Chest Imaging in CF

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Monitoring of CF lung disease using imaging

Why?
Standardization

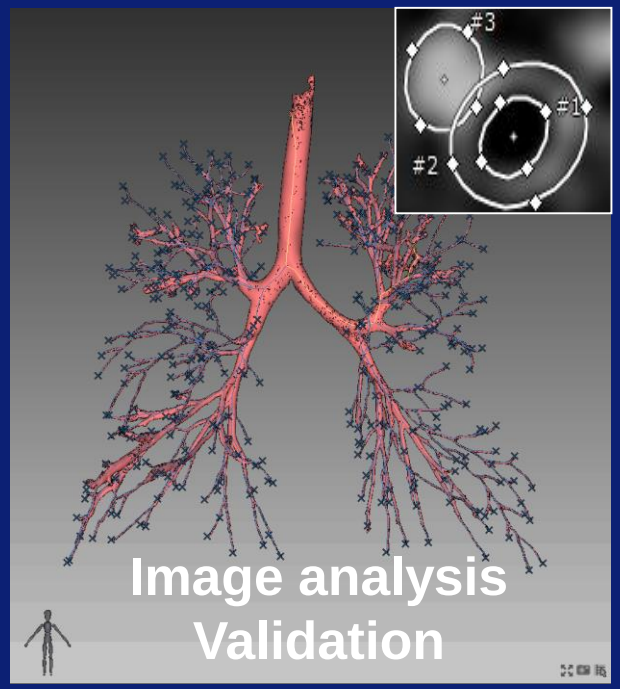
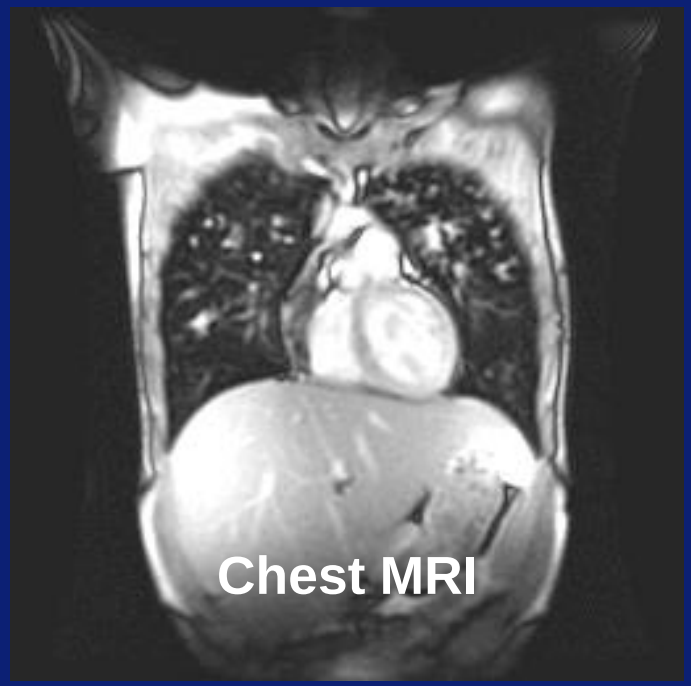


Image analysis
Validation



Chest MRI

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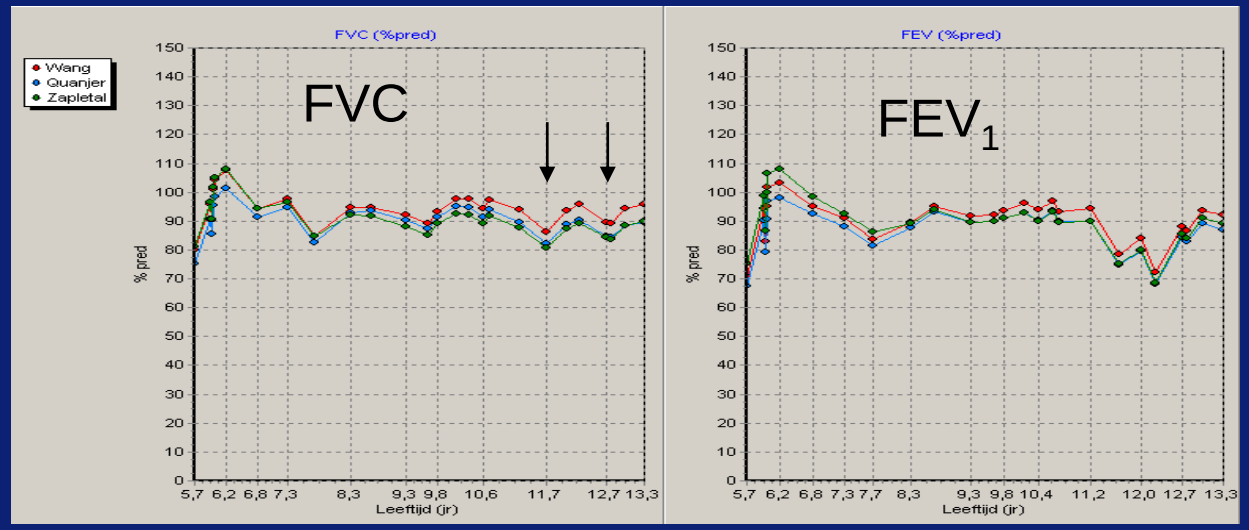
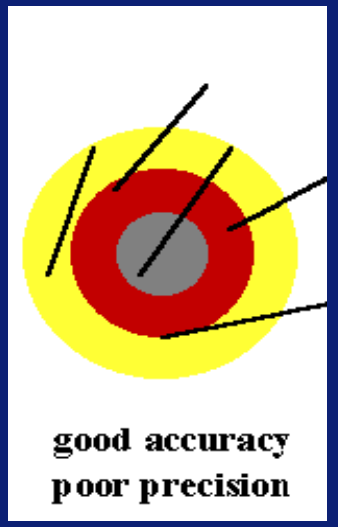
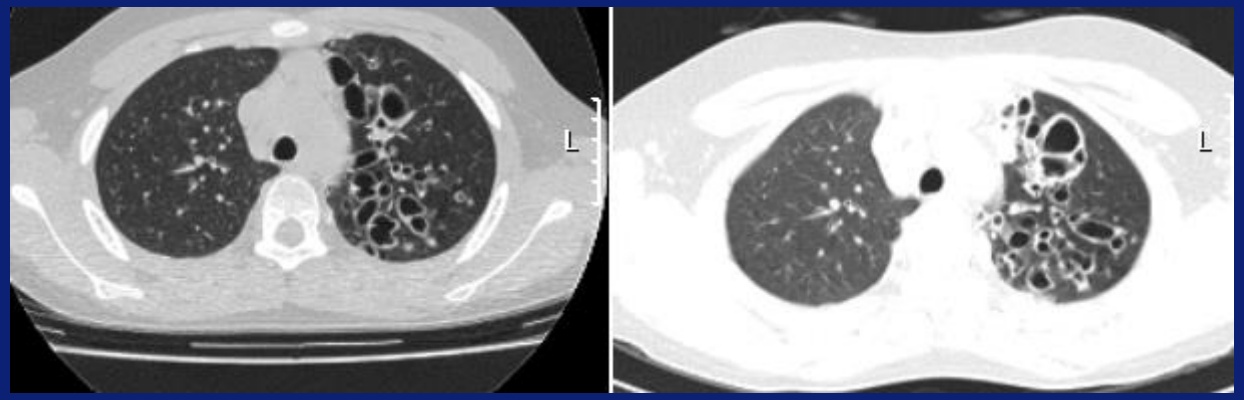
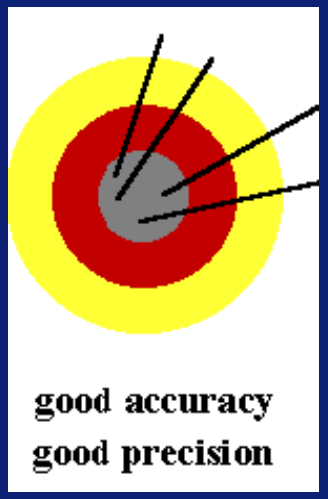
Why?: Spirometry more sensitive to detect localized structural abnormalities









Tiddens Ped Pulm 2002; De Jong ERJ 2004; De Jong Thorax 2006, Owens Thorax 2011, Thia, Abstract WS7.5

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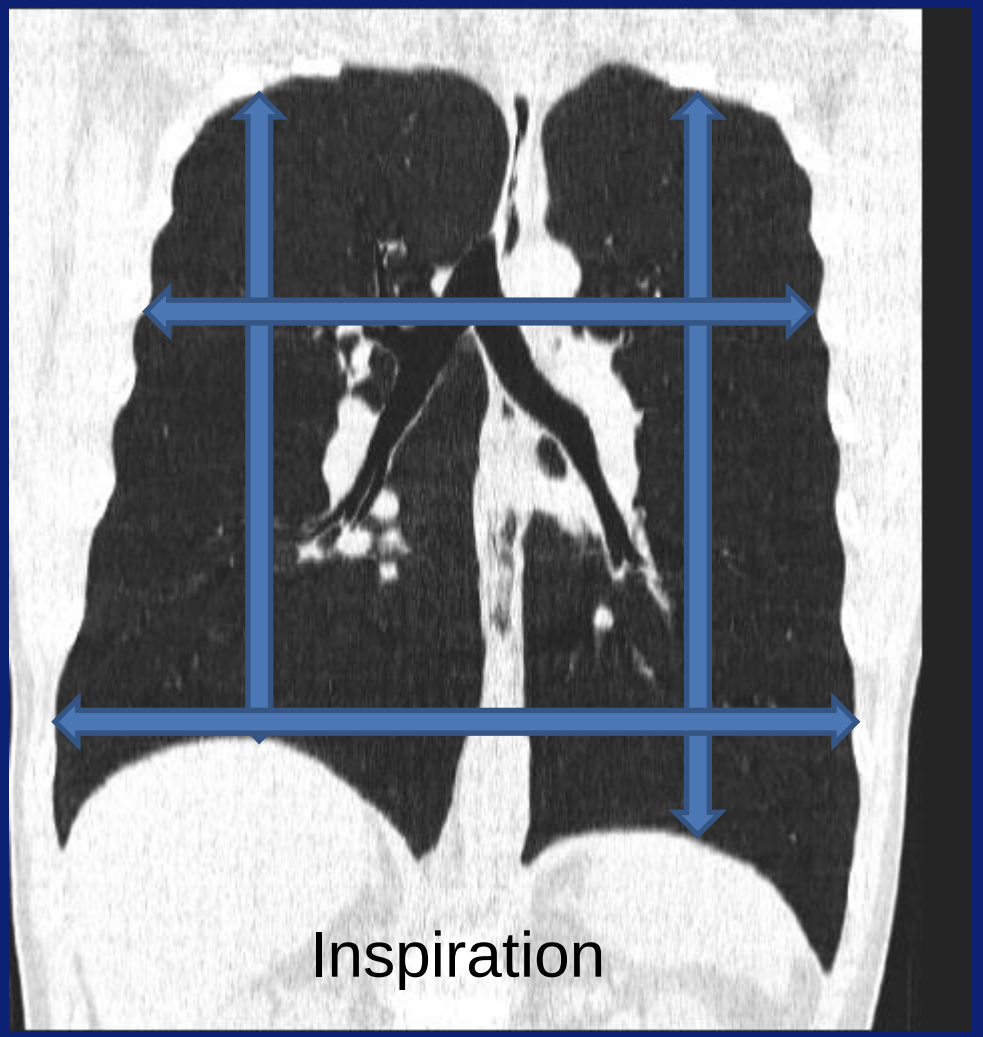
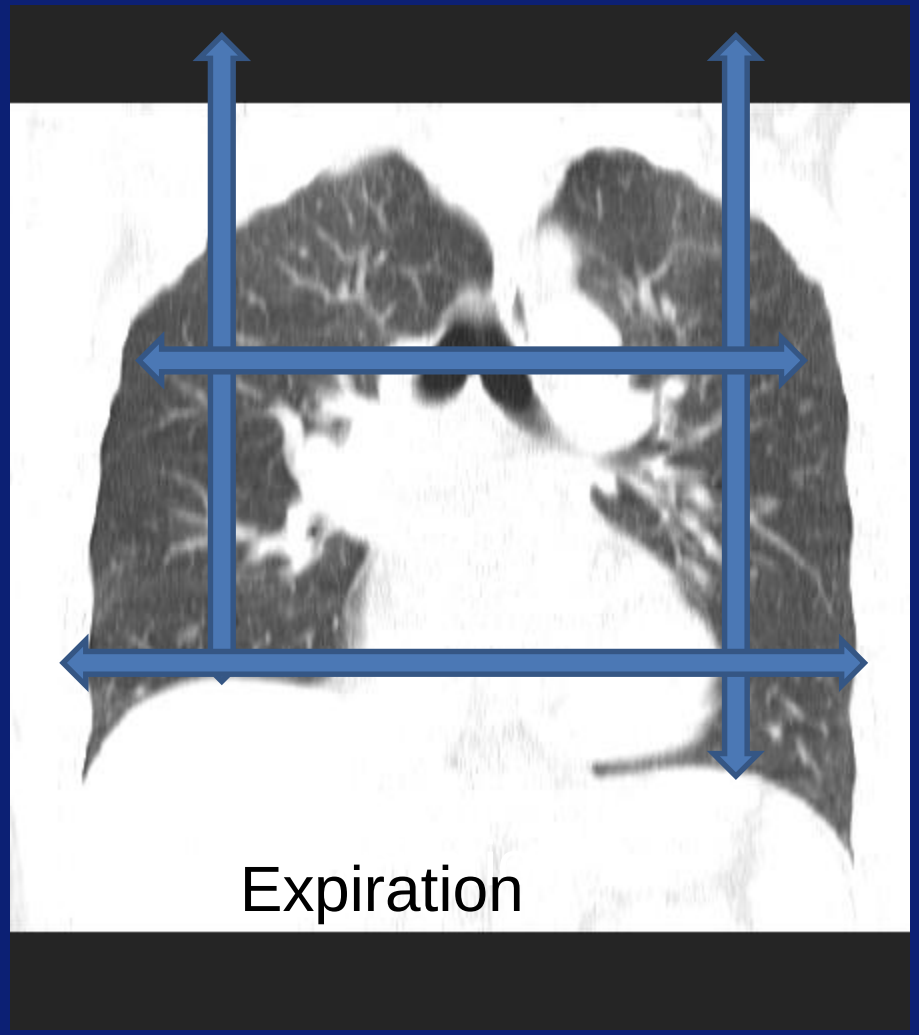
Why inspiratory and expiratory scan?





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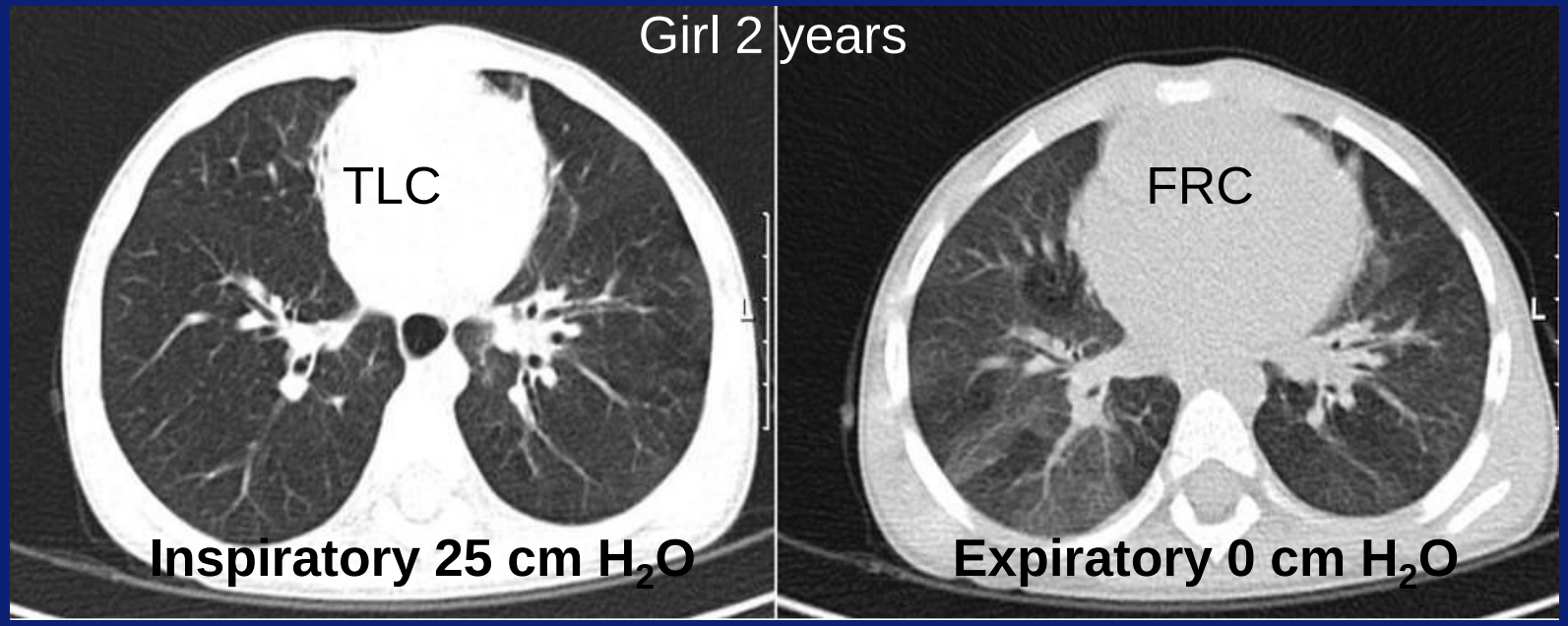
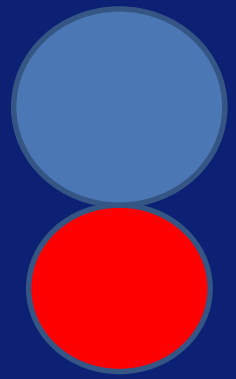
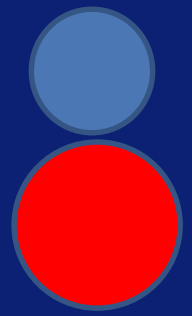
Lung volume is key determinant for diagnosis of bronchiectasis







Airway/Artery ratio >1

Airway/Artery ratio <1

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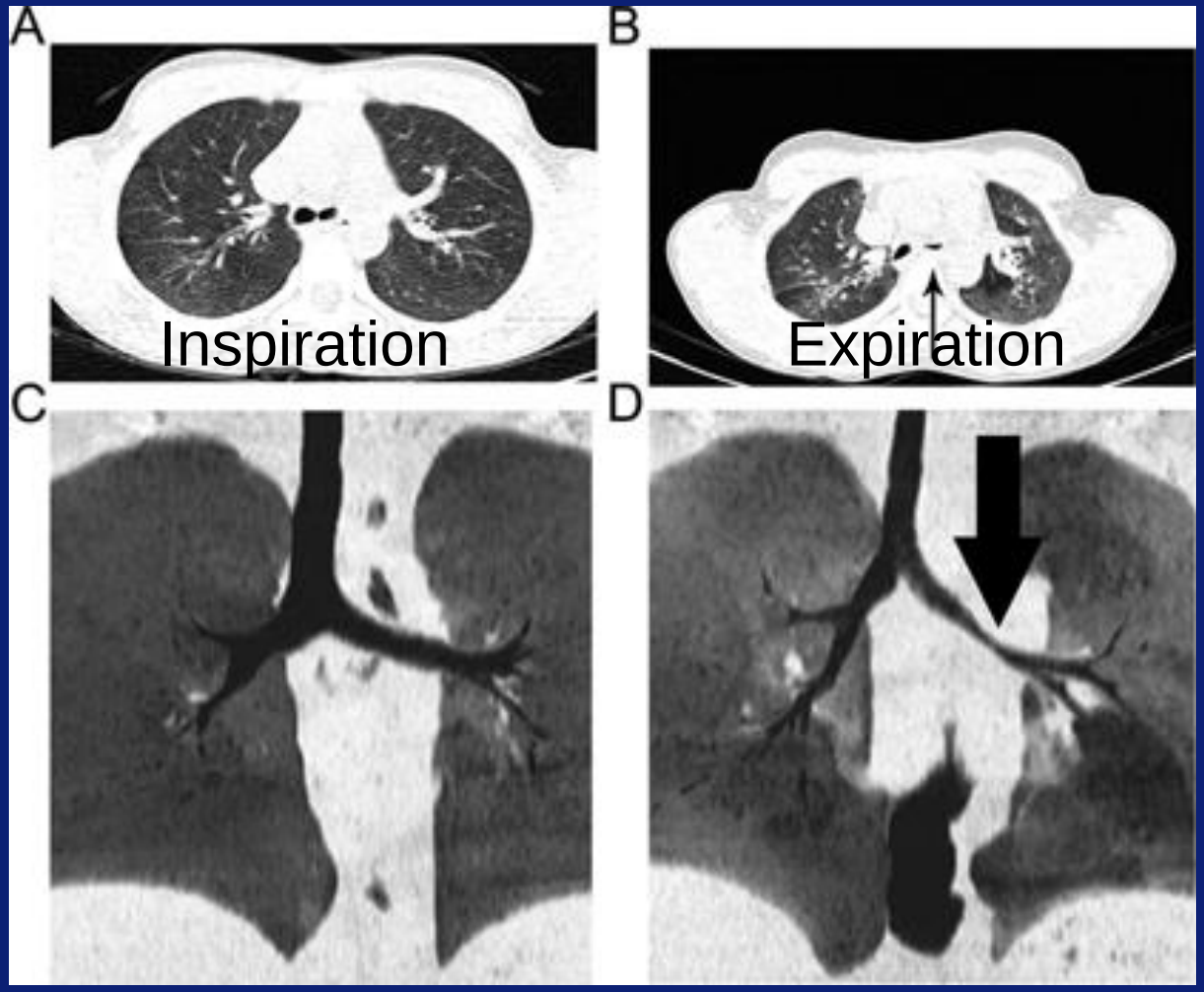
Expiration at residual volume (RV) level
Maximal contrast between normal and abnormal lung



Salamon et al, *Pediatr Pulmonol 2017*

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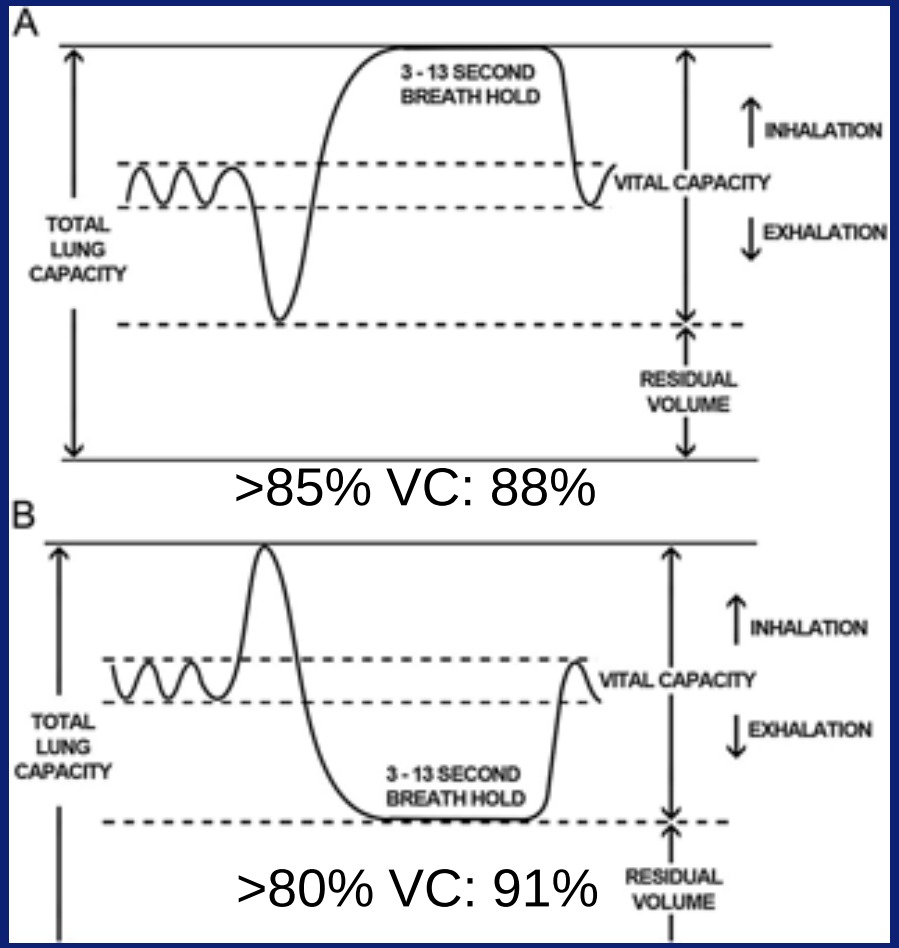
Spirometer guided chest CT and MRI: Train and coach!

N=148



Salamon et al, *Pediatr Pulmonol 2017*

Erasmus MC

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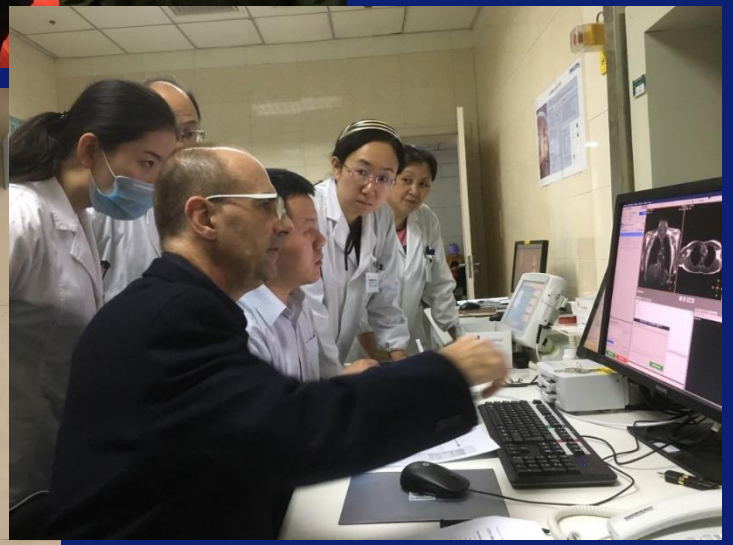

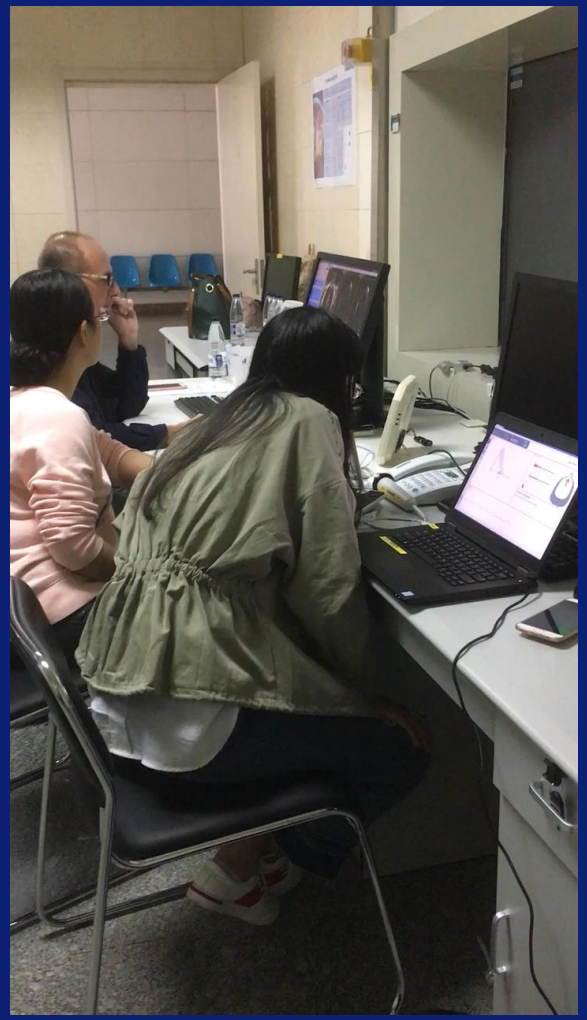

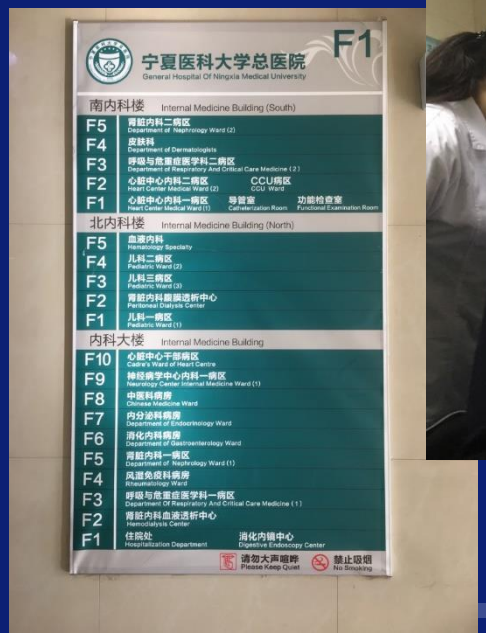

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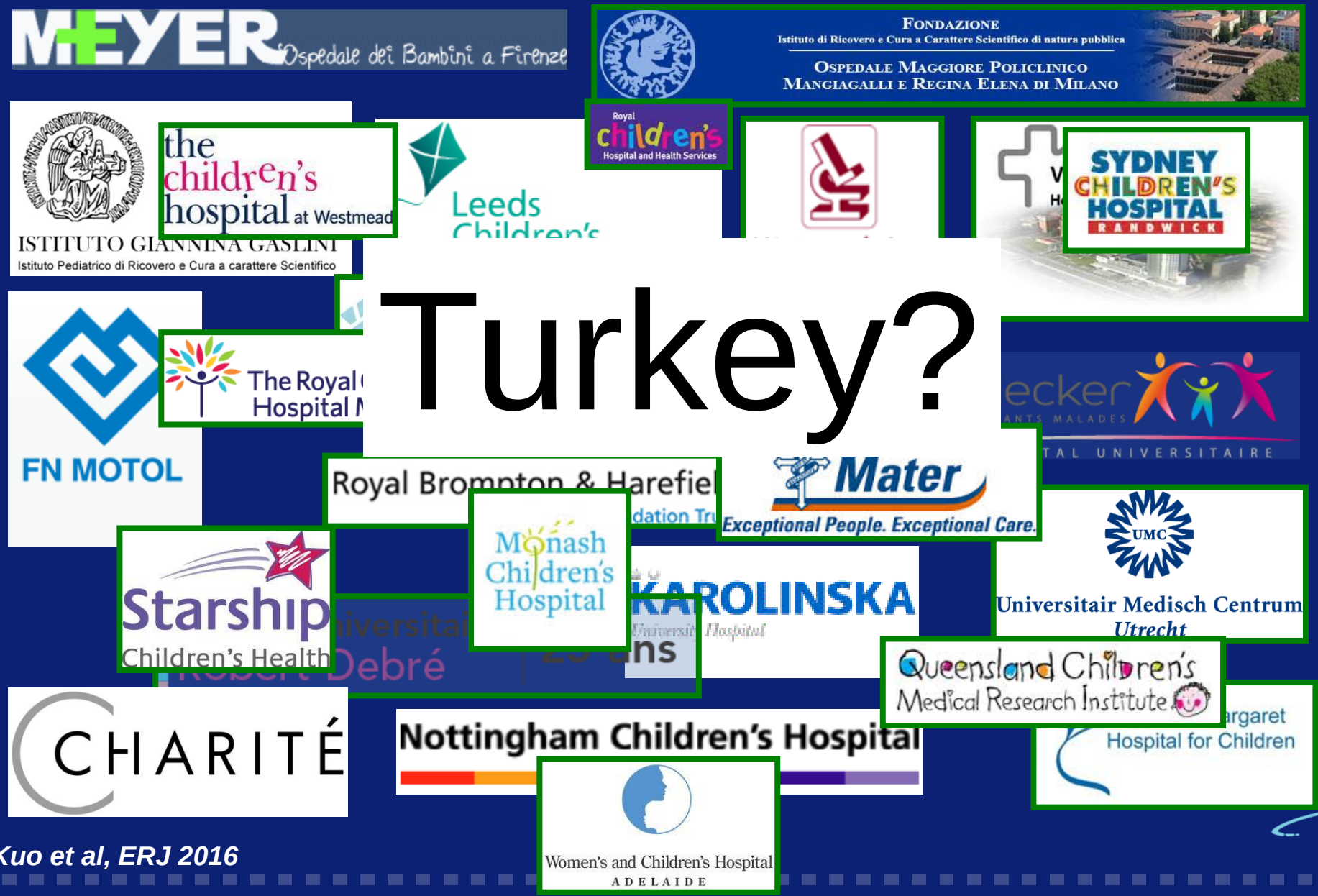
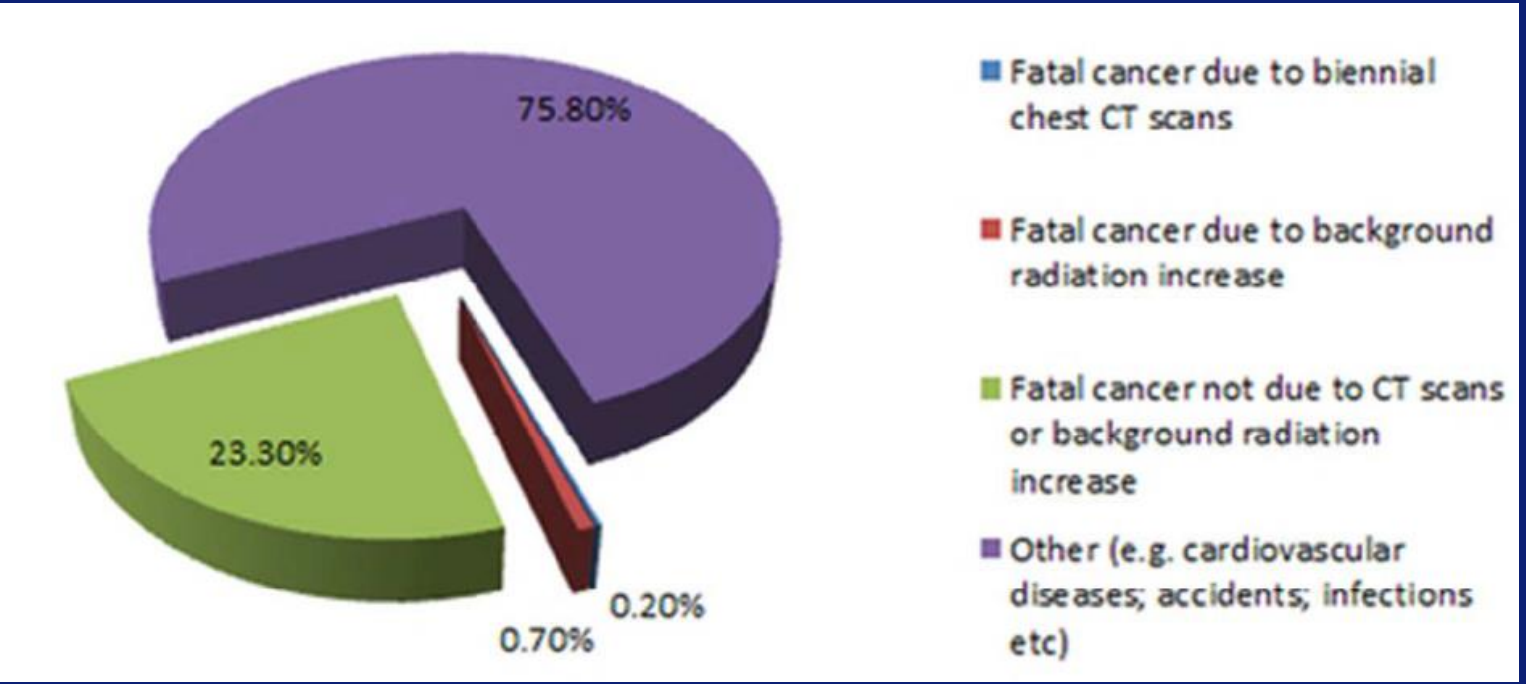
Standardization of chest CT: SCIFI-CF (EU), Australia, USA



Kuo et al, ERJ 2016

Monitoring CF lung disease using chest CT: Radiation risk in perspective



Other risks in life

- Death by motor vehicle accident 1%
- Death medical error in hospital 0.1%
- Severe reaction to contrast agent 0.18%

Kuo, *AJRCCM 2014;* Guillerman,*Thorax 2014;* De Jong, *AJRCCM 2005*

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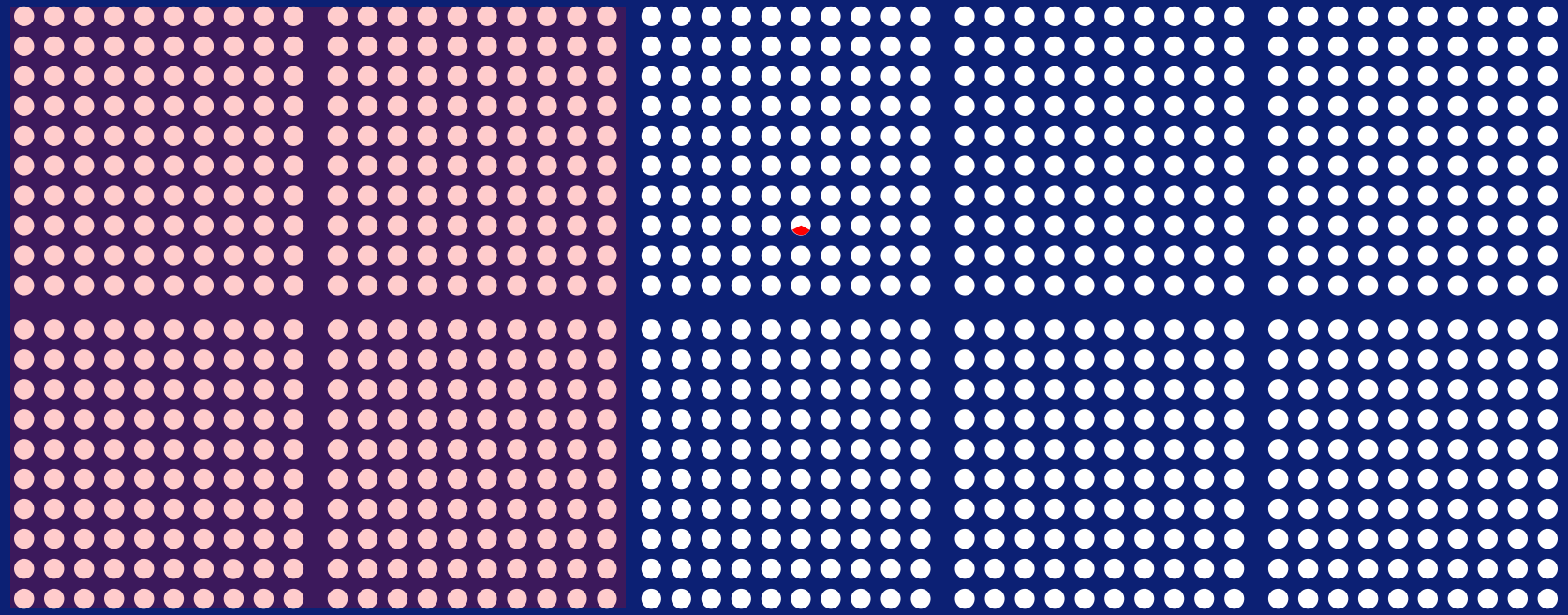
Risk relation to chest CT monitoring is low



- 1000 exposed children (dots) in total (50% male, 50% female)
- Two to four scans in total around the age of 5
- Maximum total $CTDI_{vol\ 32\ cm}$ = 3 mGy

- Life long fatal cancer risk: 200 out of 1000 persons
- Fatal cancer risk of 0.03%, i.e. 0.3 child in 1000 children exposed *

** CT-Expo, Germany and BEIR VII*

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Monitoring of CF lung disease using imaging

- Why
- Standardization

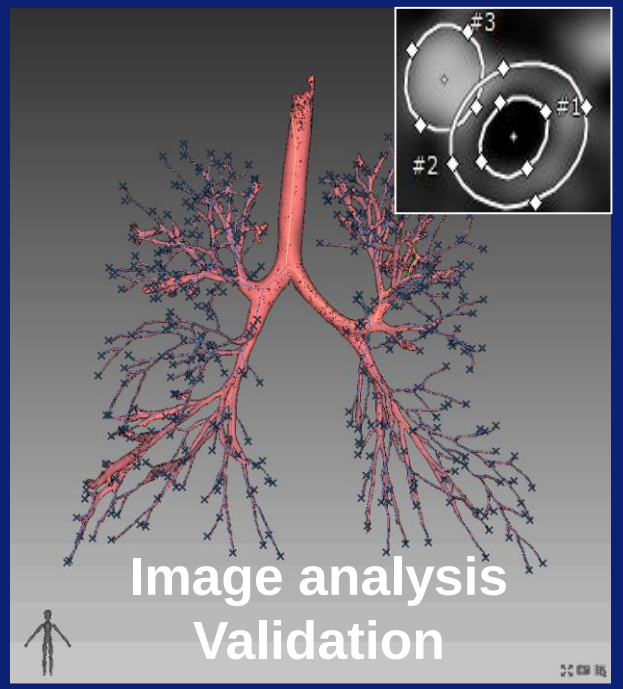
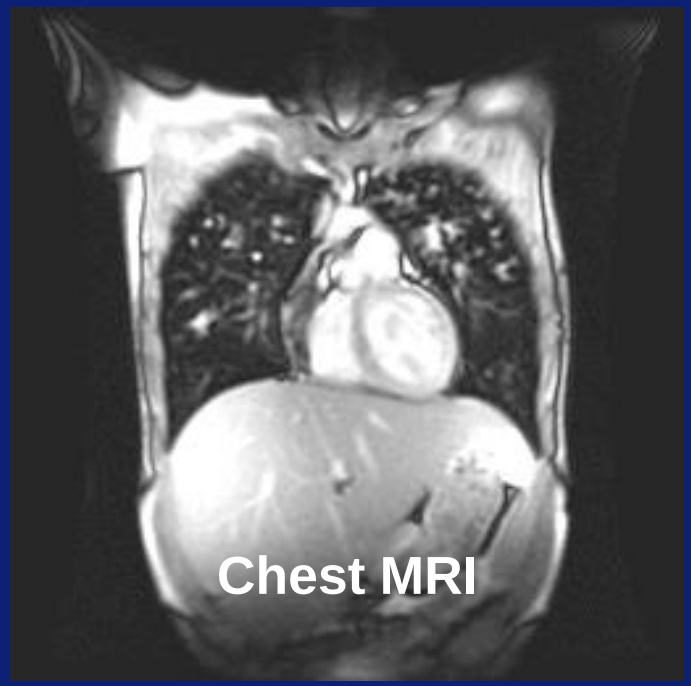


Image analysis
Validation



Chest MRI

More sensitive
Risk is low
Its doable
Improves quality
Lets do it

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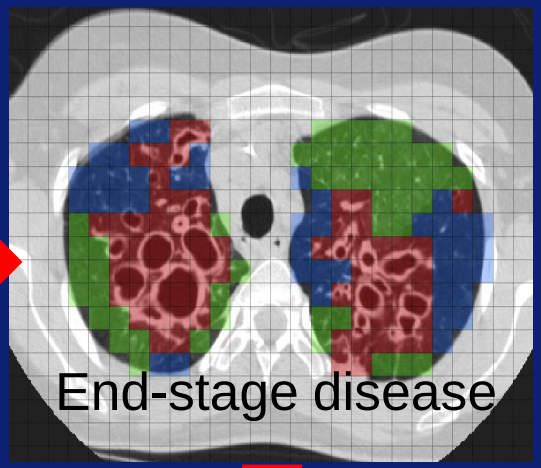
Quantification of CF lung CTs

Brody-II

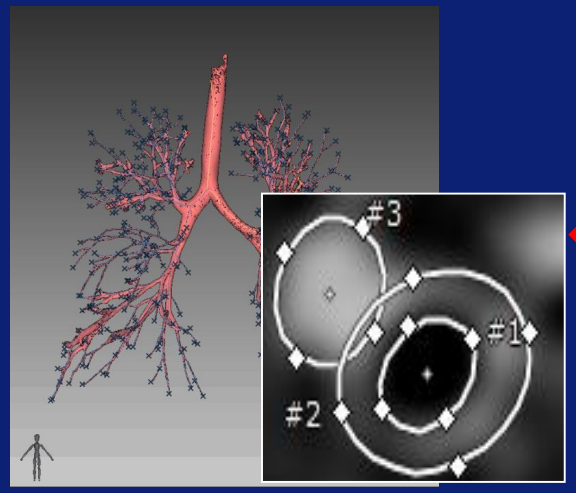
Lung ID.....Lobe:	Score			
CT abnormality	0	1	2	3
1. Bronchiectasis				
Central lung (extent of lung)	Absent	<33%	33%-67%	>67%
Peripheral lung (extent of lung)	Absent	<33%	33%-67%	>67%
Size of the largest	Absent	B<2V	B=2-3V	B>3V
Size of the average	Absent	B<2V	B=2-3V	B>3V
2. Airway wall thickening				
Severity	Absent	33%-50% V	50%-100% V	>100% V
Central lung (extent of lung)	Absent	<33%	33%-67%	>67%
Peripheral lung (extent of lung)	Absent	<33%	33%-67%	>67%
3. Mucous plugging				
Large airways (extent)	Absent	<33%	33%-67%	>67%
Small airways (extent)	Absent	<33%	33%-67%	>67%
4. Parenchyma				
Atelectasis and consolidation (extent)	Absent	<33%	33%-67%	>67%
Bulla and cysts (extent)	Absent	<33%	33%-67%	>67%
Ground glass opacification (extent)	Absent	<33%	33%-67%	>67%
5. Air trapping				
Extent	Absent	<33%	33%-67%	>67%
Pattern	Absent	Subsegmental	Segmental	Lobar

CF-CT

SALD



Rotterdam AA-method



PRAGMA-CF

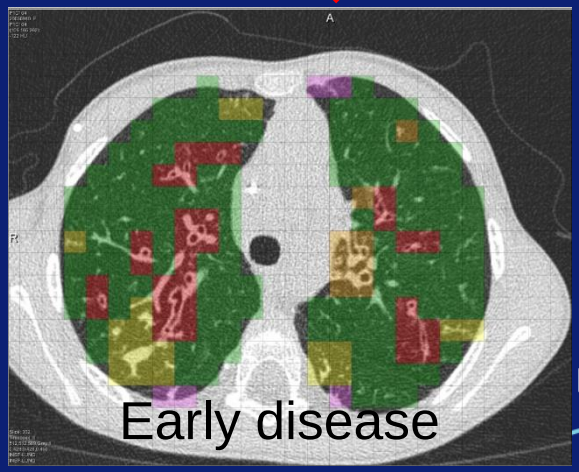
1.“Normal” lung

2.Bronchiectasis

3.Mucous plugging

4.Airway Wall Thickening

5.Atelectasis



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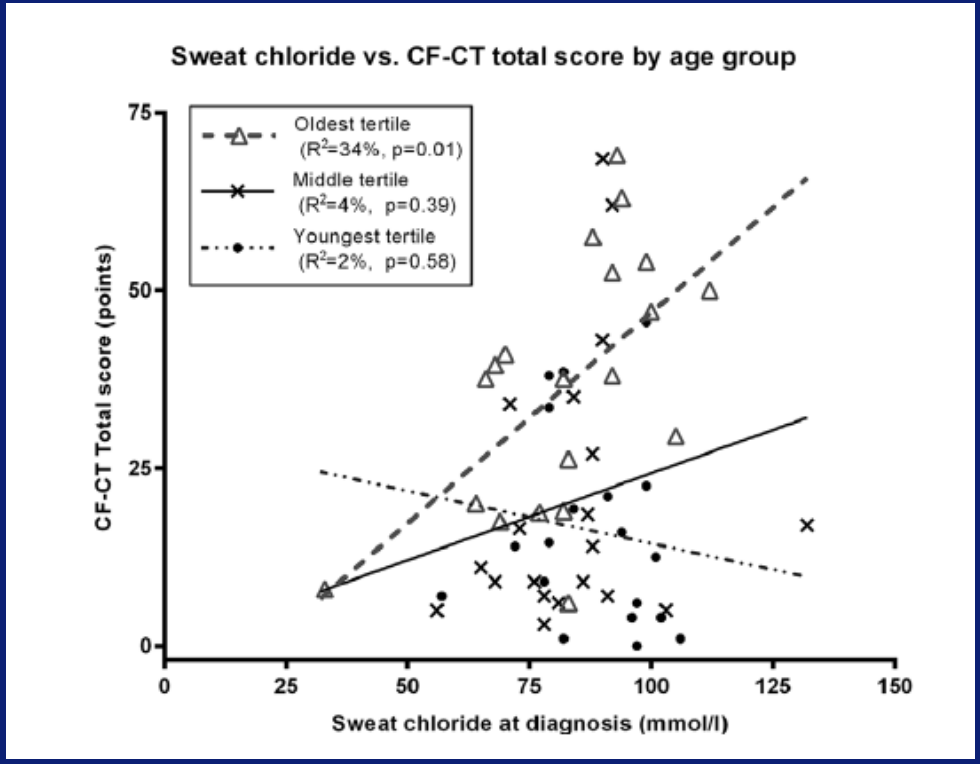
Sweat chloride predicts school age CF-CT score

- N=59, ErasmusMC CF-CT cohort routine biennial CTs
- Median age follow up 14 (6-18) years
- Linear regression: adjusted for age diagnosis and follow up
- Stratification for age of follow up in tertiles (6.2-11.1; 11.1-15.5; 15.5-18.2)



Caudri et al, *Ped Pulm 2017*

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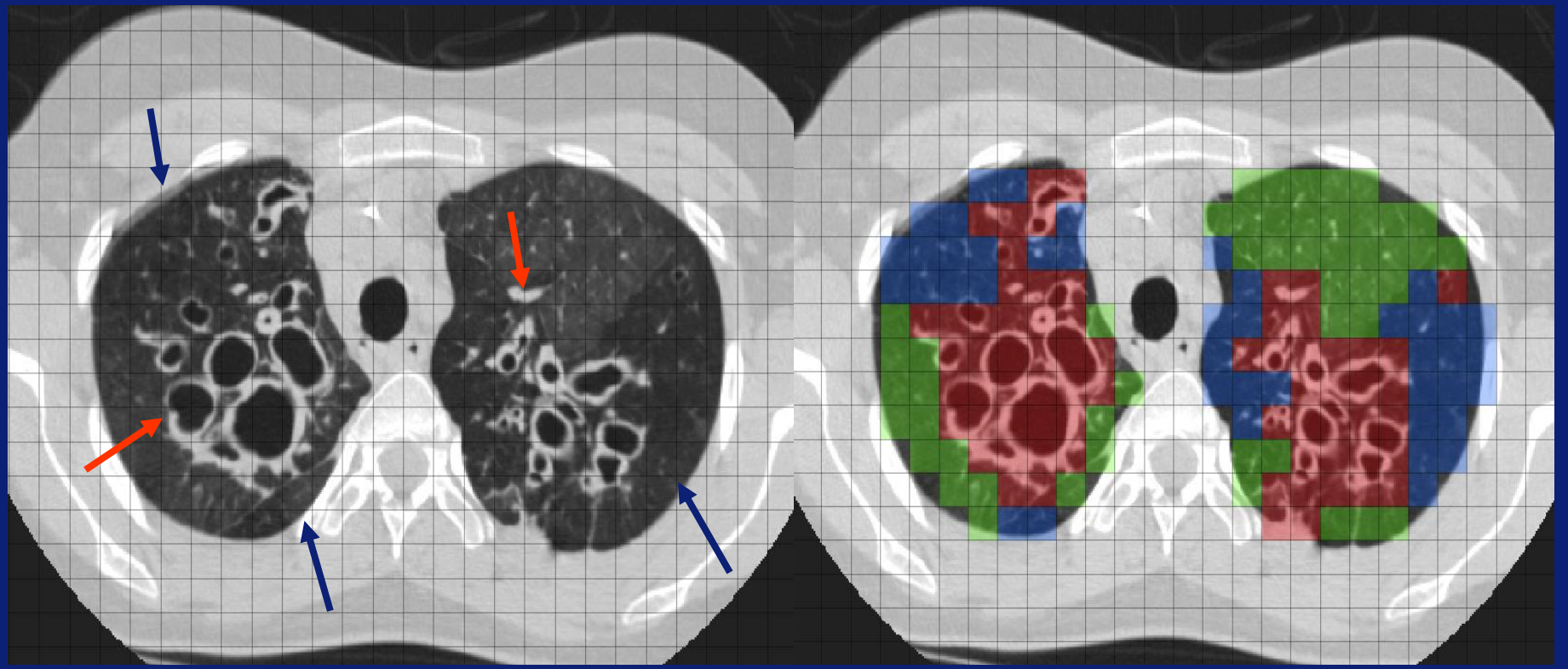
Computation of volume: SALD annotation system



1. **Infection/inflammation (red)**
2. **Air trapping/hypoperfusion (blue)**
3. **Normal/hyperperfusion (green)**
4. **Bulla/Cysts (orange)**

Loeve, *AJRCCM 2012*

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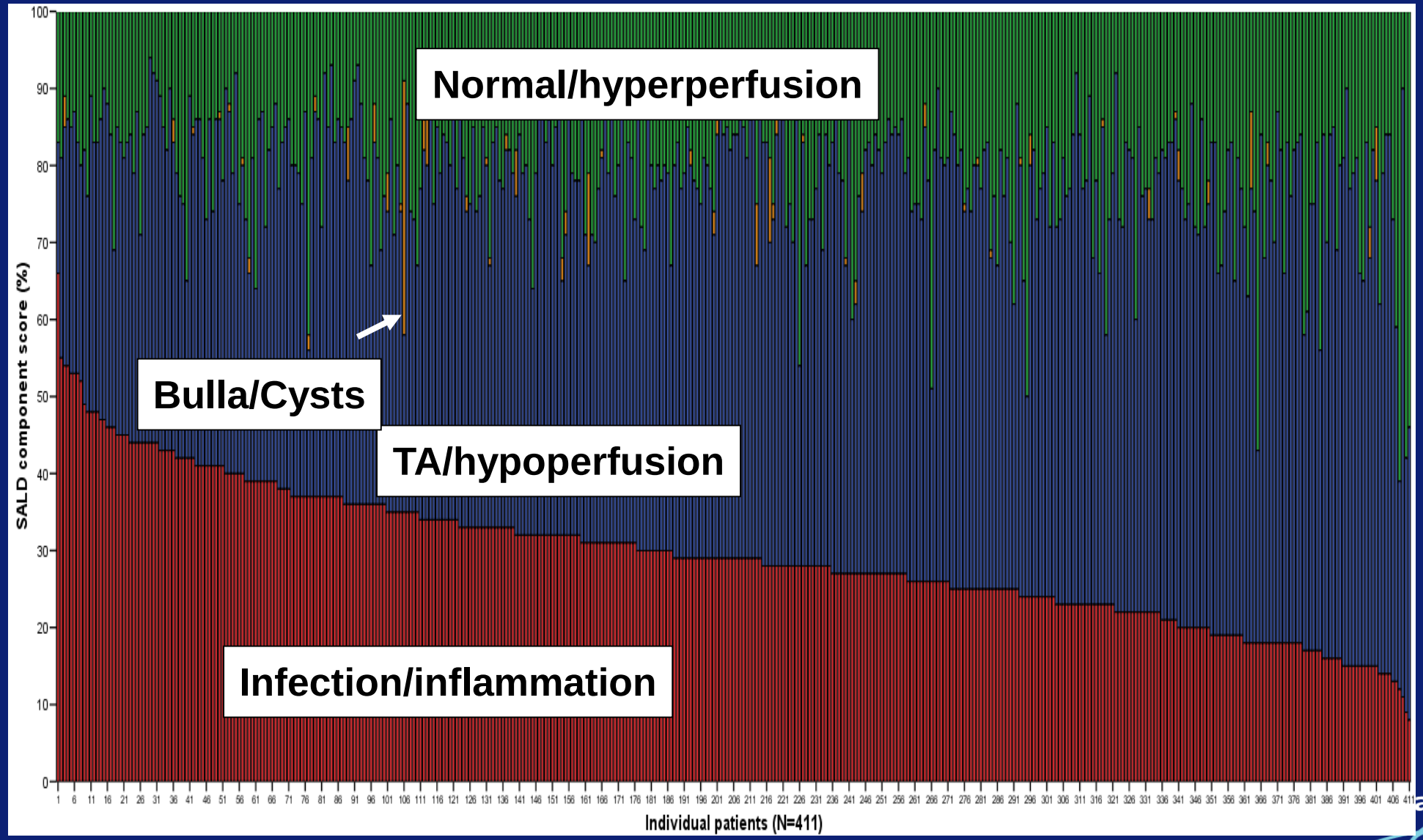
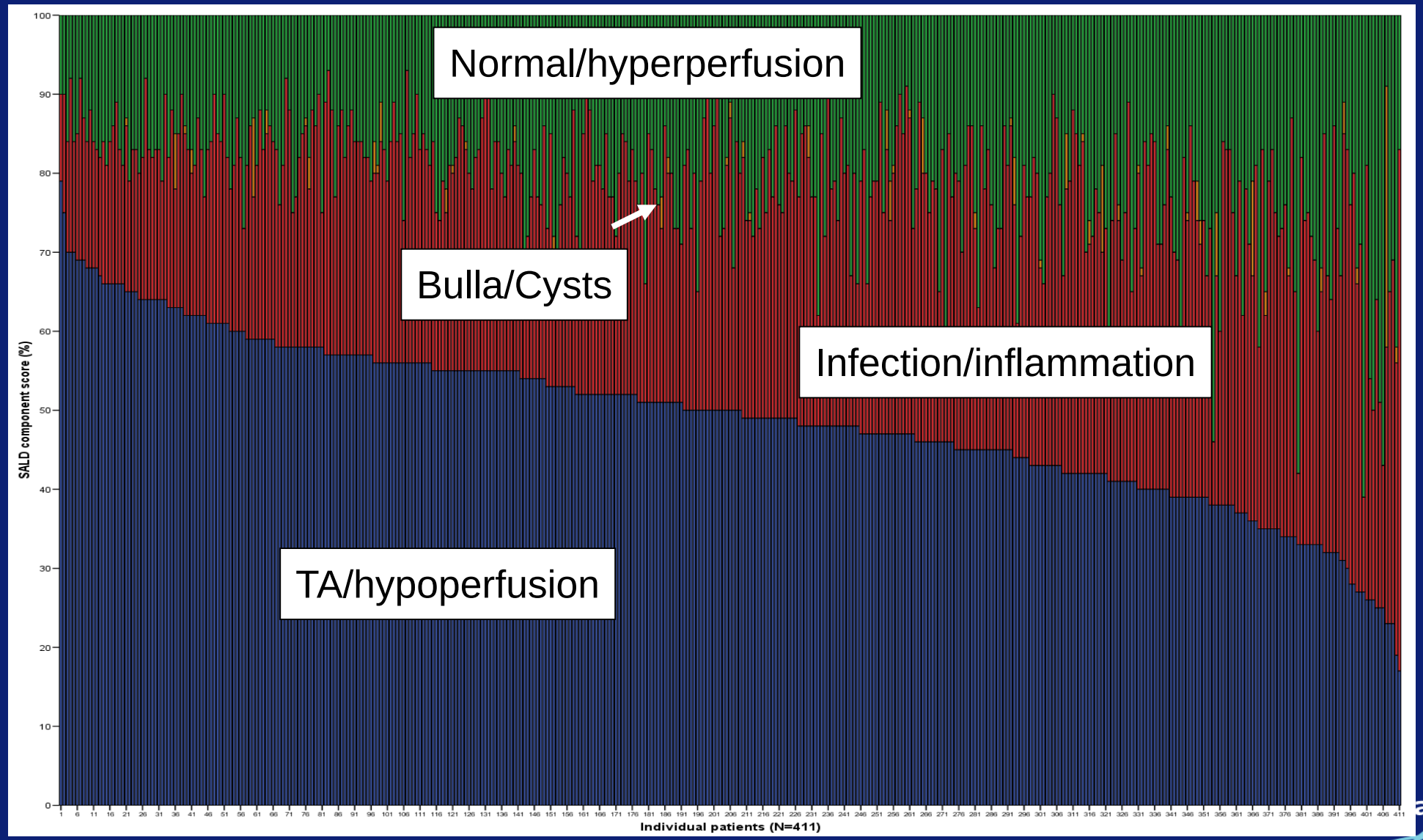
Spectrum abnormalities, 411 end stage lung disease CTs



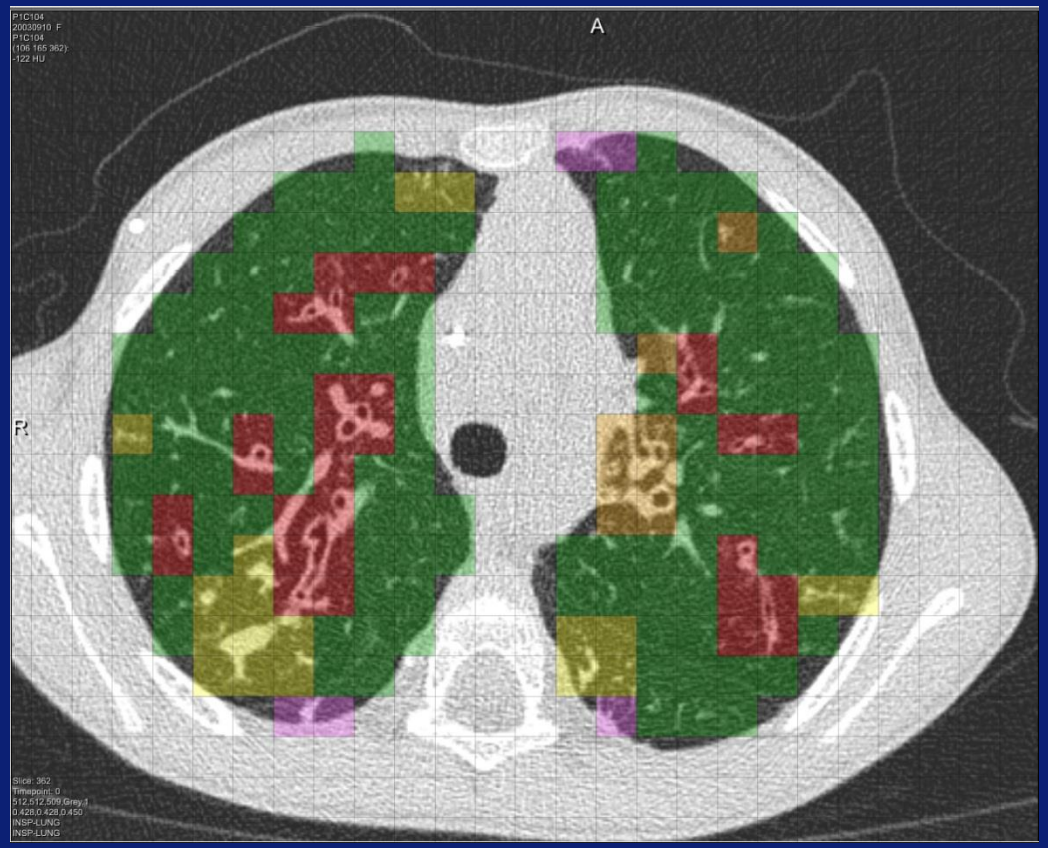
Loeve et al, *AJRCCM 2012*

Trapped Air/hypoperfusion



Loeve et al, *AJRCCM 2012*

PRAGMA-CF (Inspiratory CT)



Legend:

1. "Normal" lung
2. Bronchiectasis
3. Mucous plugging / consolidation
4. Bronchial wall thickening
5. Atelectasis

Outcome measure: Proportion lung affected with disease

%Disease = %BE + %Mucous + %Bronchial Wall Thickening

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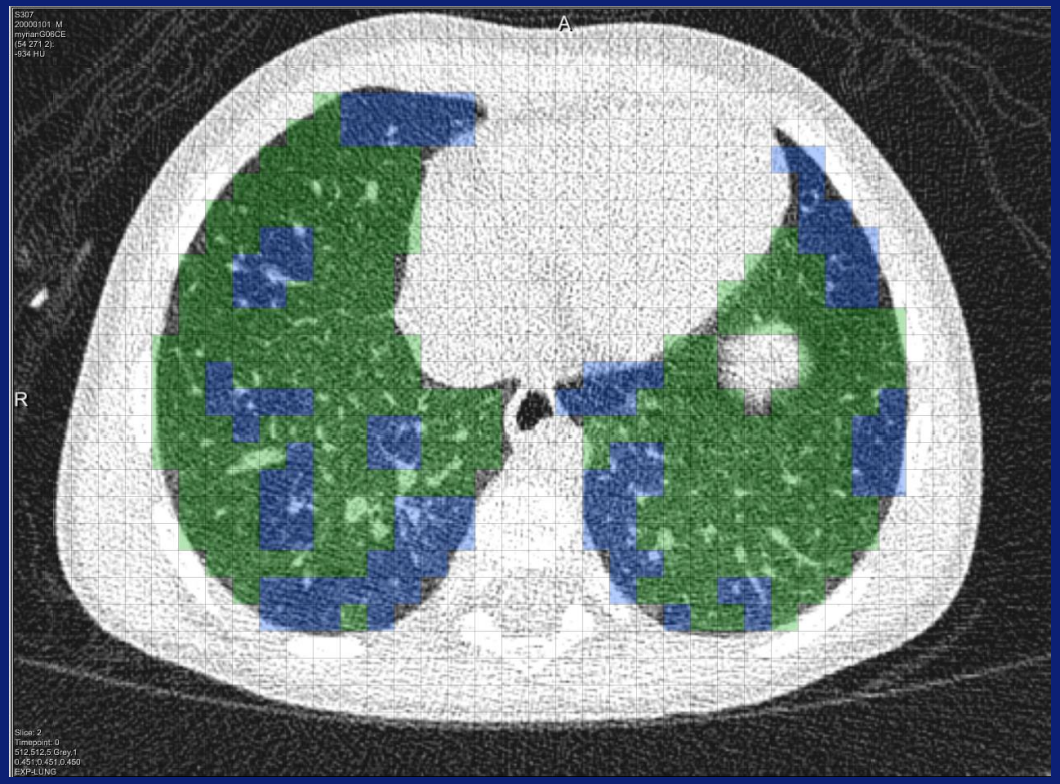
Rosenow et al, *AJRCCM 2015*

PRAGMA–CF (Expiratory CT)



Legend:

1.“Normal” lung
2.Trapped air

Outcome measure: Proportion of lung with trapped air (%TrappedAir)

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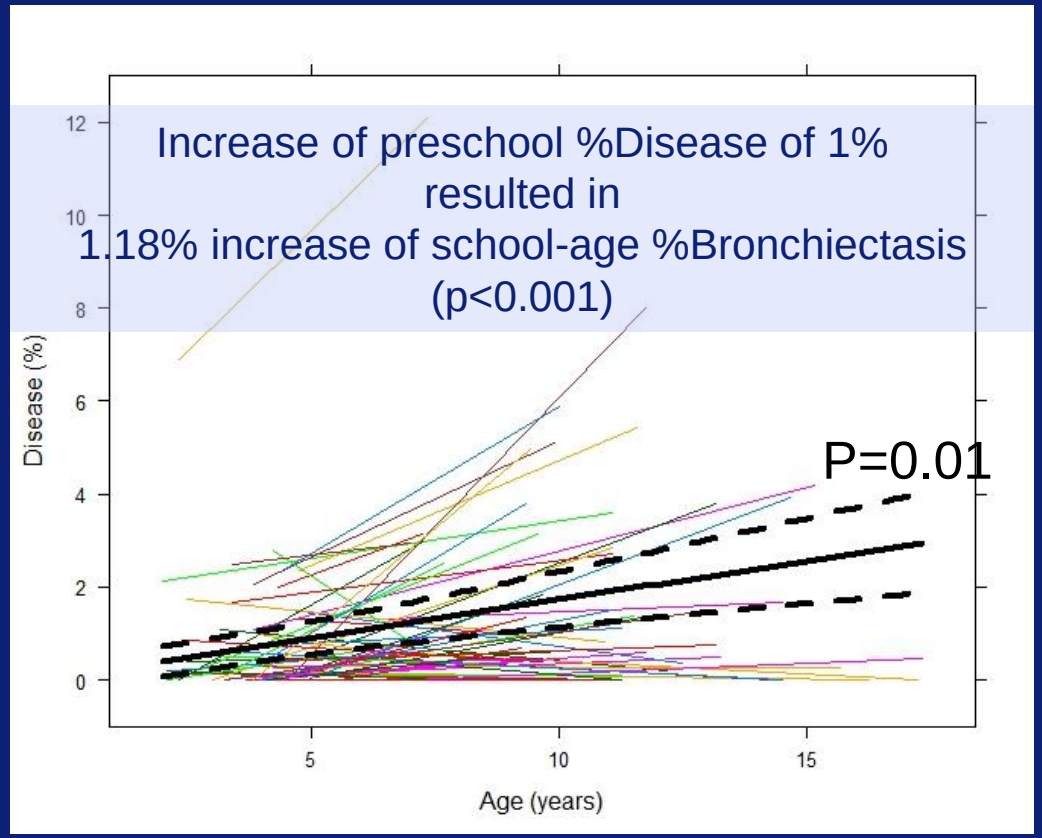
Rosenow et al, *AJRCCM 2015*

Longitudinal changes PRAGMA-CF %Dis
Erasmus-MC CF cohort

- N=61, ErasmusMC CF-CT cohort
- 122 routine biennial CTs (first scan between 3-5 years and last CT)
- Median Preschool CT age 4.07, follow up 6.6 (4-9) years
- Multivariable linear regression analysis



Bouma et al, ***Resubmitted to ERJ***

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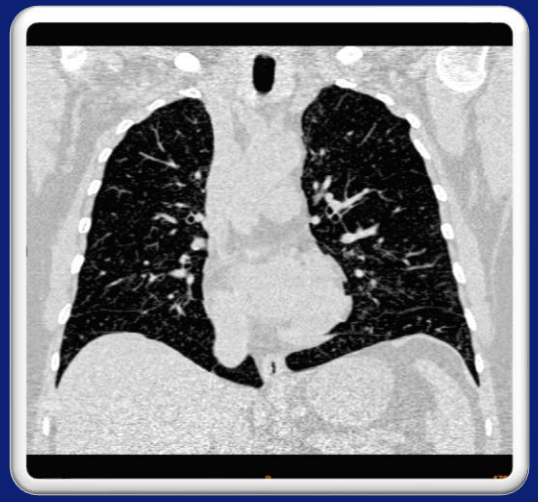
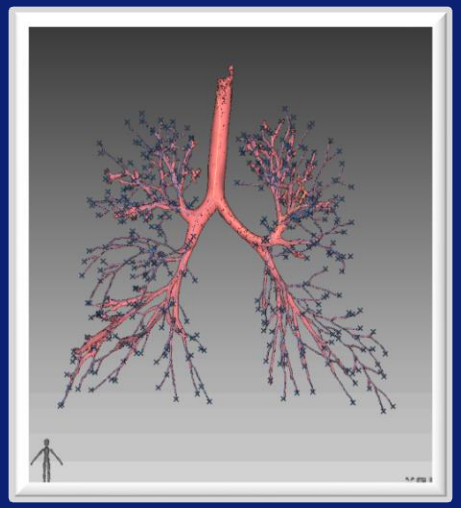
Rotterdam Airway-Artery Method (RAAM)

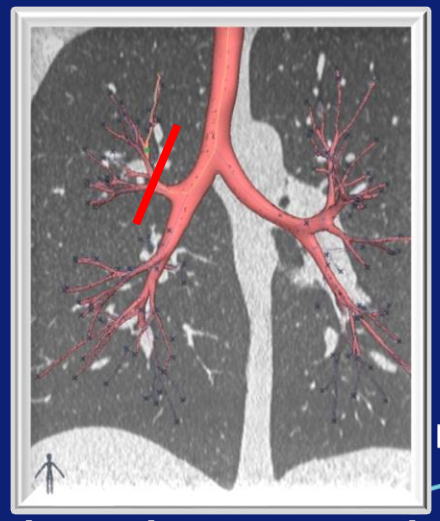
Volume controlled CT scan



Reconstruction



Segmentation



Airway in cross section

Ellipse tool

Airway Artery dimensions

Kuo et al, *Pediatric Pulmonology 2017*

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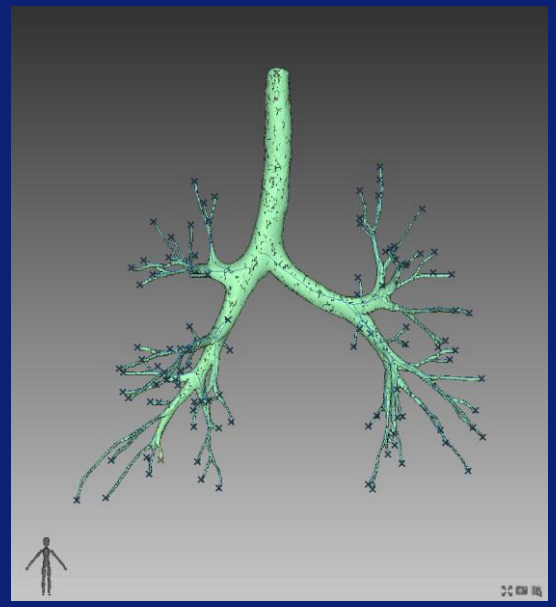
RAAM, control + CF ≥ 6 yrs:

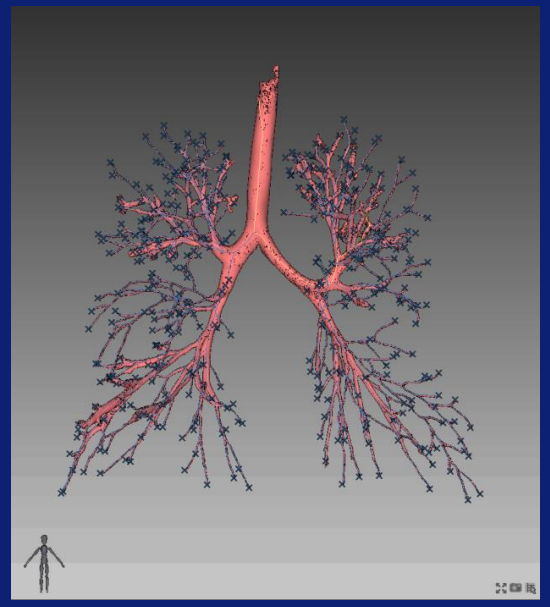
Aim:

To assess airway and artery dimensions on inspiratory and expiratory CTs of children with CF and a control group



12 controls (normal CT)

- Insp: 1516 AA pairs
- Exp: 700 AA pairs



12 CF patients

- Insp: 3528 AA pairs
- Exp: 1017 AA pairs

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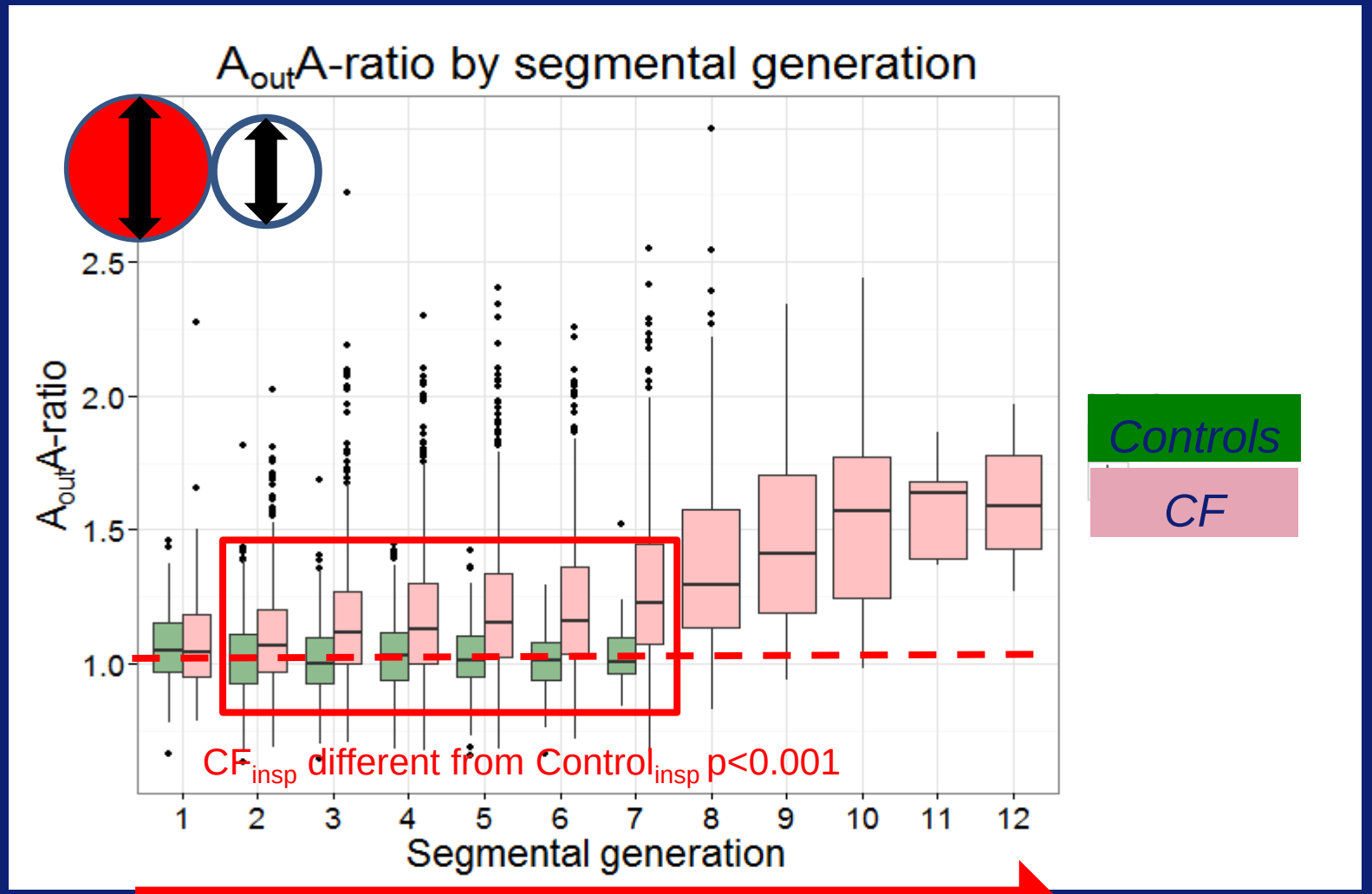
Kuo et al, *Pediatric Pulmonology 2017*

Bronchiectasis: More severe by generation



Kuo et al, *European Radiology 2017*

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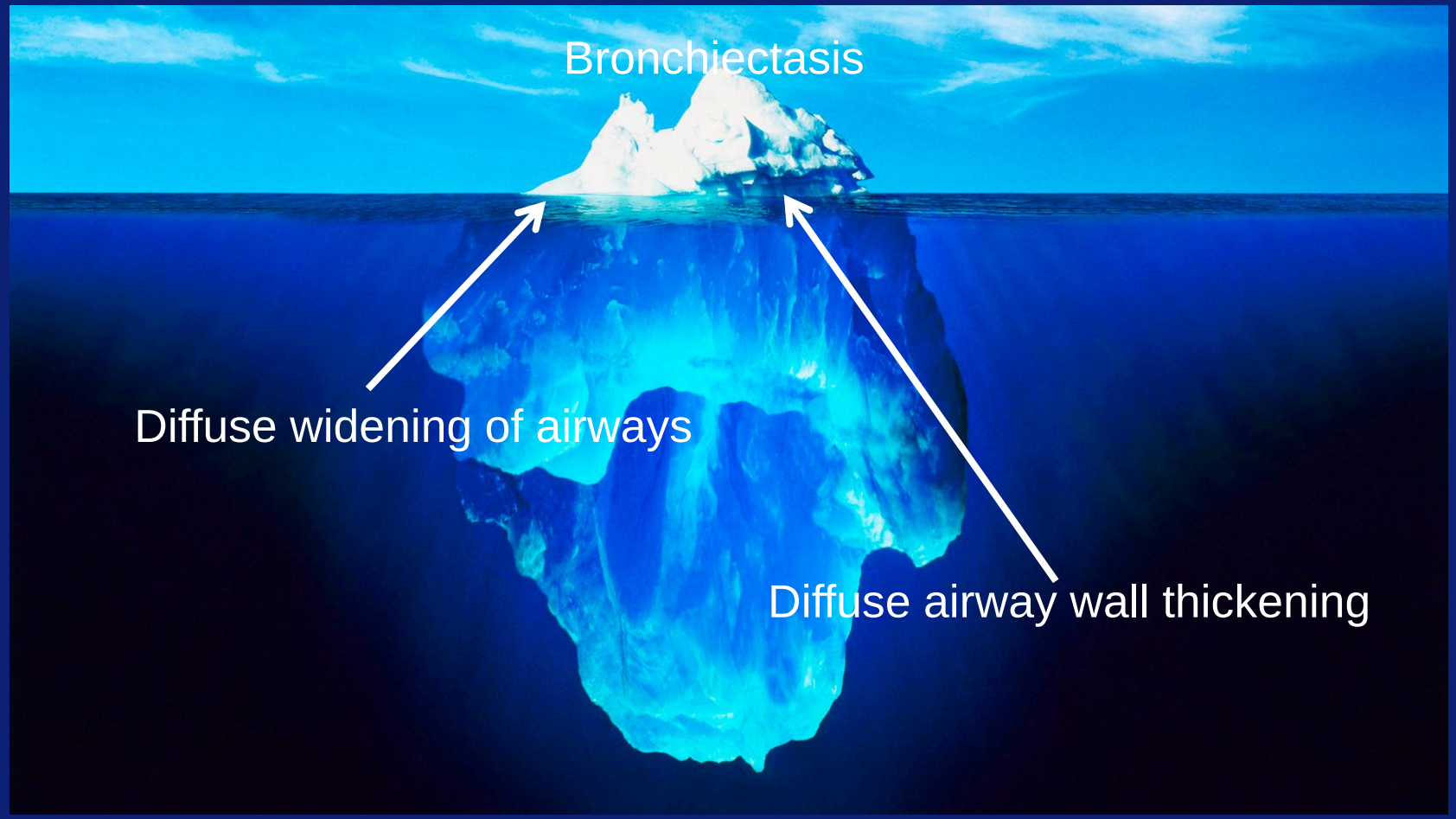
Early CF lung disease



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CT bronchiectasis: can be counted and it counts!

- ✓ Can be counted: Scoring; Pragma-CF; Airway/Artery ratio *Rosenow, AJRCCM 2014; Kuo, JCF 2016; Kuo, Ped Pulm 2017; Kuo, European Radiology 2017*
- ✓ Starts early in life: *Long J Pediatr 2004; de Jong AJRCCM 2005; Stick Pediatrics 2009; Wainwright JAMA 2011; Mott Thorax 2012; Kuo European Radiology 2017*
- ✓ Progression throughout life: *De Jong Thorax 2006, Mott Thorax 2012, Tepper ERJ 2013*
- ✓ Important component end stage lung disease; *Loeve Thorax 2009, AJRCCM 2012*
- ✓ Increased inflammatory markers in abnormal regions: *Davis AJRCCM 2007; Amin Radiology 2012; Sly, NEJM 2013*
- ✓ More sensitive endpoint than FEV_1 to detect progression: *De jong ERJ 2004 Thorax 2006; Owens Thorax 2012; Tepper ERJ 2013*
- ✓ Predictor for exacerbations: *Brody AJRCCM 2005; Loeve Thorax 2009; Tepper ERJ 2013*
- ✓ Negative impact on quality of life: *Tepper ERJ 2013*
- ✓ Correlation to mortality; *Loeve AJRCCM 2013*
- ✓ PRAGMA-CF %Disease predictor of later bronchiectasis, lower BMI
- ✓ CT but not CXR acts upon clinical decision making; *Bortoluzzi submitted*
- ✓ Prevention, slowing down progression?: *Azithro, Ivacaftor, PTC, Hypertonic saline?*

Feels, Functions
Survives

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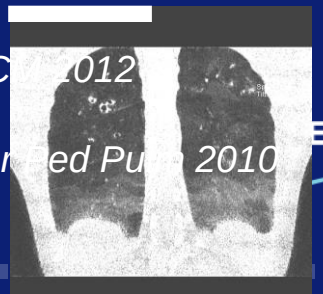
CT Trapped air: can be counted and it counts!

- ✓ Can be counted: *Loeve Radiology 2012; Mott Thorax 2012; Kuo Eur Radiolo gy2017*
- ✓ Present in 45-60% of infants and children: *Stick. J Pediatrics 2009, Wainwright, JAMA 2011; Mott Thorax 2012*
- ✓ Progression throughout life: *Mott Thorax 2012, Loeve Radiology 2012*
- ✓ Important component of end stage lung disease: *Loeve Thorax 2009; AJRCCM 2012; Boon AJRCCM 2016*
- ✓ 1/3 of trapped air in children 6 years is *irreversible*: *Mott Thorax 2012; Loeve thesis 2012;*
- ✓ 1/3 of trapped air in Arest-CF children 0-6 years is *irreversible: Mok to be submitted*
- ✓ Negative impact on CFQ children and adolescents; *Tepper ERJ 2013*
- ✓ Is not correlated to reduced survival on waiting list: *Loeve, AJRCC[illegible]2012*
- ✓ Responsiveness to therapy; *Robinson chest 2005, Altes 2011 NACFC, Nasr[illegible]ed Pu[illegible] 2010*

Feels, Functions



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Further validation studies Chest CT in CF in the last year

- Chandler et al, **Myeloperoxidase oxidation** of methionine associates with early cystic fibrosis lung disease. Eur Respir J. 2018 Sep 6.
- de Winter-de Groot et al, Stratifying infants with cystic fibrosis for disease severity using intestinal **organoid** swelling as a biomarker of CFTR function. Eur Respir J. 2018
- Newbegin et al, **Clinical utility** of surveillance computed tomography scans in infants with cystic fibrosis. Pediatr Pulmonol. 2018
- Sasihuseyinoglu et al, **Evaluation** of high resolution computed tomography findings of cystic fibrosis. Korean J Intern Med. 2018
- Chassagnon et al, An **automated computed tomography score** for the cystic fibrosis lung. Eur Radiol. 2018 Jun 4.
- Rybacka et al, Congruence Between **Pulmonary Function and Computed Tomography** Imaging Assessment of Cystic Fibrosis Severity. Adv Exp Med Biol. 2018
- Caudri et al, The association between **Staphylococcus aureus** and subsequent bronchiectasis in children with cystic fibrosis. J Cyst Fibros. 2018
- Muller et al, Evaluation of surrogate measures of pulmonary function derived from **electrical impedance tomography** data in children with cystic fibrosis. Physiol Meas. 2018
- Kuo et al, Quantitative assessment of **airway dimensions** in young children with cystic fibrosis lung disease using chest computed tomography. Pediatr Pulmonol. 2017
- Gauthier et al, **Early follow-up** of lung disease in infants with cystic fibrosis using the raised volume rapid thoracic compression technique and computed tomography during quiet breathing. Pediatr Pulmonol. 2017
- Rosenow et al, **Air trapping** in early cystic fibrosis lung disease-Does CT tell the full story? Pediatr Pulmonol. 2017

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Different specialty, different priority

Pulmonologists driven by:

Regulatory

Pharma

Lung function laboratory

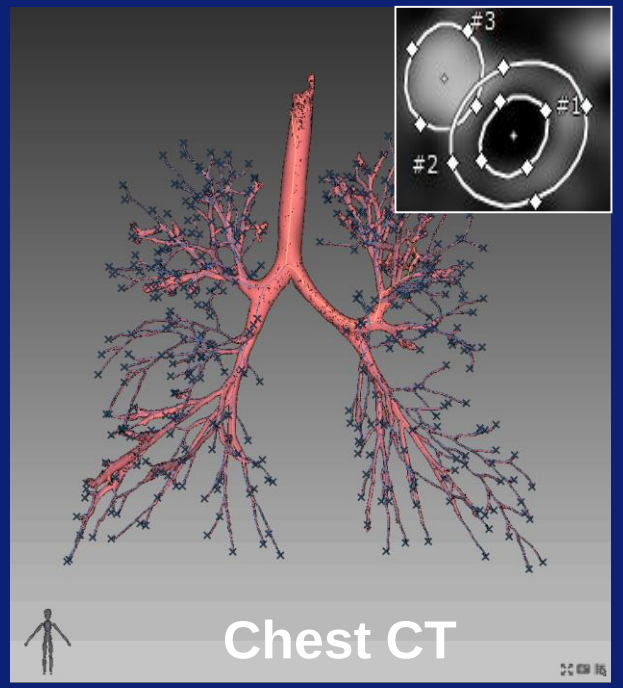
Radiologists driven by:

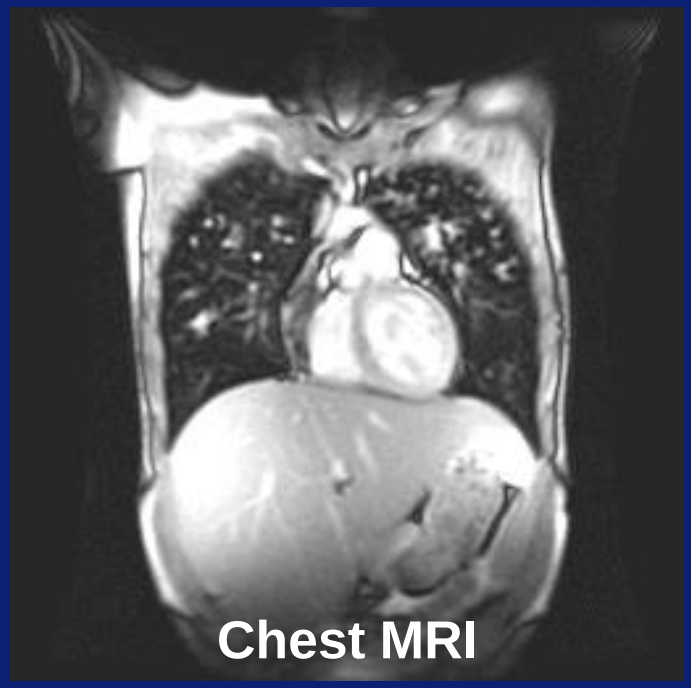
Vendors

Production

Erasmus MC

Monitoring of CF lung disease using imaging





Its doable
Improves quality
Lets do it

Analysis methods are available
Well validated
Can be automated
Get your radiologists on board!

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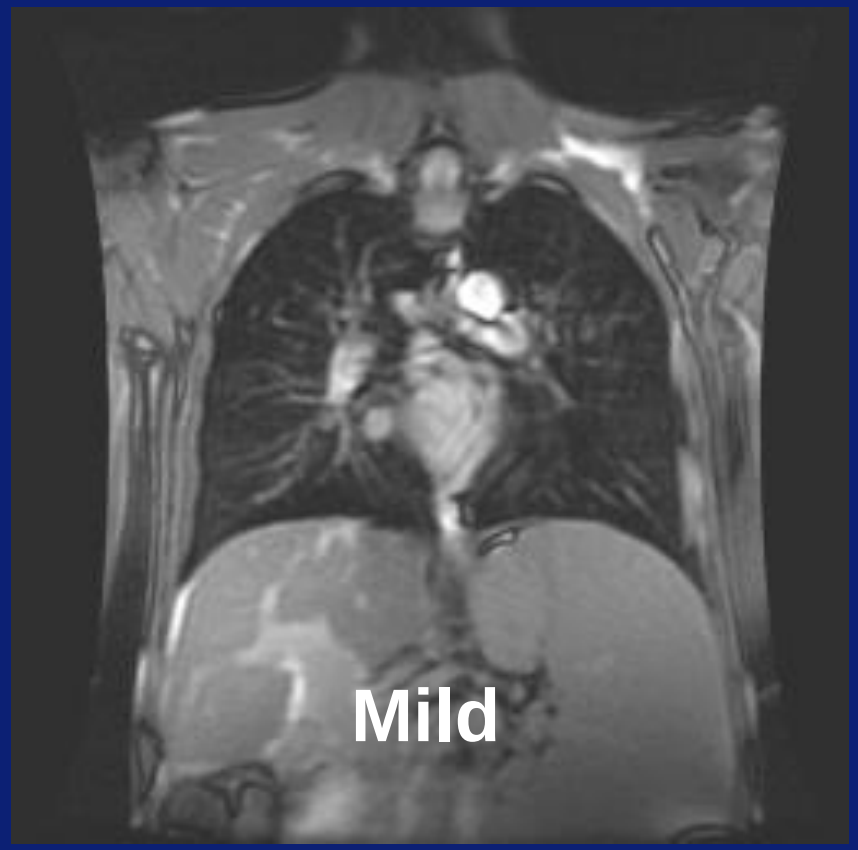
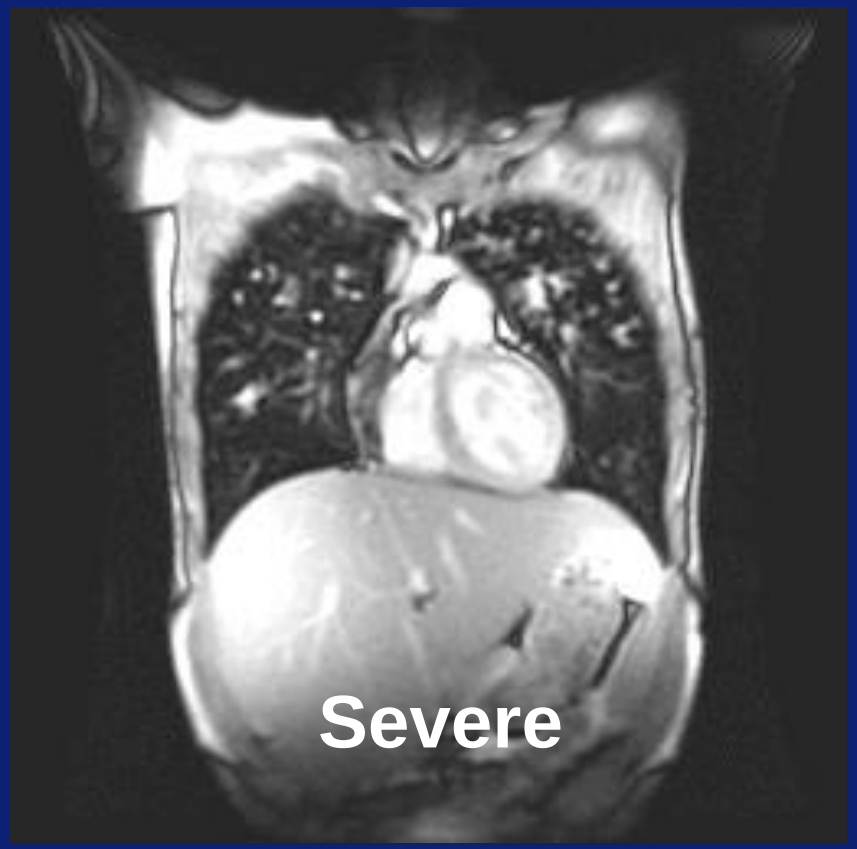
Dynamic MRI: Mild and advanced disease





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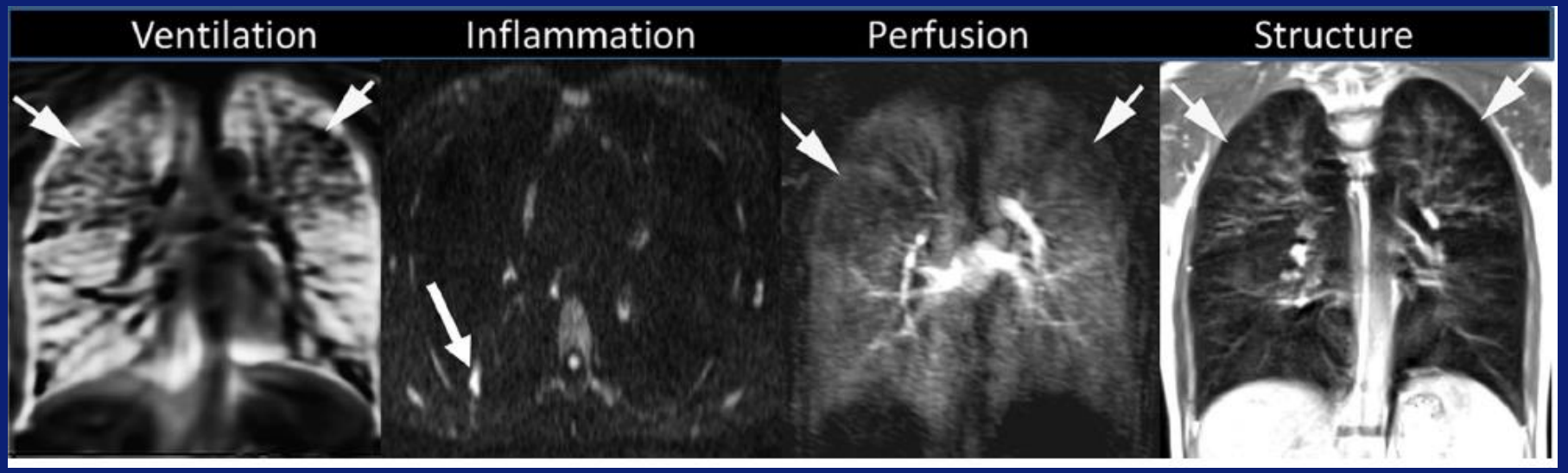
Monitoring CF lung disease: VIPS-MRI



Standardization across vendors and centres is a major challenge

Tiddens, Stick, Wild, Ciet, Parker, Koch, Vogel-Claussen, *Pediatric Pulmonology 2015*

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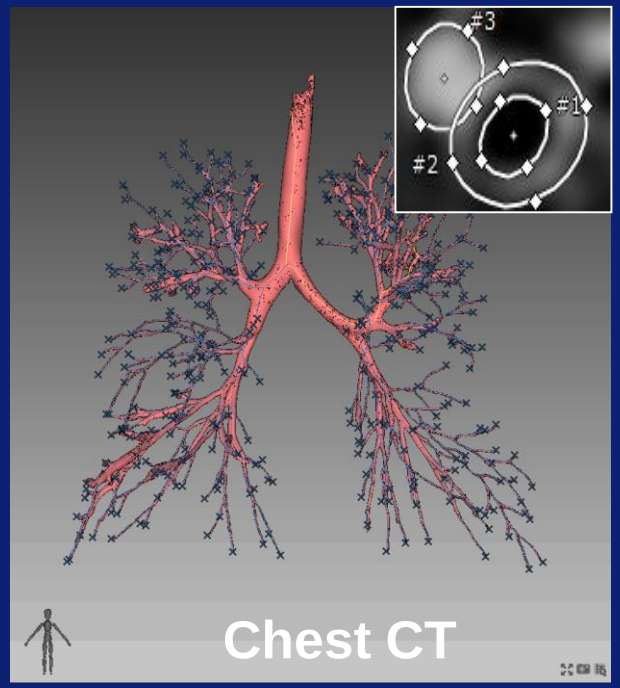
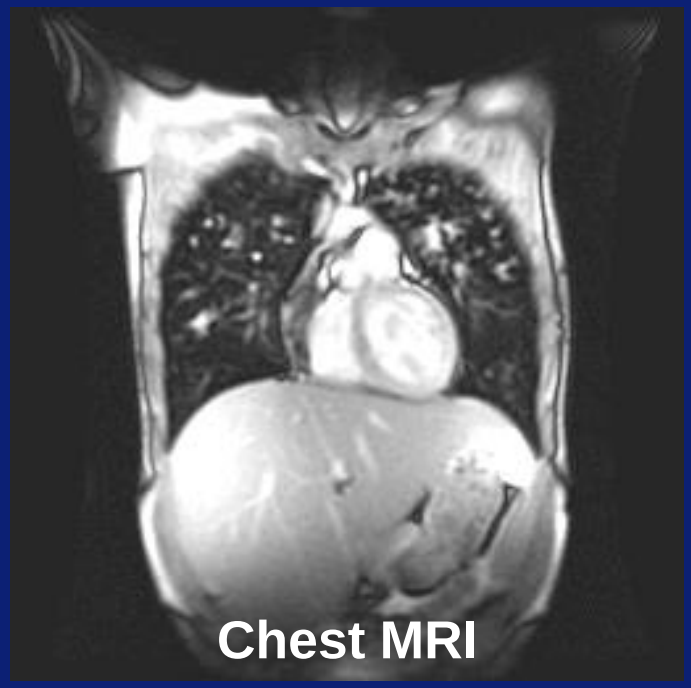
Monitoring of CF lung disease using imaging





Its doable
Improves quality
Lets do it

Analysis methods are available
Well validated
Can be automated

Its doable
Standardization?
VIPS MRI

Get your radiologists on board!

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CF chest CT and image analysis: The future is now

Courtesy: *Merlijn Bonte, ErasmusMC LungAnalysis*

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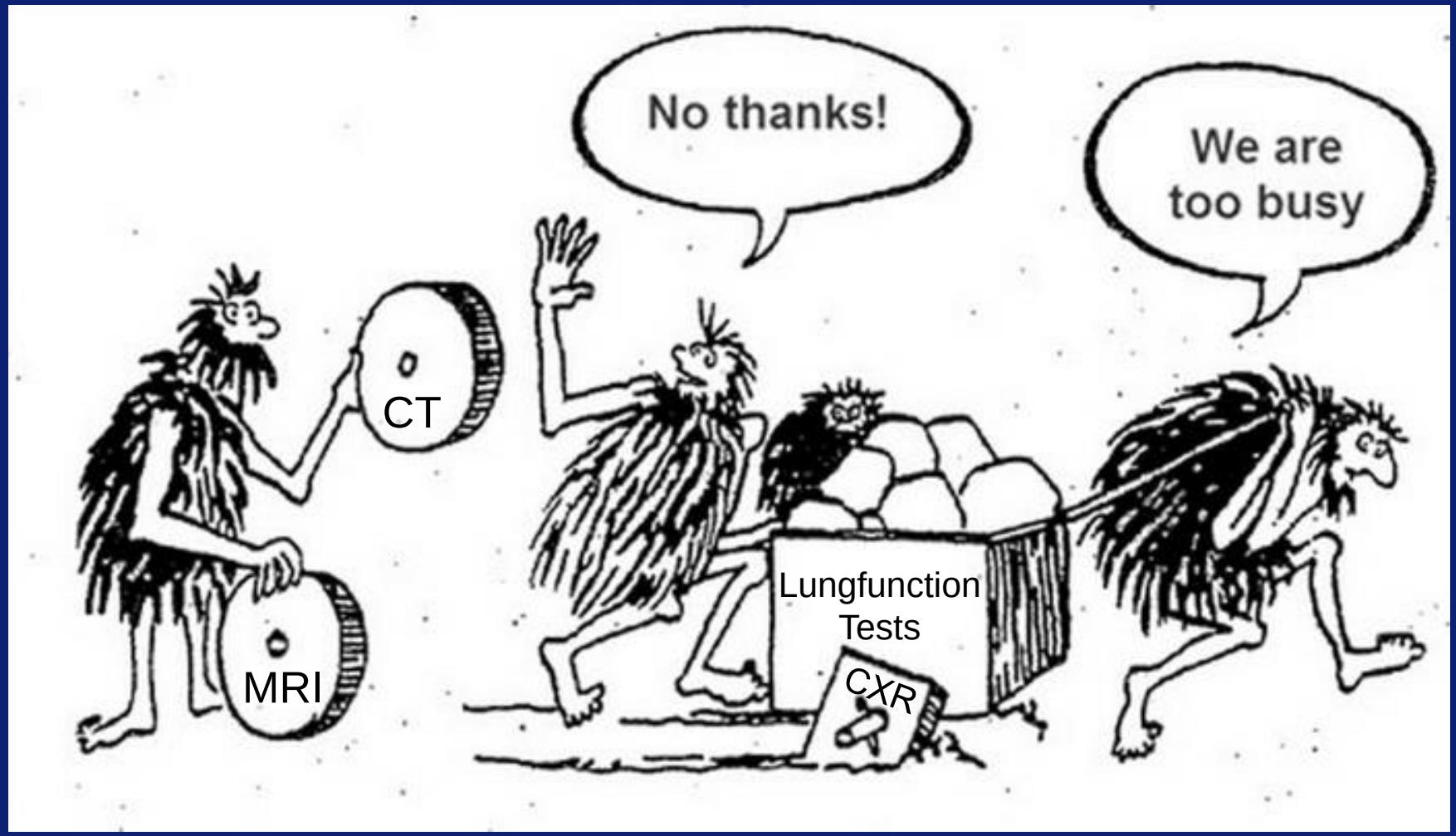

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ErasmusMC Lung Imaging Group
‘Count what Counts’

Lung Analysis

Mariette Kemner (Head)

chnician

ans (n=4)

s (BIGR)

Pediatric

Sa

Mast

Wieying

Jennife

Bernad

Clara

Hame

Sergei

Jorien va

Bad

Els van

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Post Doc)

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ead Nicu)

elstijn

Marco Schnater

Bas Pullens

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CF and bronchiectasis – from visual scoring to new imaging analysis systems

Image analysis system	Unity	Standardization Training/sets/SOP	Disease severity		Can be automated	Validation Status 1-5
			Early	Advanced		
Brody-II	Score	-	-	+	-	3
CF-CT	% Max score	+	-	+	-	5
SALD	% Lung volume	+	-	+	+	2
PRAGMA-CF %Dis	% Lung volume (Insp)	+	+	+	+	5
PRAGMA-CF TA	% Lung volume (exp)	+	+	+	+	4
AA-Ratio	% AA > 1.1	+	+	+	+	3
Airway tapering	% Airways abnormal	+	?	+	+	2
Density analysis	% lung HU Mode+300	+	?	+	+	2

- Standardization needed of chest CT protocol
- In school age standardization needed of inspiratory and expiratory lung volume chest

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Is pre-school PRAGMA-CF %Disease a predictor of later bronchiectasis?

- Erasmus MC Sophia CF cohort
- Availability of 2 routine biennial CT scans
  - Baseline CT scan: CT-scan taken at age 2-6 yrs
  - School age follow-up CT scan: Last available scan
- De-identified CT-scans annotated in random order PRAGMA-CF
- Baseline %Disease and % MUPAT (%Airway wall thickening and %Mucus plugging) predictors for school age clinical outcomes?
- School age outcomes: %Bronchiectasis, pulmonary exacerbations, quality of life, and FEV_1 %predicted
- Statistical analysis: T-tests, correlation analysis, cross-sectional analysis and linear mixed-effects model

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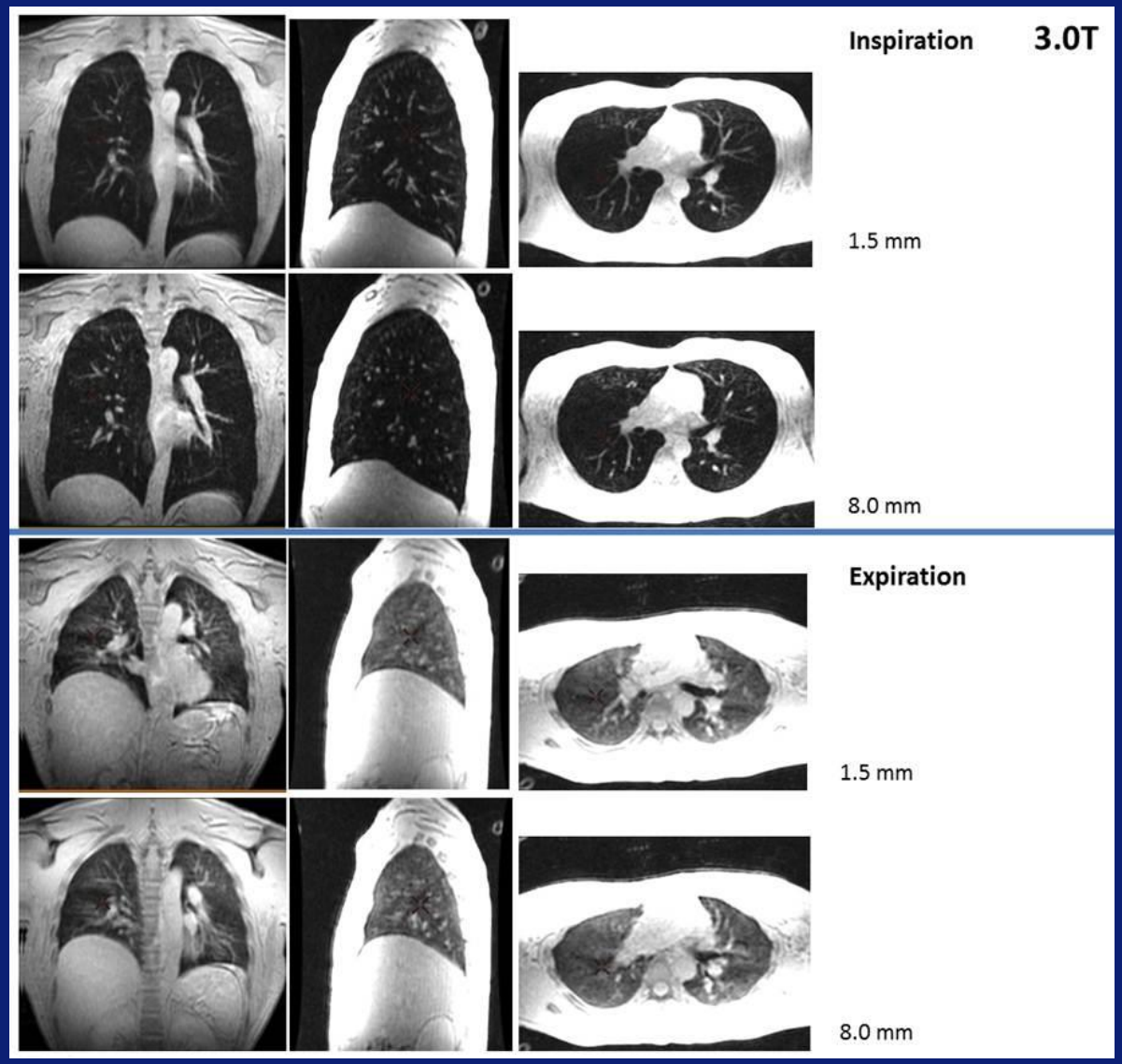
MRI and low intensity regions: Spirometer control!



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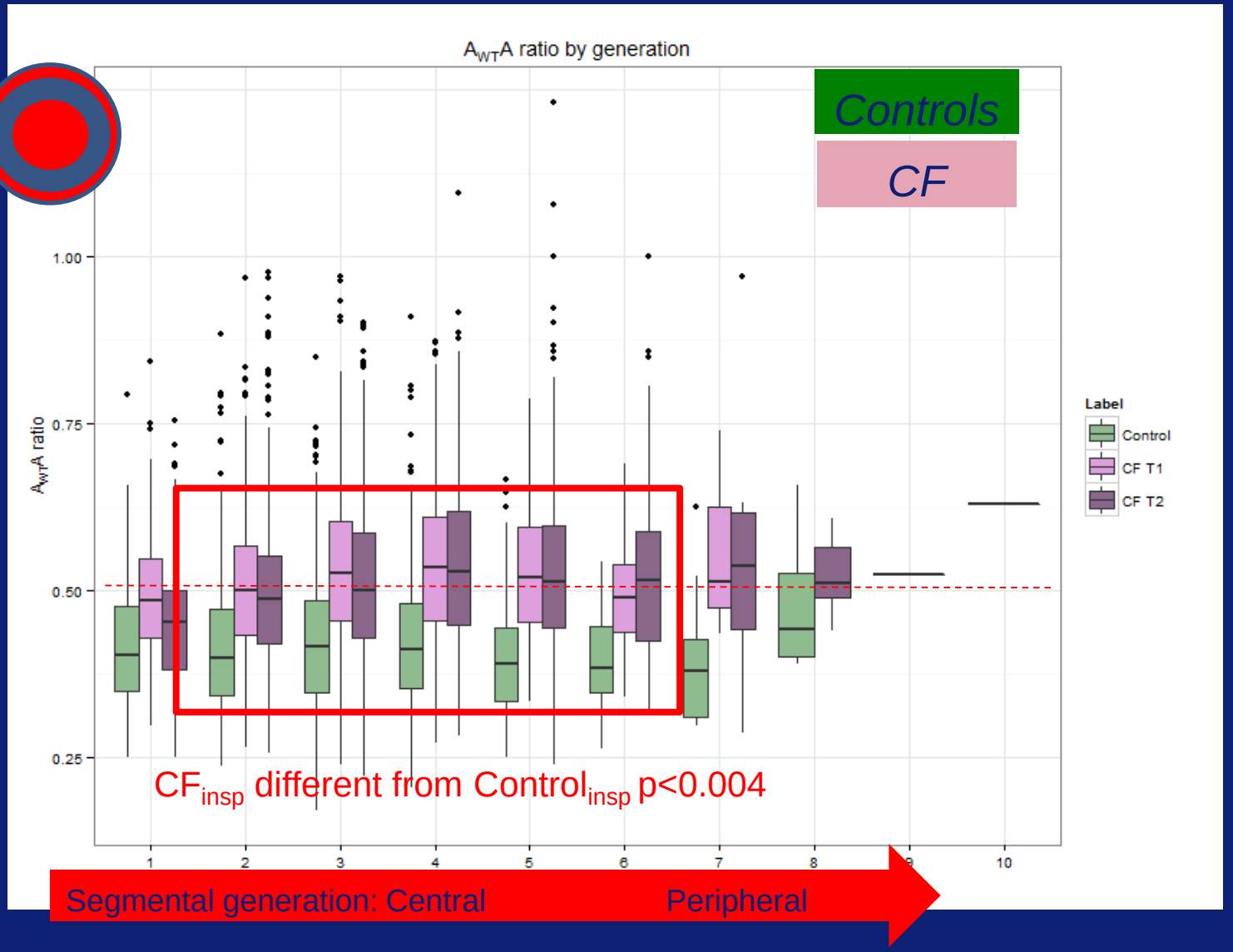
AA method (Arrest CF 2-4 years): early thickening



Kuo et al, *Pediatr Pulmonol 2017*

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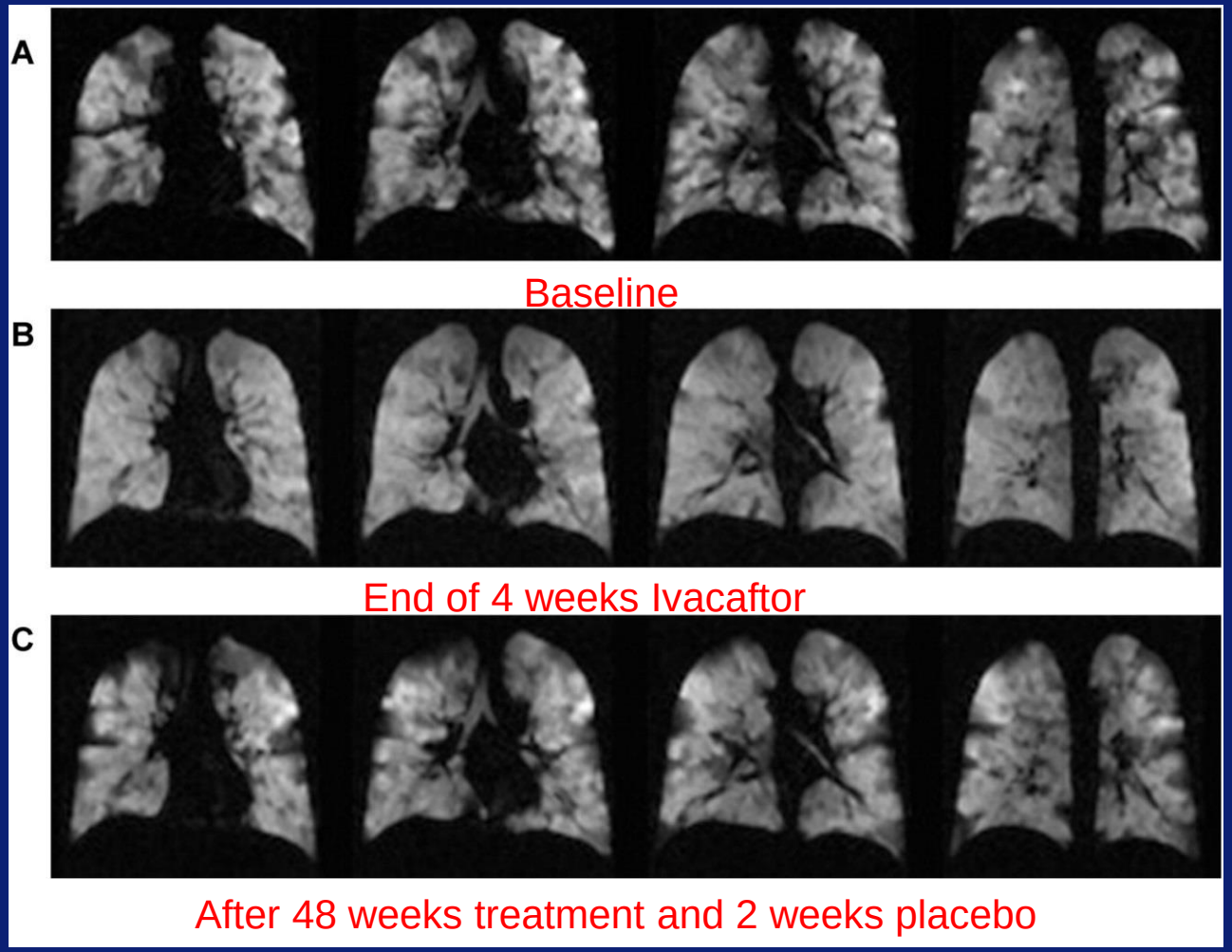
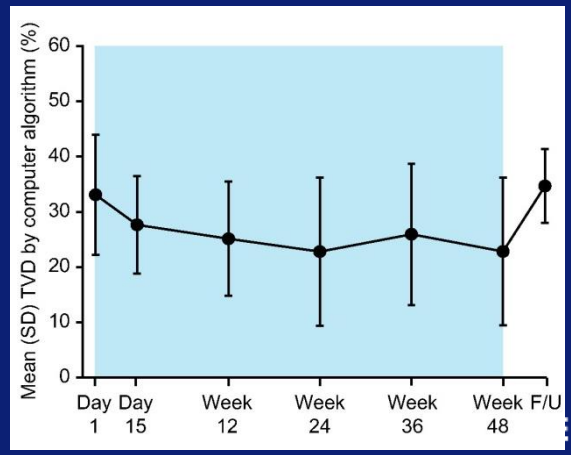
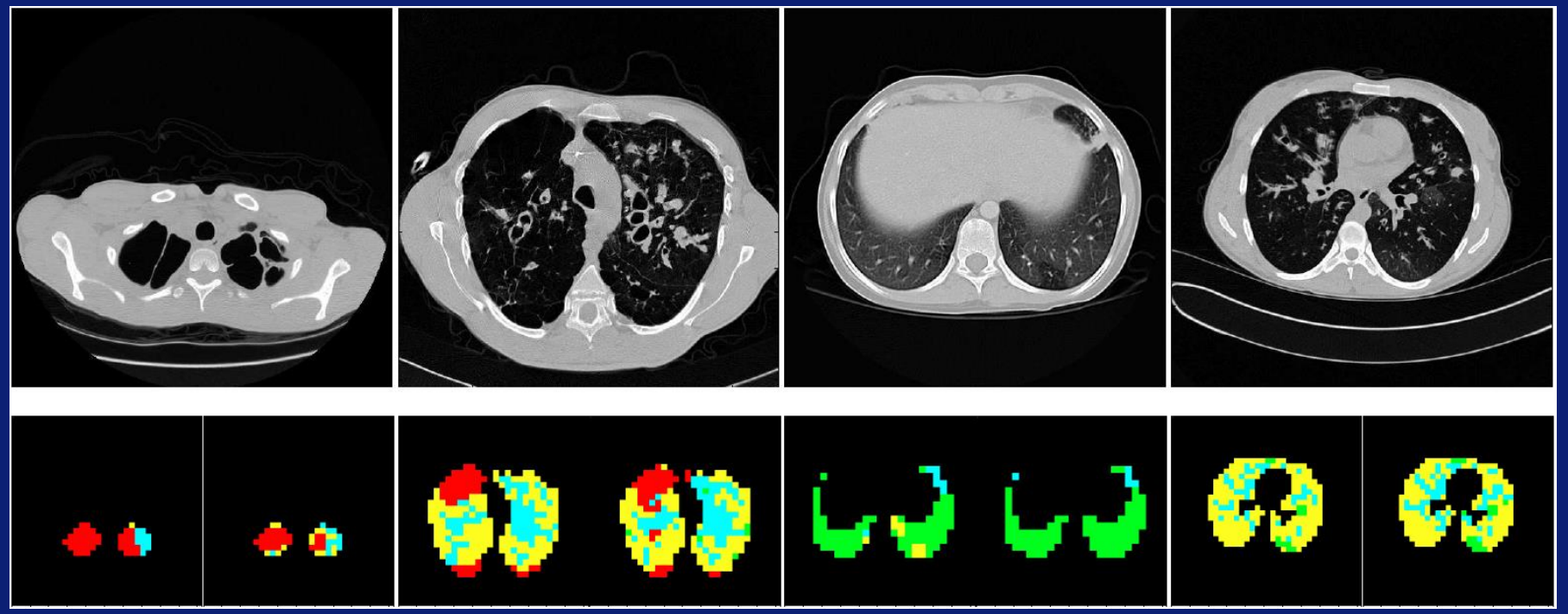
Hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with CF





Altes et al, *JCF 2017*

SALD and Computerized learning



Courtesy of De Bruijne

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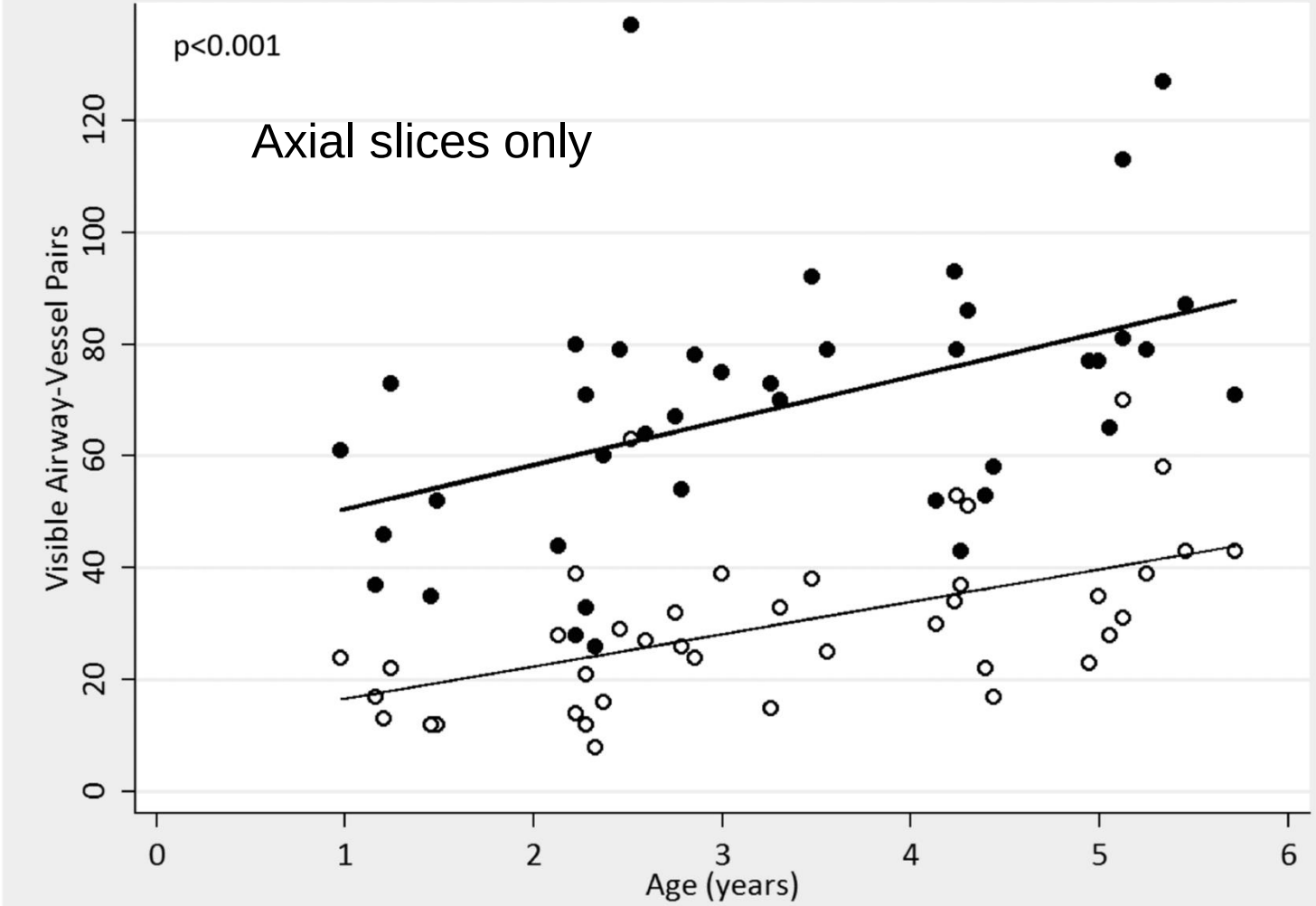
Impact of lung volume on CF-CT scoring Children < 6 years: Lower number of visible airways



Mott, *Chest 2013*

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Standardization chest CT: image quality

$$Q_{NOISE,RES,DOSE} = \frac{1}{\sigma^2} \cdot \frac{M^2 \int df\, f^2\, MTF^2(f)}{FWHM_{SSP}} \cdot \frac{1}{CTDI_{vol}}$$

MTF = axial resolution (kernel)

σ^2 = noise variance

FWHM = longitudinal resolution (slice thickness)

CTDI $_{vol}$ = CT dose index

- $Q_{noise,res,dose}$ incorporates Image noise, resolution, and dose in one formula
- 'Higher $Q_{noise,res,dose}$ is a better scanner'
- Radiation is the cost to obtain information
- Image noise; SSP, MTF are interrelated

Kuo et al, *ERJ 2016*

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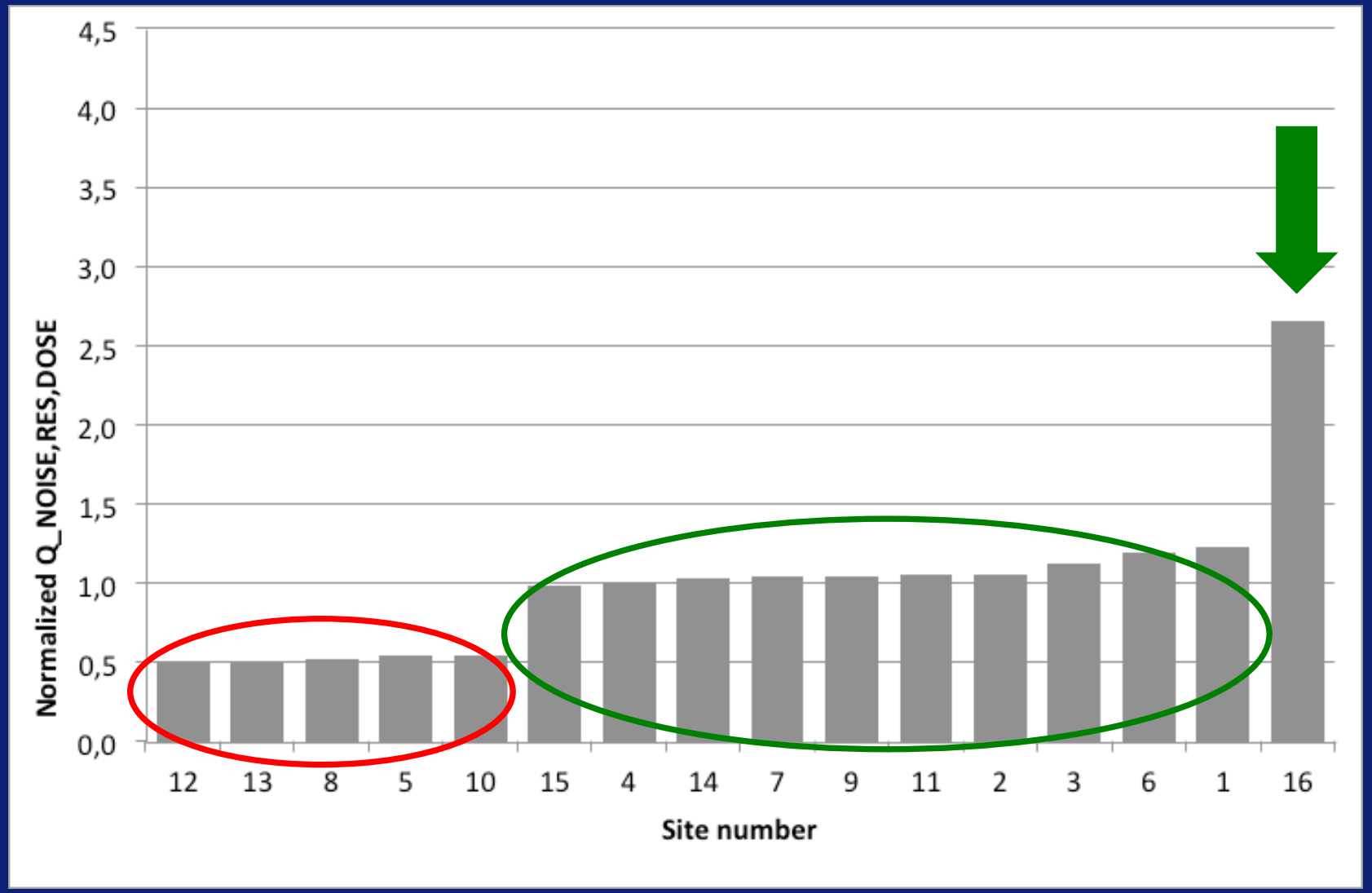
Comparison image quality: Scanners in EU



Kuo et al, *ERJ 2016*

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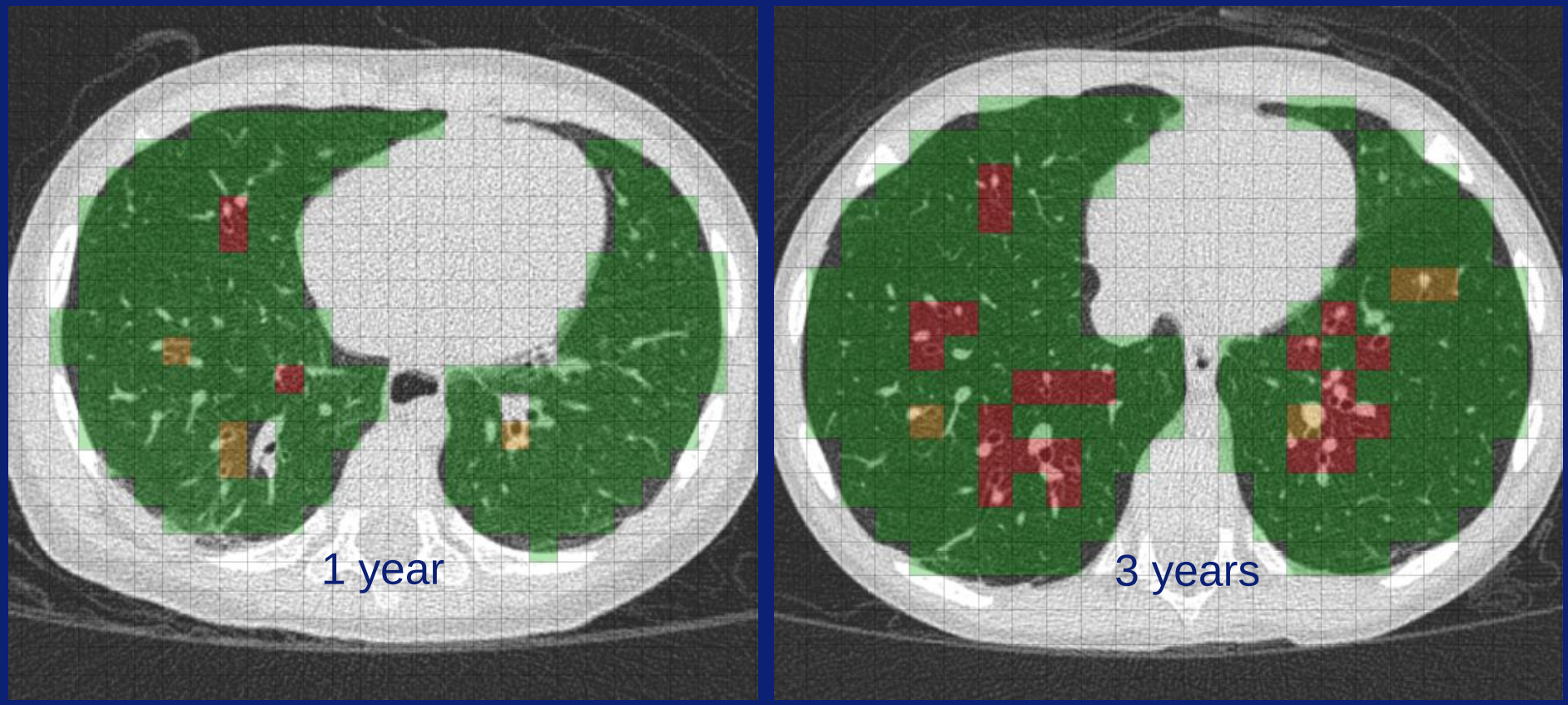
Progression of PRAGMA over time



%Dis = Bronchiectasis + Airway Wall Thickening + Mucous impaction

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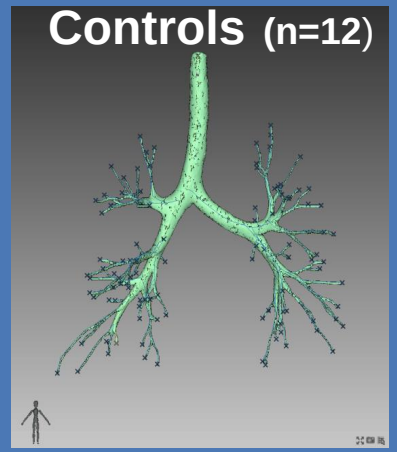
AA-method (CF-CT ≥ 6 years): Results

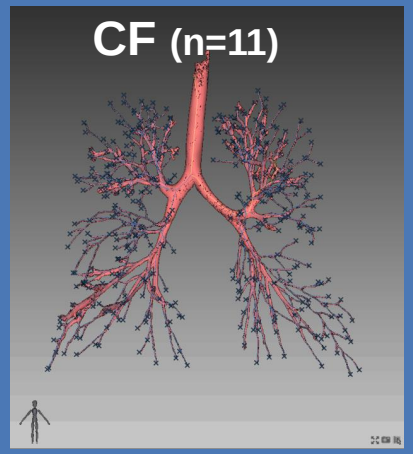
Inspiration:
1516 AA pairs
126 AA pairs/CT

Expiration:
700 AA pairs
58 AA pairs/CT



Inspiration:
3528 AA pairs
321 AA pairs/CT

Expiration:
1017 AA pairs
92 AA pairs/CT



Kuo et al, *European Radiology 2017*

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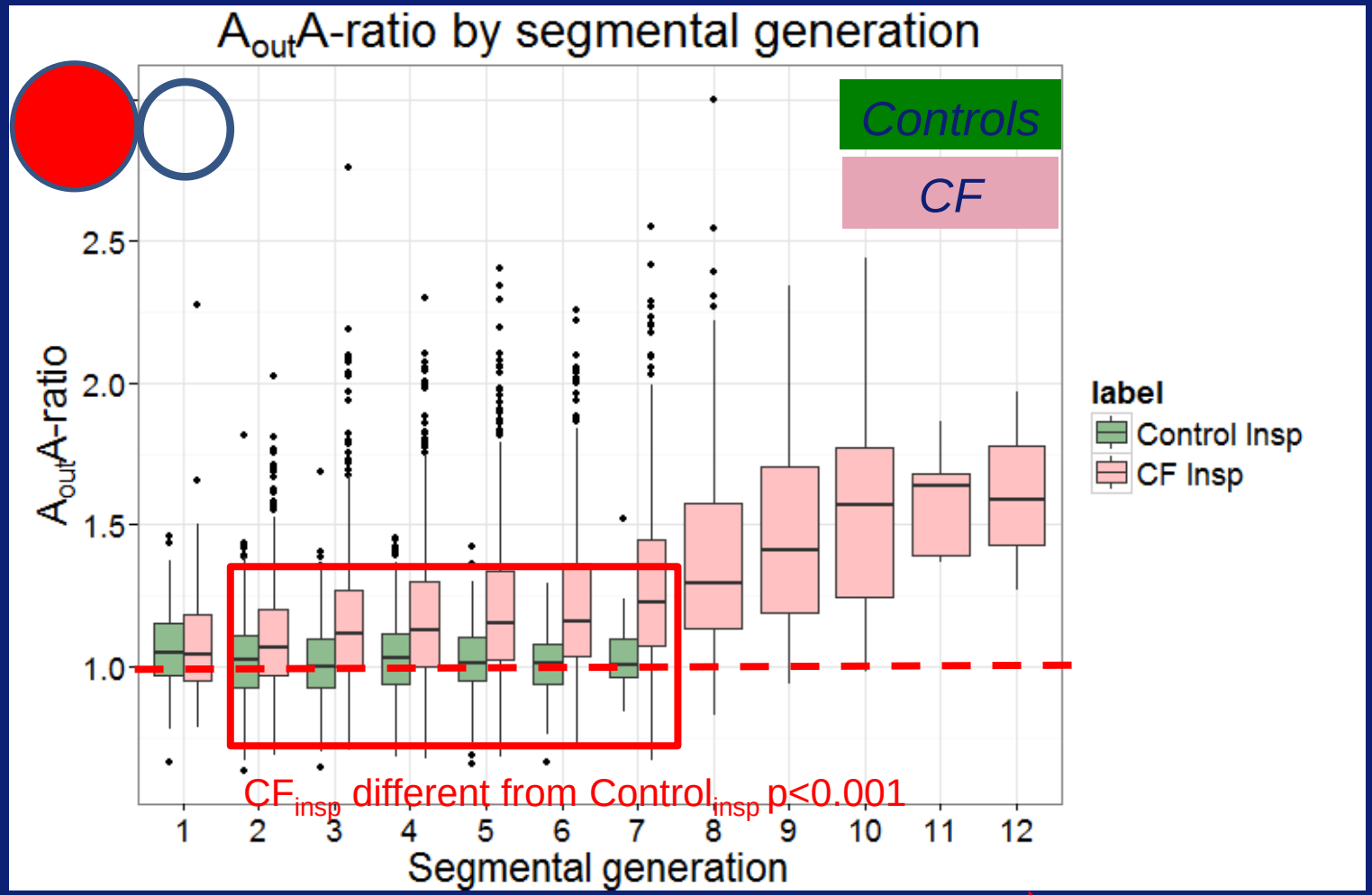
AA-method (CF-CT ≥ 6 years) : Ratio higher ≥ 2nd segmental generation



Segmental generation: Central → Peripheral

Kuo et al, *European Radiology 2017*

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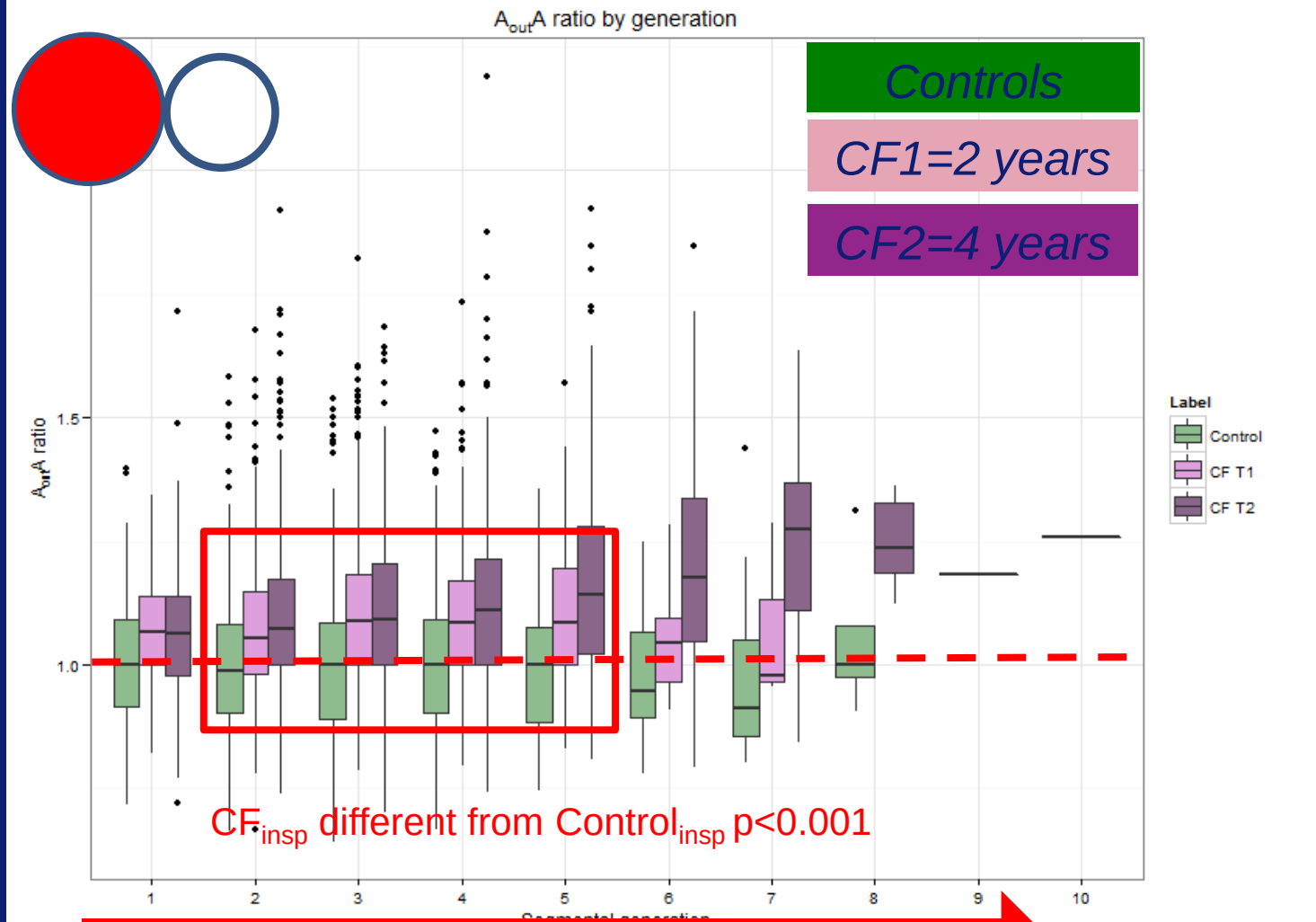
AA method (Arrest CF 2-4 years): progressive widening



Kuo et al, *European Radiology 2017*

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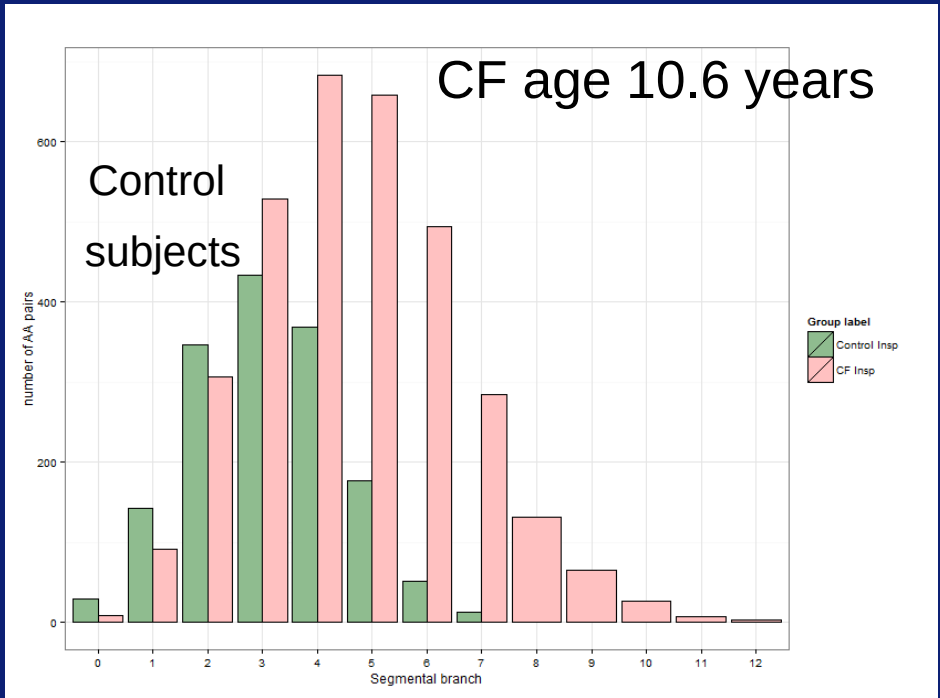
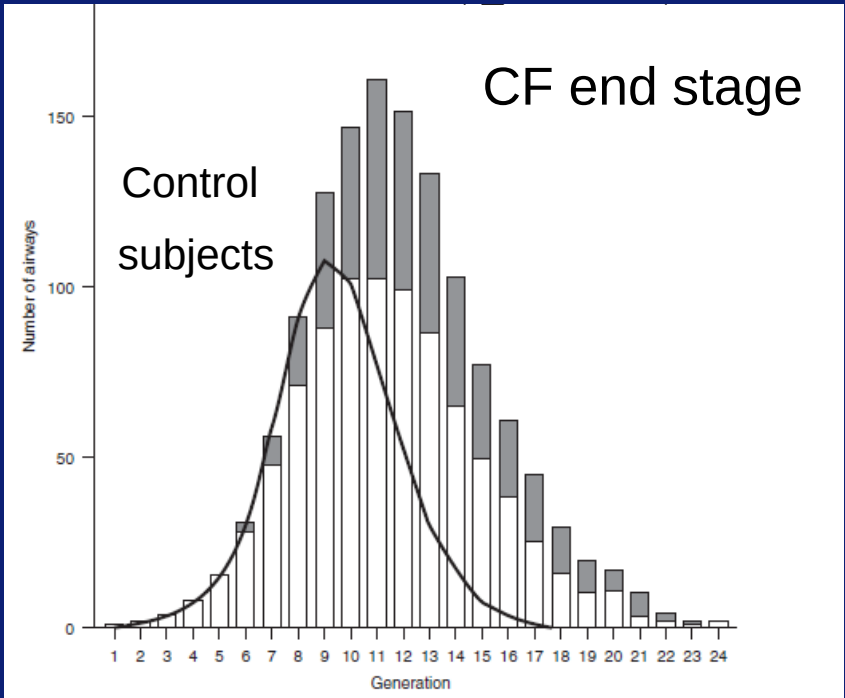
Double number of visible small airways in early and end stage CF lung disease relative to controls





Kuo et al, *European Radiology 2017;* Mott, *Chest 2013 et al,* Boon et al, *AJRCCM 2016*