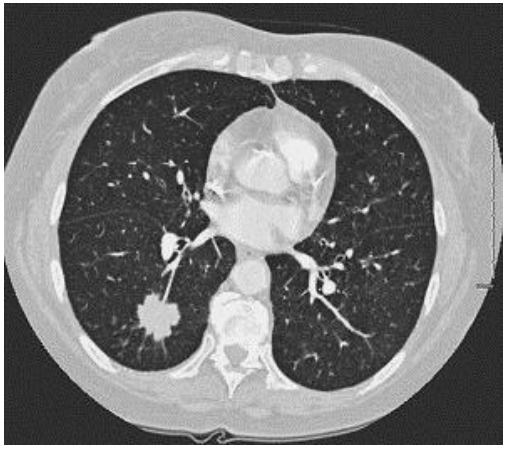


Enrollment: 8/2002-4/2004
Annual Interim Analyses: 4/2006 - 4/2010
Final: 10/2010

Study Results: Mortality



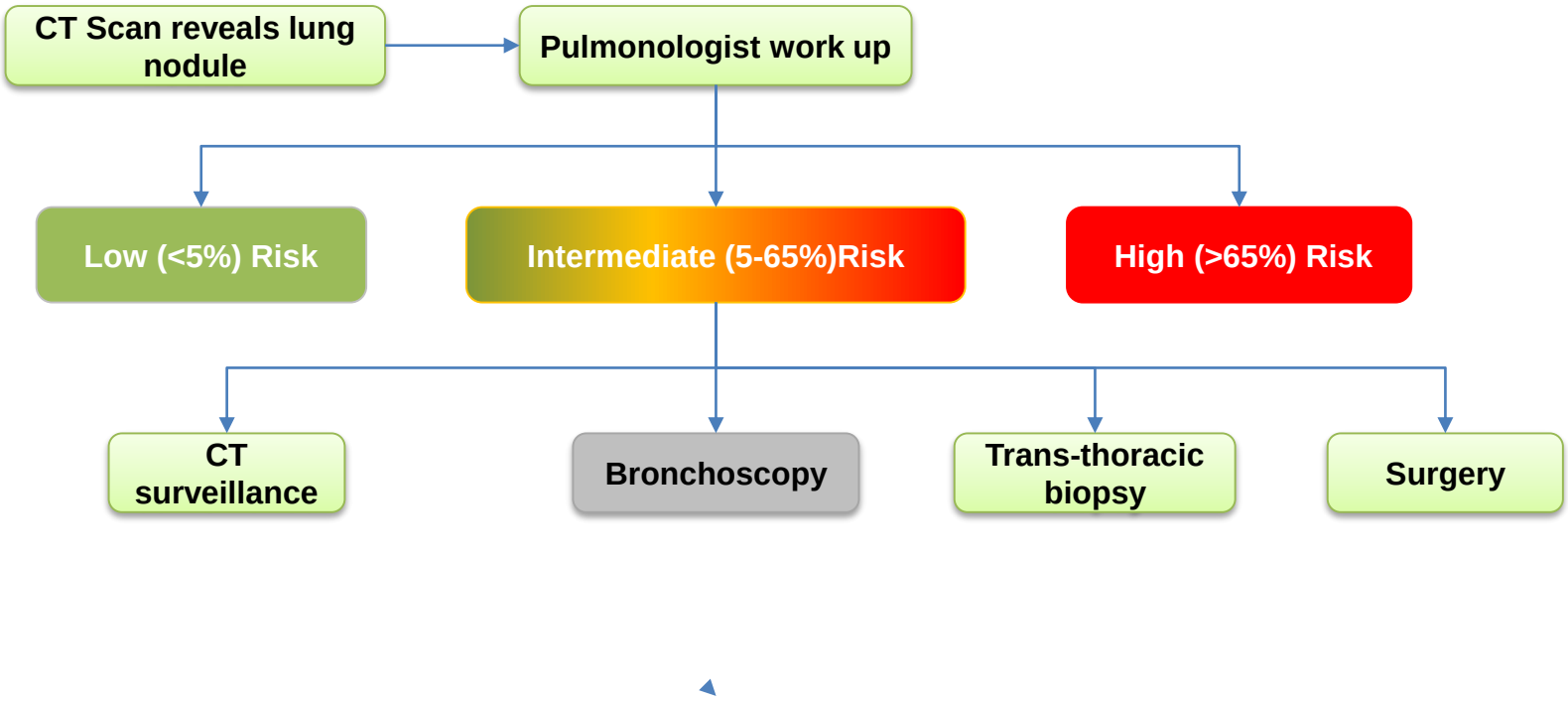
Importance of Nodule Size



Nodule Size	Confirmed Lung Cancer		PPV (%)
	Yes	No	
4-7 mm	18 (7%)	3642 (53%)	0.5
7-10 mm	35 (13%)	2079 (30%)	1.7
11-20 mm	111 (41%)	821 (12%)	11.9
21-30 mm	58 (22%)	137 (2%)	29.7
> 30 mm	45 (17%)	64 (1%)	41.3

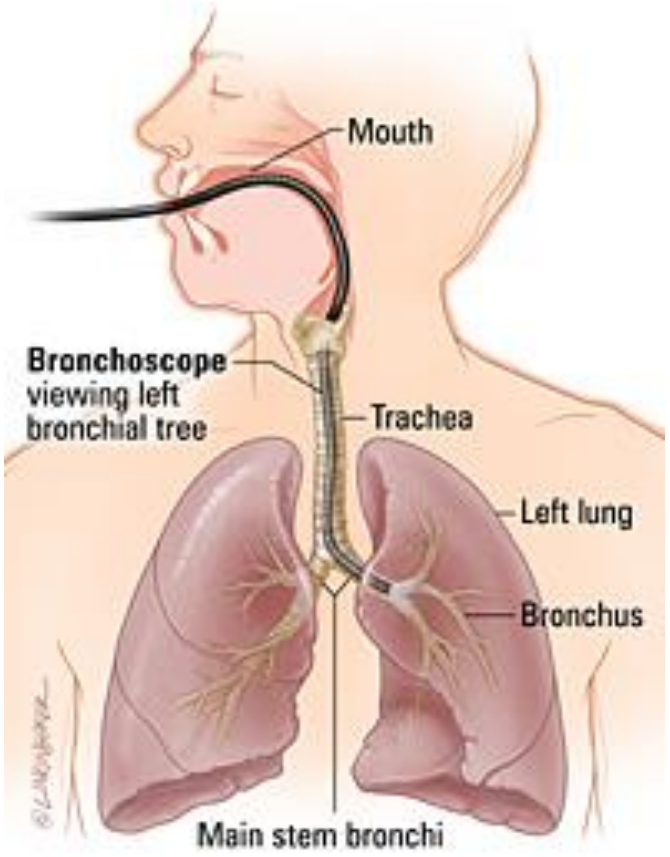
NLST Investigators. NEJM 2013

Pulmonary Nodule Evaluation



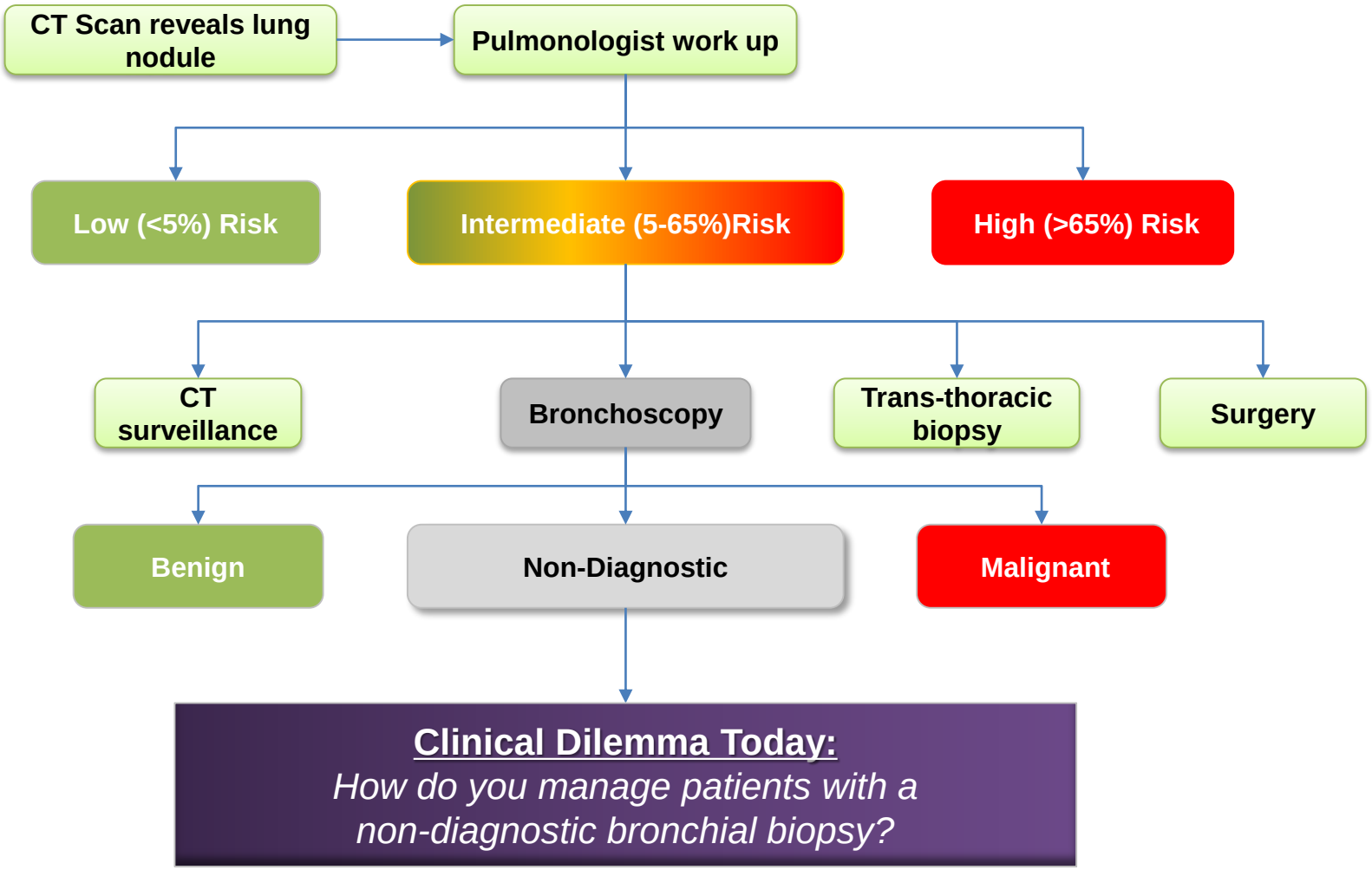
Role of Bronchoscopy in Lung Cancer

- Estimated 300,000 procedures/year on suspect lung cancer subjects
- Diagnostic sensitivity varies
  - Conventional vs guided techniques
  - Operator experience
  - Mass size or location
  - Estimates range from 50-80% (1,2)
- False-negative rate prevents rule-out of cancer
- Non-diagnostic bronchoscopy often leads to invasive follow-up procedures
- 30% of thoracotomy procedures lead to findings of benign disease

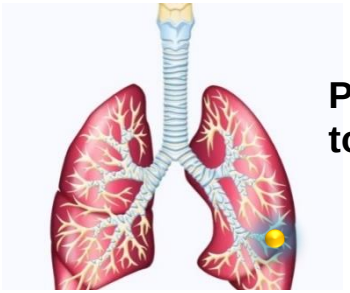


1. Ernst A, et al., CHEST. 2010;138:165-170 2. Ost DE, Ernst A, Lei X, et al. CHEST. 2011;140(6):1557-1566.

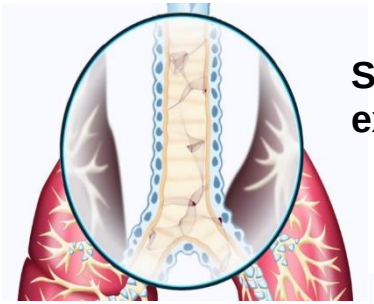
Pulmonary Nodule Evaluation



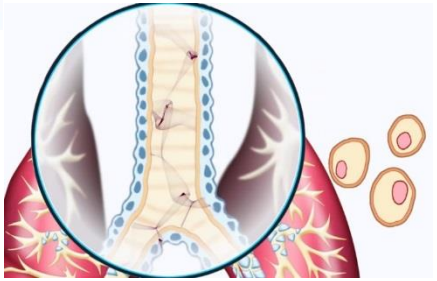
Airway Field of Injury Concept



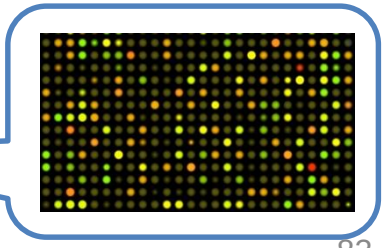
Peripheral lung nodules are difficult to biopsy



Smoking alters the epithelial cell gene expression throughout the airway



A gene signature of a cytology sample collected from the airway can predict the risk of cancer of a peripheral lung nodule



AEGIS Trial: Multi-Center Cohort Study

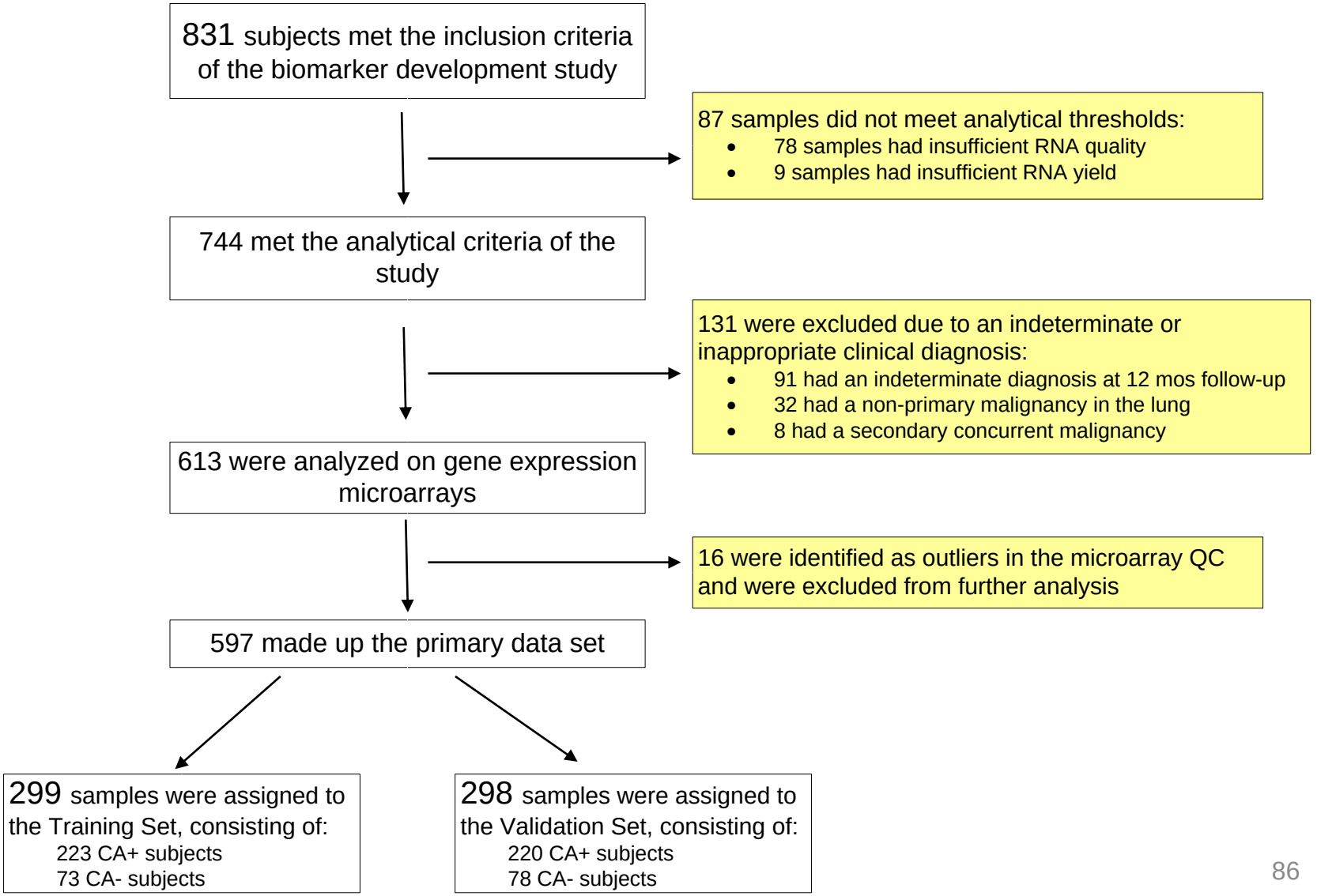
Airway **E**pithelium **G**ene Expression **I**n Lung Cancer Diagnosi**S**

- It has been shown that gene-expression in cytologically normal airway epithelial cells reflects damage in smokers (current & former)
- Development of a multivariate classifier can be used to predict cancers in the case of non-diagnostic bronchoscopy procedures and significantly improve diagnostic yield.

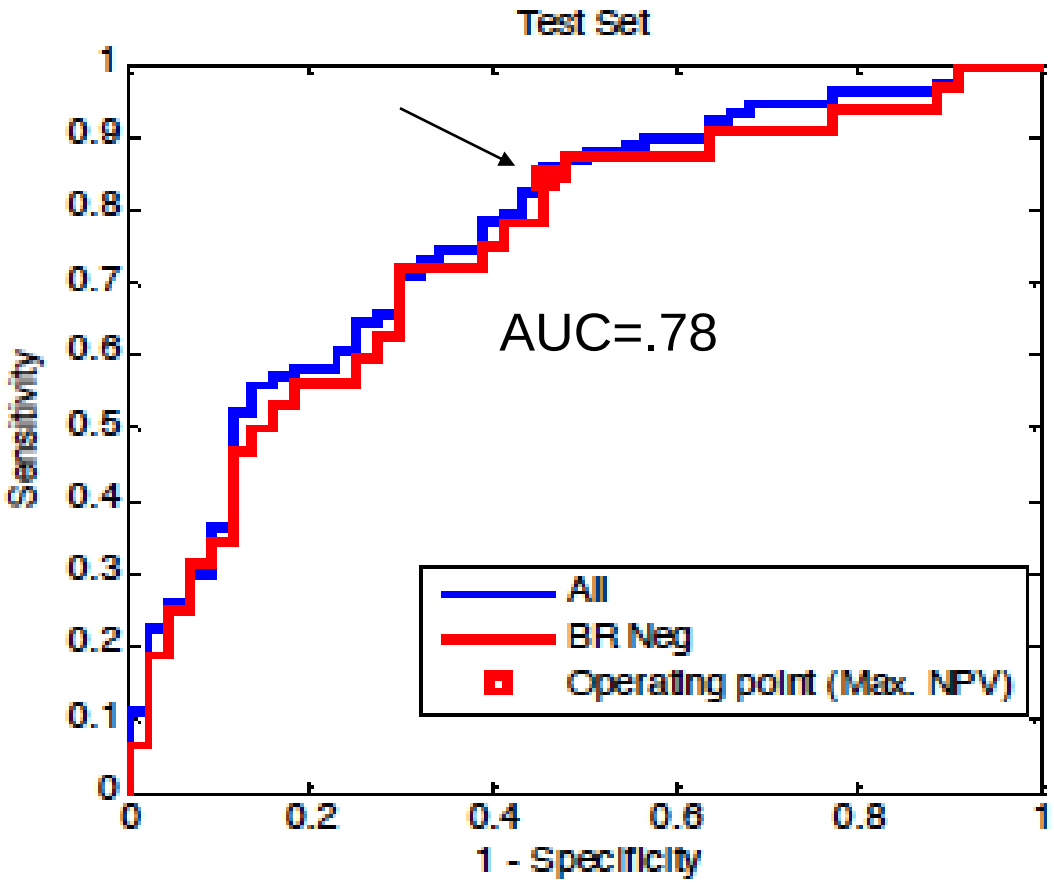
Airway **E**pithelium **G**ene Expression **I**n the Diagnosi**S** of Lung Cancer: AEGIS I and AEGIS II Clinical Trial Sites

AllegroDiagnostics
www.allegrodx.com

AEGIS 1 Study Samples



Aegis I Validation Results



Subgroup Analysis: High sensitivity in small lesions and peripheral lesions

Mass Size	N	BG	BR	Combined
<1 cm	30	93%	79%	100%
1-2 cm	87	89%	54%	98%
2-3 cm	83	92%	53%	97%
Total <3cm	***200***	***91%***	***56%***	***98%***
>3 cm	296	88%	78%	96%
Infiltrate	55	85%	75%	95%
Unk	45	97%	83%	100%

Location	N	BG	BR	Combined
Central	200	85%	80%	95%
Peripheral	176	92%	54%	96%
Both	168	93%	73%	99%
Unk	53	88%	88%	97%

Greatest added benefit observed in smaller (<3cm) and peripheral lesions, where bronchoscopy alone is least sensitive.

Subgroup Analysis: Sensitivity of the classifier is equivalent across cancer stage

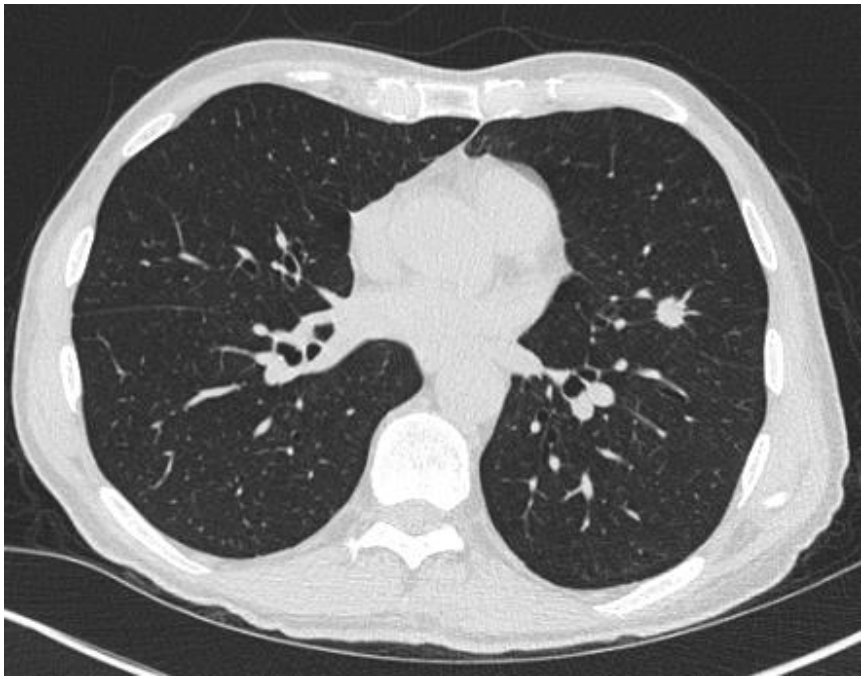
	Stage	N	BG	BR	Combined
NSCLC	IA	28	96%	29%	100%
	IB	37	81%	49%	84%
	IIA	2	100%	0%	100%
	IIB	24	92%	63%	100%
	Early stage	***91***	***89%***	***45%***	***93%***
	IIIA	54	91%	70%	98%
	IIIB	41	85%	73%	95%
	IV	110	90%	84%	98%
SCLC	Limited	31	84%	74%	97%
	Extensive	38	92%	92%	100%

Additional Results

- 34% (37/110) of surgeries were performed in benign lesions
- 23% (50/214) of subjects with negative bronchoscopy & benign disease had invasive follow-up
- **42% (21/50) patients could be saved invasive procedures by use of the Allegro lung cancer test**

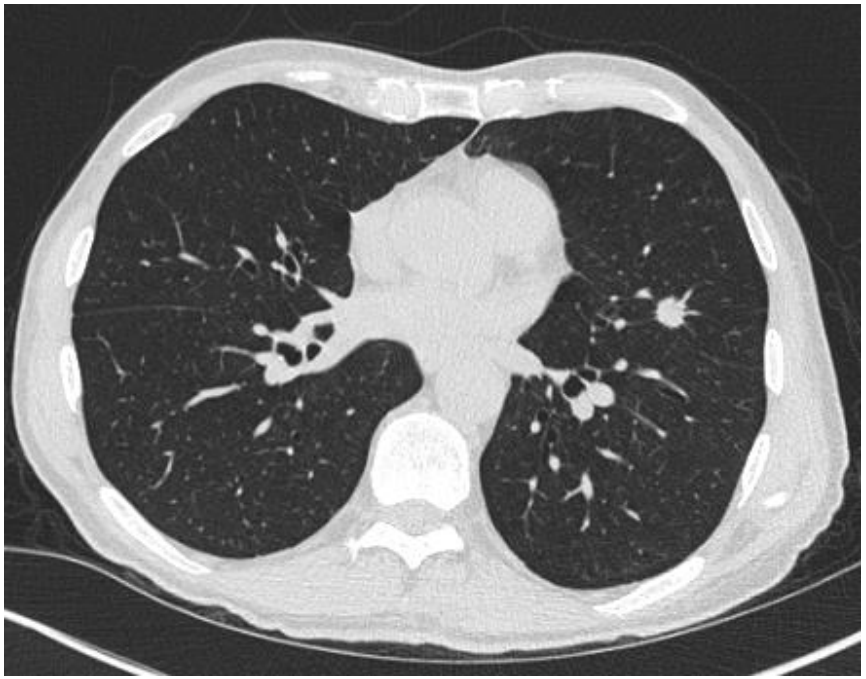
Clinical Case

- 55 y/o woman
- 20 pack year smoking history
- Early stage breast cancer 2 years ago
- Chest CT done for evaluation for shortness of breath
- 11mm LUL nodule



Clinical Case Results

- PET Scan
  - SUV ~ 2.5
  - Nonspecific lymph node uptake
- Bronchoscopy
  - Negative lymph nodes
  - Biopsy of the nodule was non-diagnostic
- VATS lobectomy
  - Benign granuloma



Summary

- Lung nodules/masses are a very common indication for pulmonary evaluation
- Bronchoscopy is non-diagnostic in in 20-50%
  - Higher non-diagnostic rate for lung nodules < 2cm
- Decision making is difficult following a non-diagnostic bronchoscopy
- Allegro's lung cancer test can lead to fewer invasive procedures following a non-diagnostic bronchoscopy

The current approach to the diagnosis of interstitial lung disease

Fernando J. Martinez, MD, MS

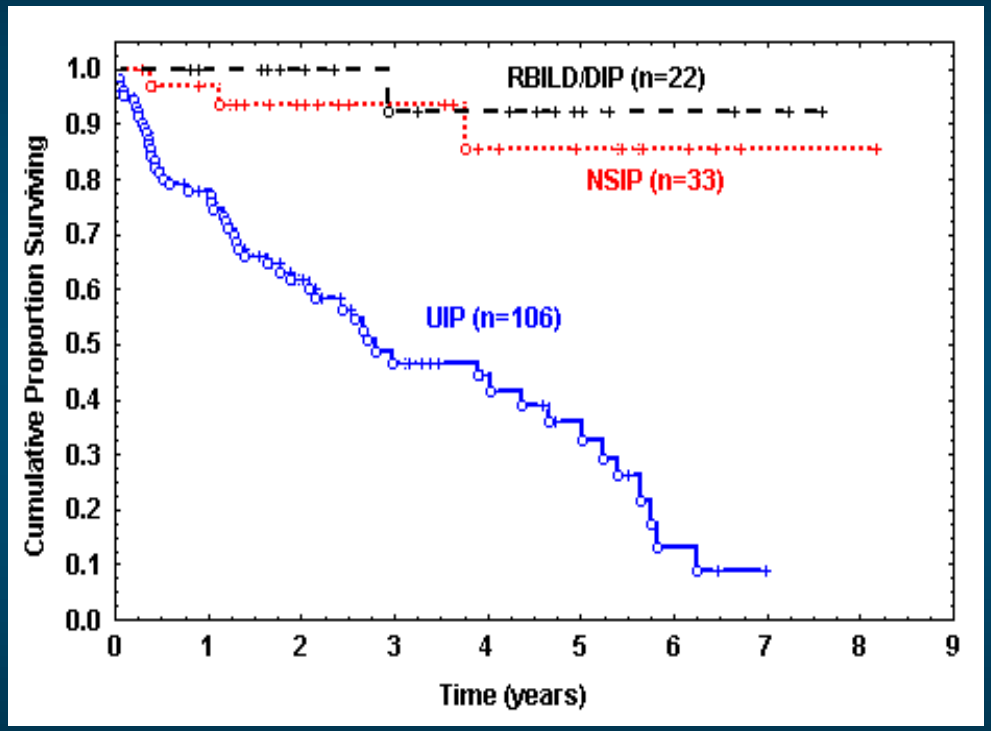
Weill Cornell Medical Center

University of Michigan Health System

Interstitial Lung Diseases - Difficulties

- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments

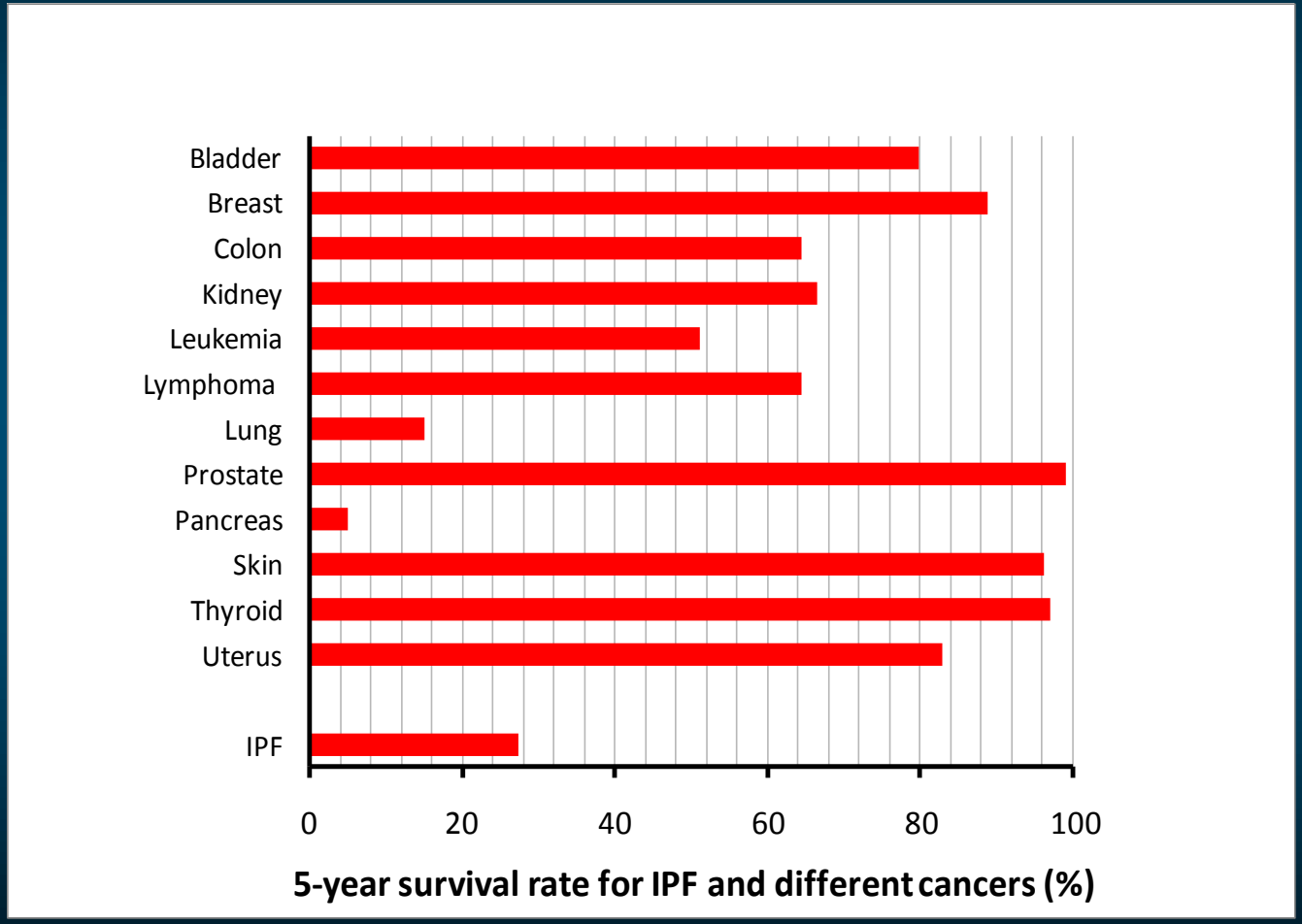
IPF confers a poor prognosis



Parameter	HR (95% CI)
IPF diagnosis	28.46 (5.5, 147)
Age	0.99 (0.95, 1.03)
Female sex	0.31 (0.13, 0.72)
Smoker	0.30 (0.13, 0.72)
Physio CRP	1.06 (1.01, 1.11)
Onset Sx (yrs)	1.02 (0.93, 1.12)
CTfib score $\geq$2	0.77 (0.29, 2.04)

Flaherty et al. *Eur Respir J*. 2002;19:275-283.

Five year survival of IPF is worse than most cancers



Vancheri et al., *Eur Respir J* 2010; 35: 496-504

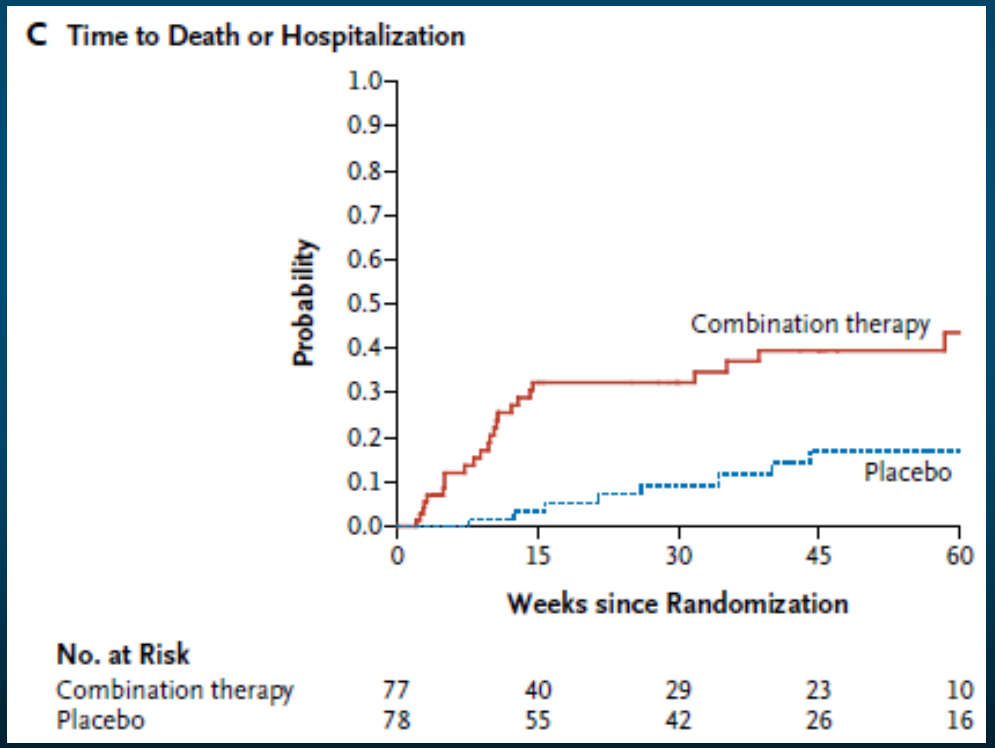
ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

- Interim Analysis with 50% data
  - Combination n = 77, Placebo n= 78
  - Increased Death 8 vs 1, p=0.01
  - Increased Hosp 23 v 7, p<0.001
  - No physio/clinical benefit

- Termination of combination therapy at mean of 32 weeks
- Recommendation against use of pred/azthioprine/N-acetyl cysteine



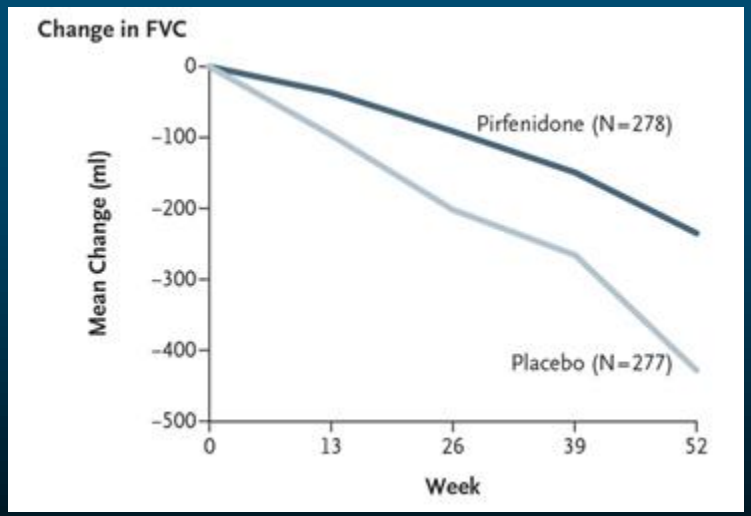
Raghu et al. *N Engl J Med* 2012; 366:1968-71

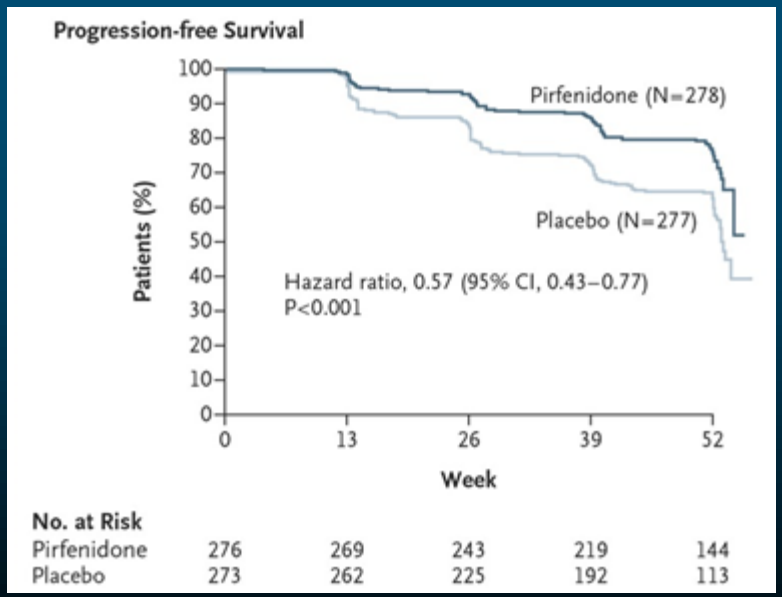
ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

Narrowly defined mild to moderate IPF without COPD





King TE Jr et al. **NEJM 2014; 370: 2083-92**

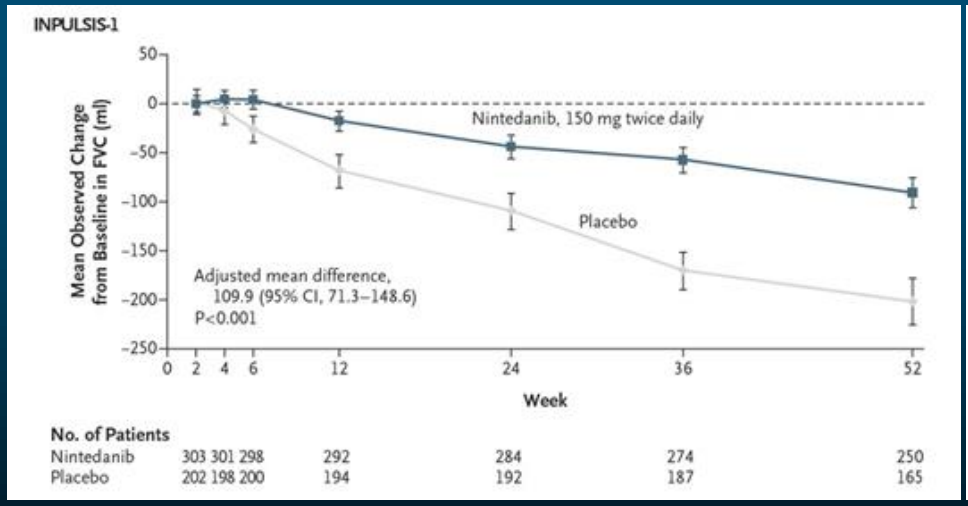
The NEW ENGLAND JOURNAL of MEDICINE

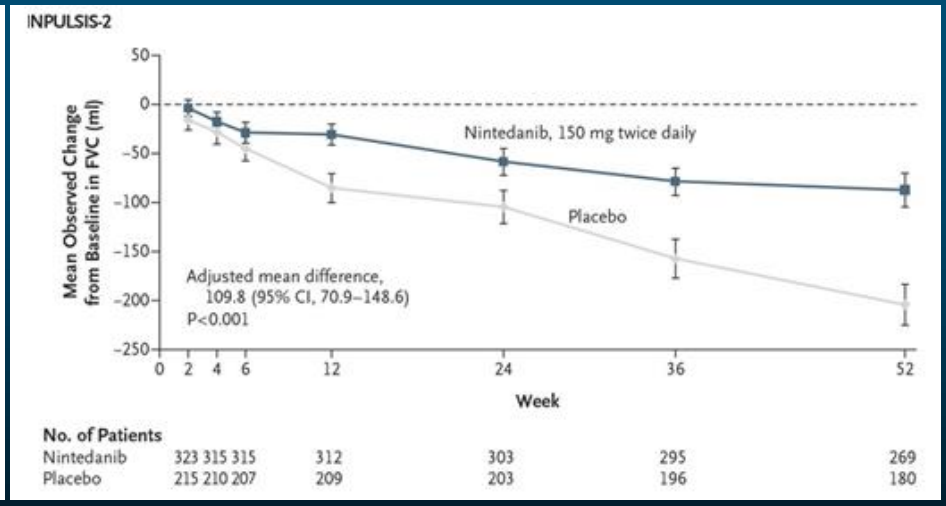
ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

Mild to moderate IPF





Richeldi L et al. **NEJM 2014; 370: 2071-82**


Chelmsford (A 414)
Chipping Ongar A 128
Brentwood
Kelvedon Hatch A 128
Industrial Estates
Secret Nuclear Bunker

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

This Official Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) Was Approved by the ATS Board of Directors, November 2010, the ERS Executive Committee, September 2010, the JRS Board of Directors, December 2010, and the ALAT Executive Committee, November 2010

This Statement has been formally endorsed by the Society of Thoracic Radiology and by the Pulmonary Pathology Society

Exclusion of other known causes of interstitial lung disease

Presence of UIP pattern on HRCT (in patients without surgical biopsy)

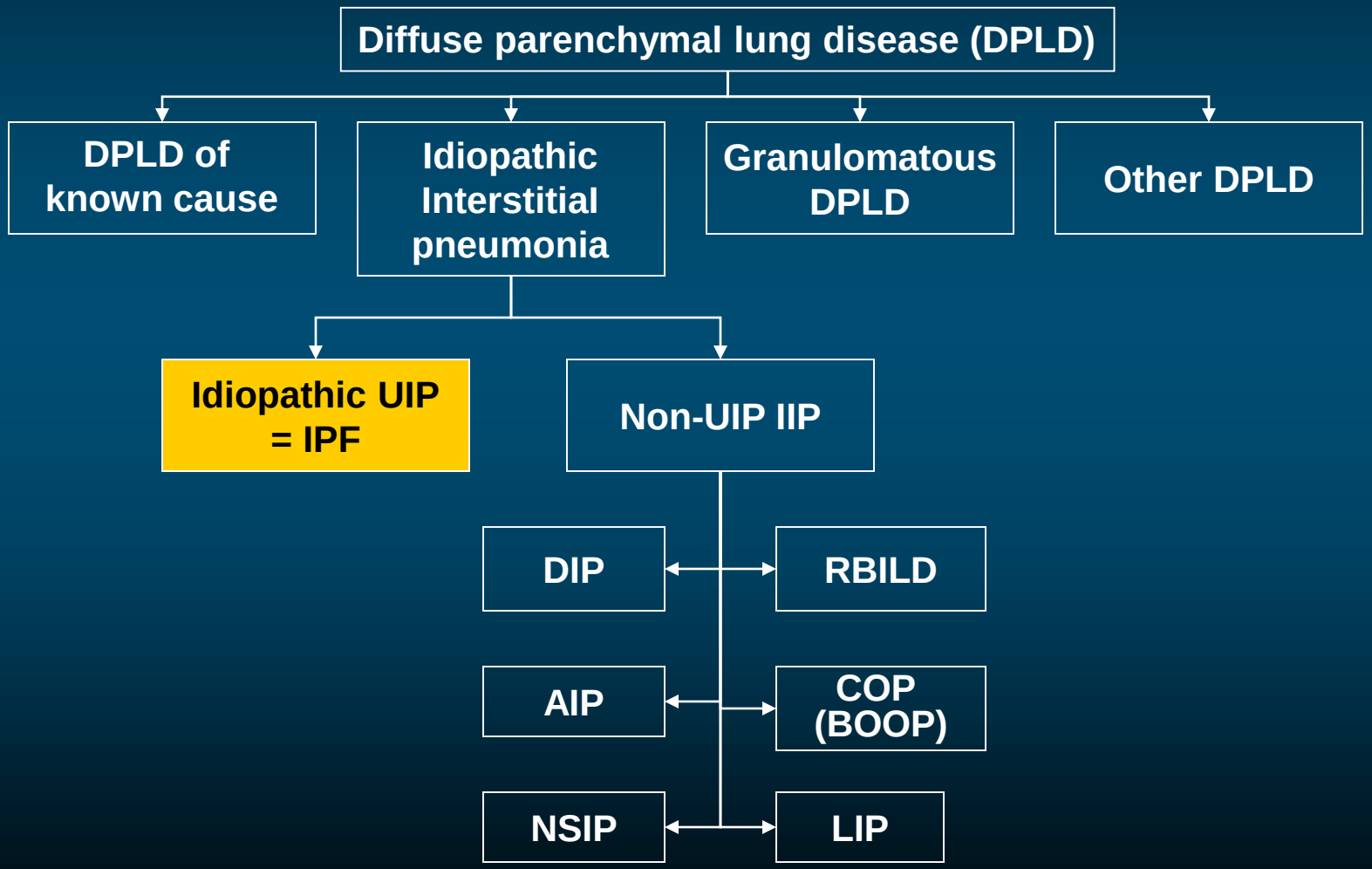
A HRCT pattern of definite/possible UIP with a Surgical lung biopsy showing Definite/Probable UIP

The Major and Minor Criteria proposed in the

2000 ATS/ERS Consensus Statement were Eliminated

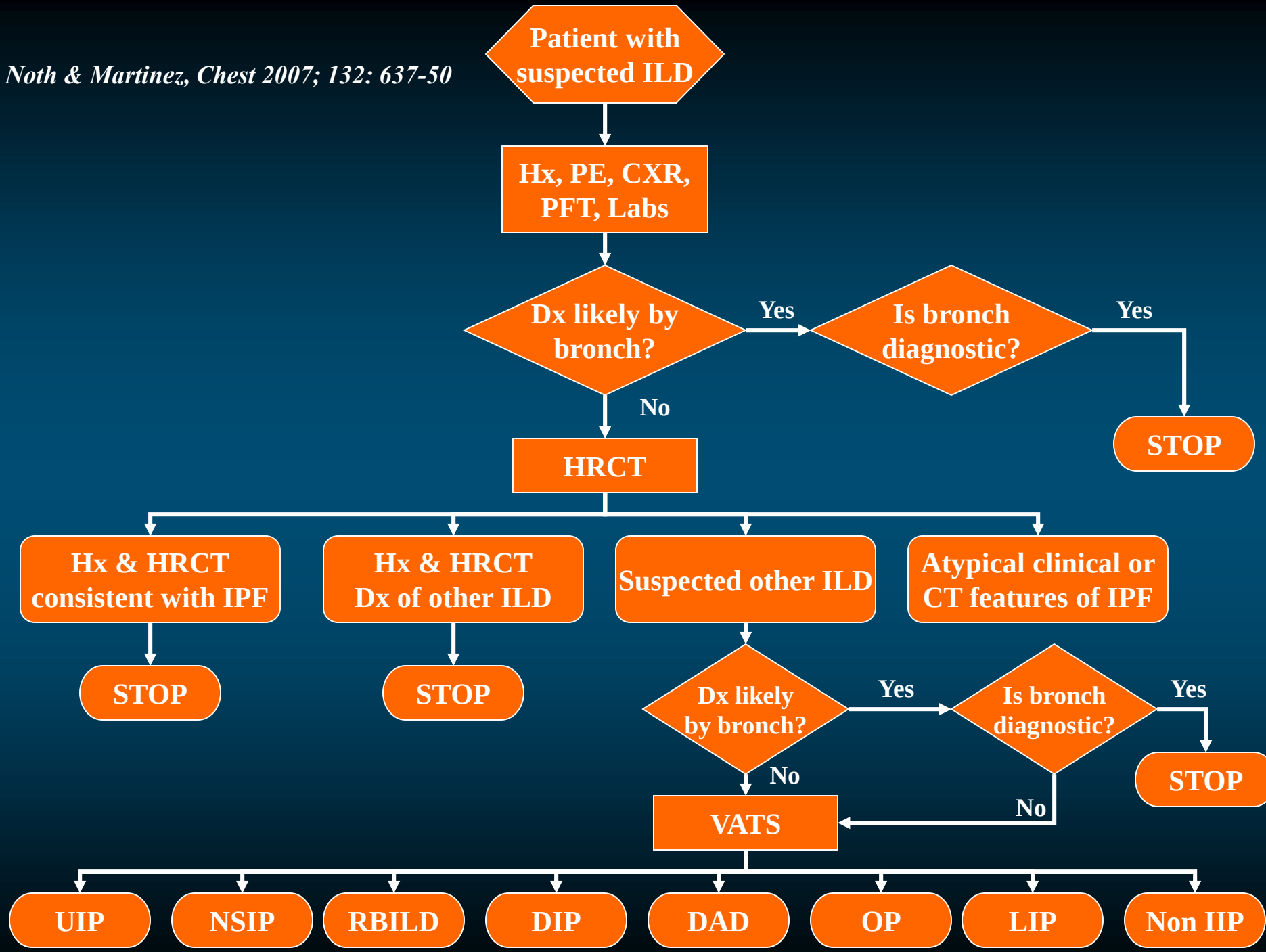
Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788-24

Classification of Diffuse Parenchymal Pulmonary Disorders



American Thoracic Society. *Am J Respir Crit Care Med.* 2002;165:277-304.

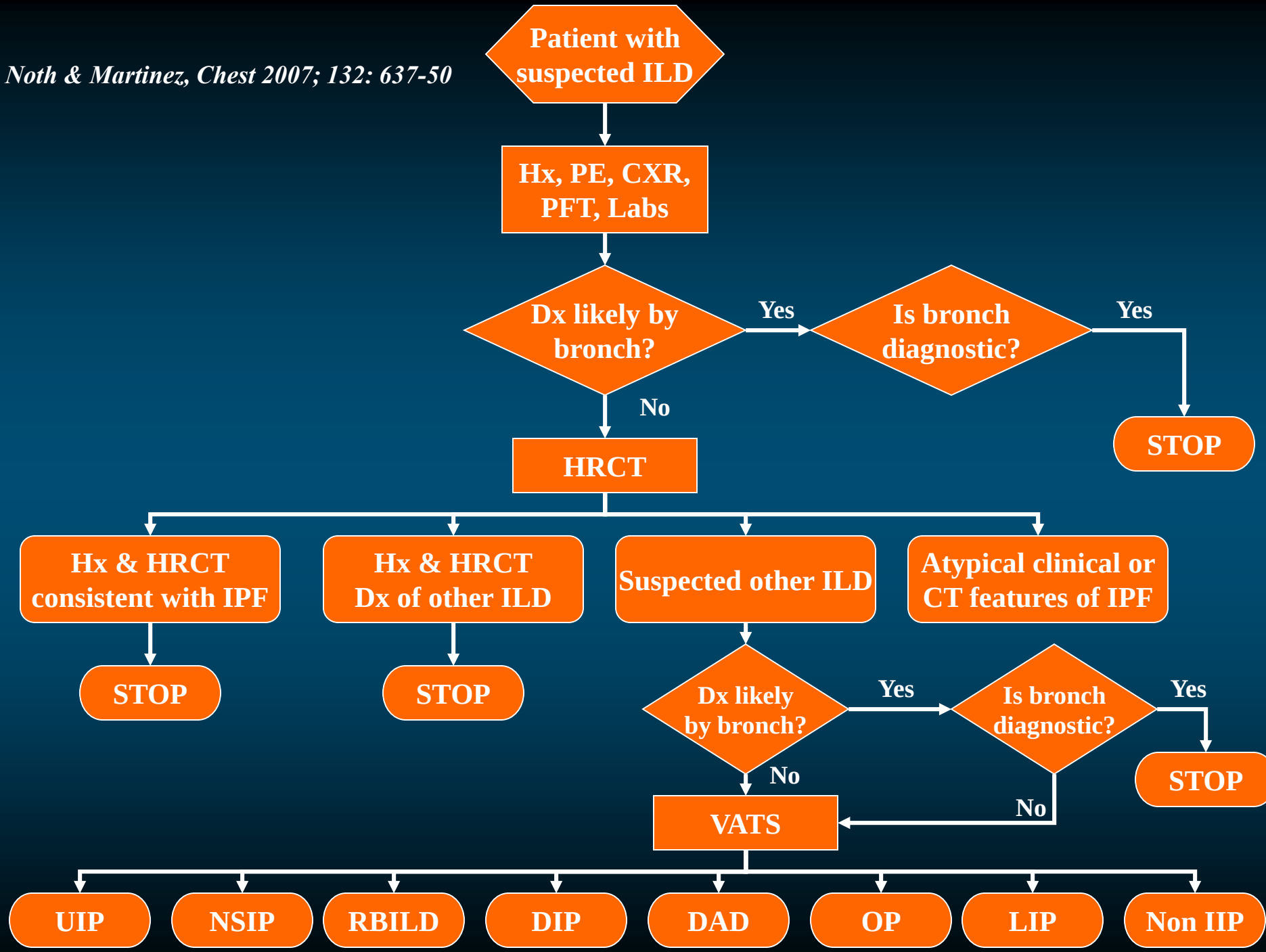
Noth & Martinez, Chest 2007; 132: 637-50



Accuracy of diagnosis of UIP

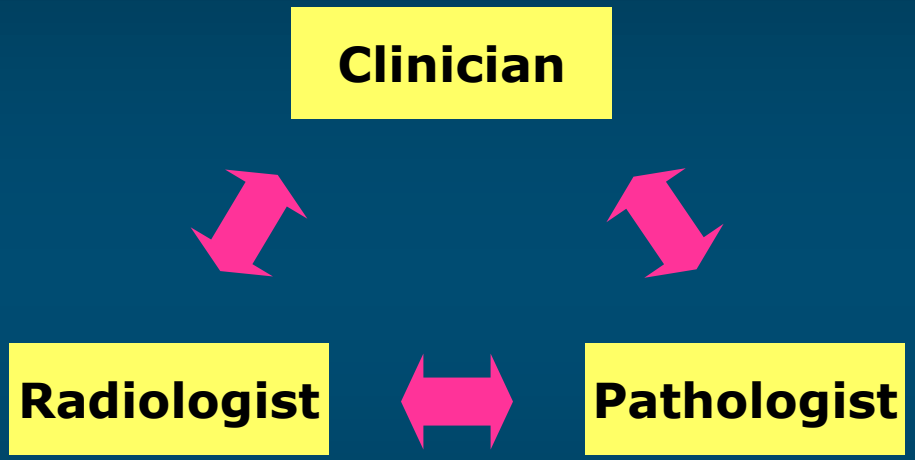
Study	Correctness of first choice diagnosis	Correctness of confident first choice	% of UIP cases with confident diagnosis
Mathieson	**89%**	**95%**	**72%**
Lee	**88%**	**100%**	**71%**
Swensen	**89%**	**100%**	**67%**
Hunninghake	**85%**	**96%**	**48%**

Noth & Martinez, Chest 2007; 132: 637-50




HORSE KILLED
11:11 41 °

The Clinical Radiographic and Pathologic Diagnosis of IIP: Clinical Gold Standard

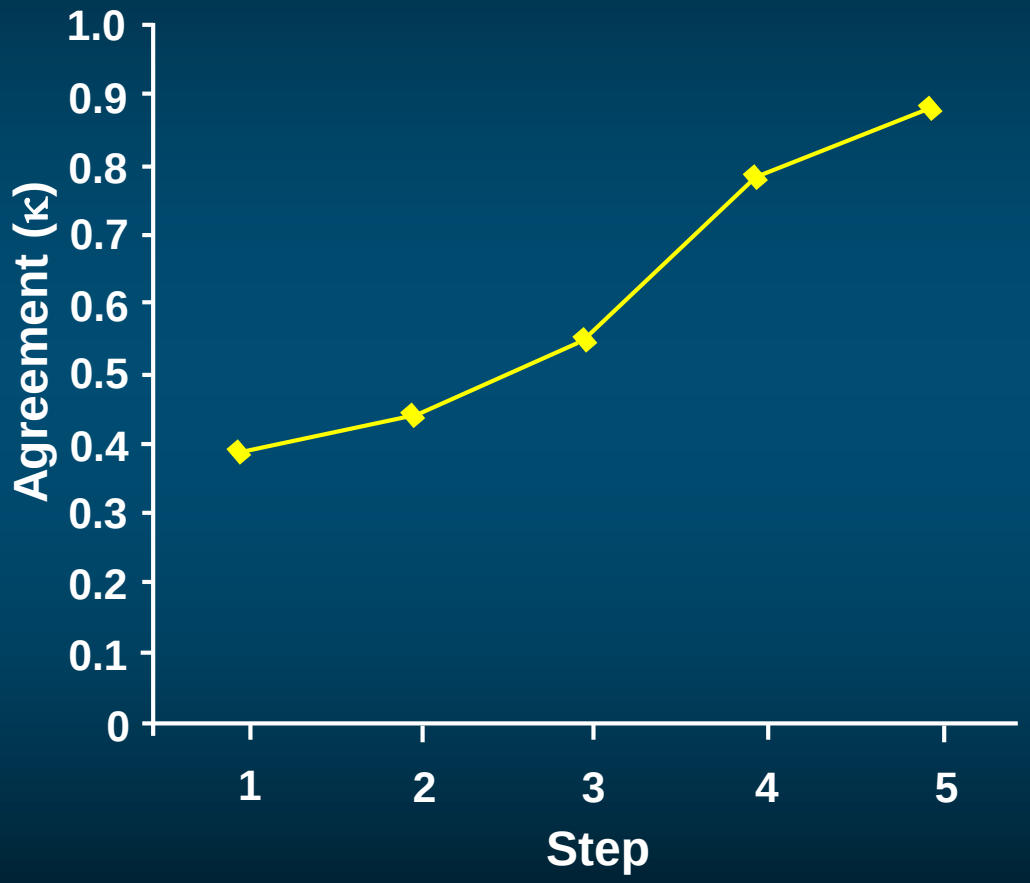


Multidisciplinary communication is essential to an accurate diagnosis

Raghu **et al.,** ***Am J Respir Crit Care Med*** **2011; 183:788-24**

Clinico/Radiological/Pathological Evaluation of 79 Consecutive IIP Patients

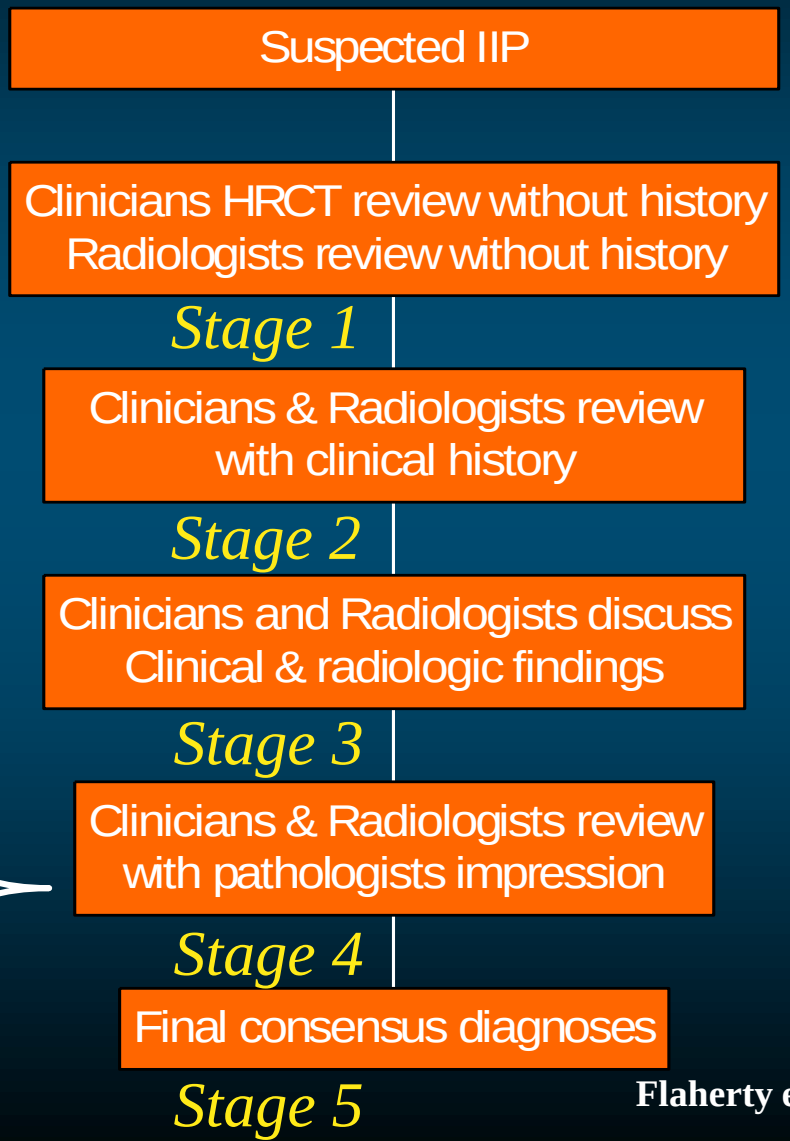
Step	Assessment Method	Information Provided
1	Individual	HRCT
2	Individual	HRCT, clinical data
3	Group	HRCT, clinical data
4	Group	HRCT, clinical data, SLB
5	Consensus	HRCT, clinical data, SLB



Flaherty KR, et al. *Am J Respir Crit Care Med.* 2004;170:904-910.

Clinico/Radiological/Pathological Evaluation:
The new gold standard?

Talmadge King
Ganesh Raghu
Kevin Brown
Athol Wells
Ron DuBois
Victor Thannickal
James Vyskocil
Frazier Wadenstorer
Jeffrey Wilt

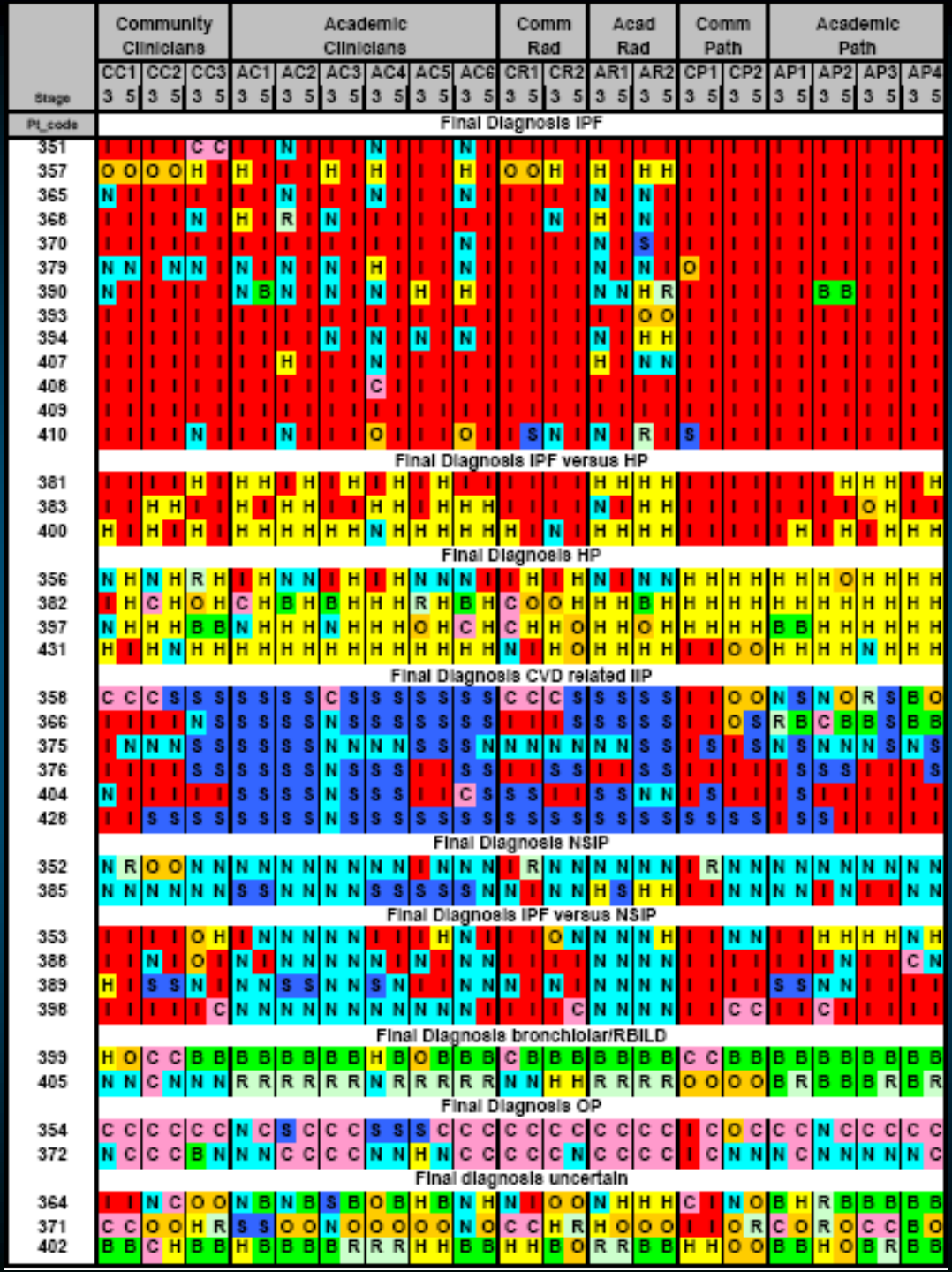


Ella Kazerooni
David Lynch
Jeffrey Quick
Edmund Louvar

William Travis
Thomas Colby
Andrew Flint
Andrew Nicholson
N. Basily
Robert Knapp

Flaherty et al., ***Am J Respir Crit Care Med. 2007; 175: 1054-60***

Academic Community Agreement

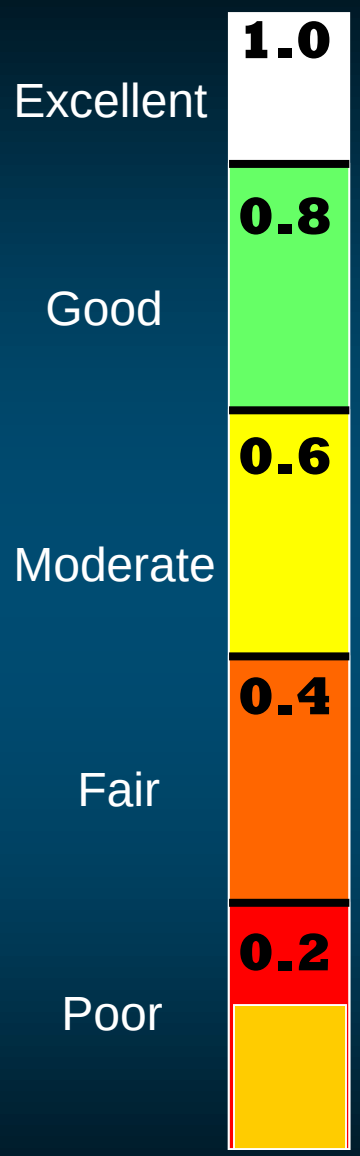


Flaherty et al., ***Am J Respir Crit Care Med. 2007; 175: 1054-60***

Final Dx Kappa – Academic radiologists compared with community-based radiologists

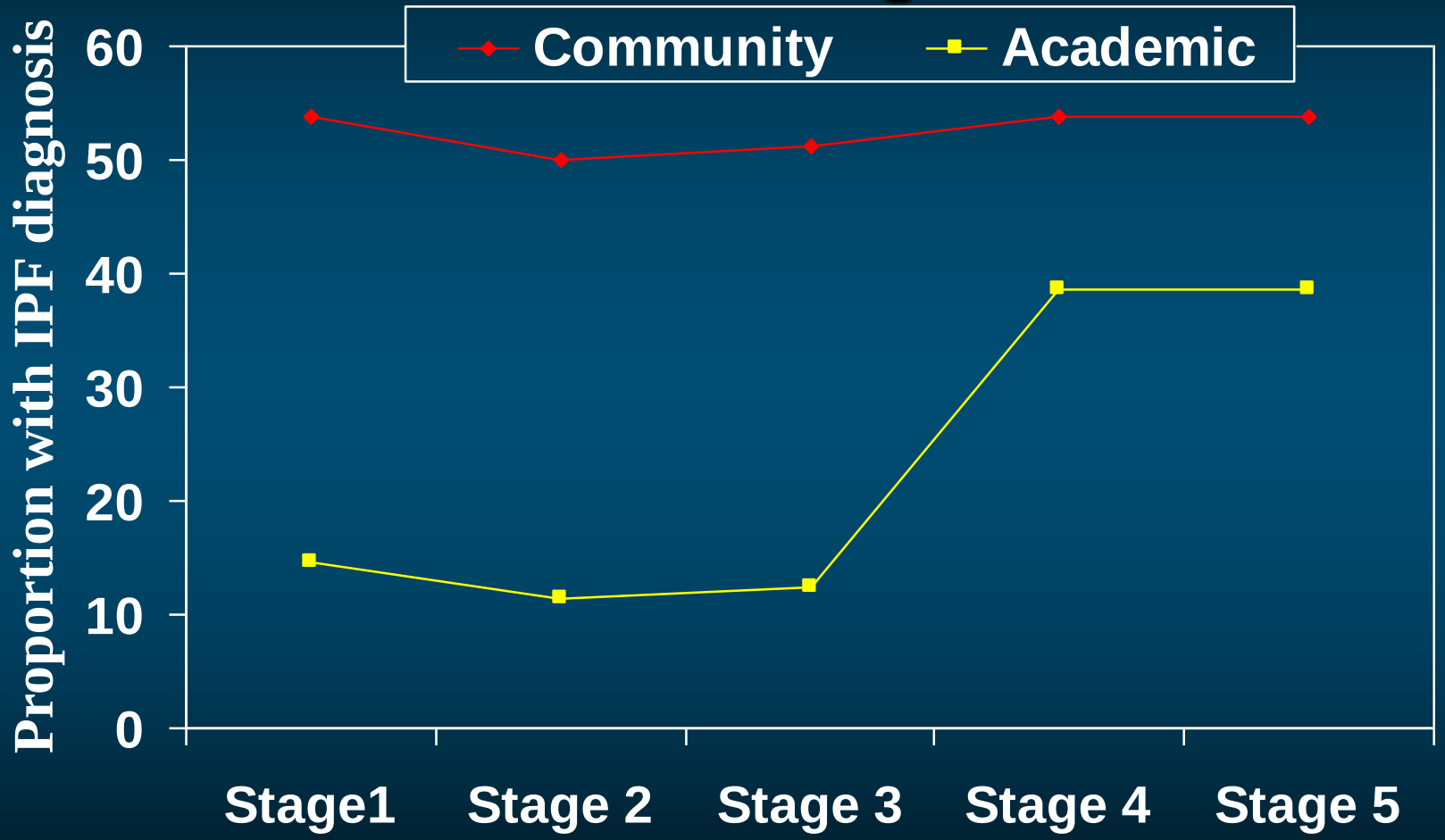
Academic Radiologist Kappa 0.55
Community Radiologist Kappa 0.32

	Academic 1	Academic 2
Community 1	0.24	0.34
Community 2	0.11	0.23



Flaherty et al., *Am J Respir Crit Care Med. 2007; 175: 1054-60*

Clinico/Radiological/Pathological Evaluation: *Radiologists*



Flaherty KR, et al. *Am J Respir Crit Care Med.* 2004;170:904-910.

Final Dx Kappa - Pathologists

Academic Pathologists Kappa 0.57
Community Pathologists Kappa 0.41

	Acad 1	Acad 2	Acad 3	Acad 4
Comm 1	0.39	0.12	0.26	0.23
Comm 2	0.47	0.46	0.48	0.46

Flaherty et al., *Am J Respir Crit Care Med. 2007; 175: 1054-60*

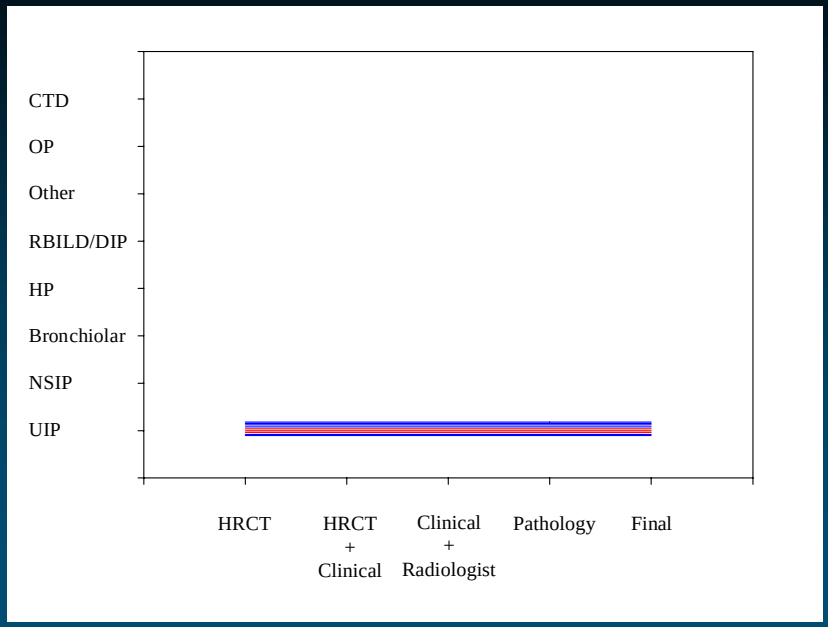
Final Dx Kappa - Clinicians

Academic Clinicians Kappa 0.71
Community Clinicians Kappa 0.44

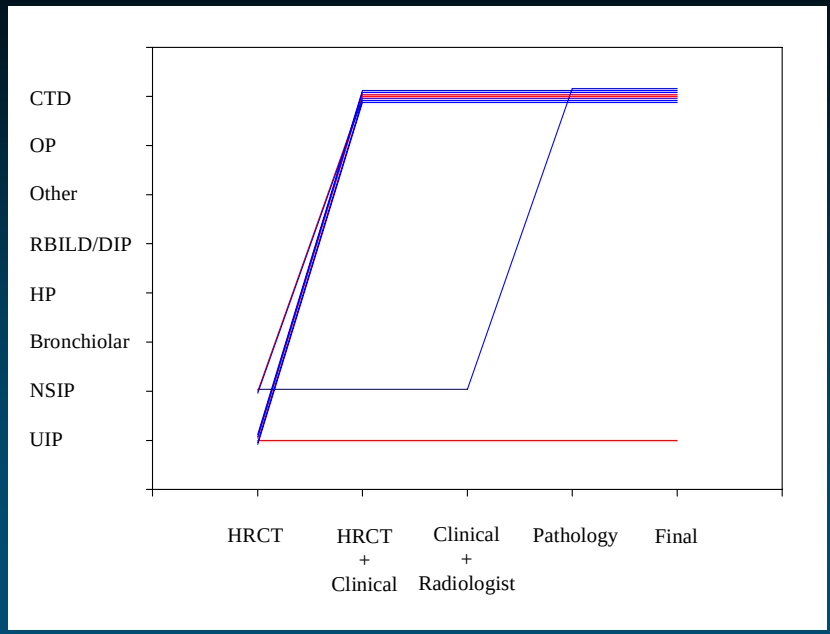
	Acad 1	Acad 2	Acad 3	Acad 4	Acad 5	Acad 6
Comm 1	0.22	0.28	0.20	0.21	0.35	0.21
Comm 2	0.39	0.38	0.38	0.39	0.50	0.25
Comm 3	0.23	0.33	0.28	0.26	0.36	0.26

Flaherty KR, et al. *Am J Respir Crit Care Med.* 2004;170:904-910.

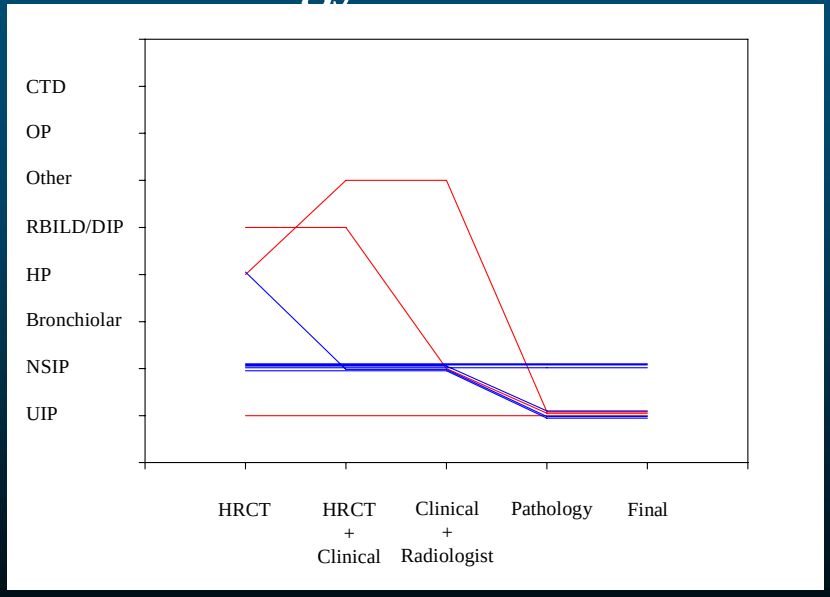
Unanimous agreement



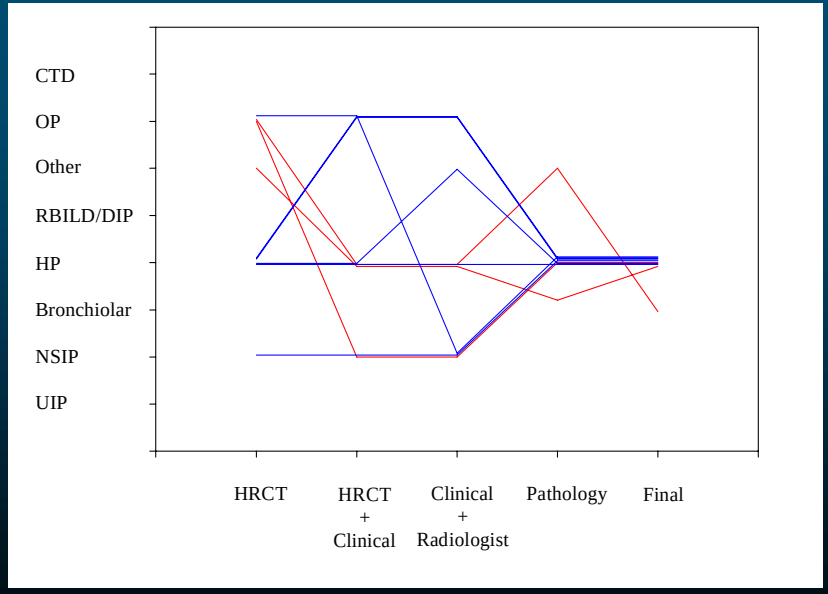
Clinical info influence



Pathology info influence

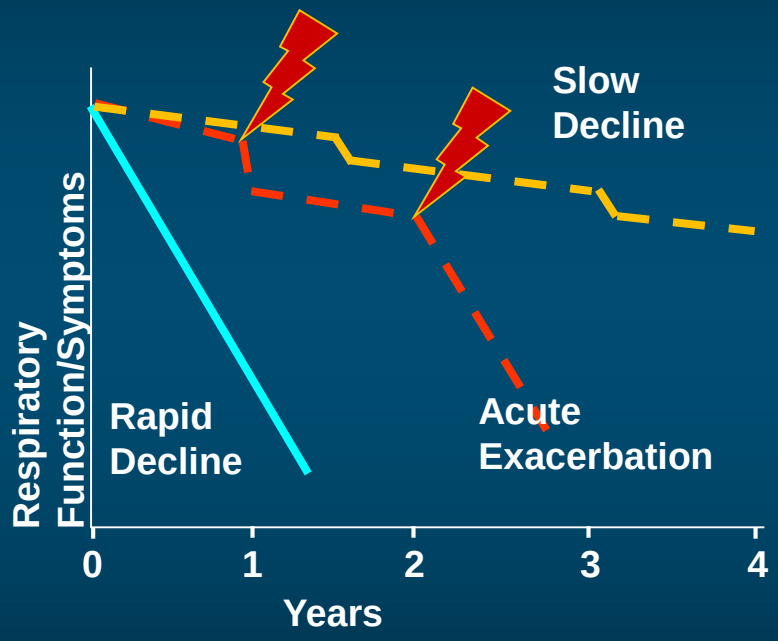


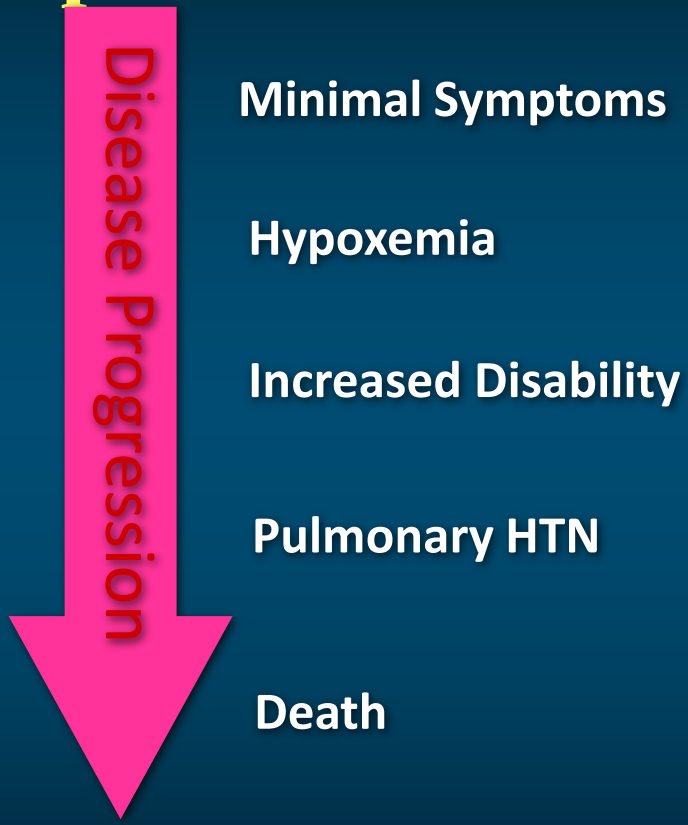
The usual result



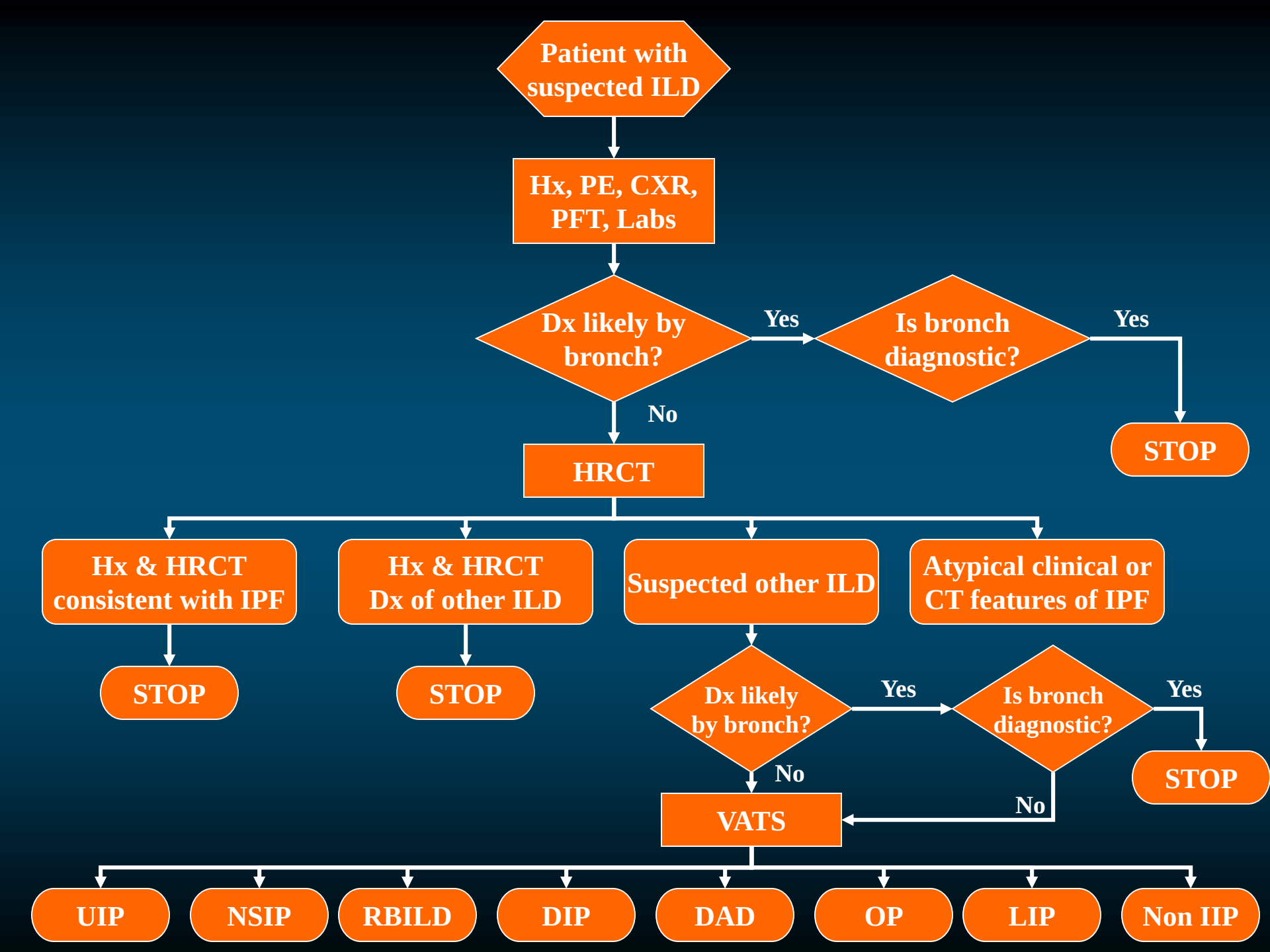

THIS WAY
OUT

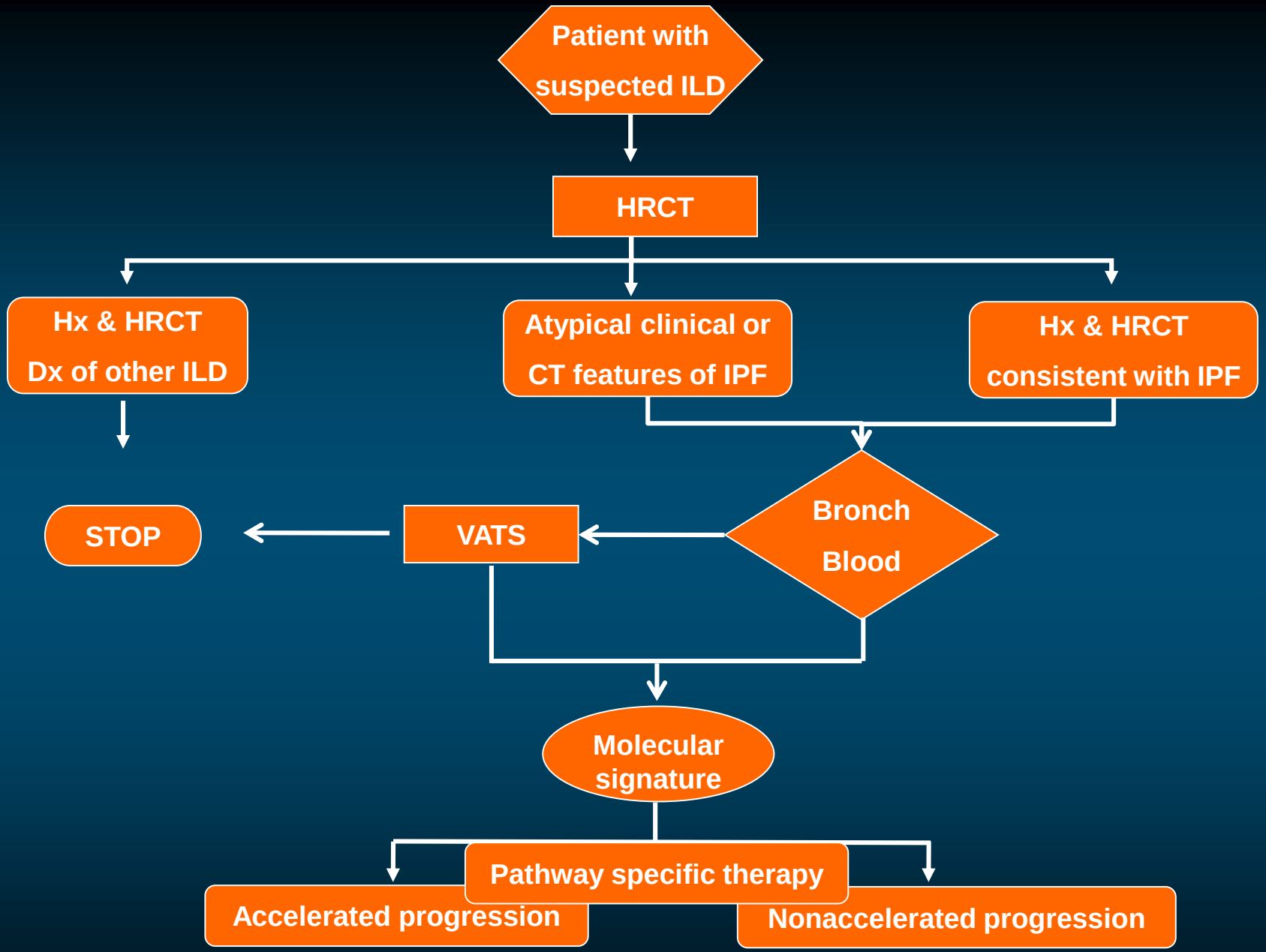
Disease Progression in IPF is Variable and often Unpredictable





Kim DS, et al. *Proc Am Thoracic Soc*. 2006;3:285-292.


Patient with suspected ILD
Hx, PE, CXR, PFT, Labs
Dx likely by bronch?
Yes
Is bronch diagnostic?
Yes
STOP
No
HRCT
Hx & HRCT consistent with IPF
Hx & HRCT Dx of other ILD
Suspected other ILD
Atypical clinical or CT features of IPF
STOP
STOP
Dx likely by bronch?
Yes
Is bronch diagnostic?
Yes
STOP
No
No
VATS
UIP
NSIP
RBILD
DIP
DAD
OP
LIP
Non IIP


Patient with suspected ILD
HRCT
Hx & HRCT Dx of other ILD
Atypical clinical or CT features of IPF
Hx & HRCT consistent with IPF
STOP
VATS
Bronch Blood
Molecular signature
Pathway specific therapy
Accelerated progression
Nonaccelerated progression


STOP

Investor Day
October 9, 2014