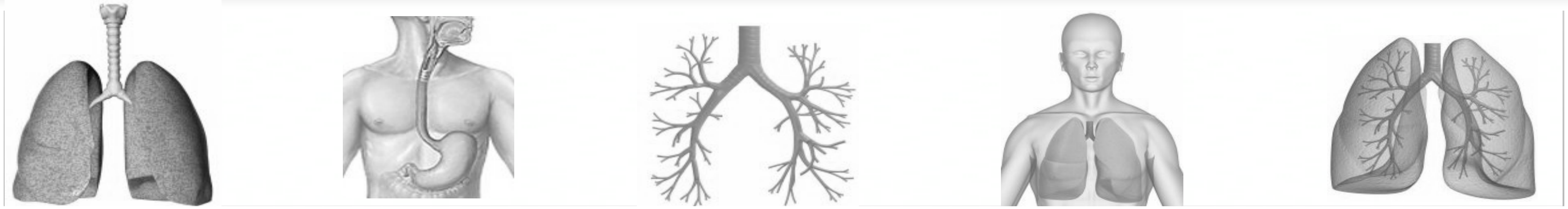

Genomics and Idiopathic Pulmonary Fibrosis

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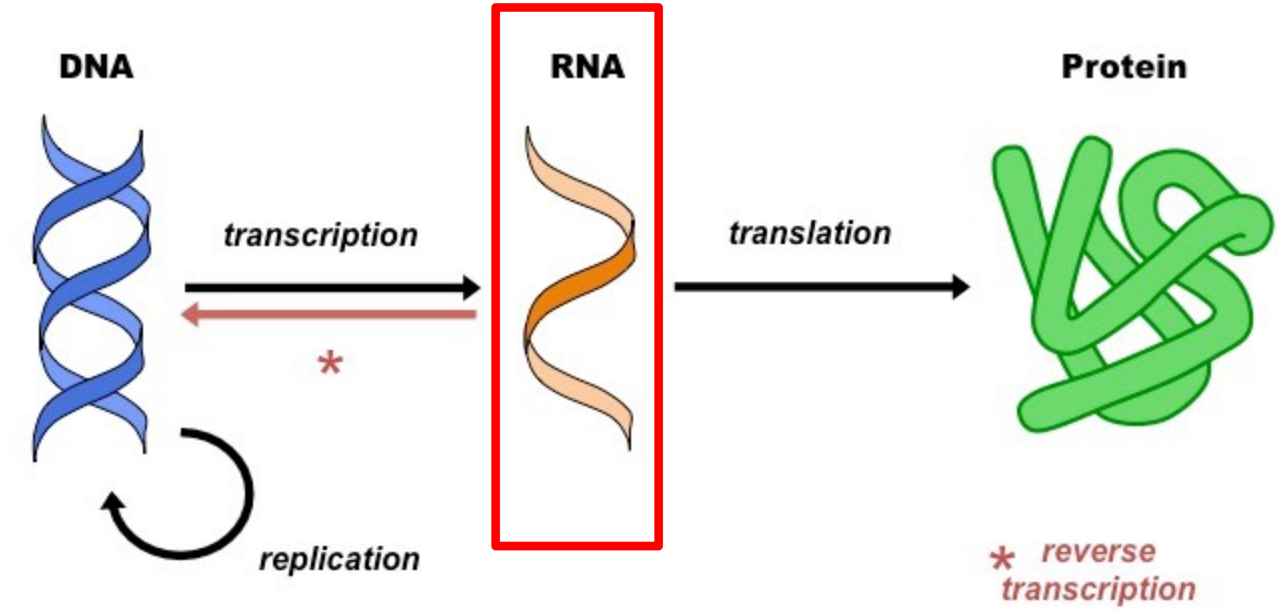
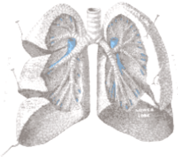
School of Medicine

Steward

Central Dogma

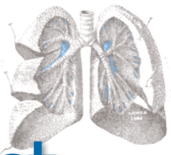


What is the study of Genomics?



- A discipline for analyzing the structure of genomes (the totality of genetic material in an organism)
- Traditional genetics or molecular biology tends to investigate single genes
- Genomics can include interactions between many genes as well as modifications not covered by the central dogma
- Tends to be bioinformatics heavy and computationally intensive

2003 – The promise of the genomic revolution after the Human Genome Project



- Variant genomic content
  - Identify cause of all single gene diseases
  - Catalog normal variants leading to complex diseases
  - I response
  - U
- Ge
  - P sponse to s
  - Identify pathways involved in disease
  - High fidelity tools for diagnosis and predictive medicine
  - Predict drug response and toxicity

Together:

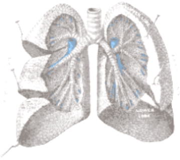
•Identify new targets for therapeutic intervention

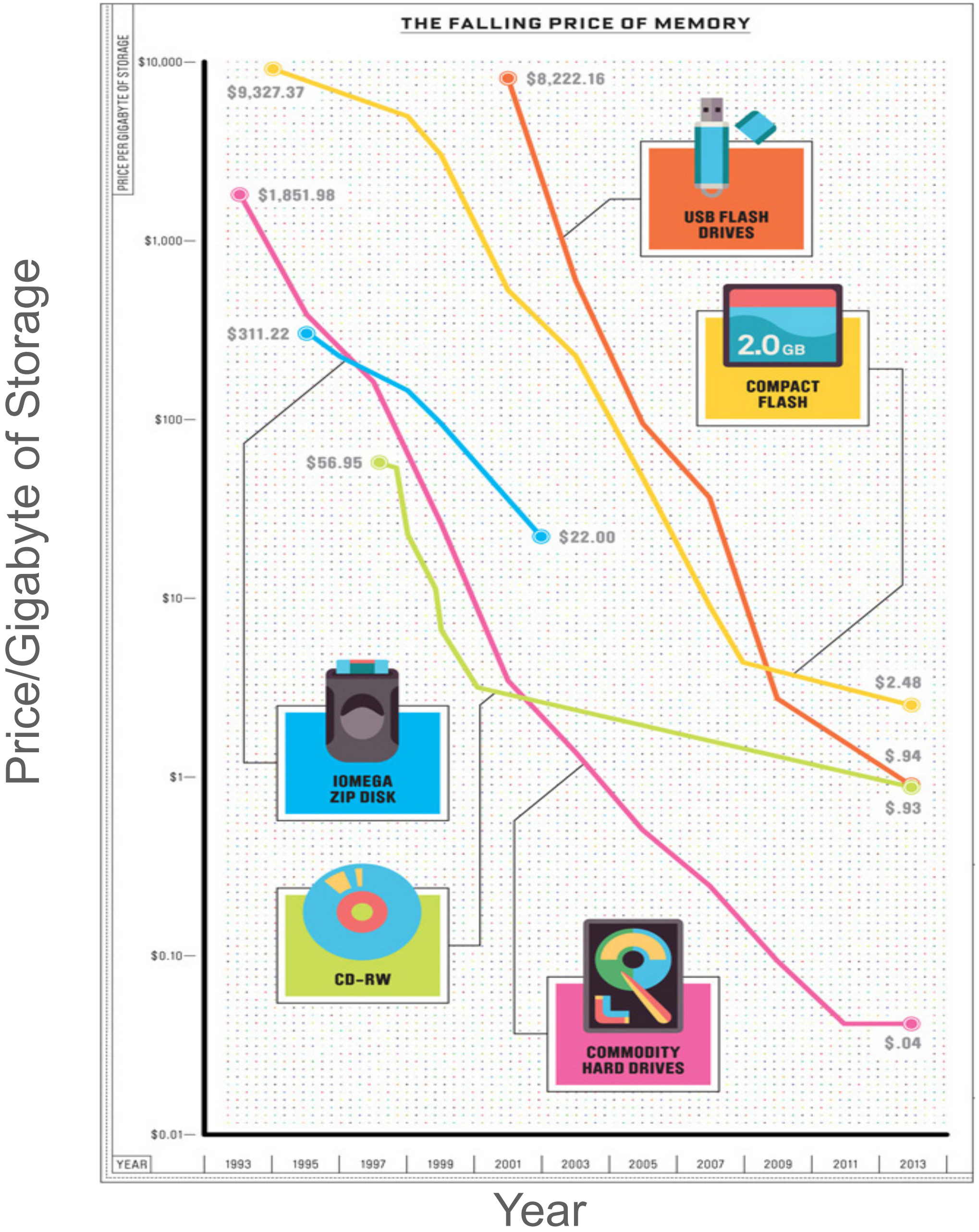
•Personalized treatment

•Predict and prevent of drug toxicities

•Detailed understanding of disease & health

Why is Genomics More Possible Now?





DNA Microarrays

- Microarrays are slides with DNA “spots” containing known sequences of genes
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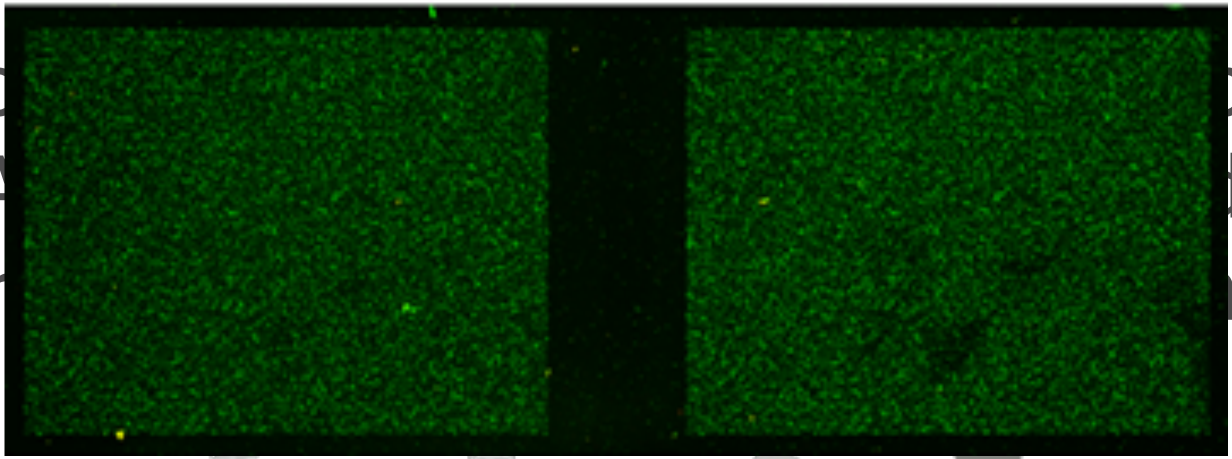
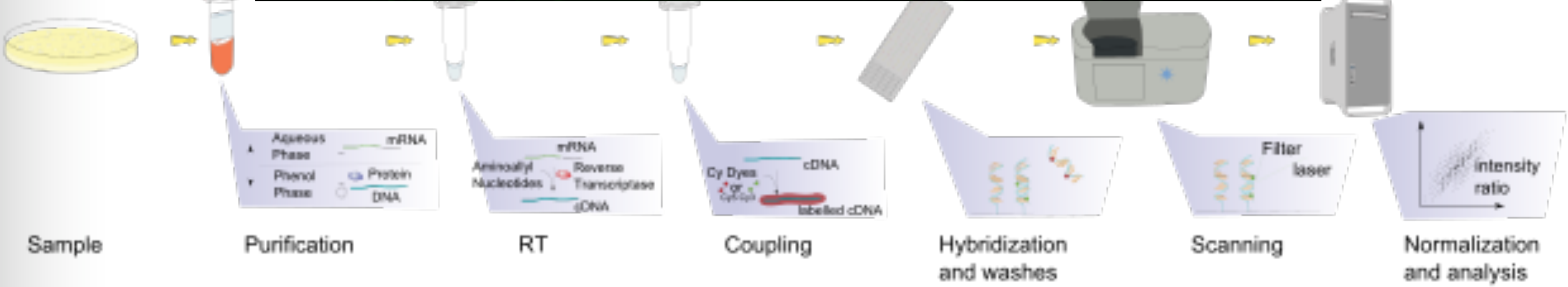
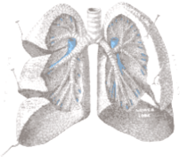




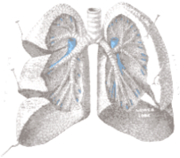
"Microarray exp horizontal" by Squidonius (talk) Licensed under Public Domain via Commons
https://commons.wikimedia.org/wiki/File:Microarray_exp_horizontal.svg#/media/File:Microarray_exp_horizontal.svg

What about the lung?



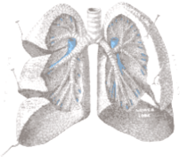
- Pubmed search
  - Gene expression profiling cancer – 52,456 articles
  - Gene expression profiling asthma – 656 articles
  - Gene expression profiling COPD – 297 articles
  - Gene expression profiling IPF – 81 articles

Why the discrepancy?



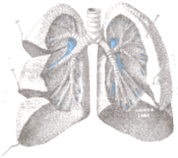
- Proliferation of fragmented phenotypes and disease definitions
- Animal models do not necessarily represent human phenotypes
- Significant understanding of molecular mechanisms did not lead to unified model
- The lung is very complex and dynamic
- The lung is relatively inaccessible
- Difficult to obtain human "Normal Controls"

IPF

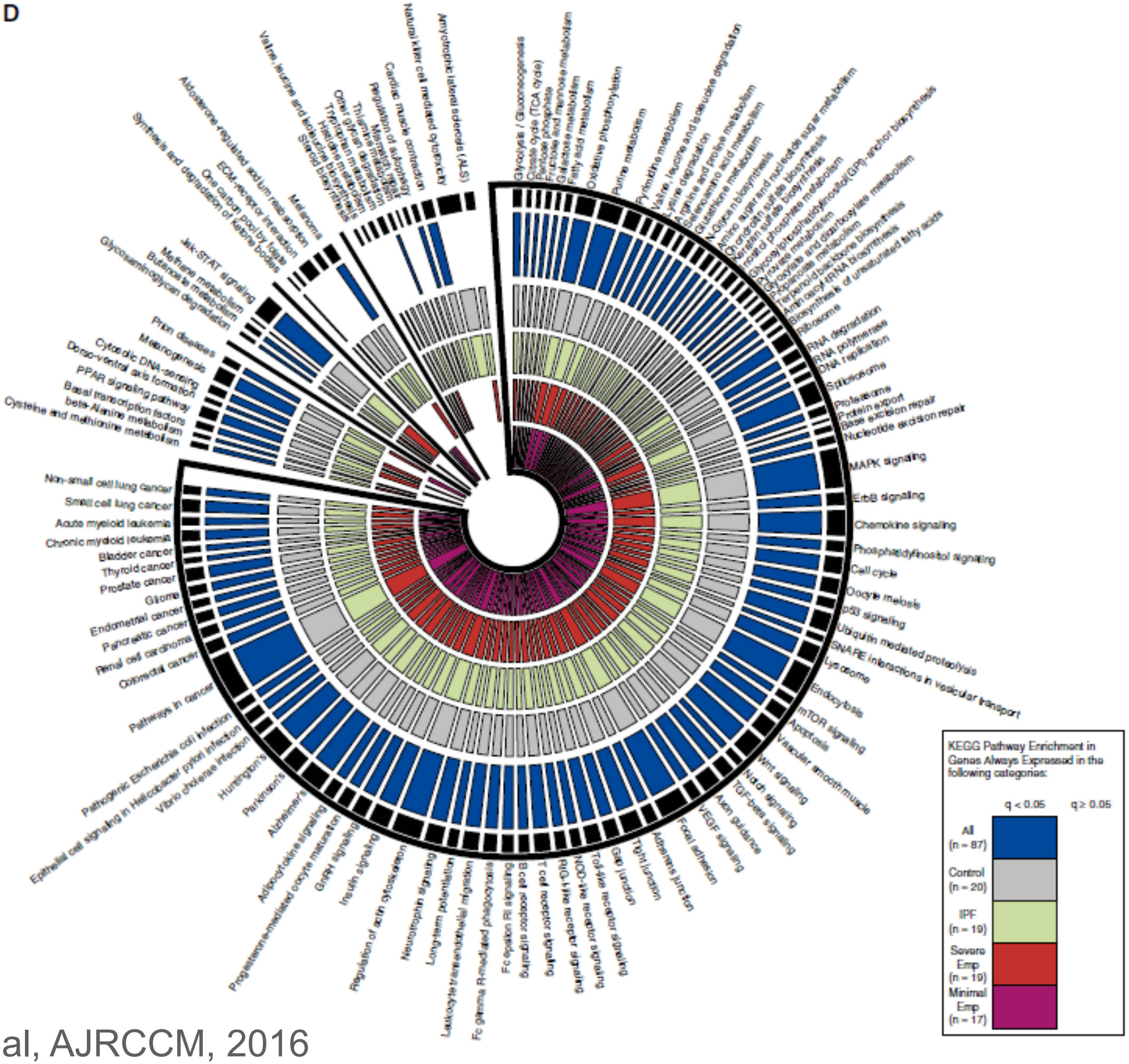


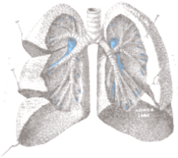
- Robust genomic signature, which makes picking a direction to analyze difficult

Lung Genomics Research Consortium



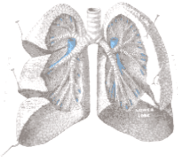
- 5 Center study
- Collect lung tissue from subjects with IPF or COPD
- Performed microarray analysis on over 500 tissue samples, as well as sequencing, miRNA analysis, methylation patterns, and genotyping

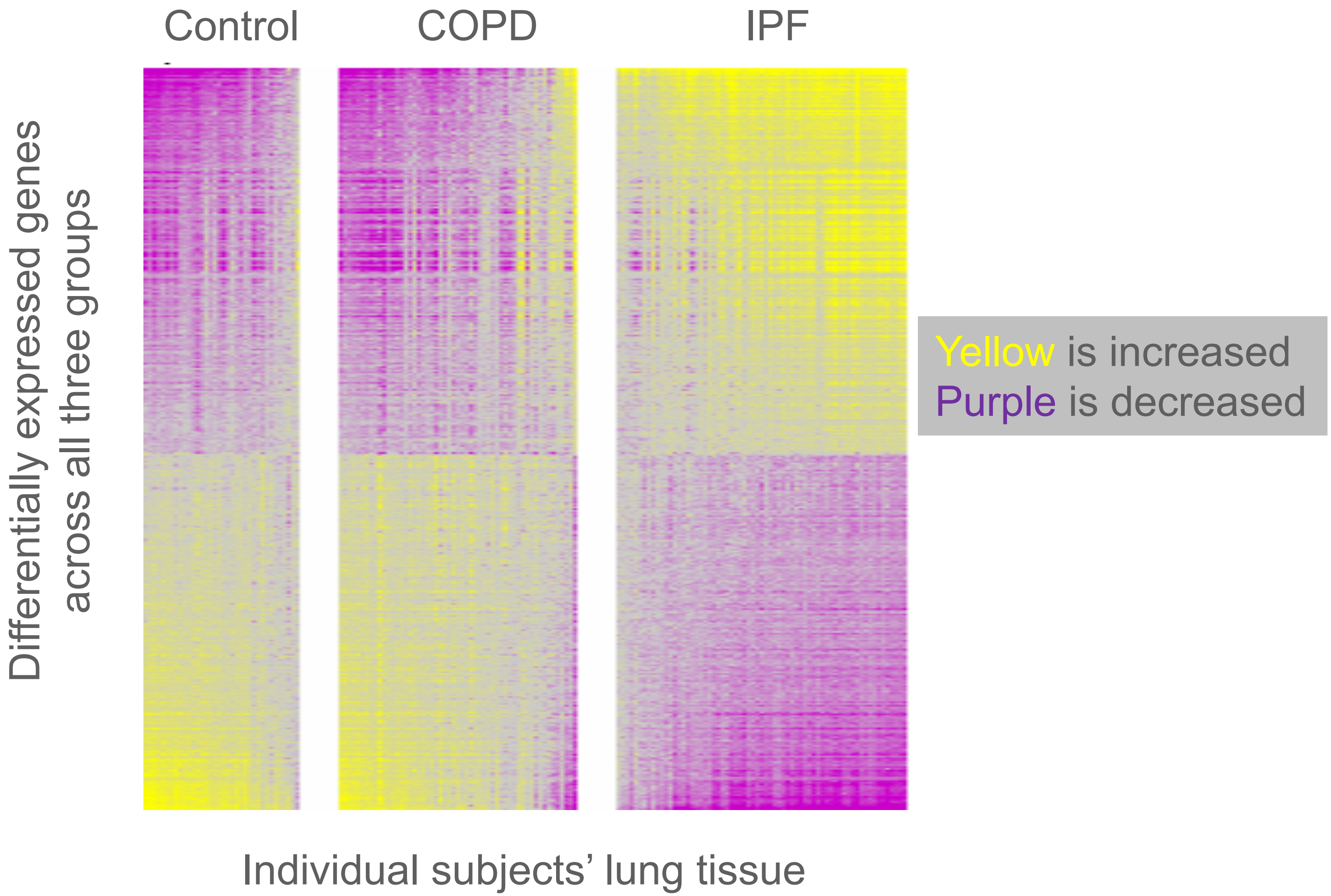




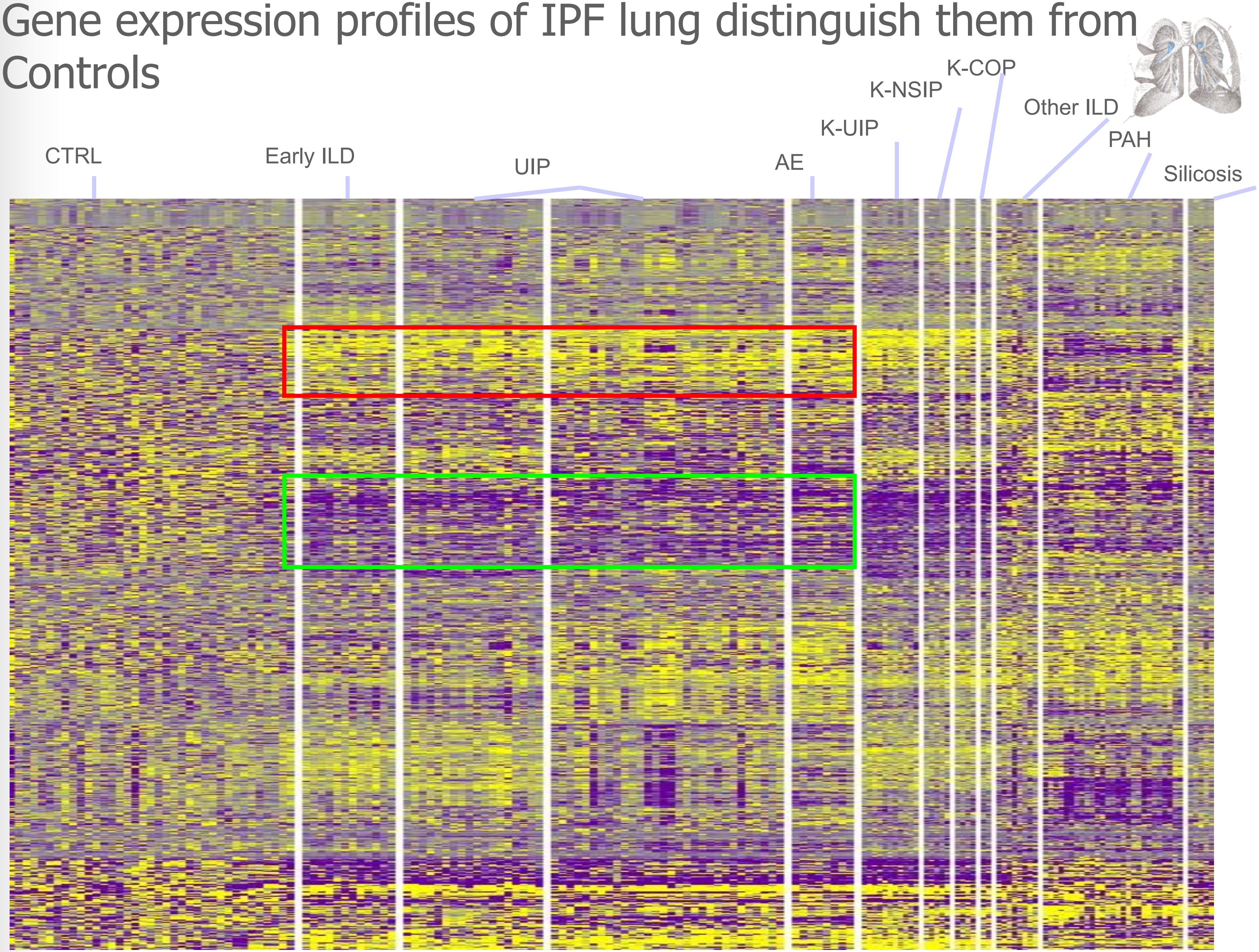
Kusko et al, AJRCCM, 2016

IPF lungs are very different from other lungs

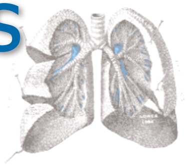


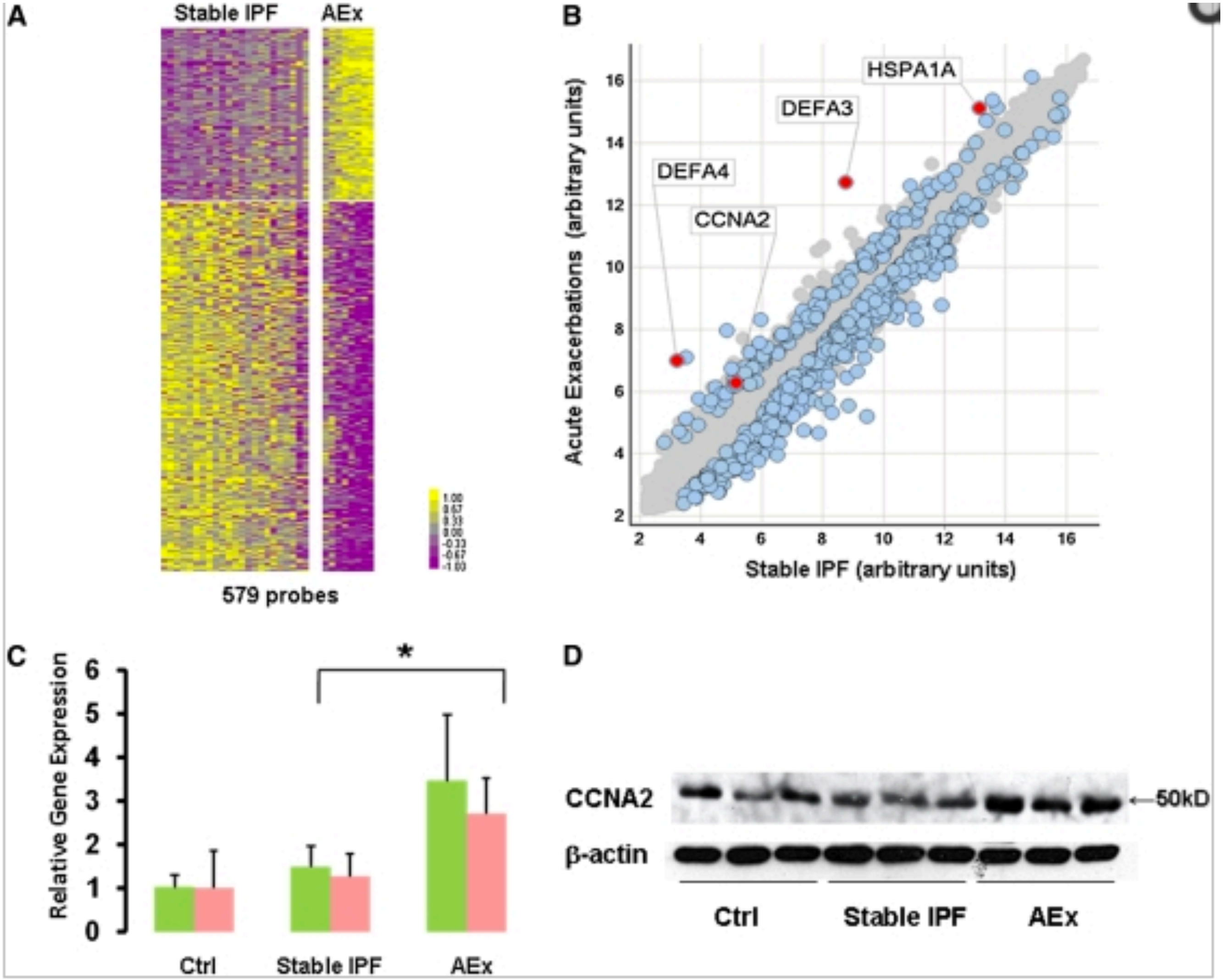


Gene expression profiles of IPF lung distinguish them from Controls



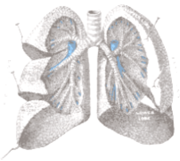
Gene expression can differentiate subjects with acute exacerbation

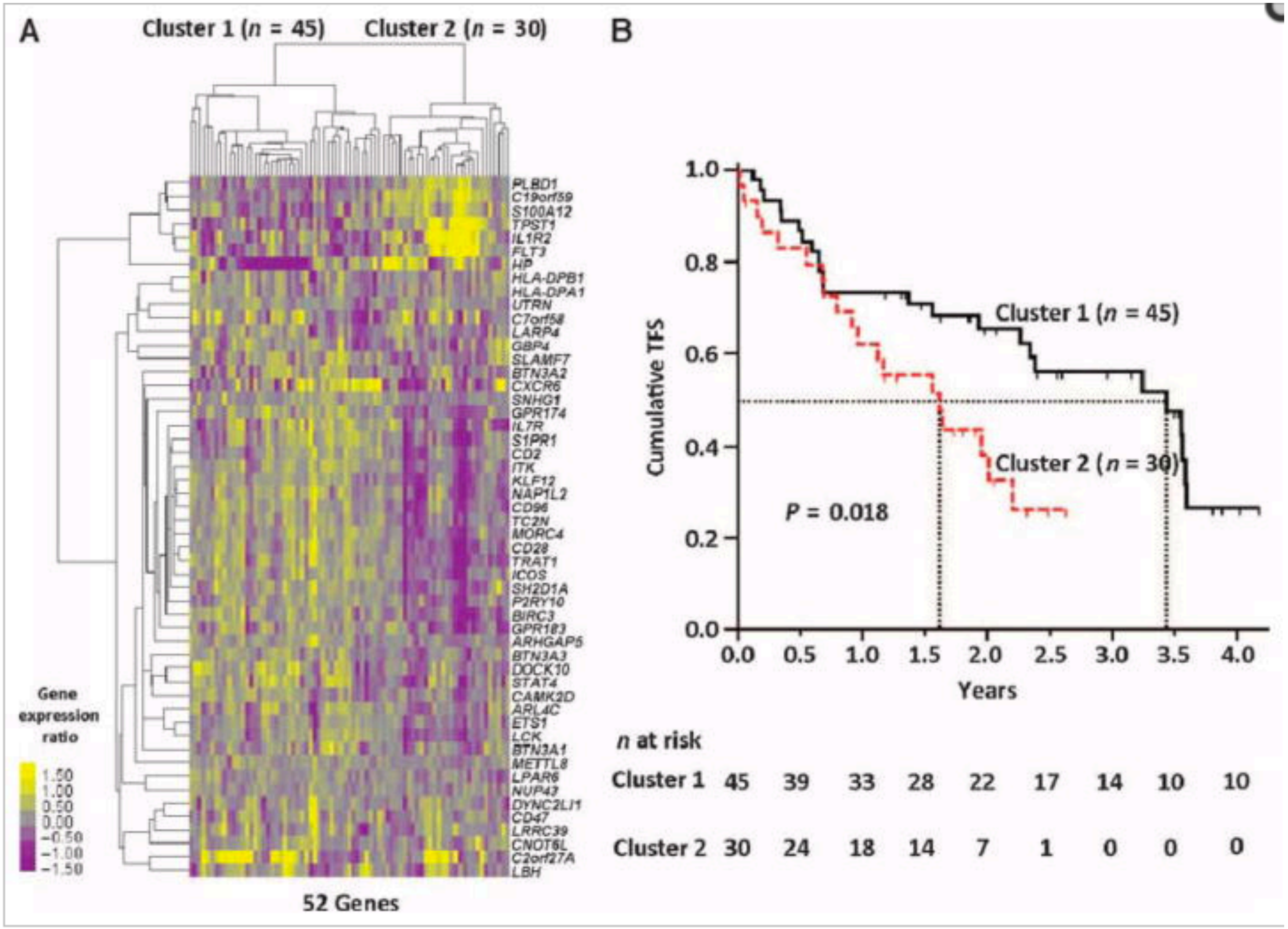




Konishi et al, AJRCCM 2009

A gene expression signature in peripheral blood could predict poor outcome in IPF subjects

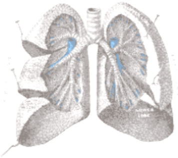




n at risk									
Cluster 1	45	39	33	28	22	17	14	10	10
Cluster 2	30	24	18	14	7	1	0	0	0

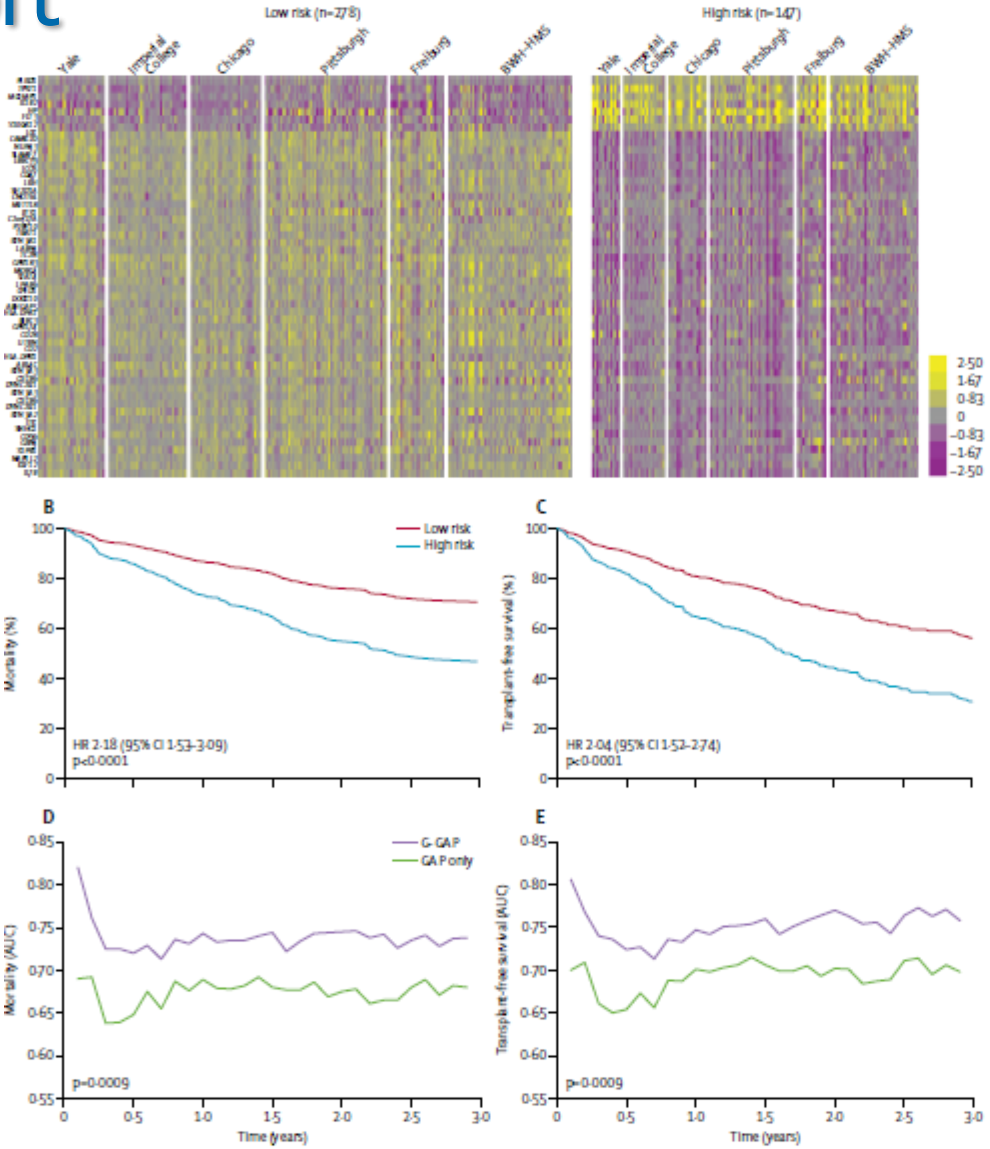
Herazo et al, AJRCCM, 2013

52 gene signature predicts outcome in 6-center cohort



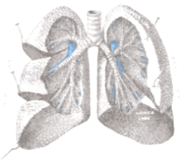
425 patients total

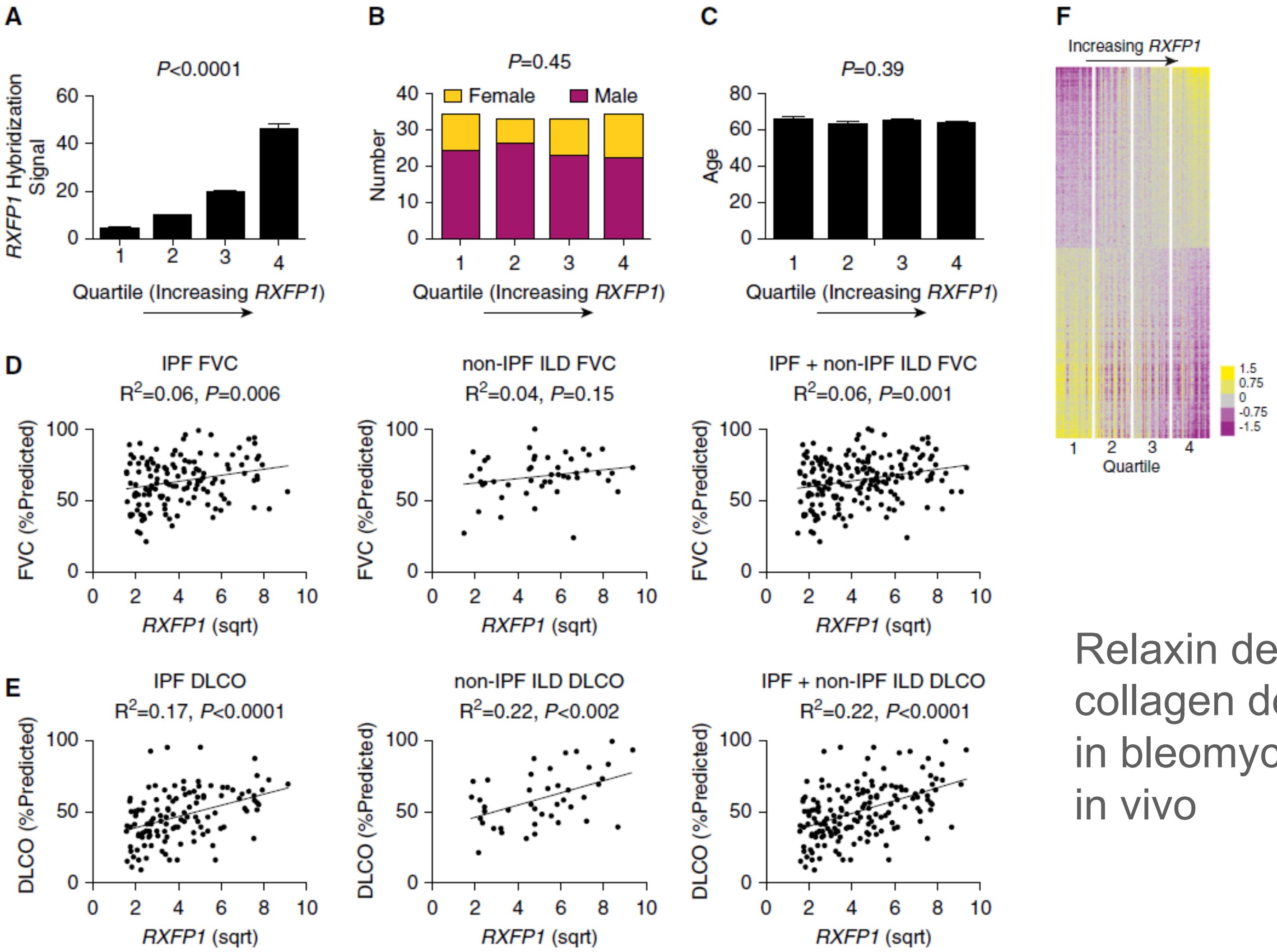
Profiles do not change with time unless treated with antifibrotic



Herazo et al, Lancet Respiratory Medicine, 2017

RXFP1 is an interesting gene for potential therapeutics

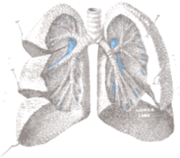




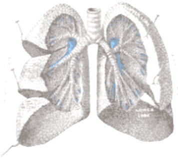
Relaxin decreases collagen deposition in bleomycin model in vivo

Tan et al, AJRCCM, 2016

Conclusion



- With increased access to biological technology and computational power, we hope genomics will provide key insights into clinical course, mechanisms of IPF, as well as the next wave of therapeutics



Thank you for your attention!