Polarean Imaging plc
"POLX"

Breathtaking Images...

Investors Symposium
June 12, 2019

POLAREAN

Agenda

- Welcome – Richard Morgan, Chairman

- Company Highlights and Update – Richard Hullihen, CEO

- Update on ^{129}Xe MRI Technology and Applications – Bastiaan Driehuys, PhD CTO

- ^{129}Xe MRI to Differentiate Diverse Cardiopulmonary Diseases – Prof Sudarshan Rajagopal MD PhD Duke University

- Cystic Fibrosis – Prof Jason Woods PhD Cincinnati Children's Hospital

- Closing, Q&A

POLAREAN

Polarean Highlights

- Revenue generating company, better than plan performance

- Phase III Clinical trial, 2 pathways, 83% and 56% complete

- Market opportunity

  - >$US500M equipment sales to top tier US institutions, plus drug sales

  - Potential for multiple pharma and device (valve/stent) company partnering deals in specific therapeutic areas

  - New applications are additive: + cardiology/Pulmonary vascular disease

  - New geographic opportunities with strategic partners emerging

- Continued buildout of IP with key patents on gas exchange and PVD

- EIS/VCT qualified

POLAREAN

Significant Interest from Researchers and Drug Companies

- From Clinicaltrials.gov

- Polarean ^{129}Xe currently being investigated in 42 clinical trials in the US, most with the Consortium and or affiliates

- Polarean ^{129}Xe currently being investigated in clinical trials with >10 drugs in IPF, PAH, Asthma, and COPD

- In process investigating corporate partnering opportunities

- Significant opportunities to reduce Pharma Phase I& Phase II trial costs

- Potential development as true biomarker

- Potential development as 'companion diagnostic'

POLAREAN

Operations

- Delivered latest research system: Univ Missouri. Total shipped/installed 24

- Built and delivered Clinical Trial Systems, per GMP

- Built and shipped 5 systems and 1 upgrade in 2018

- Received latest orders from UBC and SickKids, will deliver this year

- Pipeline up year on year

- Third year award of $US3M 3yr SBIR grant in hand

POLAREAN

Polarean's FDA Strategy

- Obtain a broad claim that allows our technology to be used in all diseases for clinical diagnosis and monitoring therapy

- We are pursuing a FDA **"structural claim"** for use of our product as a contrast agent

  - Identifying **"structural** abnormalities common to one or more disease states"

- We receive the same **"claim"** as approved 133Xe reference standard

  - **"for** the evaluation of pulmonary function, for imaging the **lungs"**

POLAREAN

Phase III Trials – Structure, Timing

- Required number of patients
  - Lung Resection – 32 subjects   56% complete
  - Lung Transplant – 48 subjects   83% complete

- Deep in Trials
  - Two experienced medical centers in trial
    - University of Virginia (largest customer)
    - Duke University (home base)
  - Adding third site June 2019: Cincinnati to speed resection pathway
  - Estimated completion of enrolment: 3Q2019
  - Estimated commercial launch: 2H2020

POLAREAN

An Update on ^{129}Xe MRI Technology and Applications

Bastiaan Driehuys, Ph.D
Chief Technology Officer

POLAREAN

Informed by a Rich Academic Research Environment

Mu He
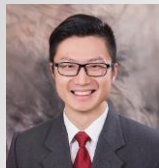
Ziyi Wang

Elianna Bier
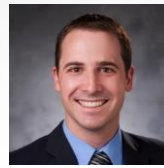
Leith Rankine

John Nouls
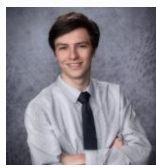
Alex Church
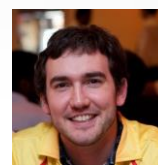
David Mummy

Brian Soher

Rohan Virgincar

Page McAdams
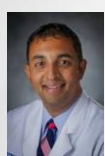
Joe Mammarapallil

Lake Morrison
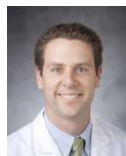
Craig Rackley
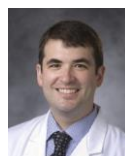
Rob Tighe
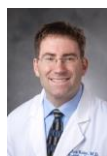
Christopher Kelsey

Tony Huang

Loretta Que
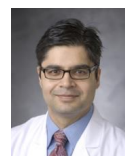
Kamran Mahmood

Sudarshan Rajagopal

Samantha Womack

Jennifer Korzekwinski

Shiva Das

Larry Marks

Lukas Ebner

POLAREAN

Hyperpolarized ^{129}Xe MRI Refresher

^{129}Xe Blend   Hyperpolarize   Dispense   Hold/Measure   Administer
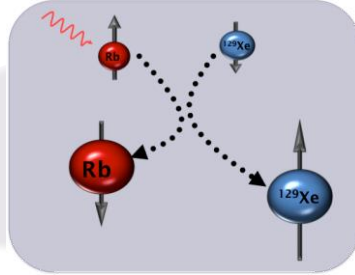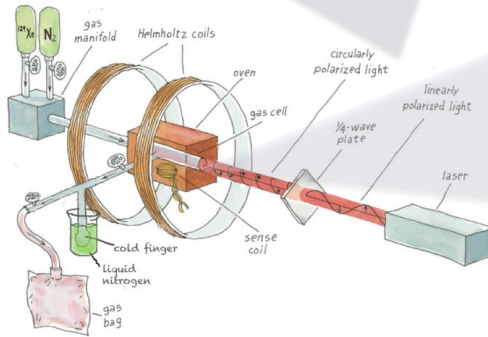
8 s breath-hold scan
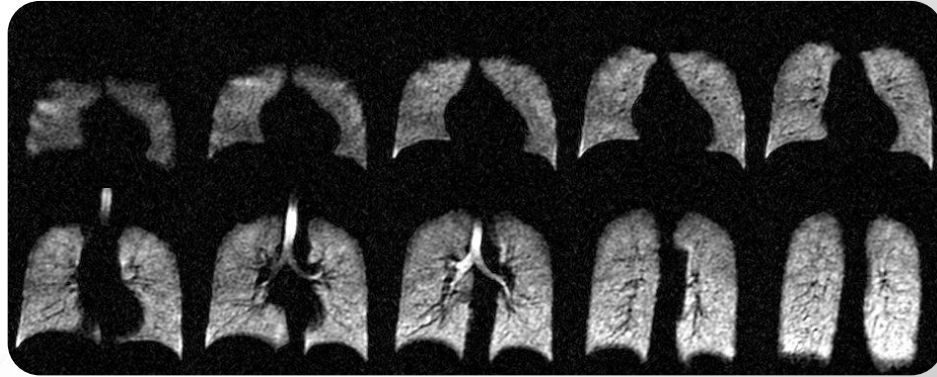
- ^{129}Xe Signal increased by ≈100,000
- Persists for ~2 hours in dose vessel

POLAREAN

Why We Need New Diagnostic Techniques for the Lung

Pulmonary Function Tests

- Airflow, lung volumes, gas exchange
- Effort-dependent
  - Varies by 5-10%
- Not spatially resolved
- Insensitive to early disease, progression and therapy response
- (Invented in 1846)

Computed tomography
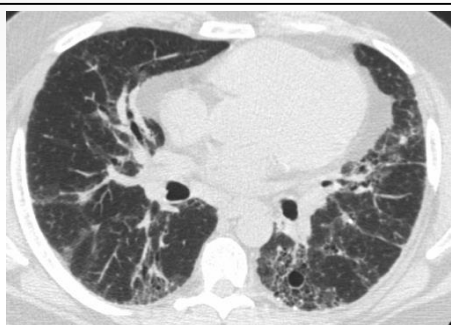
- Structural detail
- No function
- Insensitive to disease progression
- Ionizing radiation

Nuclear Scintigraphy

Xenon-posterior views

A

Xe-Initial breath/wash in   Eq 1
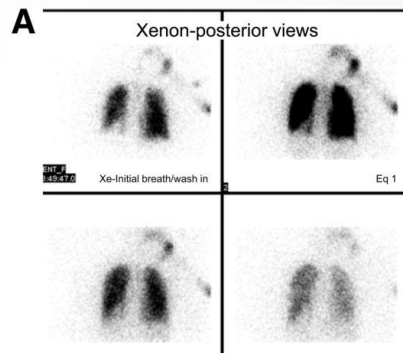
- Approved for ventilation
- 2D, low-resolution
- Only gross abnormalities
- Ionizing radiation
- Supply challenges

^{129}Xe MRI
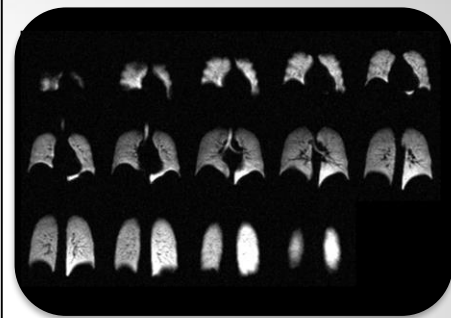
- 3D, high-resolution
- Fast, safe, repeatable
- Detects early disease
- Detect response
- In Phase III Trials

POLAREAN

Normal — FEV1 =86%

Normal — FEV1 =100%

Normal — FEV1 =121%

Asthma — FEV1 =28%

COPD — FEV1 =24%

AAT Deficiency — FEV1 =54%

Bronchiectasis — FEV1 =23%

Airway Stenosis — FEV1 =56%

Rejection — FEV1 =56%
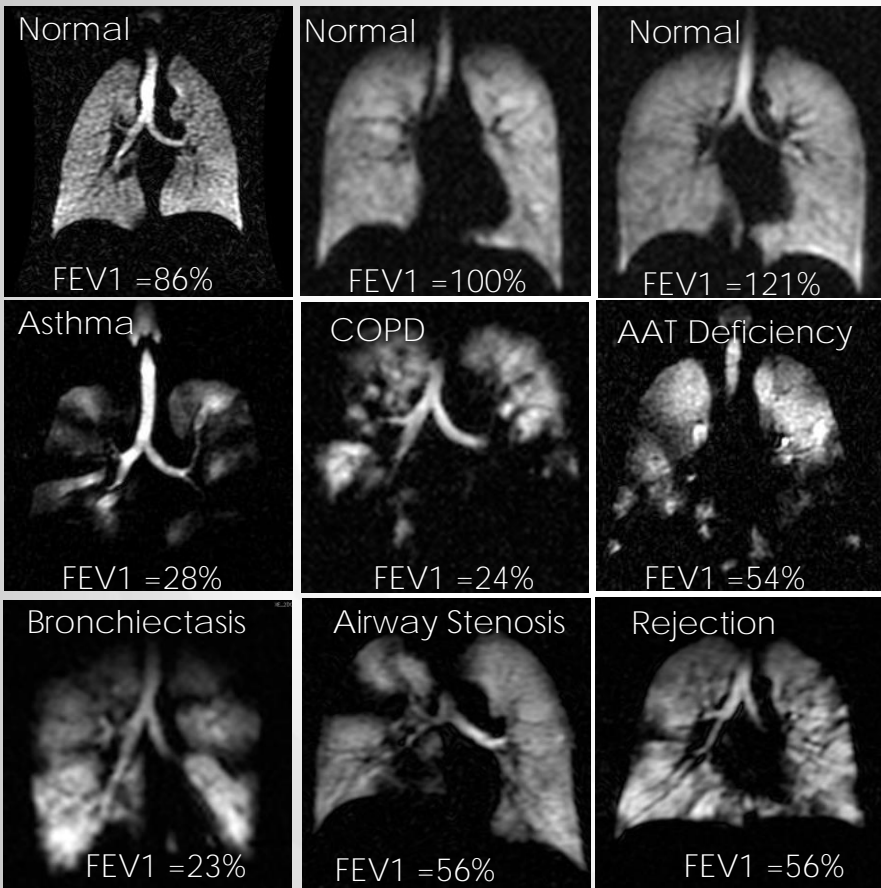
What Clinicians Want:
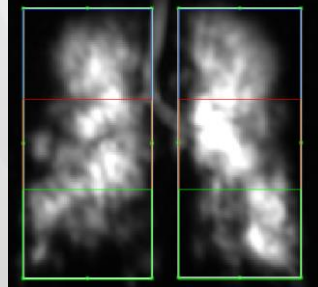- Thoracic cavity context
- Not effort dependent
  - Repeatable
- 3D resolution
  - Track disease regionally
- All 23 airway generations…

POLAREAN
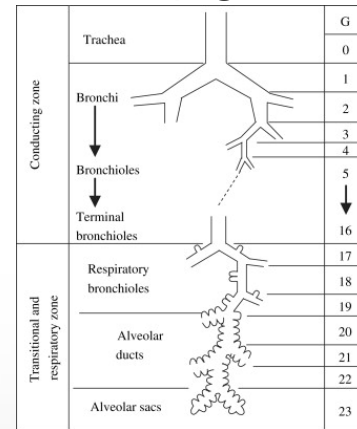
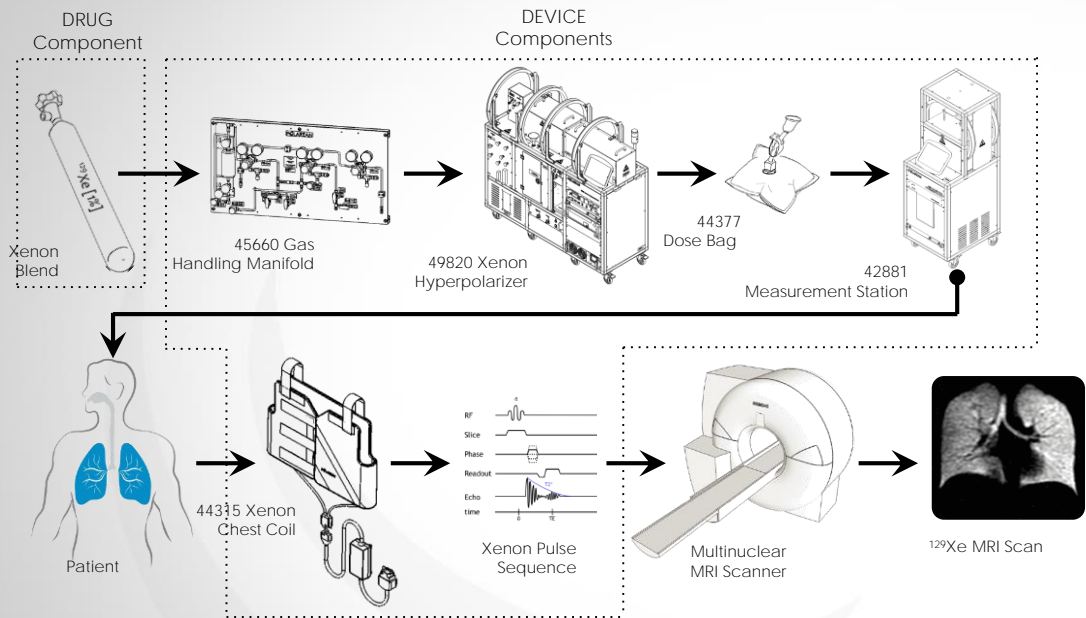# Non-inferiority Study for ^{129}Xe MRI vs ^{133}Xe Scintigraphy
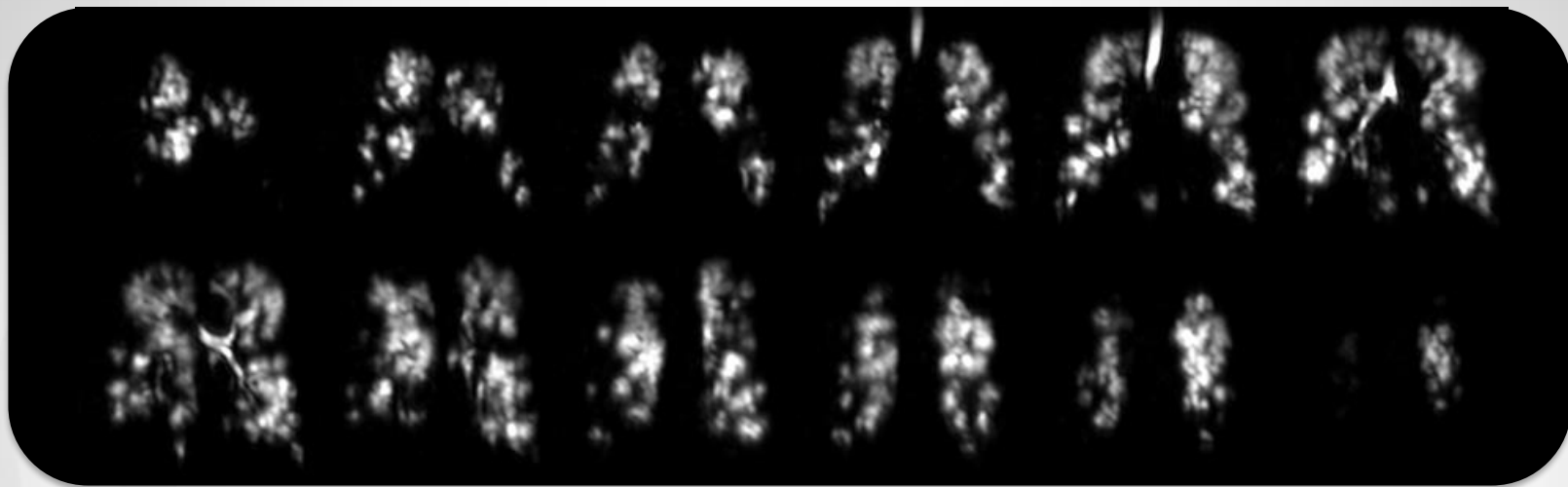
^{129}Xe MRI Projection

	Right Lung %	Left Lung %
Upper Zone	13.3	14.6
Middle Zone	24.2	22.8
Lower Zone	11.2	15.6
Total Lung	47.0	53.0

^{133}Xe Scintigraphy

	Right Lung %	Left Lung %
Upper Zone	12.7	15.2
Middle Zone	21.8	24.6
Lower Zone	10.8	15.0
Total Lung	45.2	54.8

POLAREAN

What FDA Drug/Device Approval Achieves

DRUG Component

Xenon Blend

45660 Gas Handling Manifold

DEVICE Components

49820 Xenon Hyperpolarizer

44377 Dose Bag

42881 Measurement Station

Patient

44315 Xenon Chest Coil

Xenon Pulse Sequence

Multinuclear MRI Scanner

^{129}Xe MRI Scan

- Establishes safety/efficacy of:
  - ^{129}Xe gas blend (drug product)
  - Polarizer
  - Drug container
  - Measurement station
  - Transmit/Receive Coil
  - Pulse sequences
- Approves 3D ^{129}Xe Ventilation MRI
- Physicians order ^{129}Xe MRI
- Hospitals charge for ^{129}Xe MRI
- Pharma can use the technology
- Accelerates new indications

POLAREAN

Seeding the Market with Research

NETHERLANDS

GERMANY

UK

US/CANADA

Legend
- 9600 (He)
- 9800 (Xe - *Legacy*)
- 9810 (Xe - *Upgrade*)
- 9820 (Xe - *New*)
- Anticipated

POLAREAN
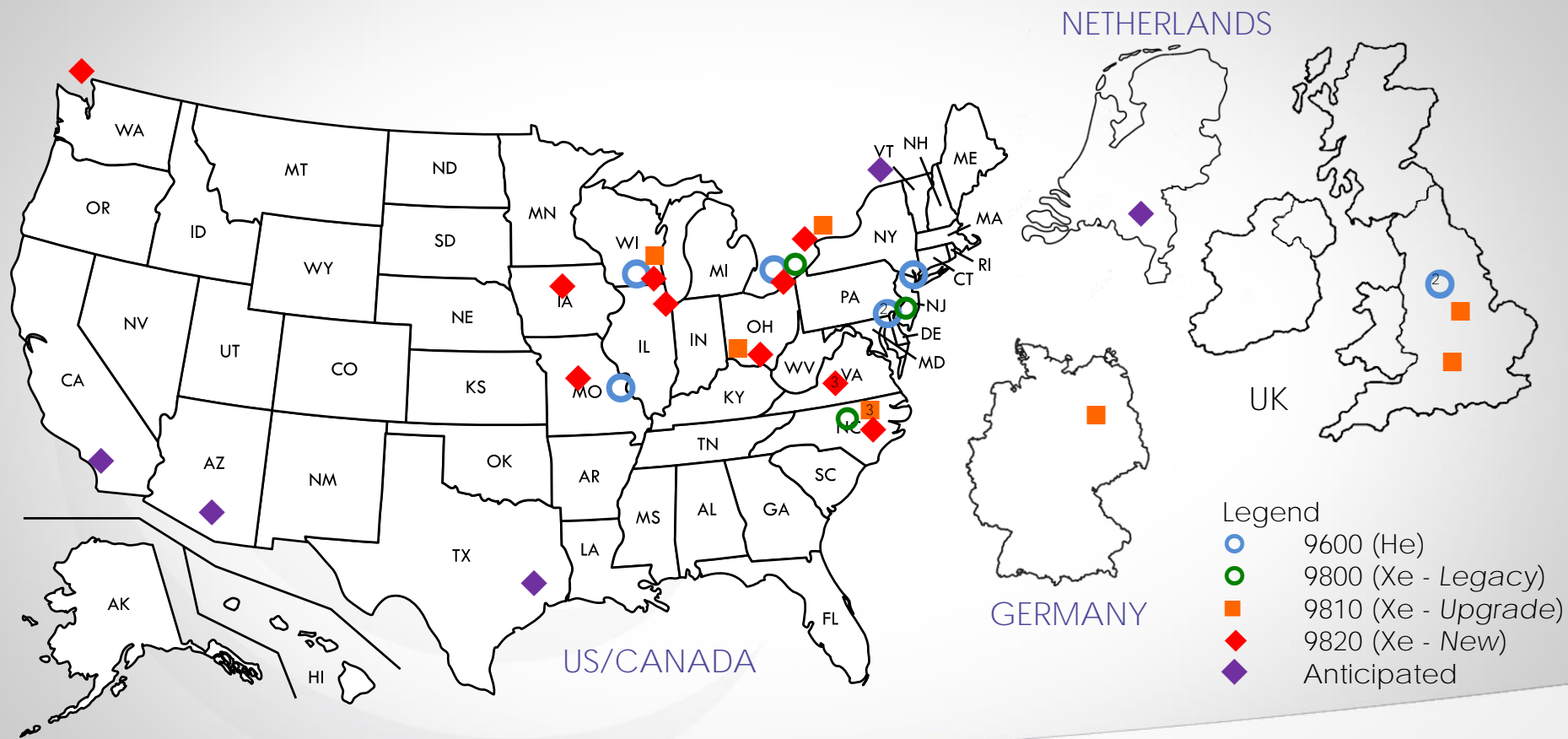
Clinical ^{129}Xe MRI Research Activity

- 42 active/pending clinical studies
- 11 different diseases/conditions
- 5 interventions being tested
- 6 funded by pharma

From Qualitative to Quantitative ^{129}Xe Ventilation MRI

a. Ventilation image   b. Bias-field corrected   c. Registered proton image   d. Detected vasculature

e. Thoracic cavity mask   f. Unscaled histogram   g. Scaled histogram   h. Binning map

He, M., et al. Acad. Radiol., 2014; He, M., Que, L., Huang, Y.C., et al. Acad. Radiol. 2016

From Qualitative to Quantitative 129Xe Ventilation MRI

Pre-

Post-

Repeat Scan

Baseline
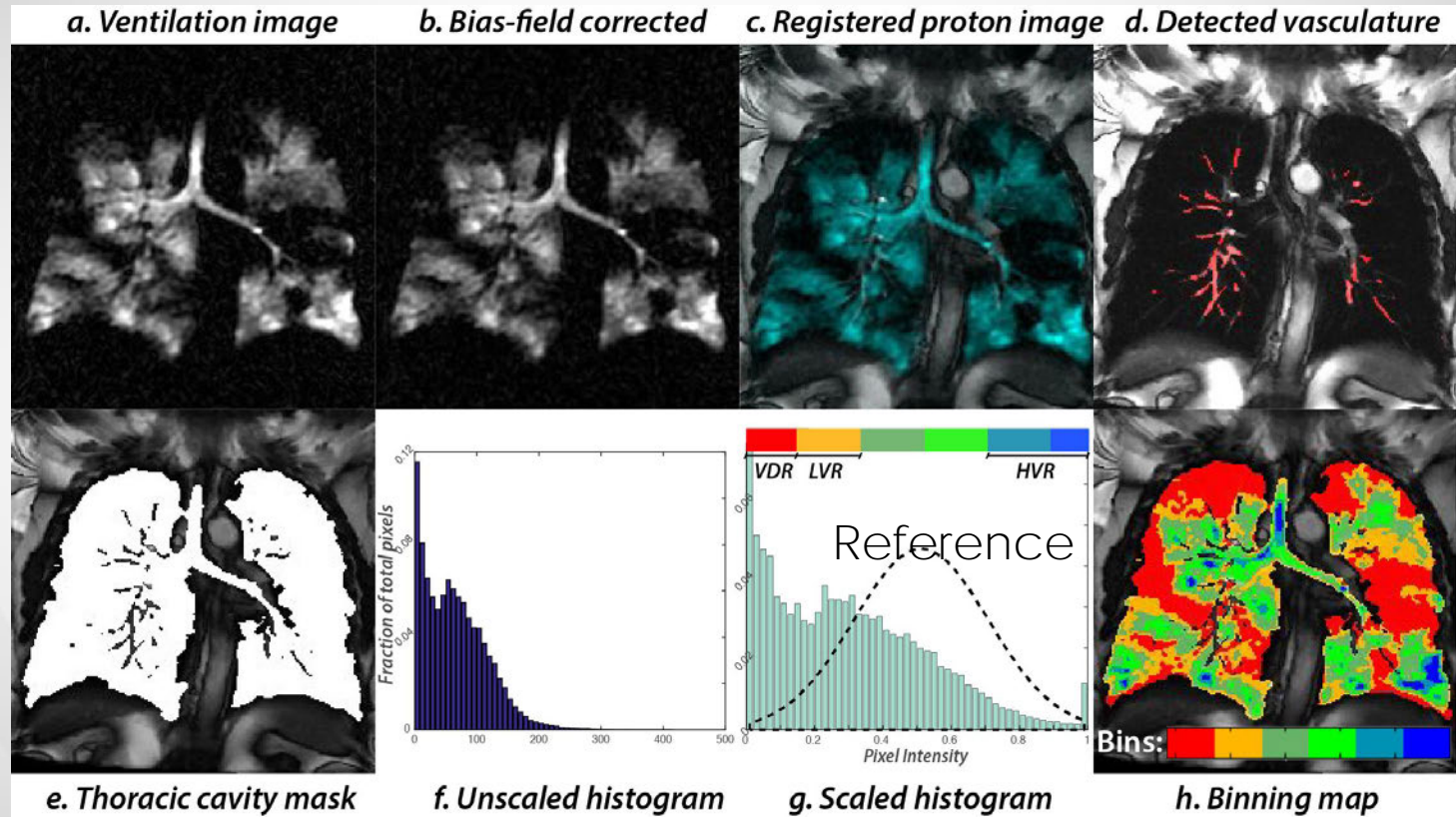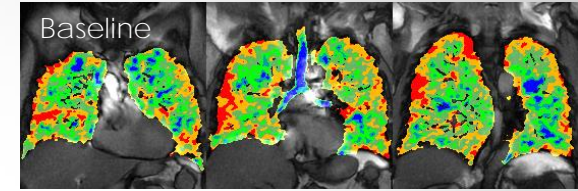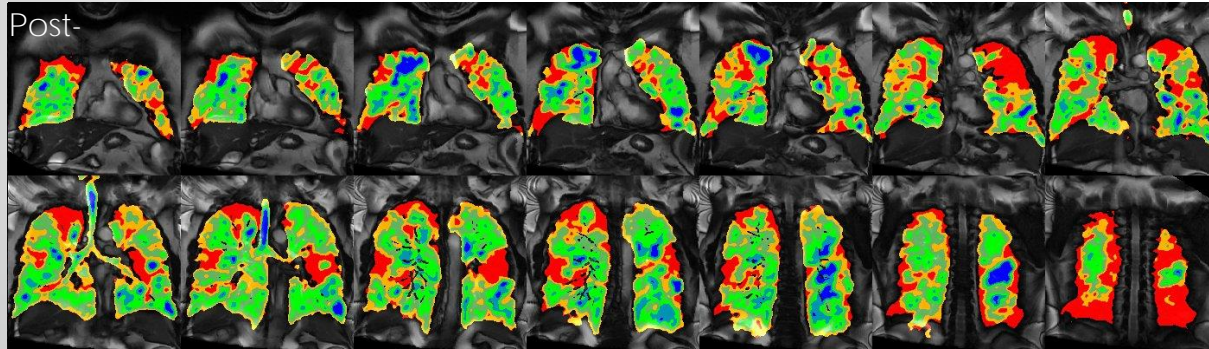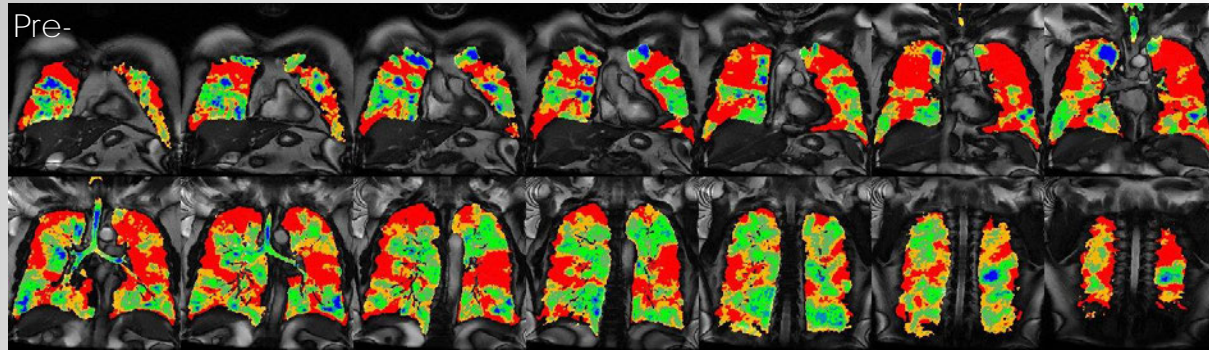
VDP =10.2%, low = 29.5%, high =9.5%, CV = 0.50

Re-test
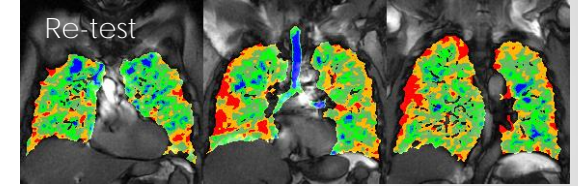
VDP = 10.9%, low = 27.2%, high =9.1%, CV = 0.49

B.

VDP = ± 1.52%

D.

FEV1 ± 7.18%
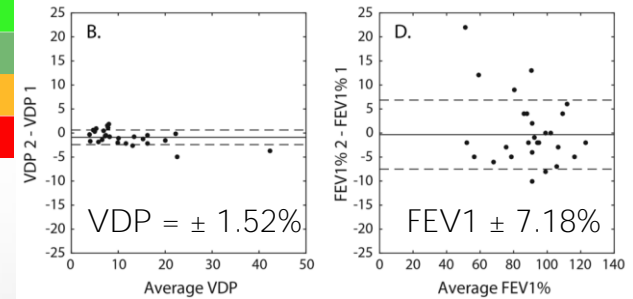
Ebner, Virgincar, Invest. Radiol. 2016

POLAREAN

Subject	FEV1(%)	VDP (%)	Low%	High%	CV	Skewness
Pre-	53	33.6	26.4	5.9	0.77	0.68
Post-	83	18.6	25.7	9.5	0.58	0.24
Reference	106.7±13	2.6±1.8	17.5±5.7	16.7±3.3	0.37±0.04	0±0.11

Imaging Guidance for Bronchoscopic Interventions

Pre-stent
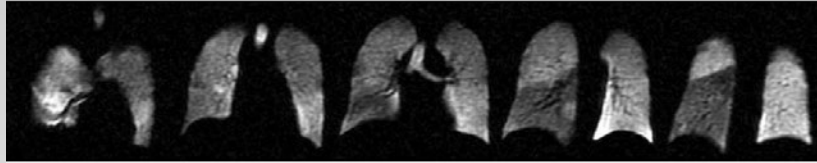
FEV1 = 51, VDP = 1.8%, LVR = 20.8%, HVR = 14.9%, CV = 0.39

Post-stent

FEV1 = 55, VDP = 2.0%, LVR = 9.3%, HVR = 14.1%, CV = 0.29

Kamran Mahmood

POLAREAN

Mahmood, Ebner, He, et al. Am. J. Transplant. 2017
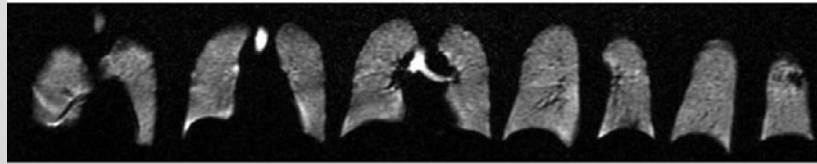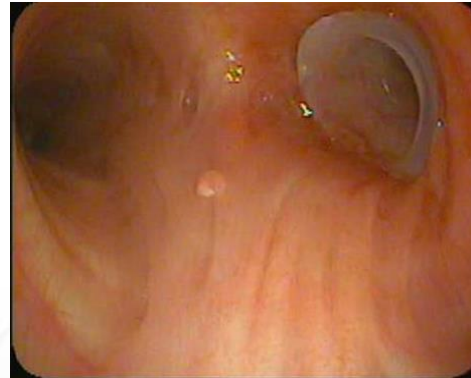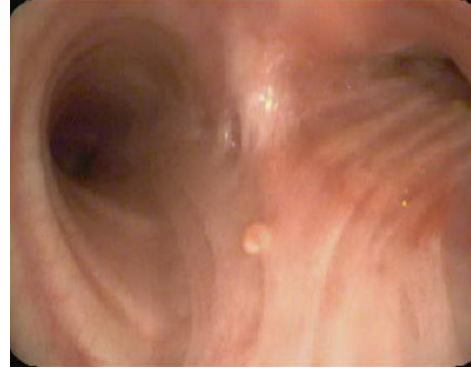
Endobronchial Valves to Treat COPD

- Potential relief for 3-4 million COPD patients with emphysema

- Pulmonx, Spiration valves – FDA approved in 2018

- $10,000 in disposables cost, operating room time, 3-5 day hospital stay.

- Paid for under major chest DRG

POLAREAN
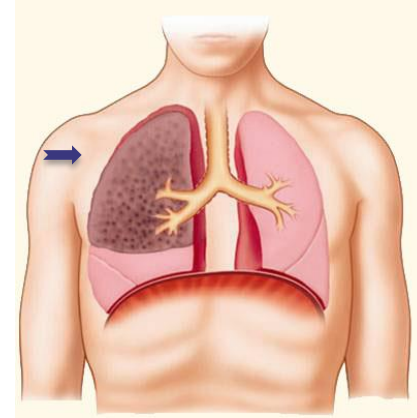
Interventional Pulmonologists want 129Xe MRI

- **Currently operating "blind"** based on inference from Chest CT

- 3D functional MRI enables
  - Candidate selection
  - Valve placement guidance
  - Follow-up monitoring

- Improves outcomes and reduces costs

Candidate 1   Candidate 2   Poor Candidate

POLAREAN
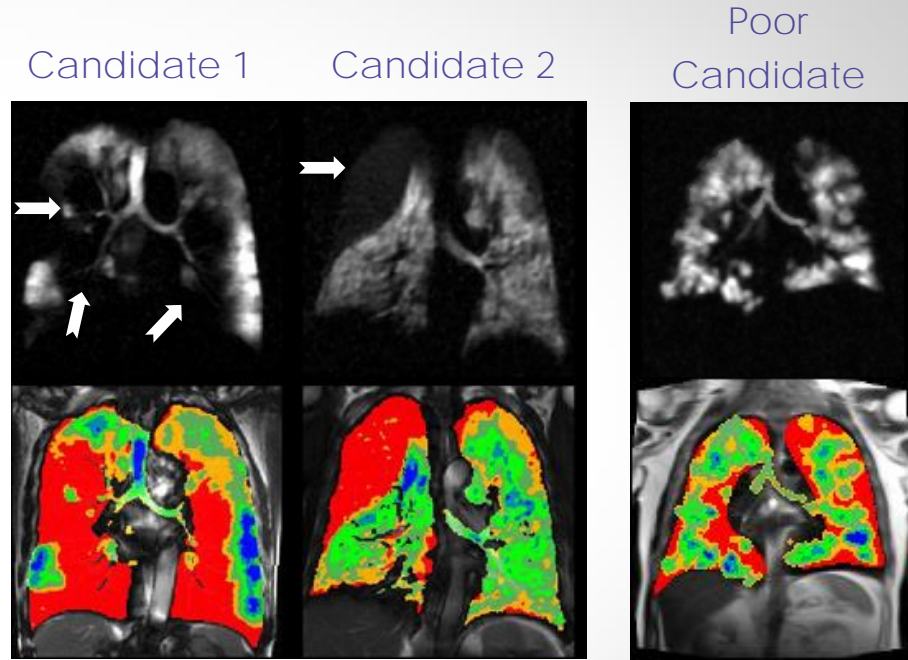
Moving Beyond Ventilation…

Clinicians increasingly asking us to address unexplained dyspnea
(3.4 million visits to ER in US each year)
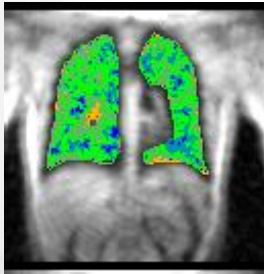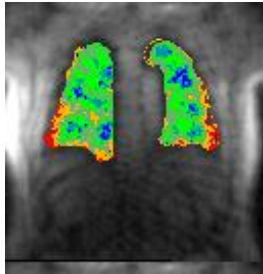
Patient 1   Patient 2   Patient 3   Patient 4   Patient 5

POLAREAN

Imaging All Aspects of Function in One Breath

POLAREAN

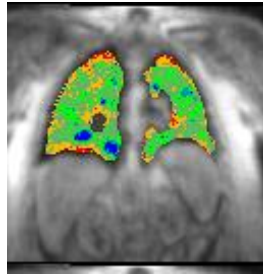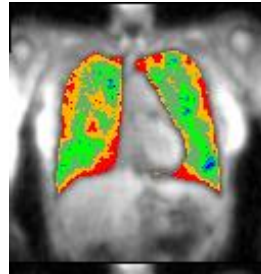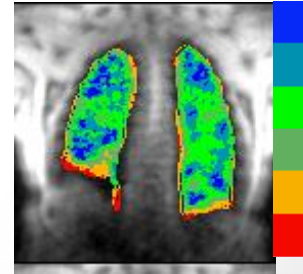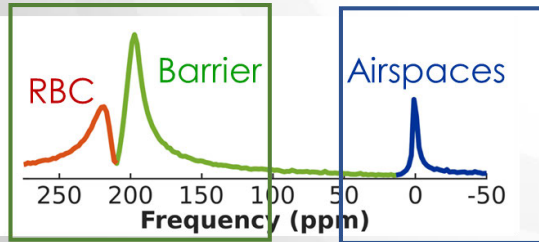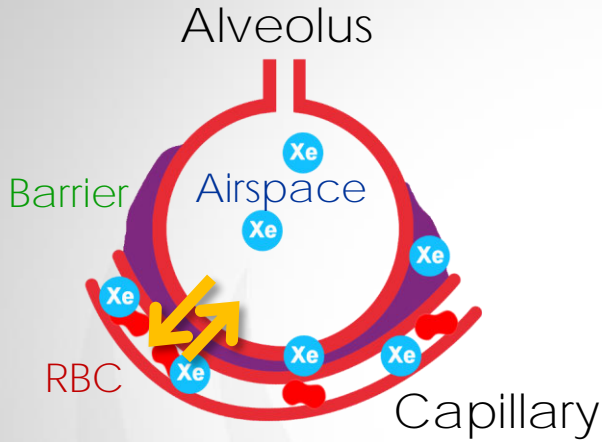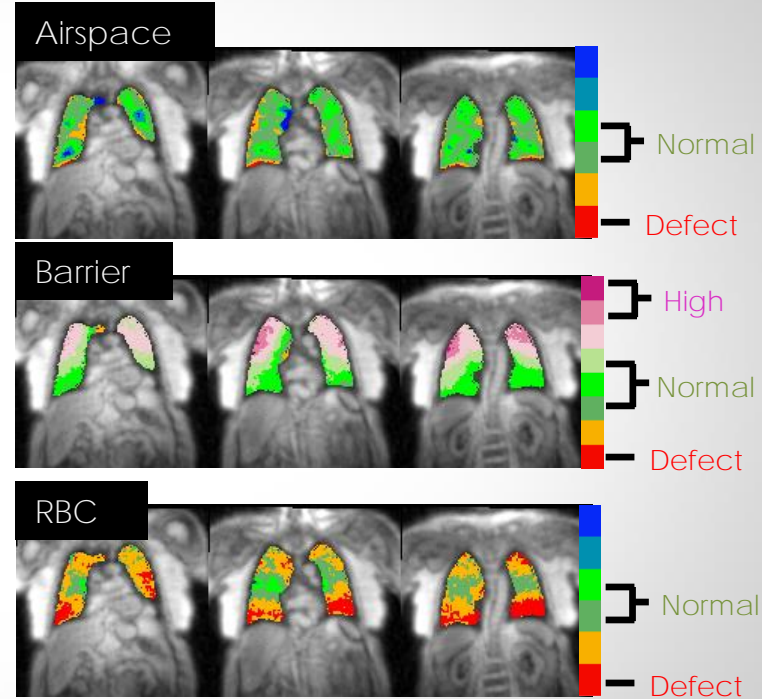# Now We See the Whole Disease Burden

POLAREAN
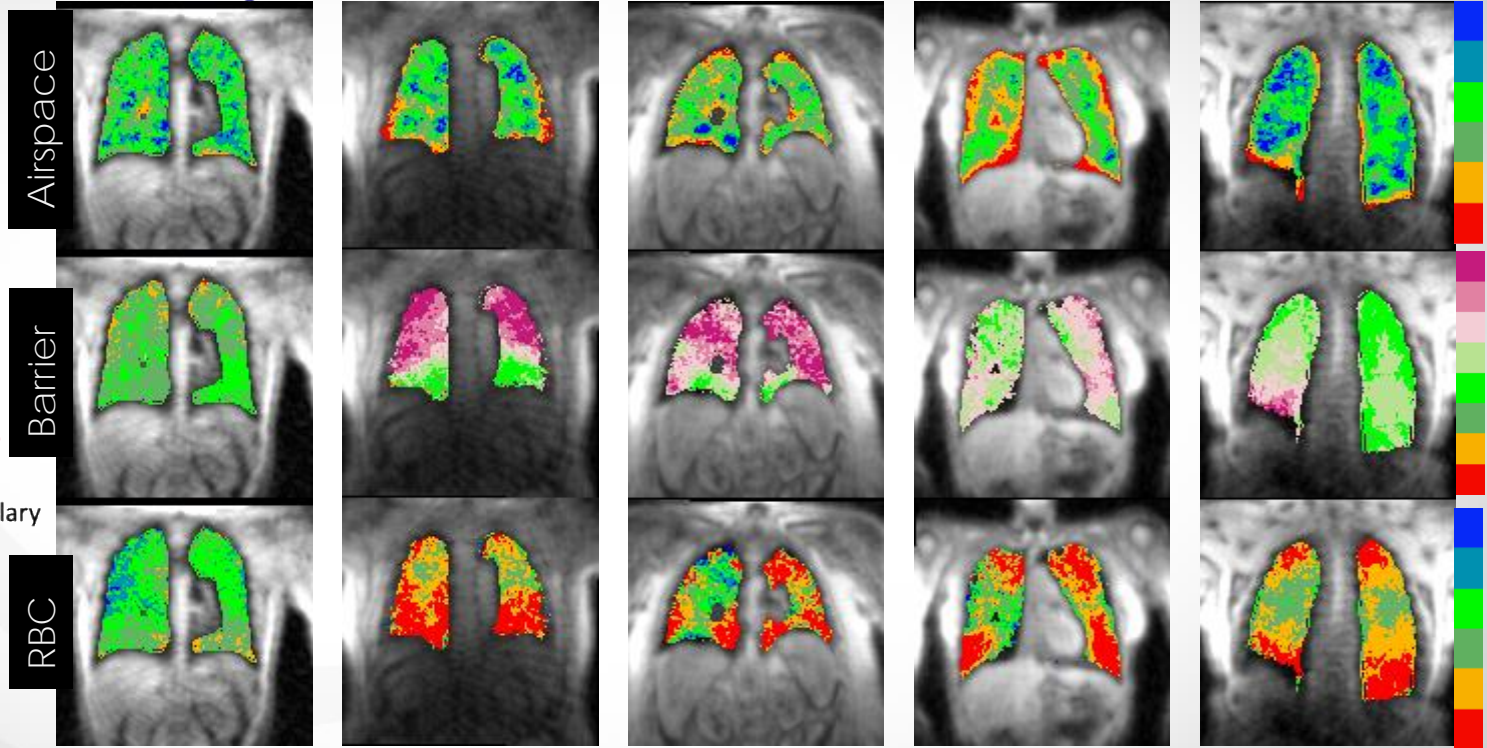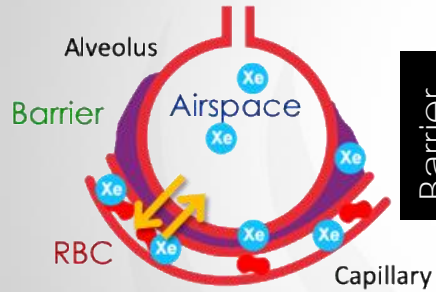
Visualizing Therapy Response in IPF
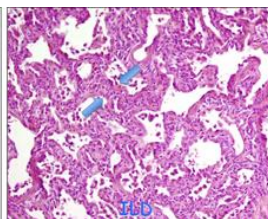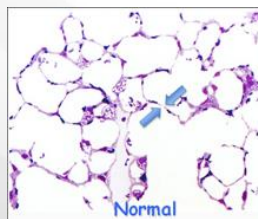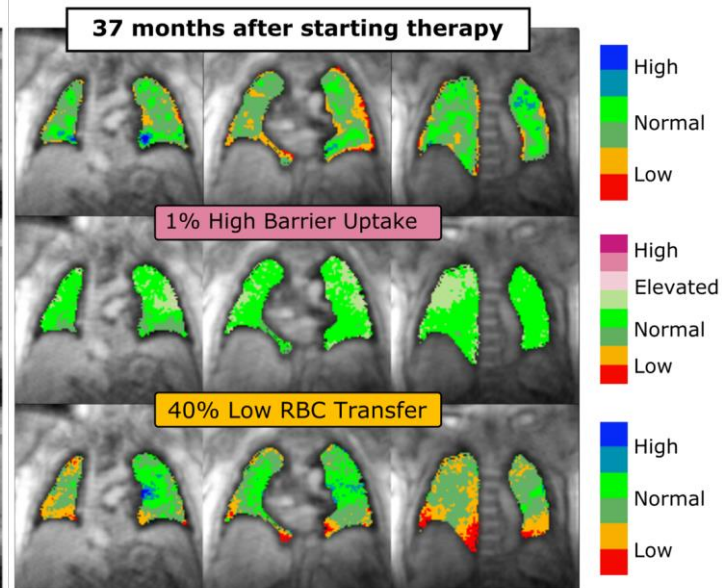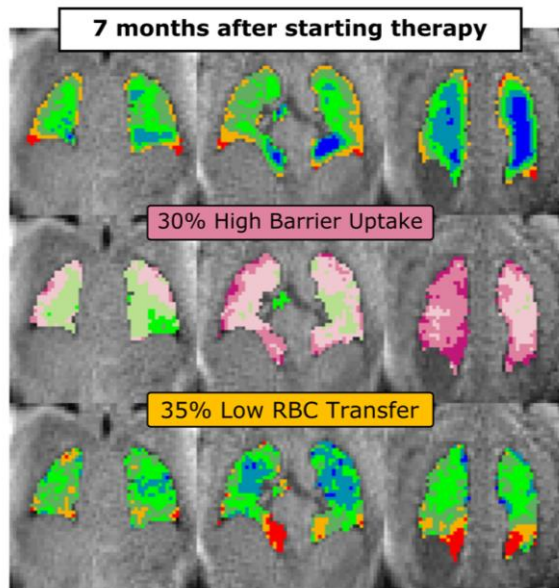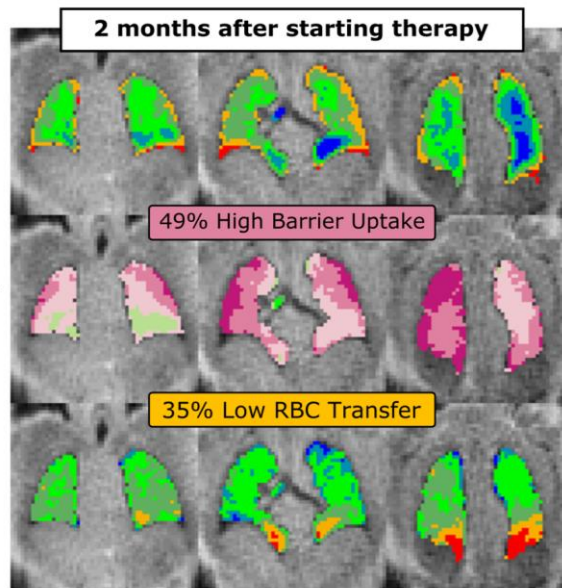
Patient Showing Continued Progression

Rankine, An. Amer. Thoracic. Soc. Under review
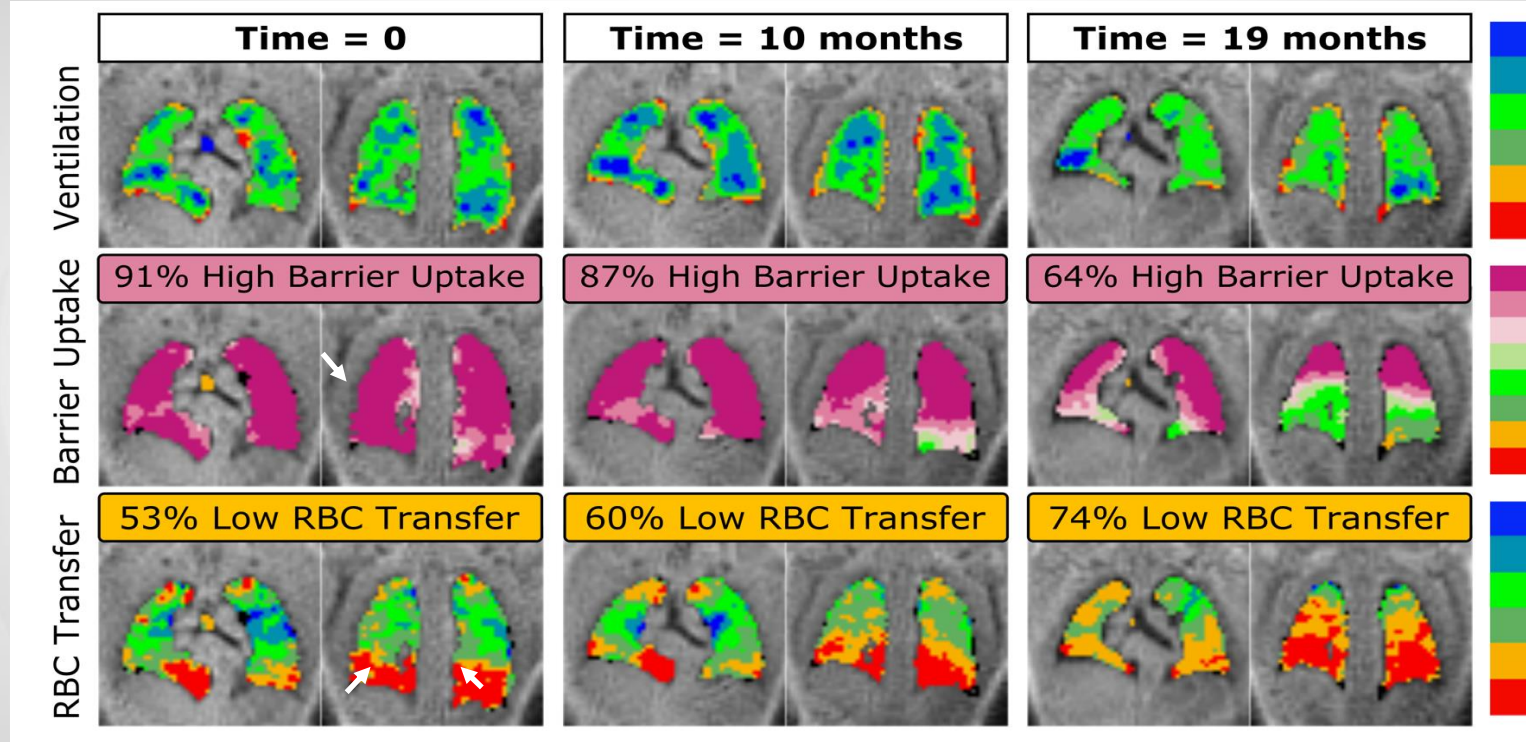
Prognostic and Predictive Information for IPF Care
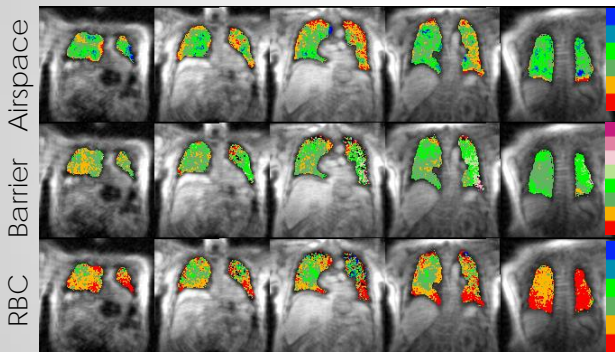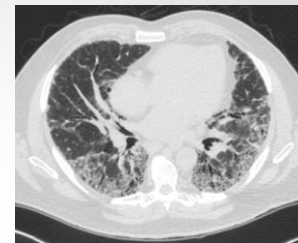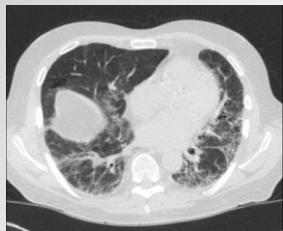
- Normal barrier, Poor RBC transfer
- Unlikely to benefit from therapy.
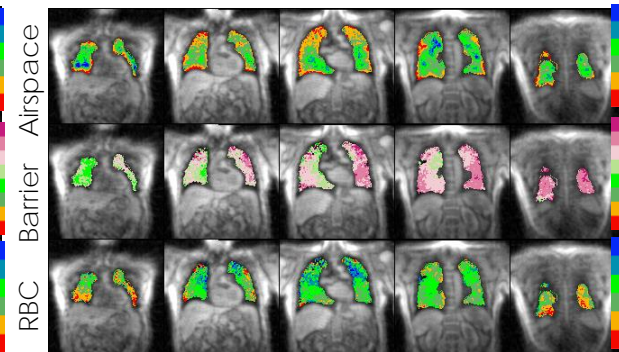
- High Barrier, Preserved RBC Transfer
- Likely to benefit from therapy
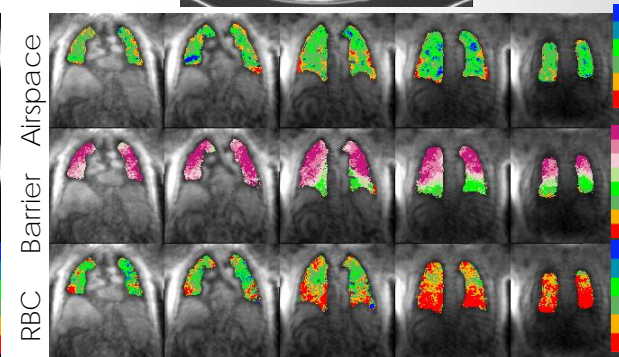
- High Barrier, Poor RBC Transfer
- May benefit from drug
- Accelerate transplant listing

Mammarappallil JG, et al, J Thorac Imaging 2019

POLAREAN

From Prognosis/Monitoring to Diagnosis …
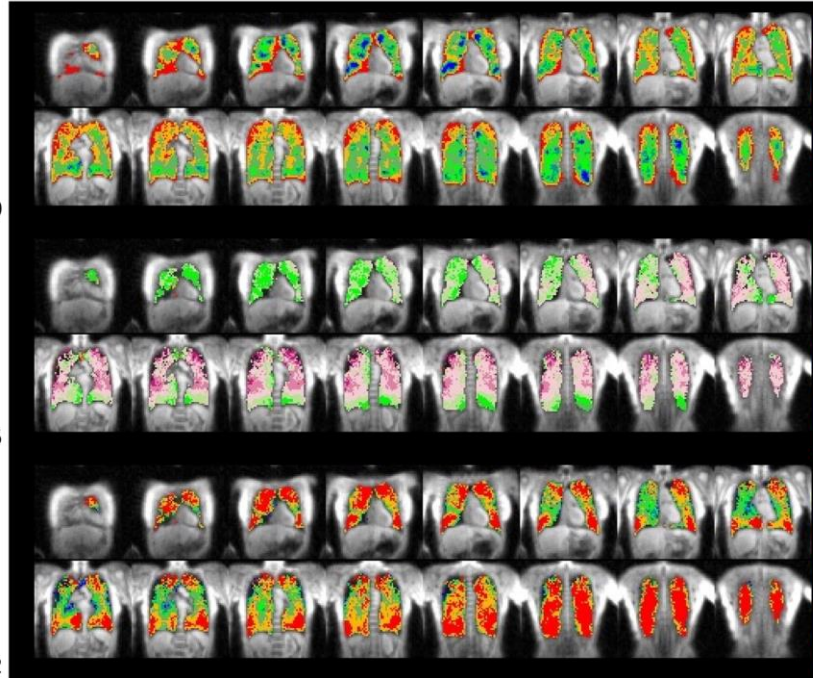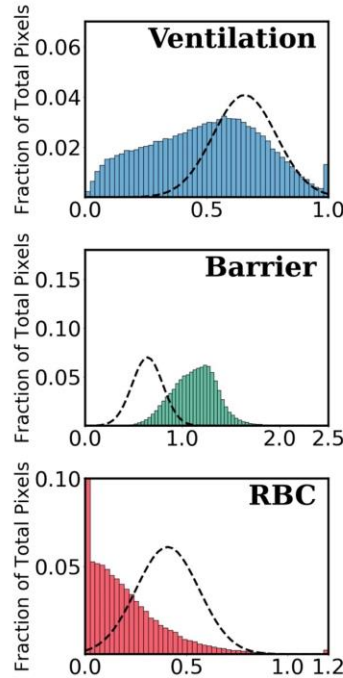
^{129}Xe Spectroscopy Adds Hemodynamics and Oxygenation
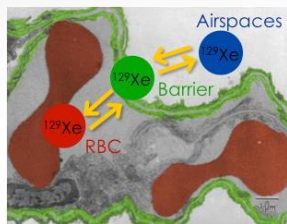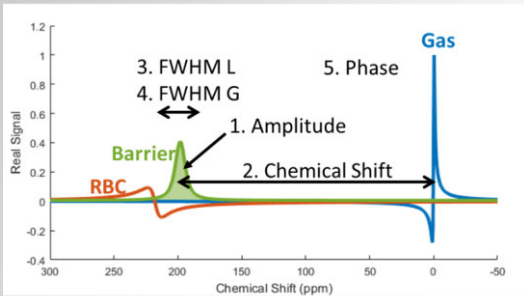
Sampling the alveolar-capillary interface every 20 ms

Bier et al., NMR in Biomed 2018

POLAREAN

^{129}Xe MRI to Differentiate Diverse Cardiopulmonary Diseases

Sudarshan Rajagopal

Co-Director, Pulmonary Vascular Disease Center
Assistant Professor of Medicine and Biochemistry
Duke University Medical Center

^{129}Xe Ventilation MRI to advance personalized medicine (CF and beyond)

Jason C. Woods, Ph.D.
Center for Pulmonary Imaging Research
Pulmonary Medicine
Radiology
Neonatology
Physics

Ranked #2 in US (consistently #1-3 in Pulm)
1000 faculty, $2.4B/yr revenue

Clinical standard for lung function:

Pulmonary Function Testing (PFT)

Used for diagnosis or management of ~100% o

Spirometry (FEV_1), Diffusion of CO (D_LCO

Global measurements (expressed as %)

Notoriously insensitive to early disease

(D_LCO even more insensitive than FEV_1)

Dated technology

Hyperpolarized ^{129}Xe MRI

Measure Ventilation

cool
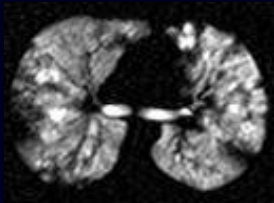
Routine clinical management of lung disease

Spirometry 2019

CAPAC

RESP

WITH A VIEW OF
OF DETE

BY

COMMU

ON

Receiv
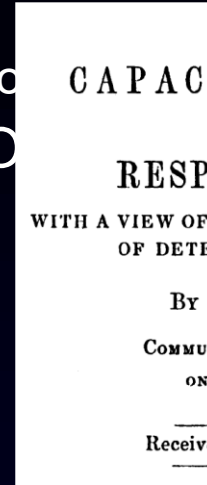
1. Cool: Ventilation MRI via ^{129}Xe

Subject in MRI Scanner

Bag of HP ^{129}Xe

Axial Slices Acquired

Inhaled ^{129}Xe

Defects identified →
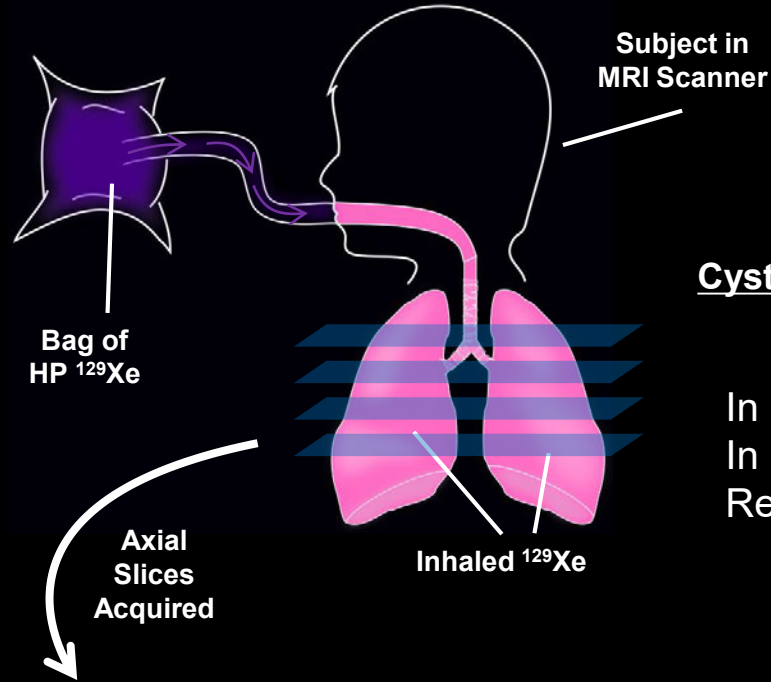
Control, 6 y.o. female
FEV$_1$ = 95%, VDP = 1.8%
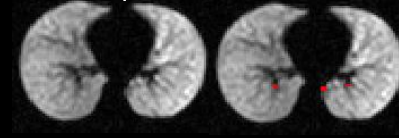
11 y.o. male
FEV$_1$ = 102%, VDP = 27.5%
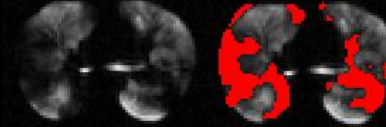
15 y.o. female
FEV$_1$ = 72%, VDP = 32.2%

Cystic Fibrosis:

In almost every CF patient, there are defects
In every patient with obstructive lung disease (asthma, COPD, ..)
Recall, PFTs (FEV$_1$) are insensitive to early obstruction

CF is a 'model' obstructive lung disease:

i)   We understand the mechanism of disease

ii) There is a predictable, steady decline in lung function (2-4%/year—more than COPD)

iii) Robust response to new treatments

1. **Thomen *et al. J Cyst Fibros.* 2016**
2. **Walkup *et al. Pediatr Radiol.* 2016**

Cincinnati Children's
changing the outcome together

Our initial Pediatric Study

- Image early CF Lung disease to understand sensitivity
- Philips 3T magnet; Polarean 9810 polarizer (9820 shown)
- Measure regional ventilation
  - Measure ventilation defect percentage (VDP, measured as <60% of avg lung signal)
  - Compare to FEV_1
  - Breath = $1/6^{th}$ predicted total lung capacity, up to 1L
- Monitor safety in pediatrics
  - SpO_2 & heart-rate throughout imaging

Group	Age, years (range)	Sex	Lung Function FEV_1% (range)
Cystic Fibrosis (n=12)	12.5 ± 2.3 (8-16)	3 M/ 9 F	101.3 ± 15.2 (72-120)
Controls (N=11)	11.5±3.2 (6-16)	7M/4F	100.3±8.5 (89-115)

Polarean 9820 ^{129}Xe polarizer
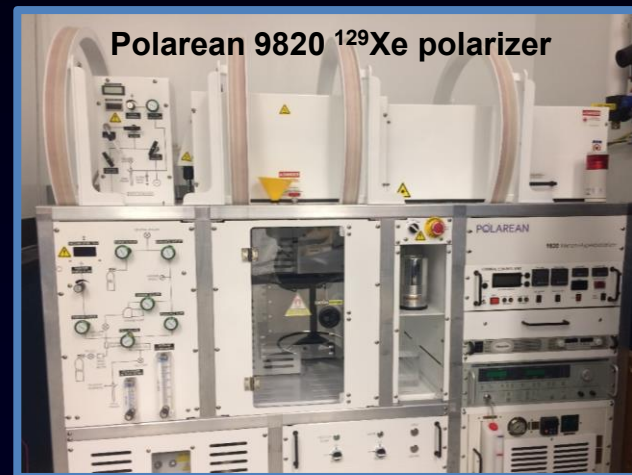
Safety & tolerability of ^{129}Xe MRI in children

- No subjects withdrew from the study
- All subjects were able to perform the coached breath-hold maneuver (max 16 sec)

Imaging dose:	Baseline SpO$_2$	Lowest SpO$_2$	2-min post SpO$_2$	P-value (baseline vs 2-min post)
All subjects (Ref 1) (11 CF & 11 Controls)	**98.1 ± 1.4 %**	92.6 ± 6.7%	**97.5 ± 1.7 %**	0.16

- No significant changes in heart-rate throughout the imaging
- Any transient side effects were mild and spontaneously resolved within 30s
  - (Tingling extremities, dizziness, euphoria– paresthetic properties of Xe)

No significant difference in the SpO$_2$ changes between controls and CF subjects

- No serious adverse events

- Results[1] are in agreement with safety assessments of ^{129}Xe MRI in adults.[2,3]
- We routinely perform ^{129}Xe MRI in adults & children as young as 5 years old (most of whom can't perform PFTs!) & have imaged over 300 subjects.

1. Walkup *et al. Pediatr Radiol.* 2016   2. *Radiology.* 2012; 262: 279.   3. *Acad. Radiol.* 2012; 19: 941.

Cincinnati Children's
changing the outcome together

Published Results: ^{129}Xe Ventilation Defects (VDP) in CF
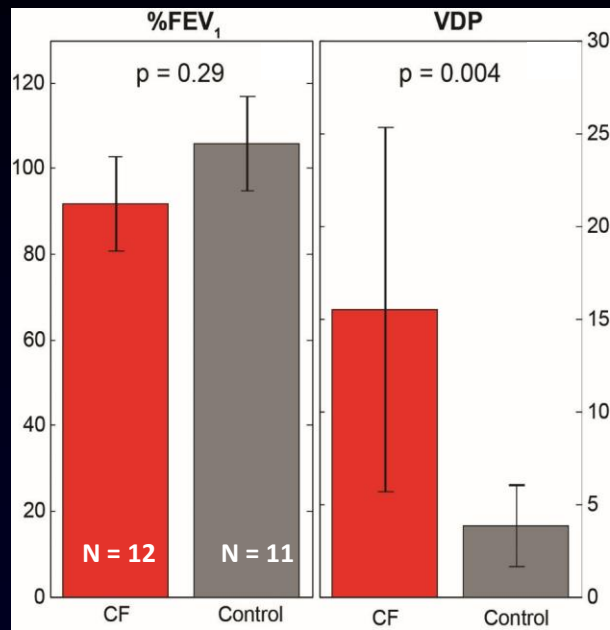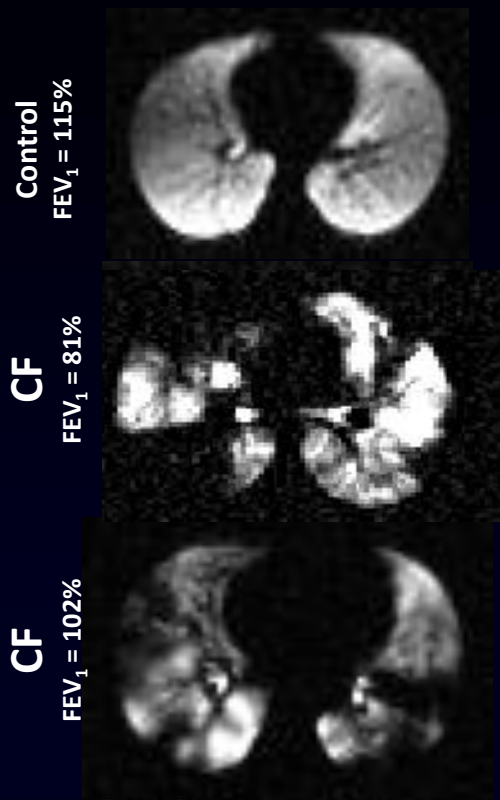
^{129}Xe ventilation MRI is a sensitive technique for measuring airway obstruction

Ages 6-16

RL Thomen et al, *J Cyst Fibros* 2017; 16: 275-282

^{129}Xe MRI data, to Dec 2018

Group	Age @ MRI (range)	FEV$_1$ %-predicted (range)	^{129}Xe VDP (range)
CF (n=48)	14.5 ± 7.9 yrs (6-45 yrs)	93% ± 21% (38-131%)	19.4% ± 9.4% (3.2-42.5%)
Control (n=11)	11.5 ± 3.2 yrs (6-16 yrs)	100.3% ± 8.5% (89-115%)	6.4% ± 2.8% (1.8-12.0%)
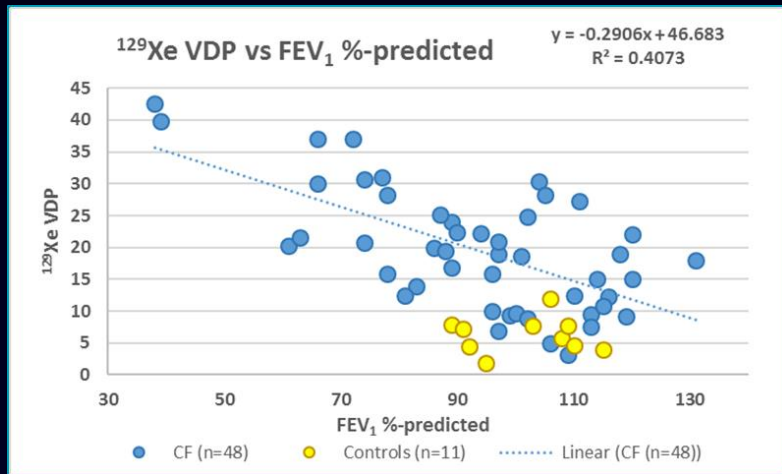
CF patients with clinically preserved lung function (FEV$_1$ ≥ 80%; N = 36)

^{129}Xe VDP vs FEV$_1$ %-predicted

$y = -0.2906x + 46.683$
$R^2 = 0.4073$

- • CF (n=48)   ○ Controls (n=11)   ····· Linear (CF (n=48))

p = 0.78

CF (n=36) 103% ± 12%   Control (n=10) 110% ± 9%

p < 10^{-7}

CF (n=36) 16% ± 7%   Control (n=10) 6% ± 3%
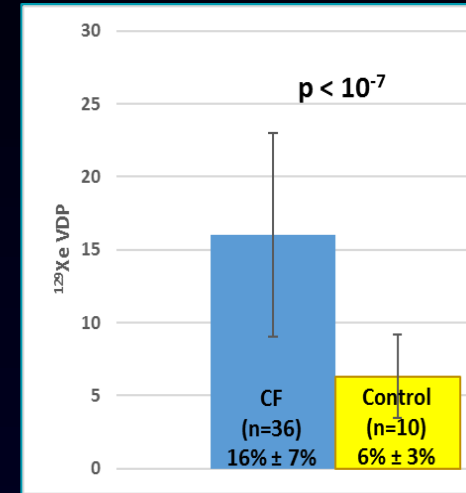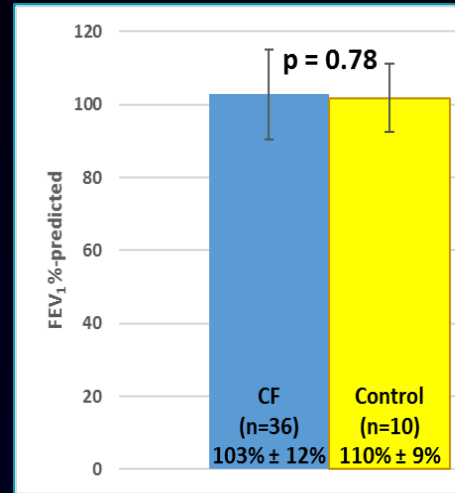
- Ventilation deficits easily detected in CF patients with normal spirometry—^{129}Xe is sensitive to early airway obstruction

Demonstration in CF (as a model disease)

Low same-day Variability (< 2%)

Disease Progression / Treatment Response
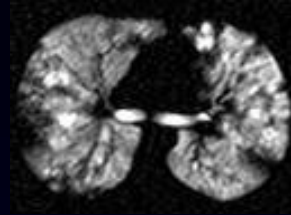
1st Acquisition
VDP=20.3%
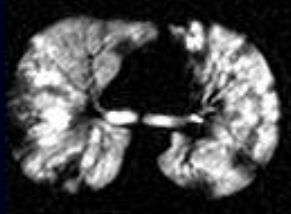
2nd Acquisition
VDP=21.5%

Baseline
VDP=12.8%
VDP=17.0%
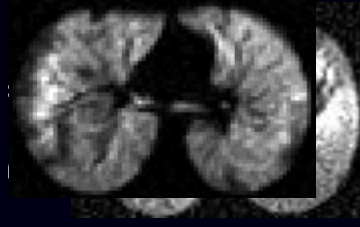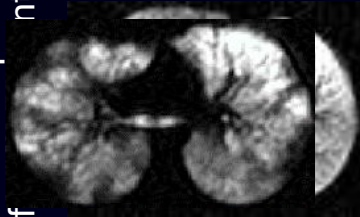
Follow Up
VDP=20.4%
VDP=18.7%
+780 days
Lumacaftor / Ivacaftor
F508del(+/+)
Cincinnati
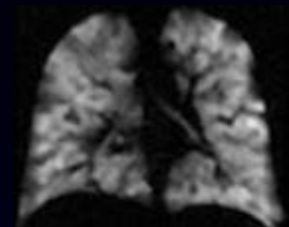
VDP=48.4%
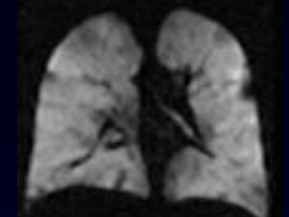
VDP=17.4%
Ivacaftor
G551D
Virginia

Images are *very* effective at patient/family communications

Is our routine management working, or should we make changes?

Is the new drug working in *my* patient? (Also, testing new pharma)

Altes TA, et al. *Proc 20th Annual Meeting of ISMRM,* 2012: 1359

Take-home message for ^{129}Xe MRI: *Sensitivity, regionality*

14 y.o. male control subject, FEV$_1$ = 103% (normal lung function) ^{129}Xe VDP = 2%
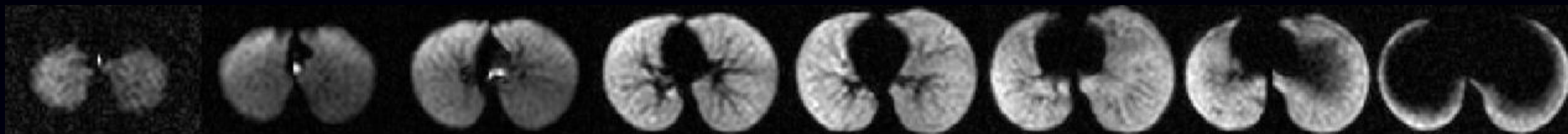
6 y.o. female control subject, FEV$_1$ = 98% (normal lung function) ^{129}Xe VDP = 3%
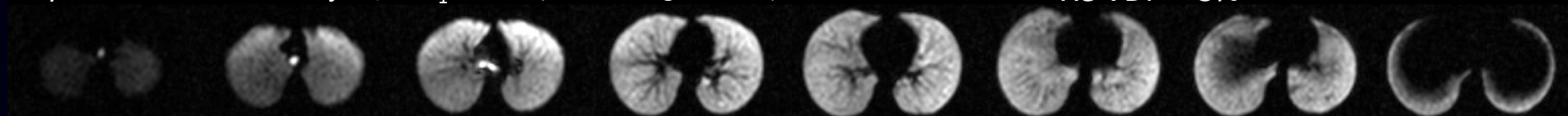
14 y.o. CF subject, FEV$_1$ = 96% (normal lung function) ^{129}Xe VDP = 16%
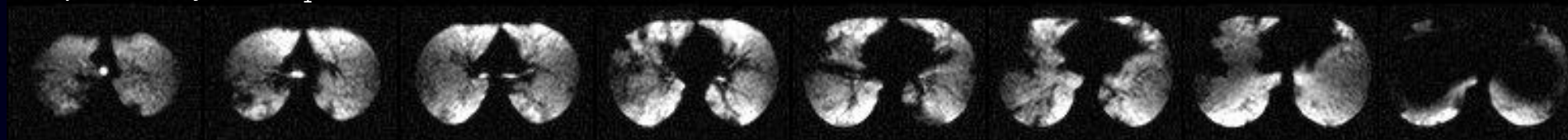
14 y.o. subject at risk for BOS (post-BMT), FEV$_1$ = 88% (normal lung function) ^{129}Xe VDP = 28%

Opens door to true individualized, precision medicine

Is "Precision Medicine" just a platitude?

No. Pulmonary medicine is entering a treatment renaissance
(think cardiology, 20-30 years ago)

CF: *highly effective* CFTR modulators for broad genotypes

Asthma: new targeted biologic therapies every few months

COPD: EB valves for volume reduction, new drugs on the horizon

Rare-lung diseases: sirolimus for LAM, GM-CSF therapy in PAP

ILDs/IPF: nintedanib and perfenidone , new treatments coming!

Cincinnati
Children's
changing the outcome together

Using ^{129}Xe MRI for Precision Respiratory Medicine

- N=1 studies

    e.g., Does *this* CFTR modulator work on *that* CF genotype?

- Regional treatments

    e.g., image-guided placement of endobronchial valves

- Phenotyped treatment

    e.g., new biologic treatment for asthma (e.g. eos atopic)

- Detection of early onset disease

    e.g., treatment of early BOS post-transplantation

- Randomized trials with fewer patients

    e.g., Does alpha-1 replacement therapy *actually* work?

Precision Medicine Example, CF

N=1 study: Does off-label drug X correct rare CF mutation?

Pre-treatment (VDP = 20%)
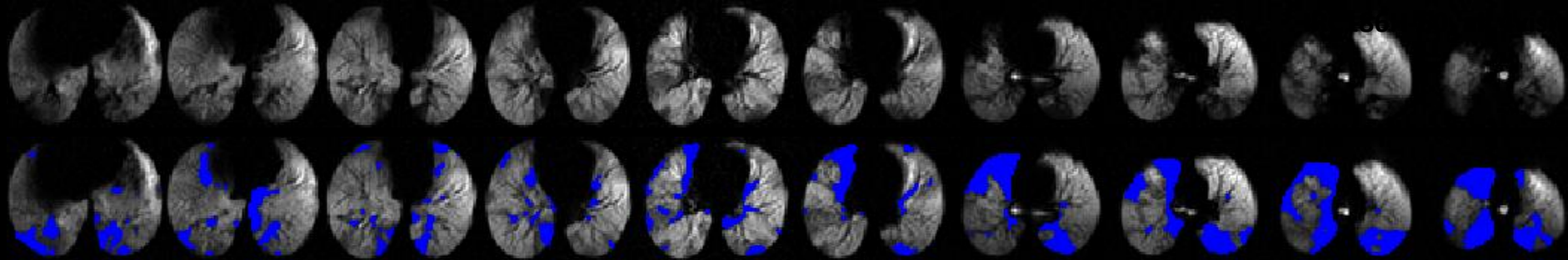
30 days post-treatment (VDP = 14%)

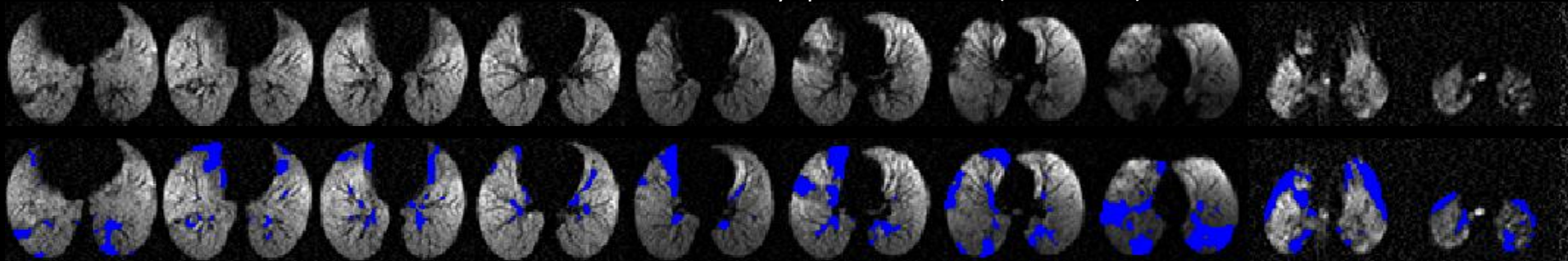MRI results consistent with PFTs, sweat chloride, other tests.
Did it correct the CFTR-mutation abnormality? A little….

Precision Medicine Example: regional response to BT
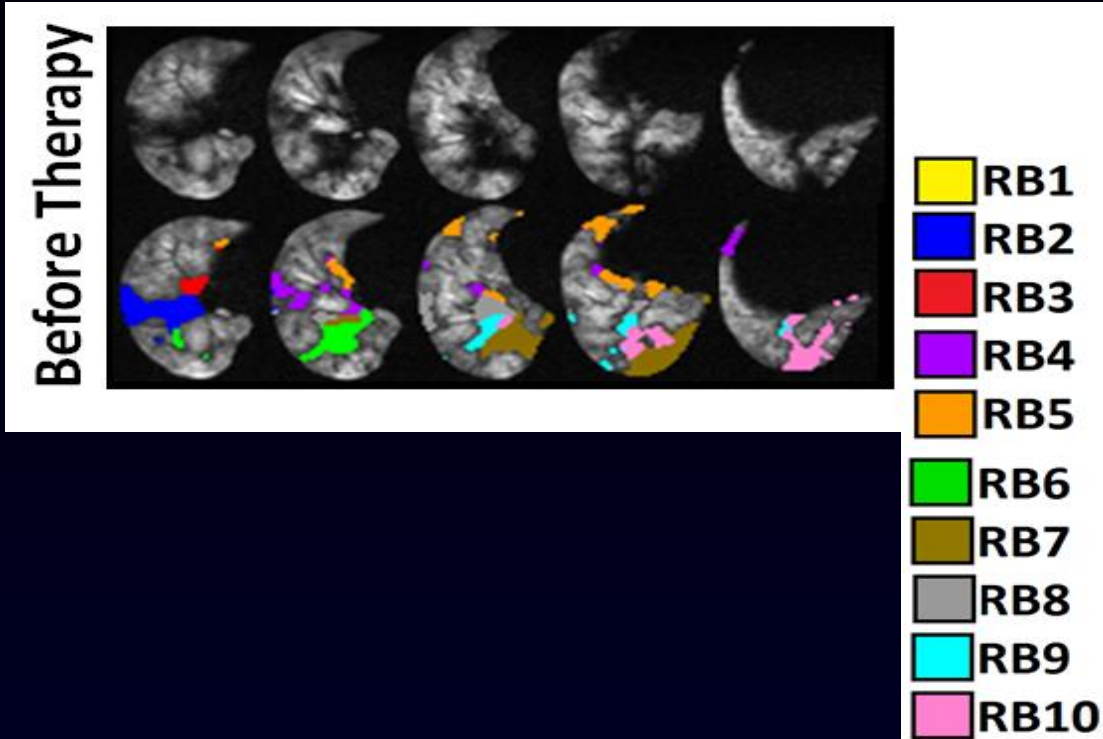
BT = bronchial thermoplasty

Bronchopulmonary segment

Precision Medicine Example: post-infectious BO

How much is the left lung participating in ventilation?
Obvious applications in lung- and bone-marrow transplantation

^{129}Xe VDP: 40.7%
Near absence of ventilation in left lung!

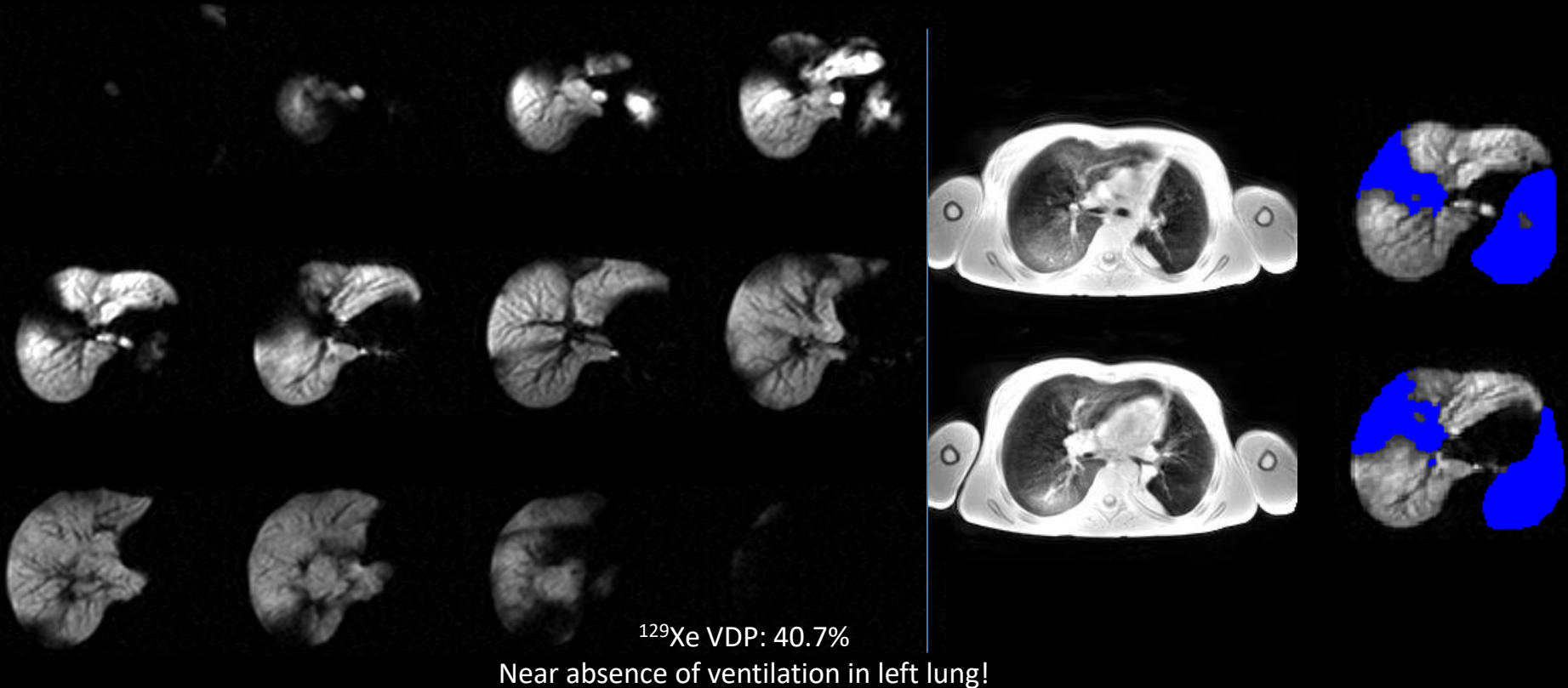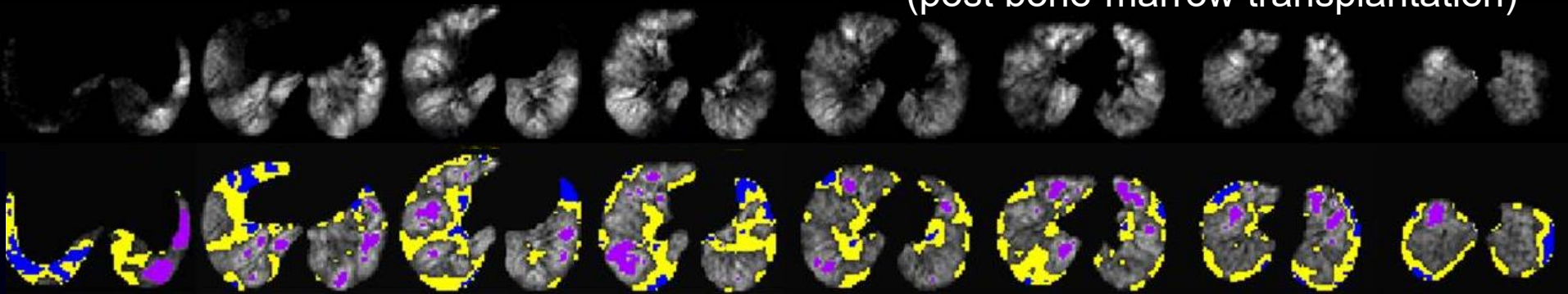# Precision Medicine Example: early BOS

(post bone-marrow transplantation)

03-06-2017
^{129}Xe VDP −28%

Treatment response?

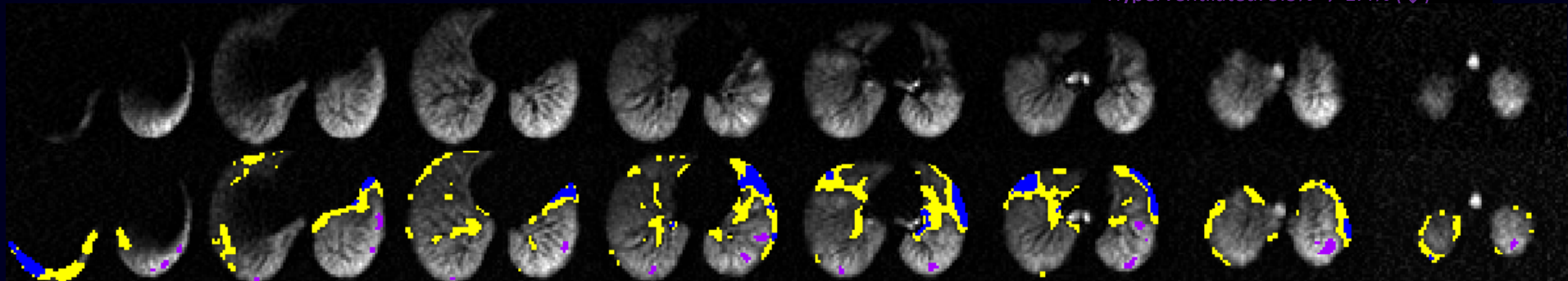05-08-2017
^{129}Xe VDP −18%

March → May
VDP: 28% → 18% (↓)
Complete defect: 5.4% → 3.7% (↓)
Partial defect: 22.8% → 14.3% (↓)
Hyperventilated: 5.3% → 1.4% (↓)

LL Walkup, *et al., Eur Respir J 2019*, in press.

Conclusions

Healthy   Cystic Fibrosis

$FEV_1 = 98\%$ $FEV_1 = 96\%$

^{129}Xe Ventilation MRI

- Very sensitive measure of early lung obstruction
  - More sensitive than any other traditional testing
  - Regional information unavailable by any other test
- Potential for routine clinical management
  - e.g., in CF lung disease
- Evaluate present & future regional treatments:
  - asthma, COPD, CF, post-transplantation, etc.
- Potential for true precision medicine, matching patient to treatment (recall, treatment is easier at early disease)

Cincinnati **Children's**
changing the outcome together
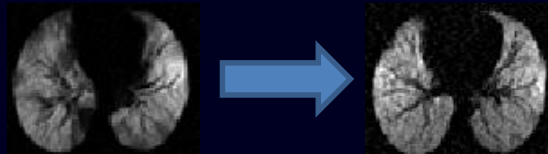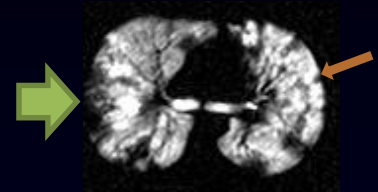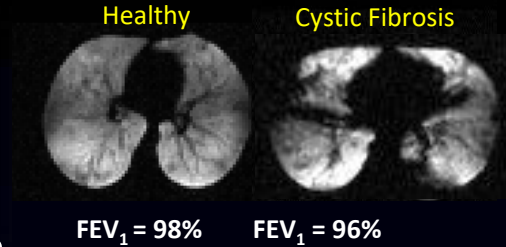
2018

Center for Pulmonary Imaging Research
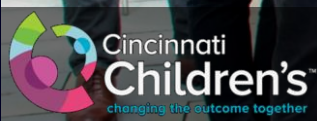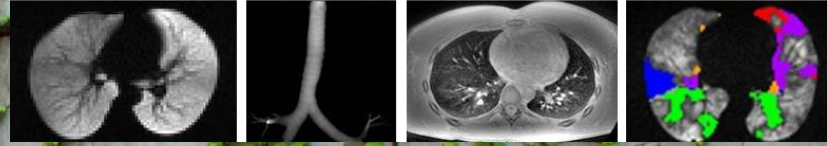
Cincinnati (not pictured): JP Clancy MD, Frank McCormack MD, Bruce Trapnell MD, Theresa Guilbert MD, many others
Washington University: Mario Castro, MD

Cincinnati Children's
changing the outcome together

Closing

- Revenue generating company, drug device combination company

- Completing non-inferiority Phase III clinical trial, NDA build already underway

- Added new IP for key clinical applications gas exchange and PAH

- Rapid progress path to breakeven post approval

- Combination of Pharma, implantable device, geographic market partner, and MRI manufacturers will fund future expansion

POLAREAN

Polarean Imaging plc
"POLX"

Breathtaking Images...

Investors Symposium
June 12, 2019

POLAREAN