Developing clinically useful genomic tests

That change what happens next for patients

... patients like Ashley
Five clinical indications
Addressing unmet needs throughout the care continuum

* Investigational product
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RNA = “The Living Genome”

- **Compare RNA-seq and DNA Whole Exome Seq (WES) in 17 lung cancer tissues**
  - Identify variants that are expressed or silent.
  - Also find allelic imbalance – alleles that are biased towards the variant or wild type allele
  - Somatic drivers like KRAS are found to be variant biased
  - Overall mutation rate of highly expressed genes is lower than non expressed genes (4 vs 14 mutations per Mbp), suggesting Transcription-coupled repair mechanism or other selection pressures
The “Unified Assay” RNA sequencing platform allows us to measure a rich source of transcript diversity

- Uses 425,437 enrichment probes to enable sequencing of 214,126 exons in 21,415 human genes
- The assay covers 98.3% of the RNA Exome
The power of RNA sequencing was needed in Afirma GSC

RNA Transcriptome Sequencing (aka RNaseq)
- protein-coding
- non-coding

**GENE EXPRESSION**

**SEQUENCE VARIANTS**
- AUUCGA
- UACAGU
- CGUAAC

**MITOCHONDRIAL GENOME**

**LOSS OF HETEROZYGOSITY**
- Normal: One copy from each parental chromosome
- Loss-Of-Heterozygosity (LOH): One copy from each parental chromosome

**FUSIONS**

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Improving patient outcomes from biological complexity

565k Patients evaluated for suspected thyroid cancer annually¹

>110,000 Diagnosis Uncertain¹

Benign
>91% sensitivity
Reduce unnecessary surgeries by identifying ~70% truly benign patients

Suspicious
Xpression Atlas
(BRAF, NTRK, RET, RAS, etc.)
Inform surgery and treatment decisions

¹ Company estimates
Algorithmic approach needs to fit the problem

**Simple Biology**

- Strong, unique signature

**Complex Biology**

- Diverse and complex signature
Afirma GSC utilizes >10,000 genes among multiple classifiers

**PARATHYROID**
mRNA expression

**MTC**
mRNA expression

**BRAF**
mRNA expression + Variants

**RET/PTC FUSION**
Fusion Transcripts

**FOLLICULAR CONTENT INDEX**
mRNA expression

**ENSEMBLE MODEL**
mRNA expression

**HÜRTHLE CELL INDEX**
mRNA expression + Mitochondrial Transcripts

**HÜRTHLE NEOPLASM INDEX**
mRNA expression + Chromosomal Level Loss of Heterozygosity

**Initial Classifiers**
identify rare neoplasms and lesions with >95% risk of malignancy for more informed treatment decisions

**Follicular Content Index**
identifies samples with sufficient follicular content

**Ensemble Classifier**
leverages multiple algorithms to derive the final benign or suspicious result

**Hürthle Classifiers**
enable correct classification of significantly more Hürthle cell lesions as benign

Afirma GSC was validated on 191 of the 210 samples with remaining RNA from Alexander EK, et al. *NEJM* 2012

Four key elements should be considered in clinical validation studies:

- **BLINDED**
- **REPRESENTATIVE**
- **MULTICENTER**
- **PROSPECTIVE**


Clinical evidence is essential for adoption and reimbursement

Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study

Prof Ganesh Raghu, MD  Prof Kevin R Flaherty, MD  Prof David J Lederer, MD  Prof David A Lynch, MBChB  Prof Thomas V Colby, MD  Prof Jeffrey L Myers, MD  et al.  Show all authors

A Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer

Cecilia A. Silvestri, M.D., Anil Vachani, M.D., Duncan Whitney, Ph.D., Ed Persson, Ph.D., Amanda Mitro, Ph.D., Edith Quan, M.D., Scott Ferguson, M.D., and Aartje Spaz, M.D., for the AEGIS Study Team
Applying the model to Lung Cancer
Early detection of lung cancer improves survival

5-YEAR SURVIVAL RATE SIGNIFICANTLY HIGHER WHEN LUNG CANCER DETECTED AT A LOCAL STAGE

NATIONAL LUNG SCREENING TRIAL DEMONSTRATED 20% MORTALITY REDUCTION WITH CT SCREENING

The NEW ENGLAND JOURNAL of MEDICINE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team

2. Aberde et al. NEJM 2011
Noninvasive nasal swab test based on “Field of Injury” science
NASAL SWAB CLASSIFIER

New risk assessment & diagnostic approach to improve standard of care

750,000 patients with suspicious nodules* are sent to Pulmonologist for workup (~25% risk of cancer)

High Risk
Send patient directly to Surgery and/or Treatment

Intermediate Risk
Conduct Bronchoscopy

Low Risk
Monitor with Low Dose CT

Planned launch in 2021

* Suspicious nodules include LungRADS3, 4 nodules and Intermediate/High risk nodules
1 Cancer Epidemiol Biomarkers Prev. 2012 July ; 21(7): 1049–1059. doi:10.1158/1055-9965.EPI-12-0343
3 Gould et al., ATS Journal, 2015
### Training: 411 patients

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<th>Sub-category</th>
<th>Benign</th>
<th>Malignant</th>
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### Independent Test Set: 261 patients

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Subsequent Independent Test Set Performance using Classifier with two cut-offs:

**Sensitivity > 96% for Classification as Low Risk**

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<th>Sensitivity</th>
<th>Specificity</th>
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<td>All (N=261)</td>
<td>96.6% [93.1 – 98.6]</td>
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**Specificity > 94% for Classification as High Risk**

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<td>All (N=261)</td>
<td>50.0% [42.9– 57.1]</td>
<td>94.7% [85.4 – 98.9]</td>
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Test performance is optimized for desired outcome to avoid:

Test with HIGH SPECIFICITY (98%)
But LOW SENSITIVITY (50%)

- 30% Cancer prevalence
- Post CT today

Positive results – 50% of cancers - 2% FP
Negative results – 50% FN

Test with HIGH SENSITIVITY (98%)
But LOW SPECIFICITY (50%)

- Positive results – 50% FP
- Negative results – 2% FN

Dx Workup
No Workup

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NASAL SWAB CLASSIFIER
New risk assessment & diagnostic approach to improve standard of care

1.6m
Incidentally detected by imaging

10m
Eligible for Lung Cancer Screening Low Dose CT (only 1.2m currently screened)

750,000 patients with suspicious nodules* are sent to Pulmonologist for workup (~25% risk of cancer)

Nasal Swab

Planned launch in 2021

High Risk – ~50% of cancers classified with > 94% specificity (~100,000 pts)
Send patient directly to Surgery and/or Treatment

Intermediate Risk Reduced by 50% (~25-30% risk of malignancy)
Conduct Bronchoscopy (~60% inconclusive)

Low Risk – ~40% of benign nodules classified with >95% sensitivity (~250,000 pts)
Monitor with Low Dose CT

* Suspicious nodules include LungRADS3, 4 nodules and Intermediate/High risk nodules
1 Cancer Epidemiol Biomarkers Prev. 2012 July; 21(7): 1049–1059. doi:10.1158/1055-9965.EPI-12-0343
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