BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

Quantitative Assessment of Emphysema Progression

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HMS

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Brigham and Women's Hospital – The Lung Center

Disclosures

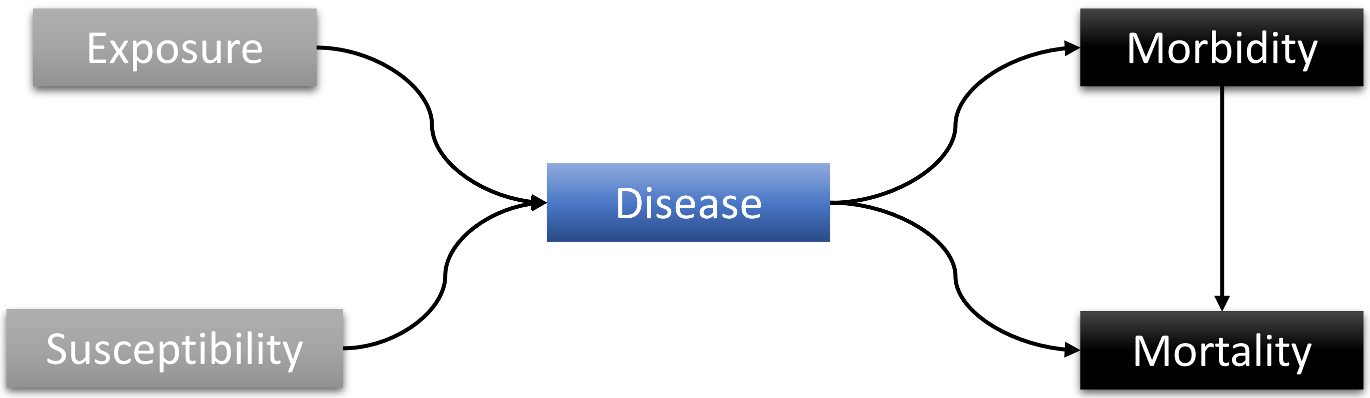
- Research funding
  - Pulmonary fibrosis foundation
  - NIH-NHLBI
- Other
  - Quantitative Imaging Solutions - scientific advisor/owner

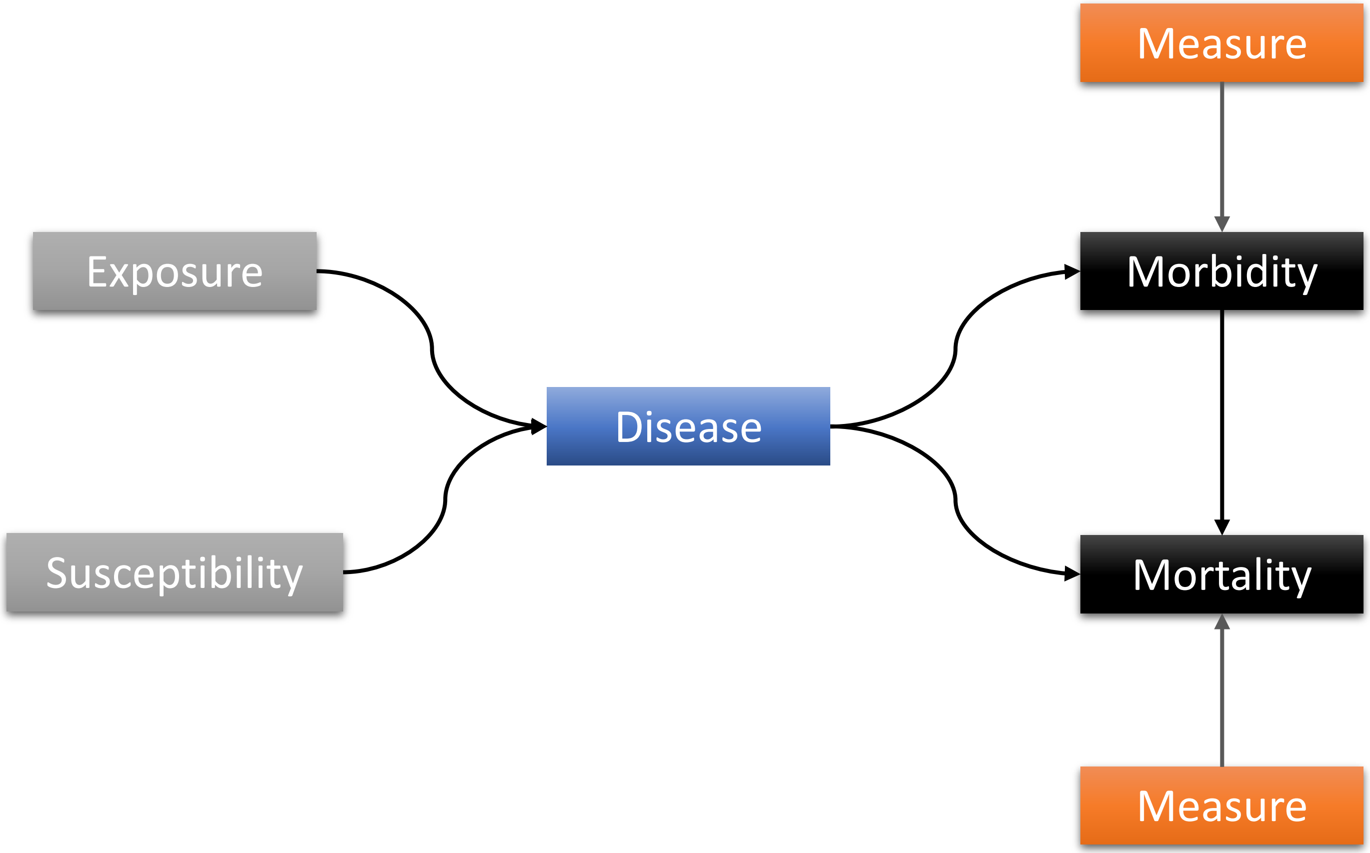
Background

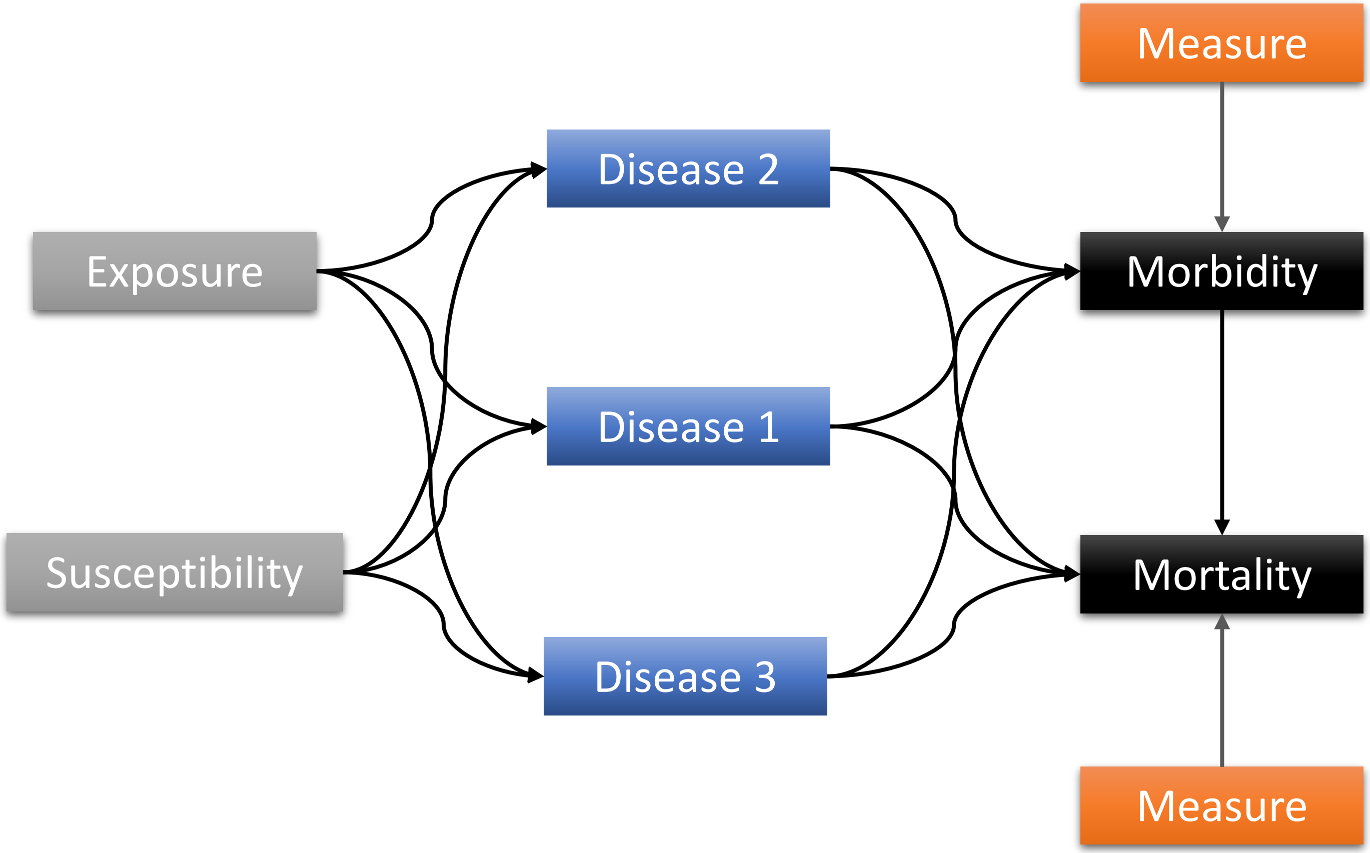
Roles for objective thoracic medical image analysis*

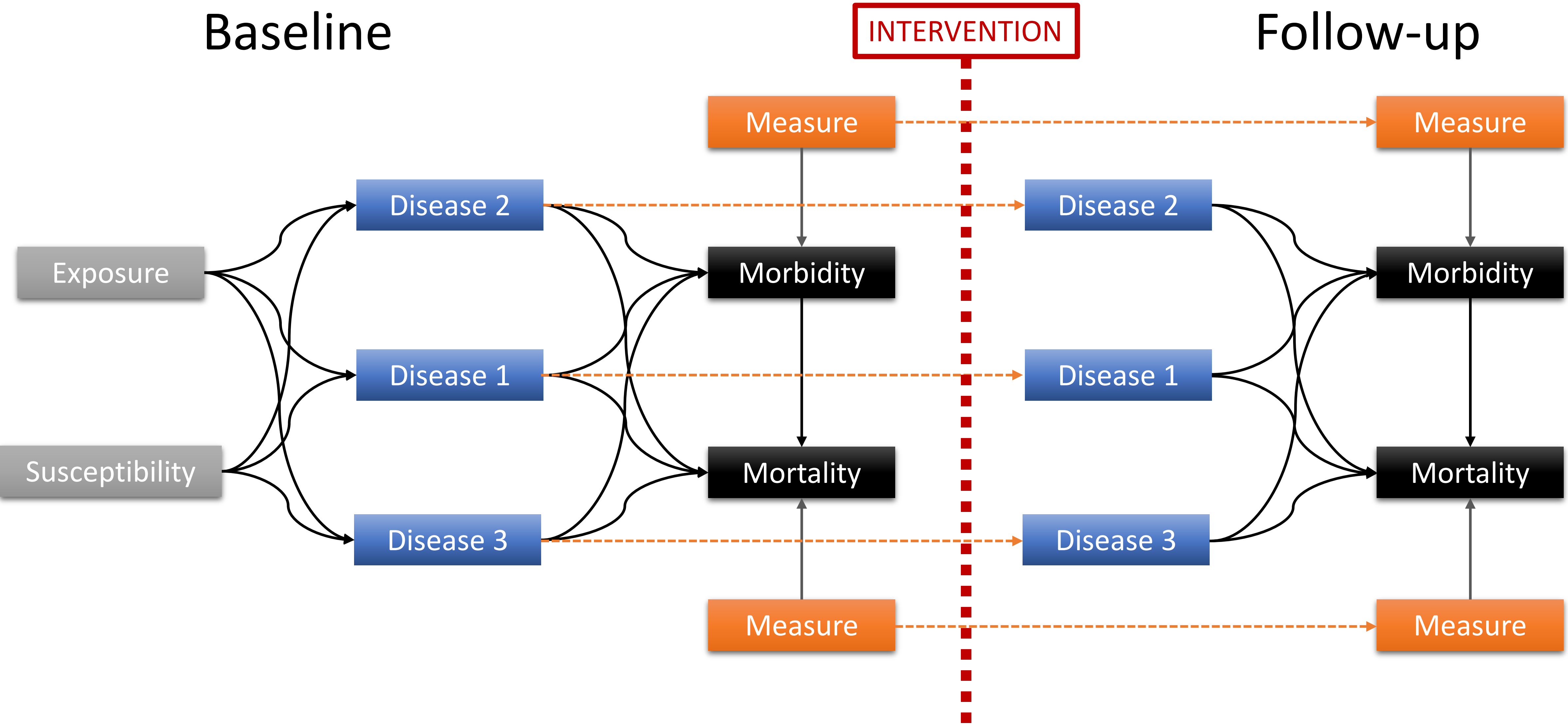
**an incomplete list*

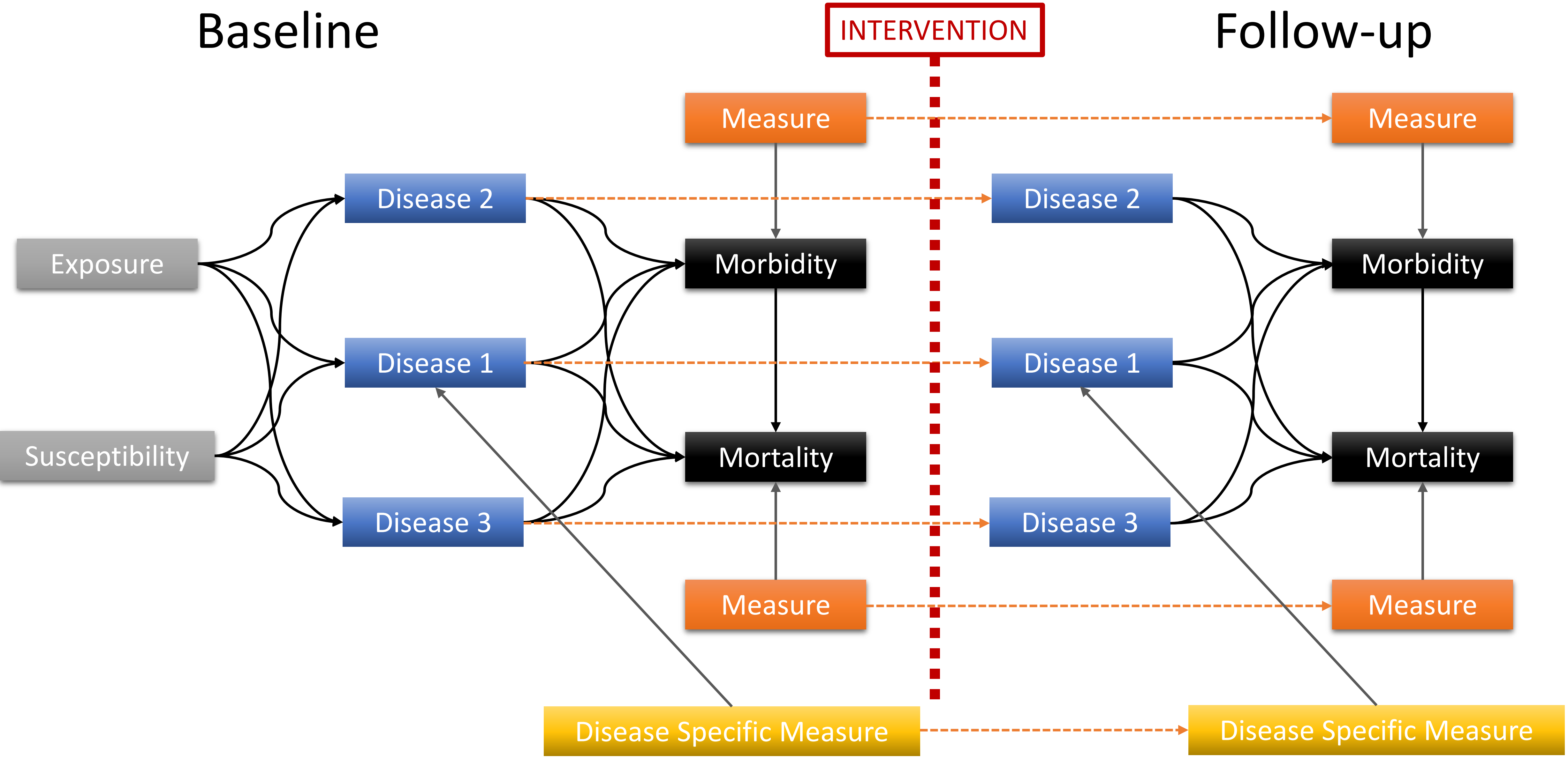
- *In vivo* understanding of structure/function and disease pathogenesis
- Disease diagnosis
  - Primary disease
  - Secondary diseases
- **Measurement of disease severity**
  - Cross sectional
  - **Longitudinal**
    - Response to therapy
- **Association with and prediction of outcomes**
  - Likelihood of response to intervention

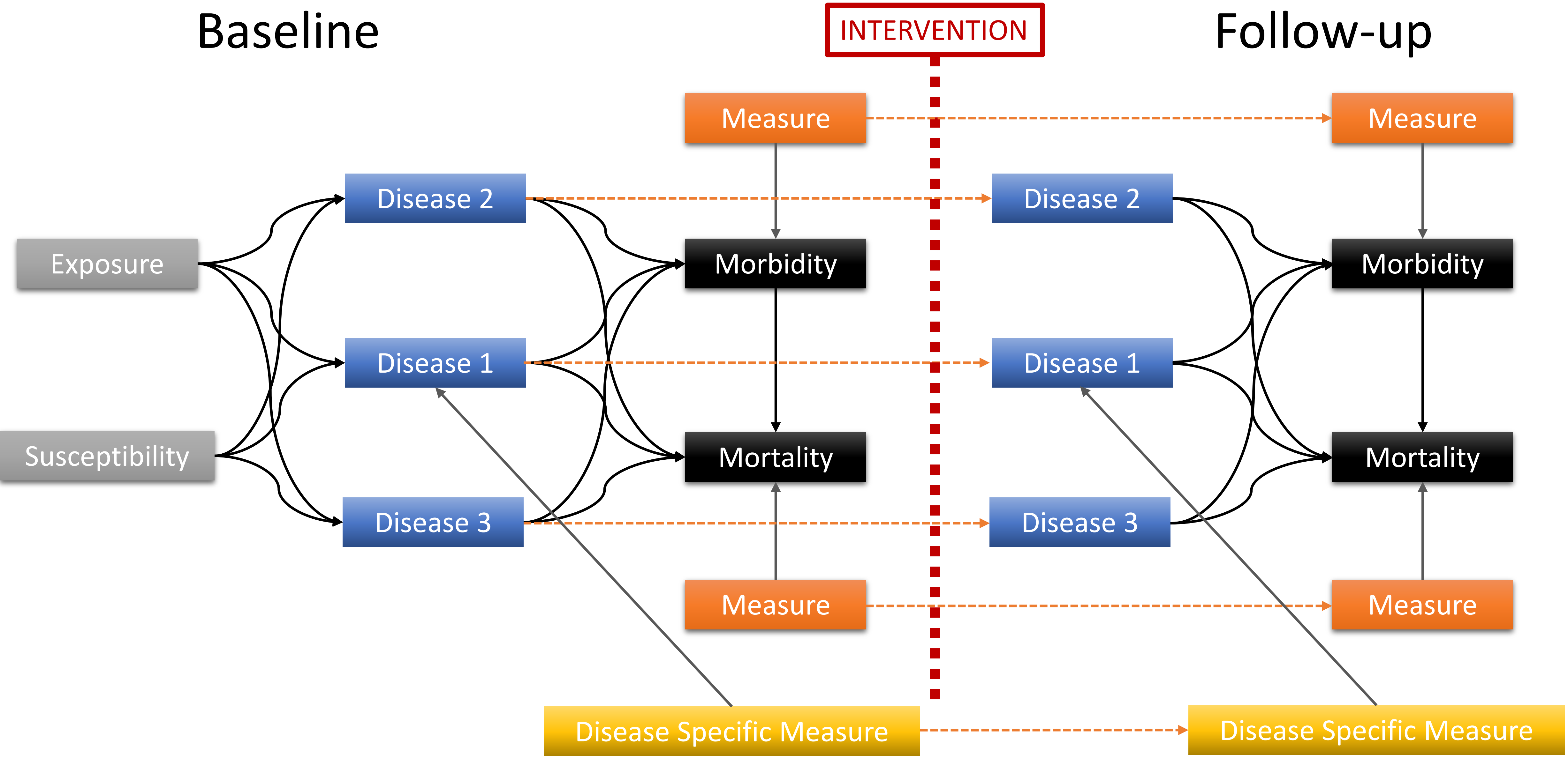

Exposure
Susceptibility
Disease
Morbidity
Mortality


Measure
Exposure
Morbidity
Disease
Susceptibility
Mortality
Measure


Measure
Disease 2
Exposure
Morbidity
Disease 1
Susceptibility
Mortality
Disease 3
Measure

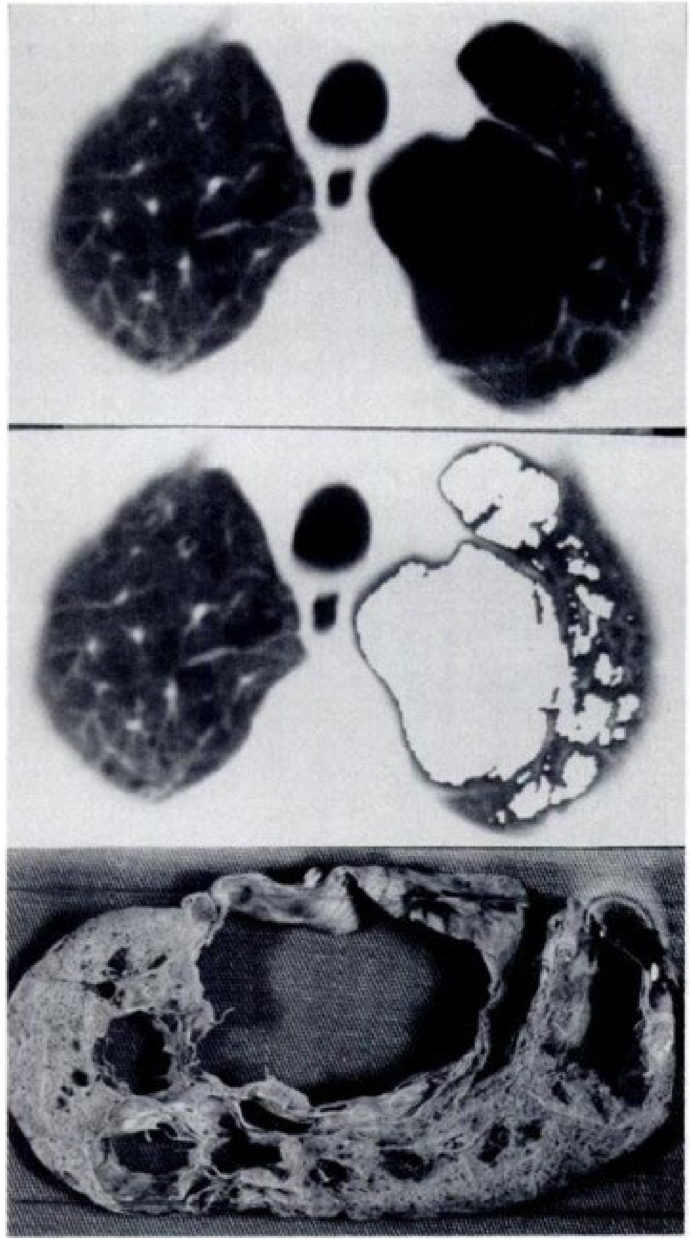

Baseline
INTERVENTION
Follow-up
Measure
Measure
Disease 2
Disease 2
Exposure
Morbidity
Morbidity
Disease 1
Disease 1
Susceptibility
Mortality
Mortality
Disease 3
Disease 3
Measure
Measure

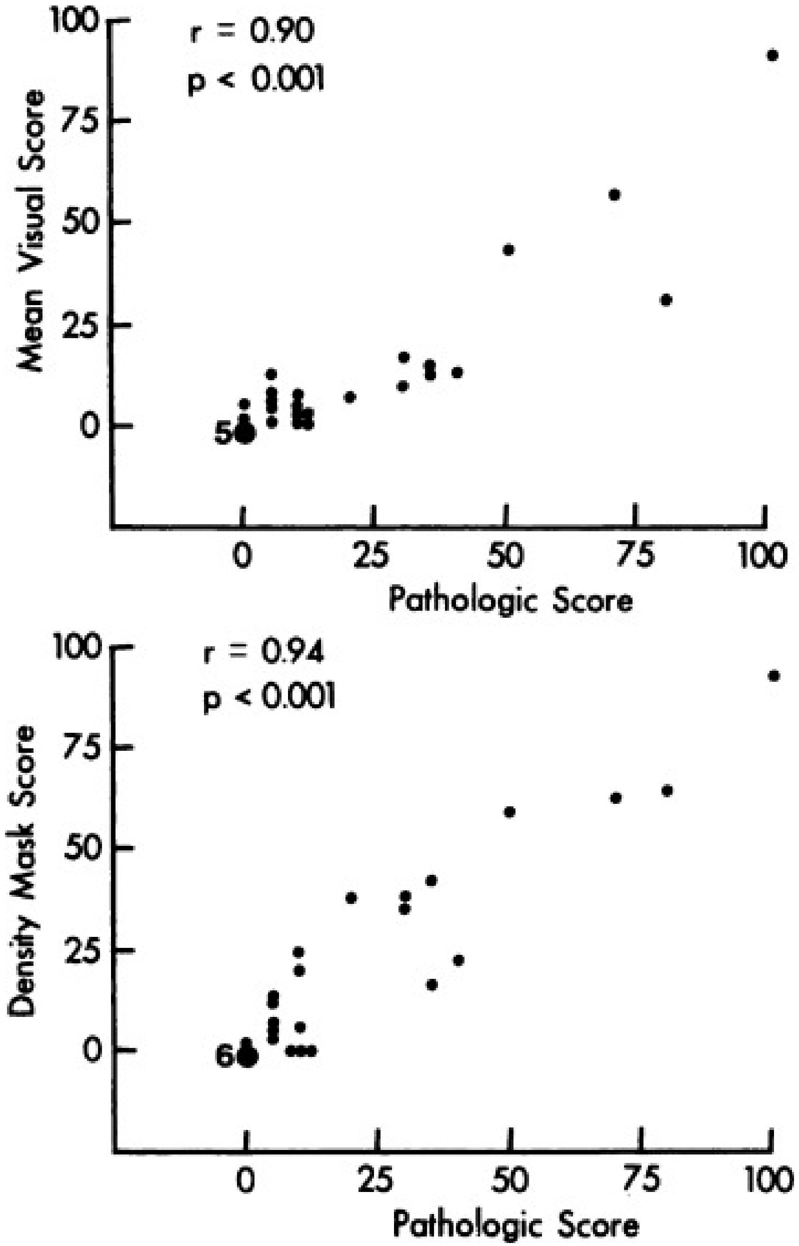

Baseline
INTERVENTION
Follow-up
Measure
Measure
Disease 2
Disease 2
Exposure
Morbidity
Morbidity
Disease 1
Disease 1
Susceptibility
Mortality
Mortality
Disease 3
Disease 3
Measure
Measure
Disease Specific Measure
Disease Specific Measure


Baseline
INTERVENTION
Follow-up
Measure
Measure
Disease 2
Disease 2
Exposure
Morbidity
Morbidity
Disease 1
Disease 1
Susceptibility
Mortality
Mortality
Disease 3
Disease 3
Measure
Measure
Disease Specific Measure
Disease Specific Measure

What is the clinical significance of this change?

Disease Specific Measure → Disease Specific Measure




r = 0.90
p < 0.001
Mean Visual Score
Pathologic Score
5
r = 0.94
p < 0.001
Density Mask Score
Pathologic Score
6

Muller 1988

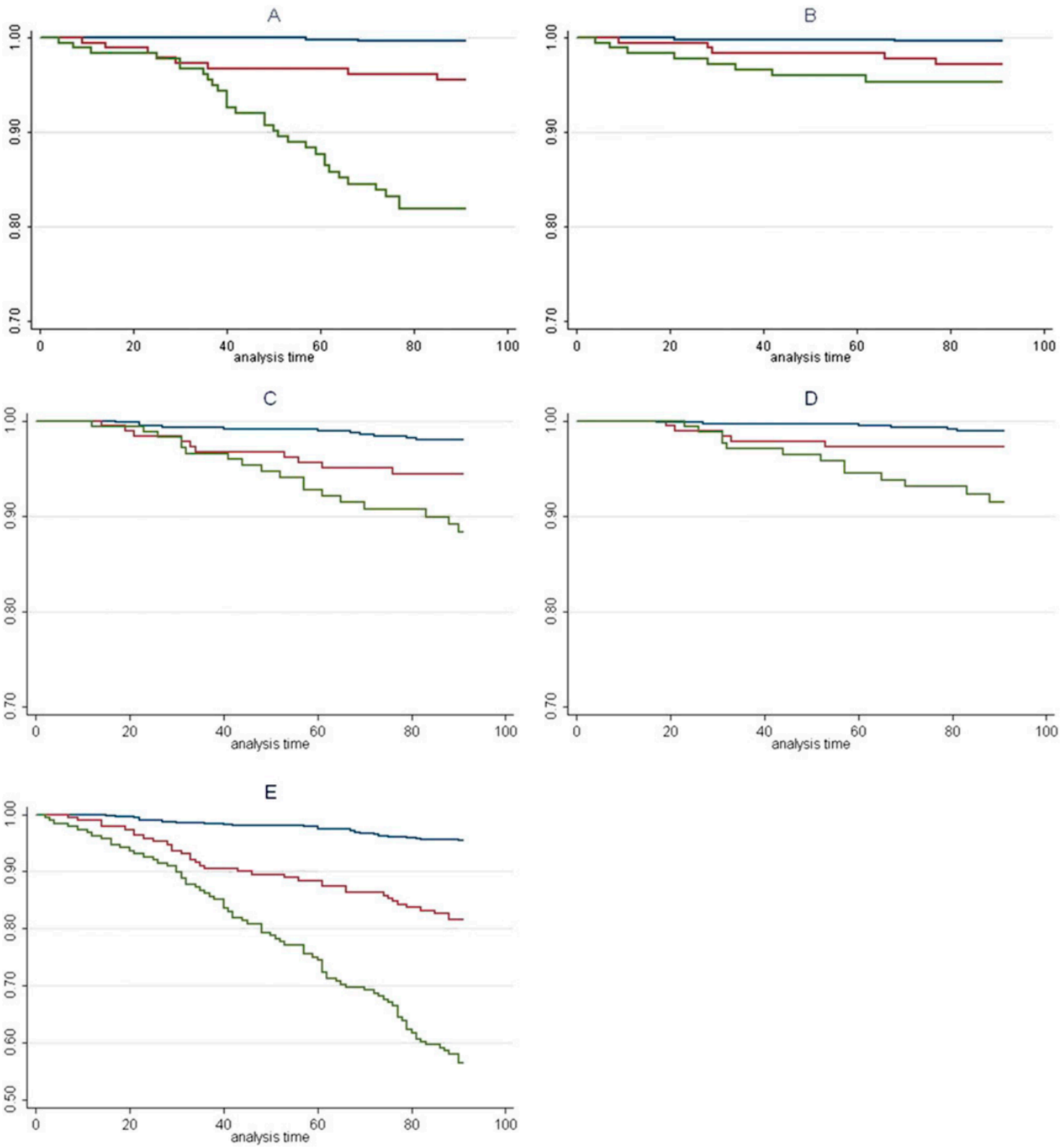


Figure 1. Kaplan-Meier survival estimates by low-attenuation area (%LAA) tertiles, n = 947 subjects from the GenKOLS study 2003–2005. (*A–E*) Respiratory mortality (*A*), cardiovascular mortality (*B*), cancer mortality (*C*), lung cancer mortality (*D*), and all-cause mortality (*E*) from baseline through June 2011. *Blue line*, low %LAA (<3); *red line*, medium %LAA (3–10); *green line*, high %LAA (>10).

Johannessen 2013

Barriers to Use of Quantitative Thoracic Imaging as Biomarker

Technical

- Image acquisition parameters
- Variation in manufacturers
- Variable reconstruction algorithms
- Device calibration
- Image quality assurance
- Patient/scanner interaction

Clinical

- Association of change with clinically relevant outcome
- Clinical reproducibility/patient level confounders

Barriers to Use of Quantitative Thoracic Imaging as Biomarker

Technical

Quantitative Imaging Biomarkers Alliance
RSNA

QIBA Profile:
Computed Tomography: Lung Densitometry

Clinical

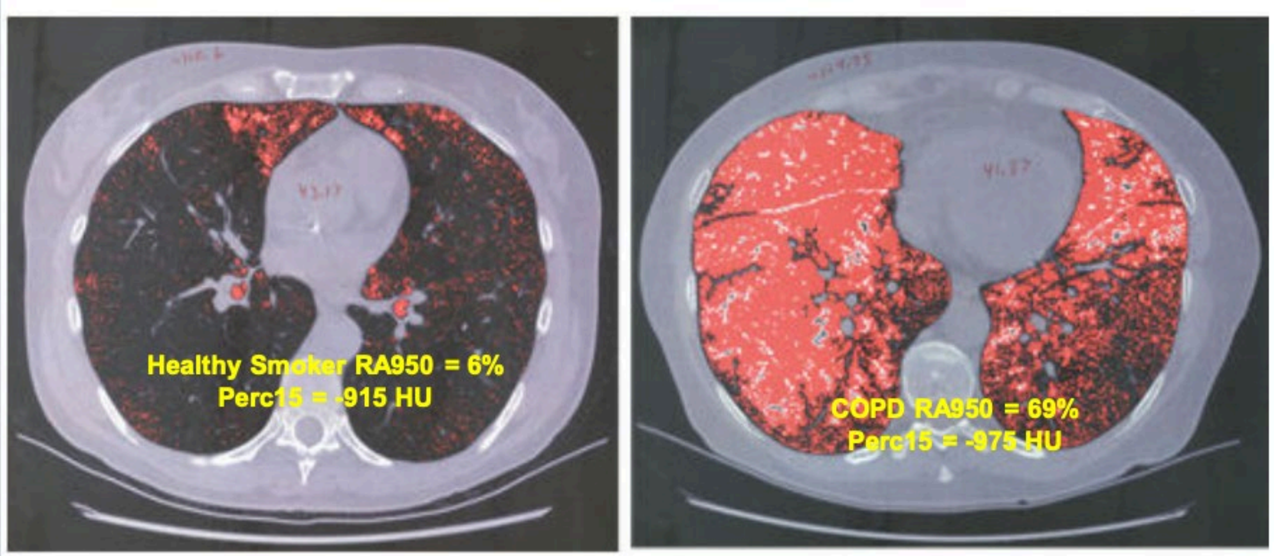
- Association of change with clinically relevant outcome
- Clinical reproducibility/patient level confounders

TABLE 1. LUNG PARENCHYMAL PARAMETERS COMMONLY EMPLOYED TO ESTIMATE EXTENT OF EMPHYSEMA USING QUANTITATIVE COMPUTED TOMOGRAPHY

Measured Parameters		Confounding Factors	Derived Parameters	
Volume	Sum of voxels	Spatial resolution; inspiration level	Mass =	Volume × CT density
Total lung	Both lungs or right/left		Tissue volume =	Mass/tissue density
Lobar	Sum of voxels on specific lobes		Air volume =	Total volume − tissue volume
X-ray attenuation	Hounsfield units (HU)	Image noise; depth of inspiration	CT density	(HU+1,000)/1,000
			Specific lung inflation	1/CT density – 1/tissue density
Low attenuation area	% voxels <predefined threshold (i.e., −950 HU)	Image noise; depth of inspiration	Low attenuation cluster analysis	Slope of regression line of cumulative number of low attenuation clusters vs. size of low attenuation cluster
Percentile	HU at predefined percentile value of frequency distribution of X-ray attenuation values (e.g., lowest 15th percentile)	Image noise; depth of inspiration		

Coxson 2009

Lung Density Perc15



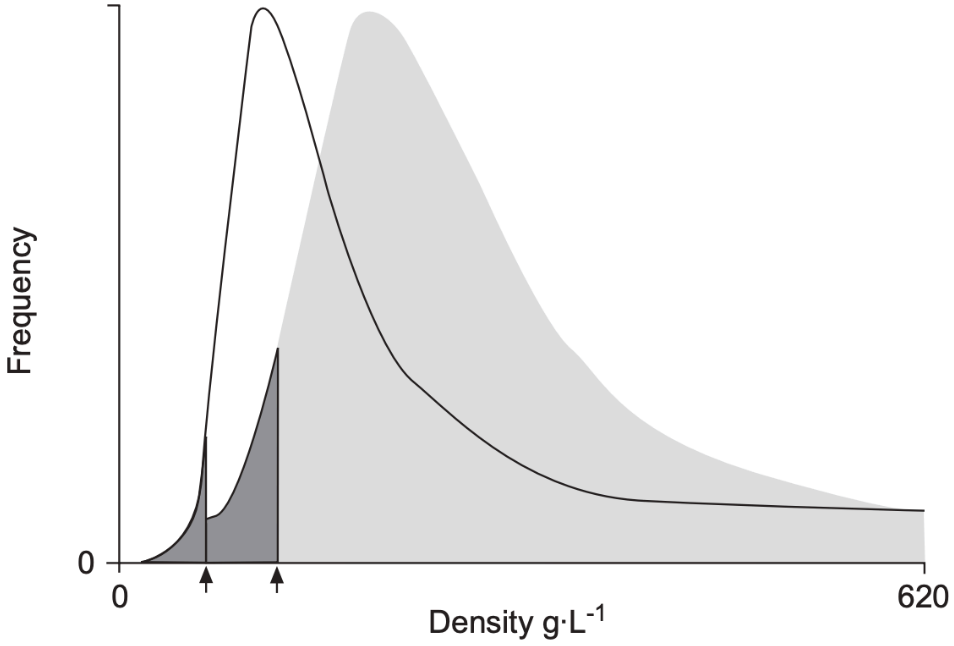


FIGURE 1. Density distribution in the lung. Histogram of densities from a subject with normal lungs (■) and a patient with emphysema (——). The 15th percentile point (■) is the density value on the x-axis that covers 15% of all densities of the histogram. ↑: 15th percentile point.

Fain 2014
Stolk 2007

Barriers to Use of Quantitative Thoracic Imaging as Biomarker

Technical

Quantitative Imaging Biomarkers Alliance
RSNA

QIBA Profile:
Computed Tomography: Lung Densitometry

Clinical

PIVOT
PATIENT-INSPIRED VALIDATION OF OUTCOME TOOLS
COPD FOUNDATION

Study Design

- Objective:
  - Determine if emphysema progression over 3-5 years is associated with subsequent:
    - Mortality
    - Respiratory specific mortality
- Cohorts:
  - COPDGene Study
  - Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)
- Groups:
  - Ever smokers **with emphysema** (primary analyses)
  - All ever smokers (secondary analyses)
  - *Never smokers for development of MCID*

Methods

- Predictor:
  - Lung Density Perc15 adjusted for lung volume based on the sponge model
    - Annualized rate of change (continuous)
    - Progressor vs. non-progressor (dichotomous)

- Definitions:
  - Emphysema at baseline: those with low attenuation area (LAA) > the upper limit of normal defined by the MESA study
  - **Progression:**
    - **Absolute Lung Density Perc15 decline of more than the mean repeatability coefficient from QIBA (11 g/L)**
    - **Rate of Lung Density Perc15 decline ½ SD more than the mean rate in 'never-smoking normals'**

Dirksen 2008
Hoffman 2014

Mortality by Progression Rate

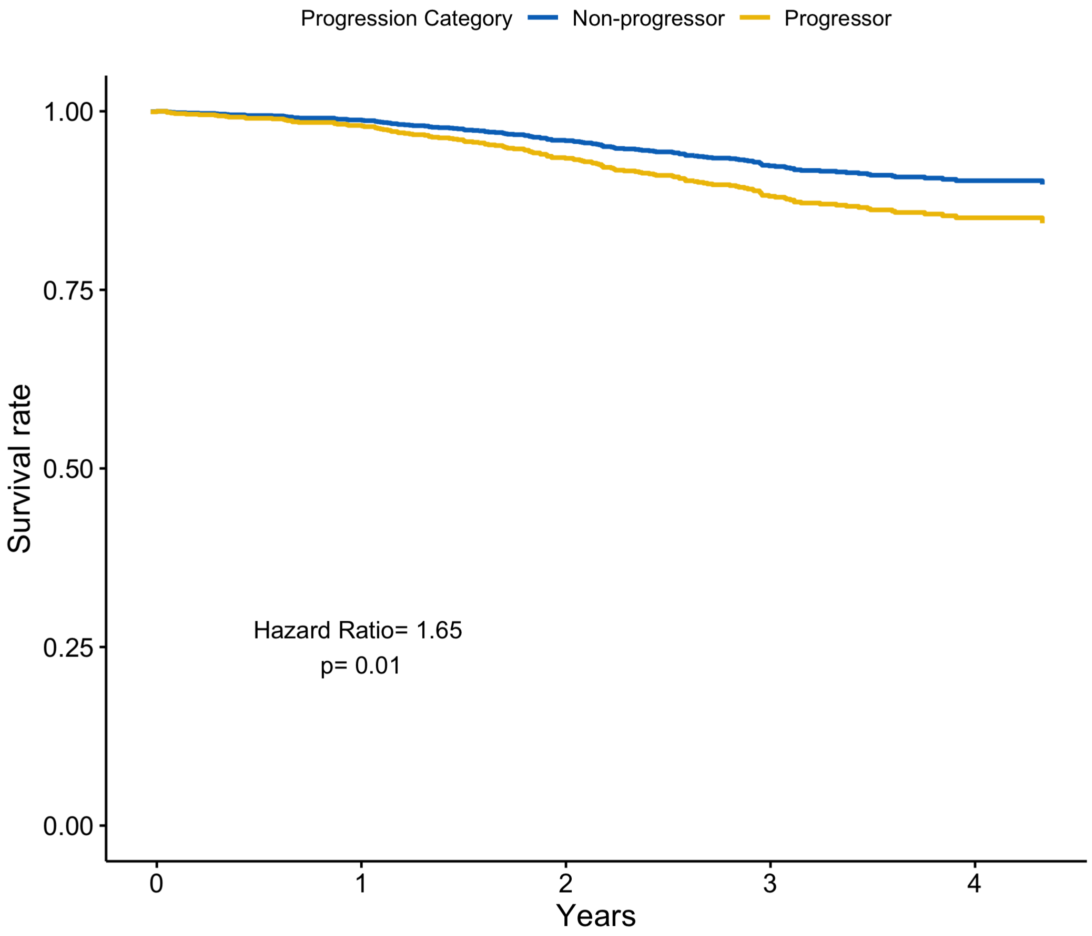
		Confidence Interval		
All Cause Mortality	**Hazard Ratio**	**Lower**	**Upper**	**p**
COPDGene	1.08	1.01	1.16	0.03
ECLIPSE	1.06	1.00	1.13	0.045
Respiratory Specific Mortality				
COPDGene	1.22	1.13	1.31	< 0.001

[1] Effects expressed as change in the risk of all-cause mortality per 1 g/L/year faster rate of change in density
[2] Mortality assessed as time since follow-up visit
[3] All cause mortality models adjusted for: a) Race and gender; b) Baseline age, smoking status, pack years, forced expiratory volume in one second, six minute walk distance and volume adjusted lung density measured at the 15th percentile of the CT lung density histogram (Lung Density Perc15); c) Change in smoking status, rate of change in forced expiratory volume in one second and rate of change in six minute walk distance.
[4] Respiratory specific mortality models adjusted for race, gender and age, and performed using the Fine and Gray method of accounting for competing risk.
[4] Results shown are in those with emphysema at baseline

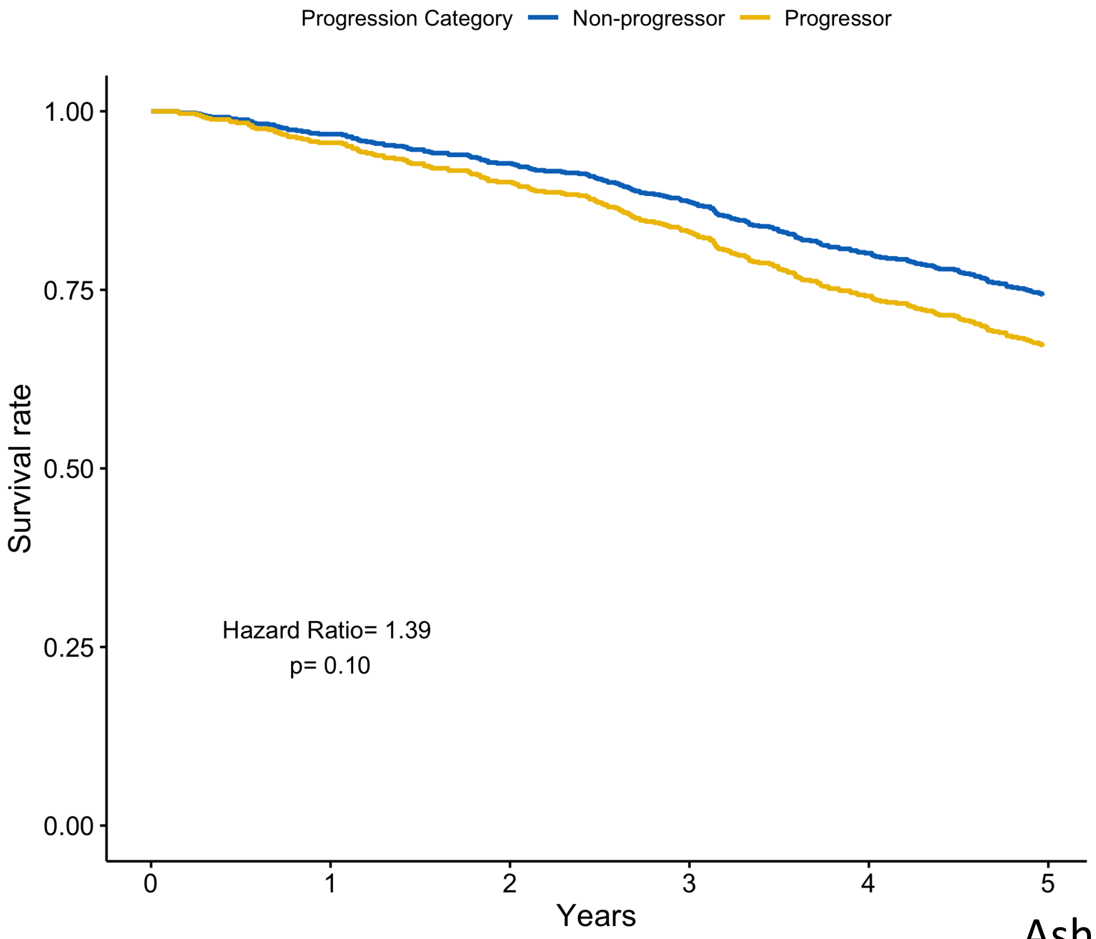
Ash *In press*

Mortality by Progression Category

Adjusted Survival Curve for Change in Lung Density
Perc15 Relative to the Repeatability Coefficient
COPDGene - Those with emphysema at baseline



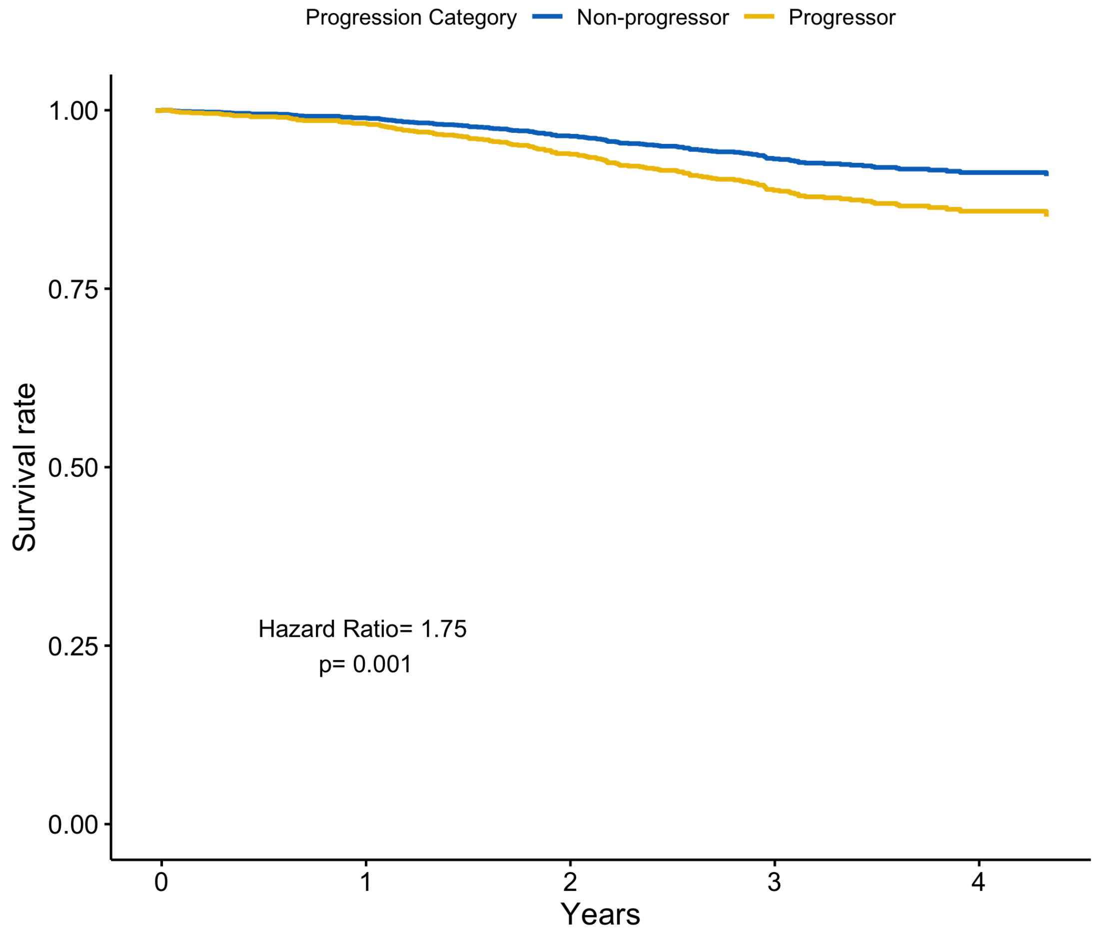
Adjusted Survival Curve for Change in Lung Density
Perc15 Relative to the Repeatability Coefficient
ECLIPSE - Those with emphysema at baseline



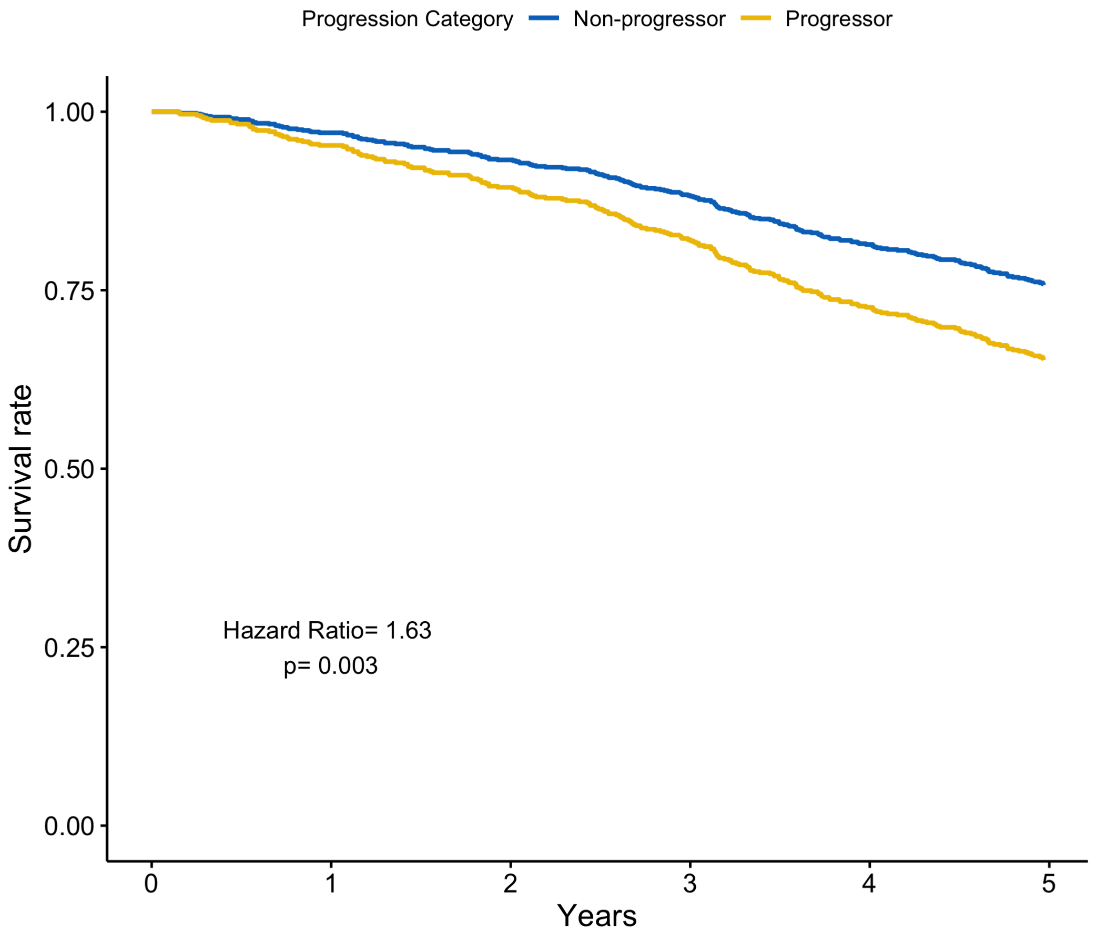
Ash *In press*

Mortality by Progression Category

Adjusted Survival Curve for Rate of Change in Lung Density Perc15 Relative to Minimum Clinically Important Difference
COPDGene - Those with emphysema at baseline



Adjusted Survival Curve for Rate of Change in Lung Density Perc15 Relative to Minimum Clinically Important Difference
ECLIPSE - Those with emphysema at baseline



Ash *In press*

Comparison of Model Performance - COPDGene

Comparison	NRI	p: First Model vs. Second Model (non-nested only)	p: Second Model vs. First Model
Baseline vs. Baseline			
Baseline Spirometry vs. Baseline Imaging	-0.12	0.08	0.92
Baseline Spirometry vs. Baseline Spirometry + Baseline Imaging	0.07	N/A	0.02
Baseline Imaging vs. Baseline Spirometry + Baseline Imaging	0.19	N/A	< 0.001
Longitudinal vs. Longitudinal			
Longitudinal Spirometry vs. Longitudinal Imaging	-0.04	0.20	0.80
Longitudinal Spirometry vs. Longitudinal Spirometry + Longitudinal Imaging	0.13	N/A	0.01
Longitudinal Imaging vs. Longitudinal Spirometry + Longitudinal Imaging	0.15	N/A	< 0.001
Baseline vs. Longitudinal			
Baseline Spirometry vs. Longitudinal Spirometry	0.18	N/A	0.002
Baseline Imaging vs. Longitudinal Imaging	0.23	N/A	< 0.001
Baseline Spirometry + Baseline Imaging vs. Longitudinal Spirometry + Longitudinal Imaging	0.25	N/A	< 0.001

Comparison of Model Performance - ECLIPSE

Comparison	NRI	p: First Model vs. Second Model (non-nested only)	p: Second Model vs. First Model
Baseline vs. Baseline			
Baseline Spirometry vs. Baseline Imaging	-0.09	0.17	0.83
Baseline Spirometry vs. Baseline Spirometry + Baseline Imaging	0.15	N/A	< 0.001
Baseline Imaging vs. Baseline Spirometry + Baseline Imaging	0.21	N/A	< 0.001
Longitudinal vs. Longitudinal			
Longitudinal Spirometry vs. Longitudinal Imaging	-0.08	0.15	0.85
Longitudinal Spirometry vs. Longitudinal Spirometry + Longitudinal Imaging	0.12	N/A	< 0.001
Longitudinal Imaging vs. Longitudinal Spirometry + Longitudinal Imaging	0.24	N/A	< 0.001
Baseline vs. Longitudinal			
Baseline Spirometry vs. Longitudinal Spirometry	0.21	N/A	< 0.001
Baseline Imaging vs. Longitudinal Imaging	0.17	N/A	< 0.001
Baseline Spirometry + Baseline Imaging vs. Longitudinal Spirometry + Longitudinal Imaging	0.18	N/A	< 0.001

Emphysema Current Status

- Letter of intent for qualification of volume adjusted lung density Perc15 resubmitted to the FDA after initial favorable comments
- CBQC transitioned to PIVOT
- White paper consensus document in progress

Summary

- Densitometric emphysema progression is associated with all cause and respiratory specific mortality in ever smokers with emphysema
- In combination with extensive prior work on densitometry, this suggests that volume adjusted Lung Density can be used as an imaging biomarker
- Additional work is needed in clinical cohorts and to determine what interventions might change the course of emphysema progression

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