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Functional Respiratory Imaging Biomarkers by FluidDA:

Mode of action of Daxas® in COPD patients: a randomized placebo controlled trial

Takeda Meeting

August 7th, 2013

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OBJECTIVES OF TODAY'S MEETING

- Explain Functional Respiratory Imaging (FRI) and mode of action application
- Daxas Study Results
  - Review protocol
  - Discussion of Results
- Next steps

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CONCLUSIONS OF THE STUDY

- Daxas improves the patient compared to placebo
- Daxas group has responders and non-responders
- Study provided hypothesis for the mode of action of response and for the phenotype of the responders
- Hypothesis were supported by the data (statistically significant)

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CHALLENGES IN RESPIRATORY DRUG DEVELOPMENT

Limited sensitivity of current Pulmonary Function Tests (FEV1,…)

Very difficult to demonstrate efficacy of novel compounds, resulting in **high number of patients needed in clinical trials**

Excessive respiratory drug development cost > $1.5 billion

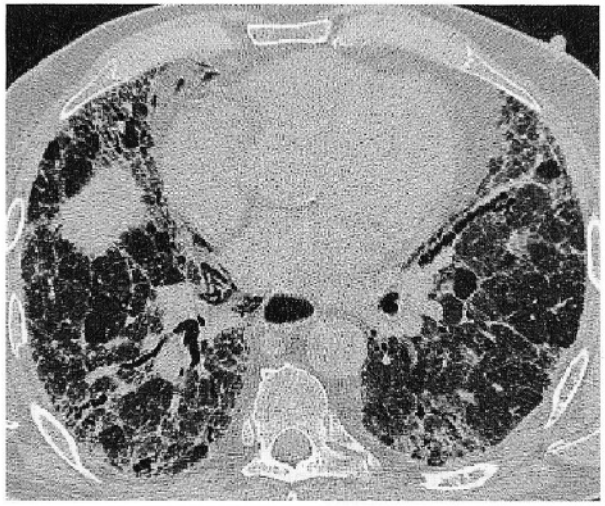
[1]Adams CP, Brantner VV. Health Aff (Millwood). 2006 Mar-Apr;25(2):420-8.

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FRI Analysis using CT scans as input

- High-resolution CT images are converted into patient-specific 3D computer models





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FluidDA's Process Flow:

From CT Images

to

CFD Analysis

CT images





Segmentation

- voxel tresholding
- mask operations
- dynamic region growing algorithms





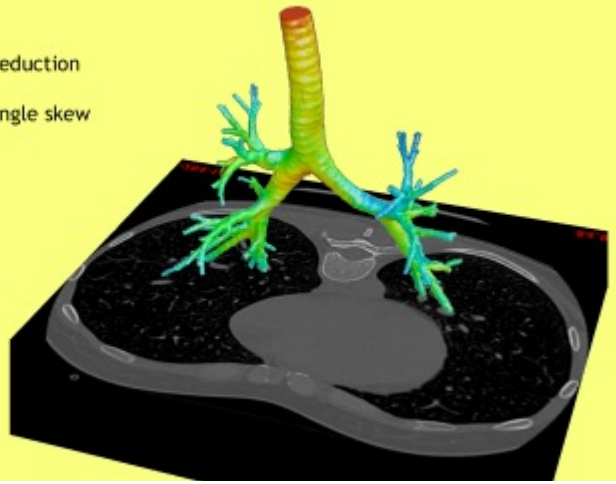
3D reconstruction

- staircasing effect
- highly skewed elements

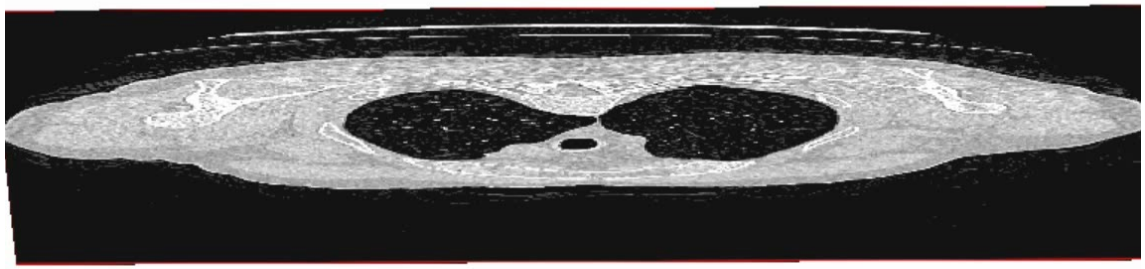


Post processing

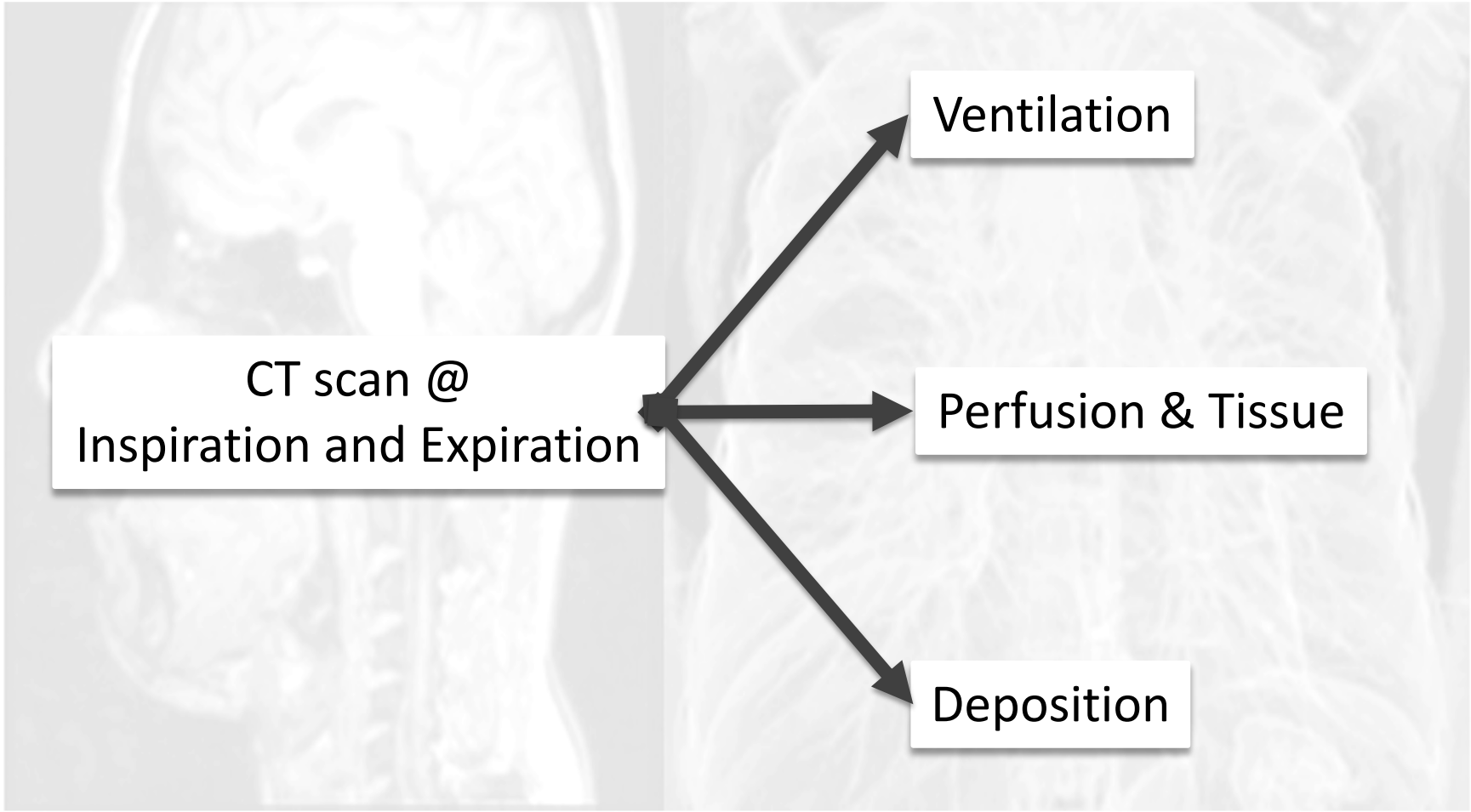
- smoothing with volume reduction compensation
- remeshing to reduce triangle skew



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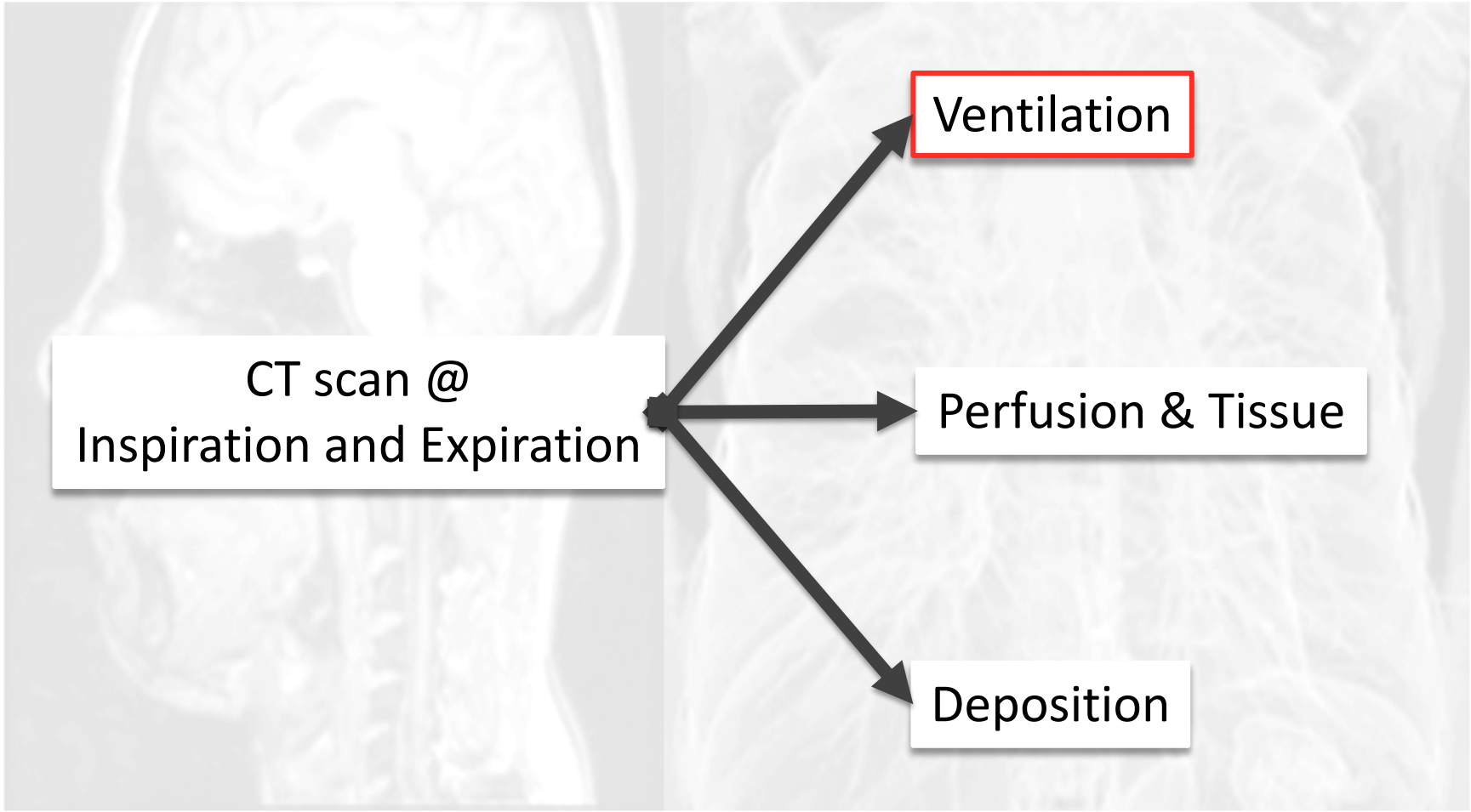


FRI: OUTCOME PARAMETERS



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FRI: OUTCOME PARAMETERS

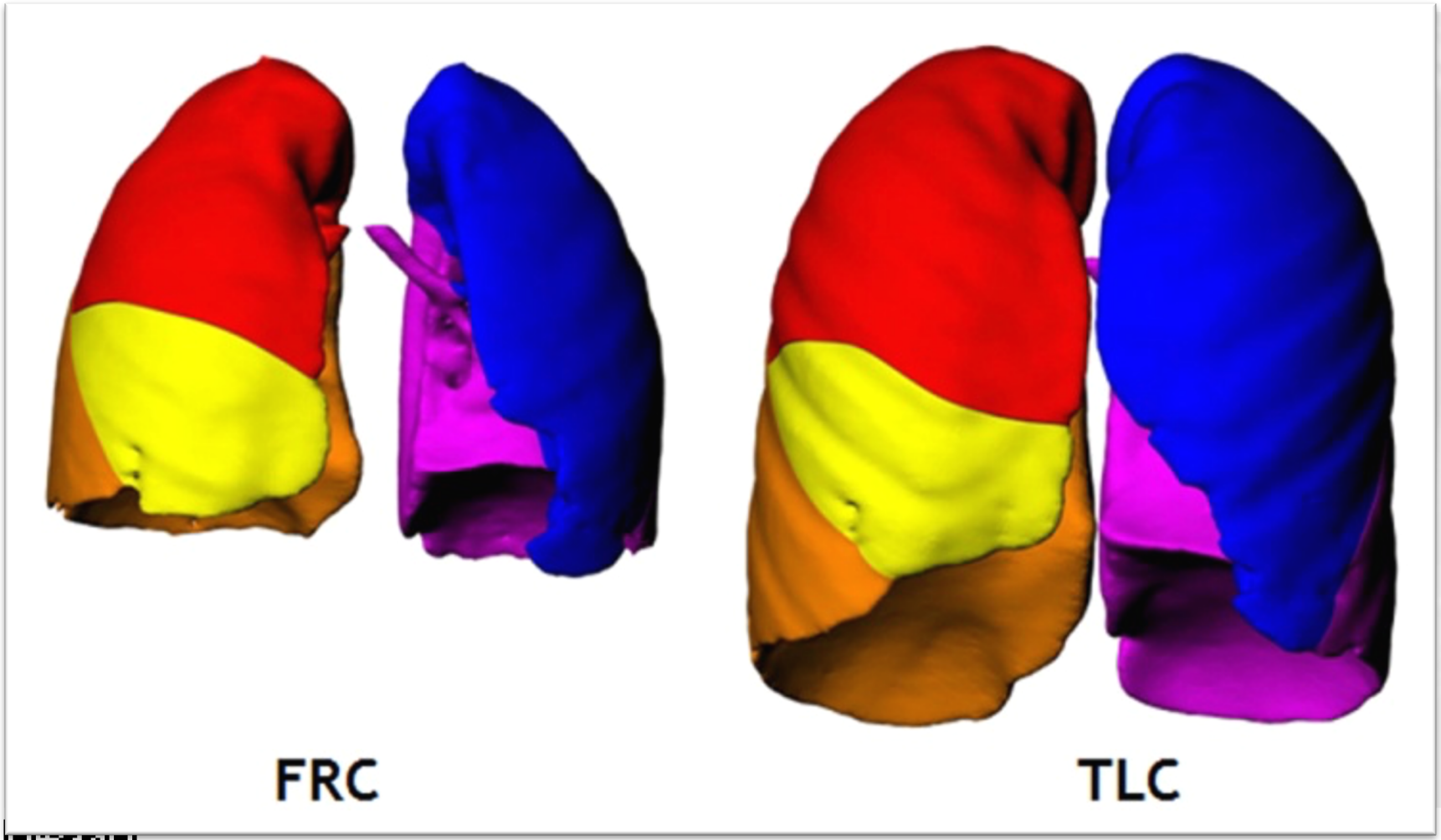


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FRI: VENTILATION

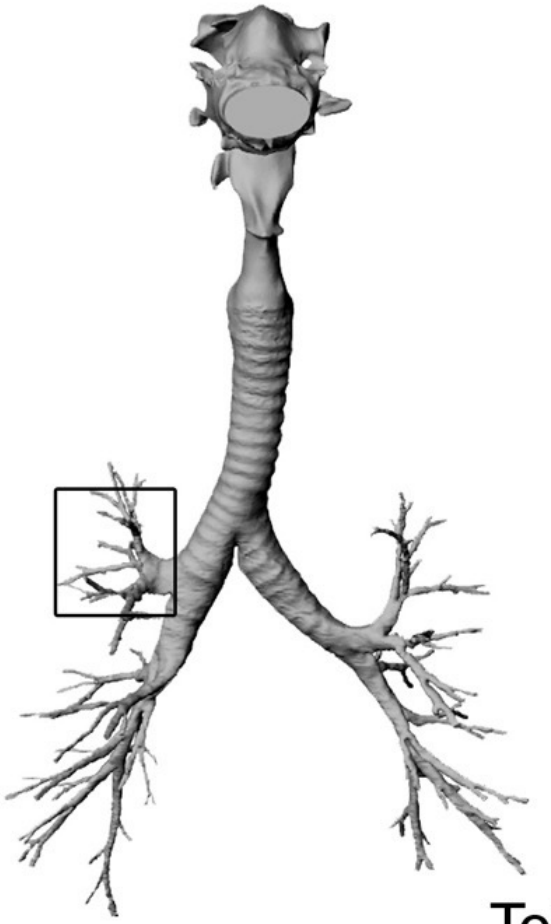
LOBAR VOLUMES

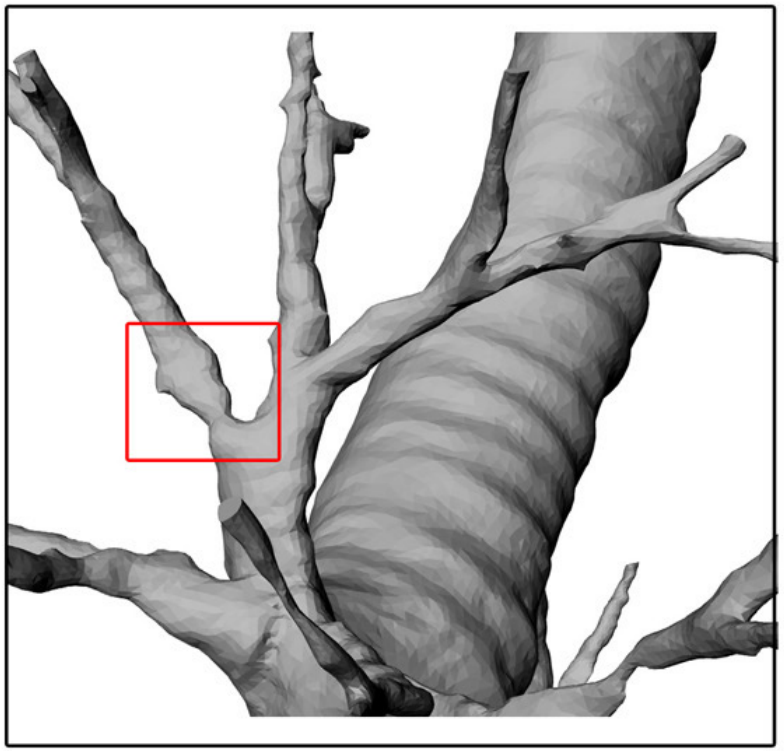


Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

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AIRWAY VOLUMES: Mild Asthmatic Case with airway narrowing



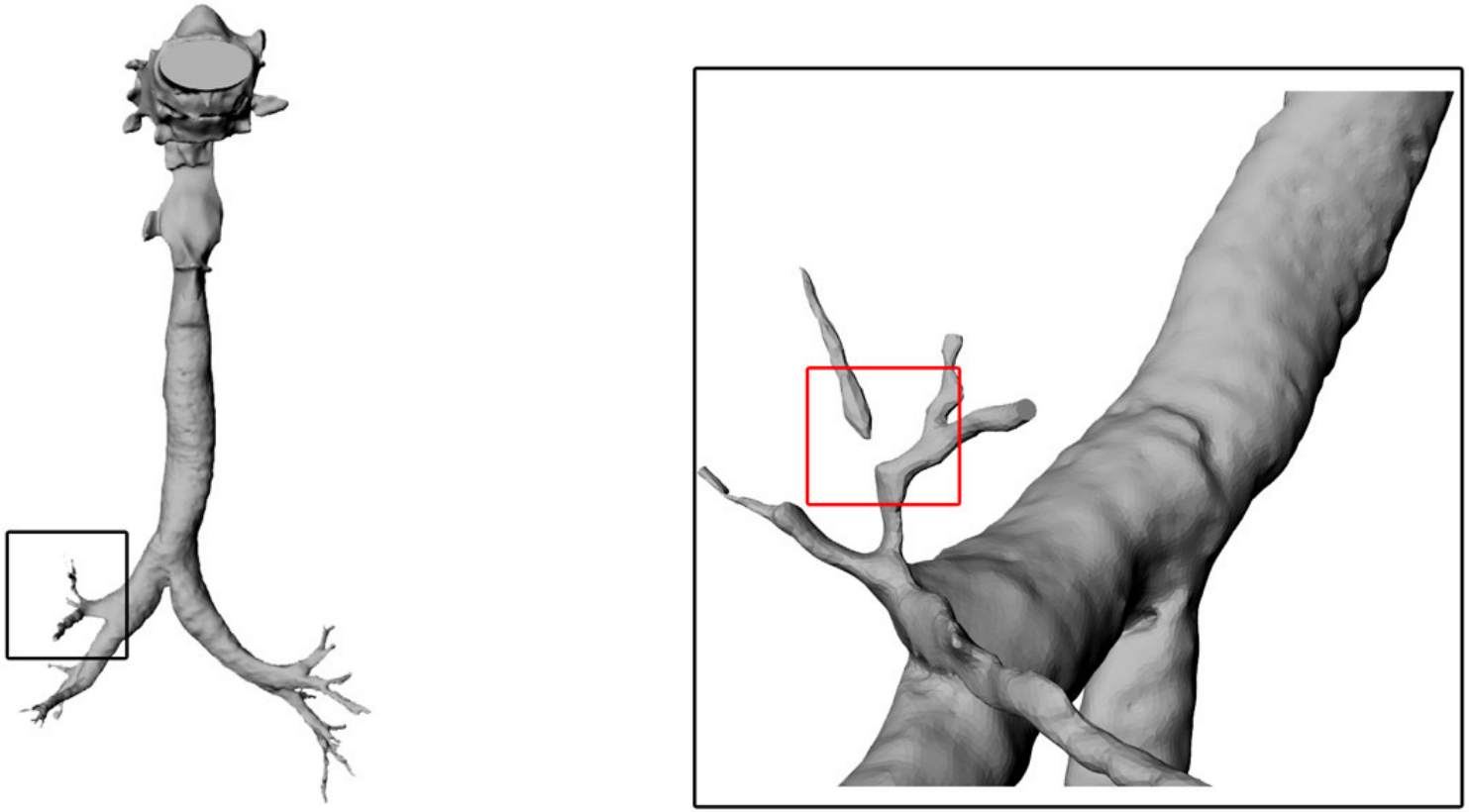


Total Lung Capacity

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AIRWAY VOLUMES: Mild Asthmatic Case with airway closure



Functional Residual Capacity

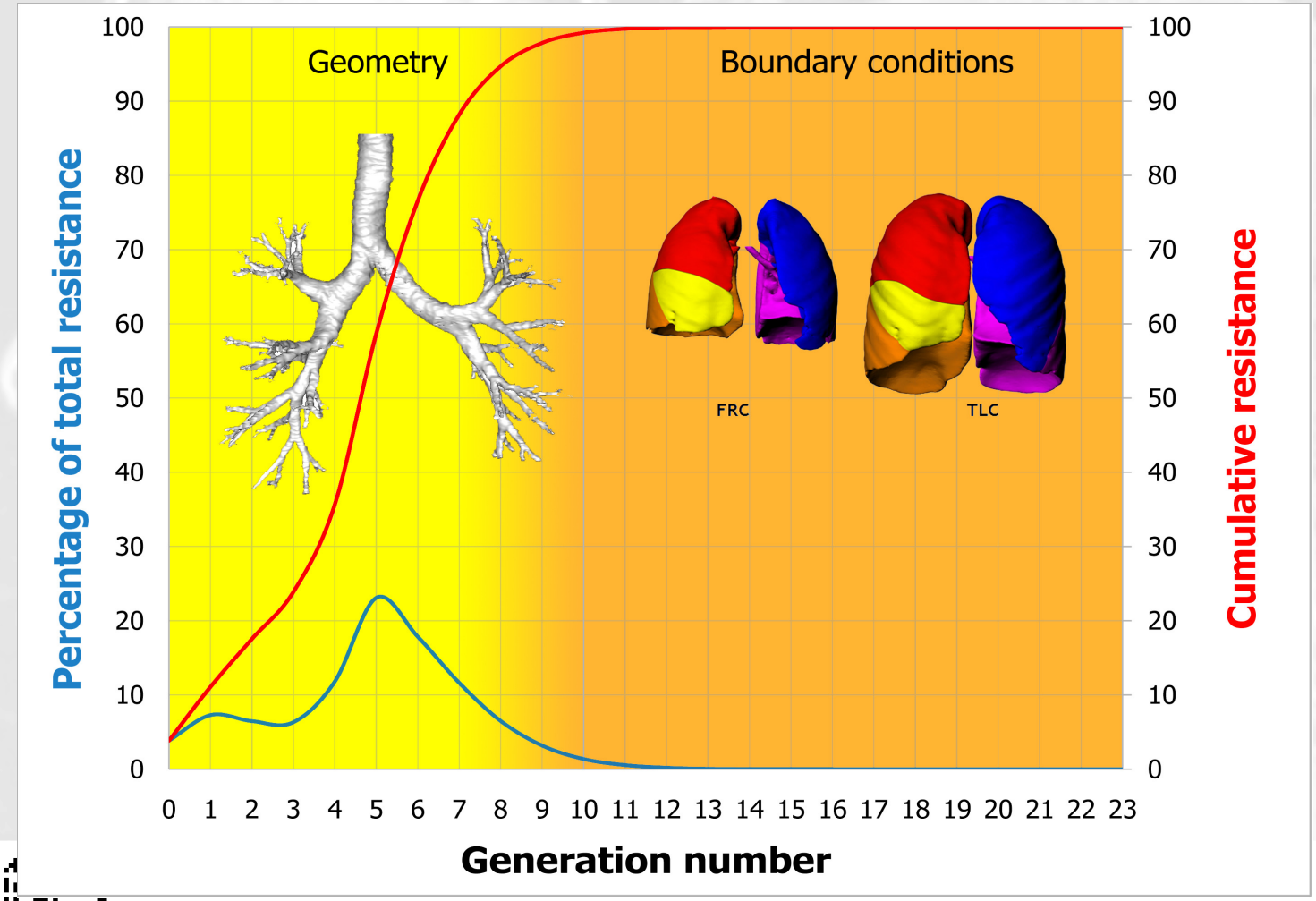
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FRI: VENTILATION

AIRWAY RESISTANCE and INTERNAL AIRFLOW DISTRIBUTION



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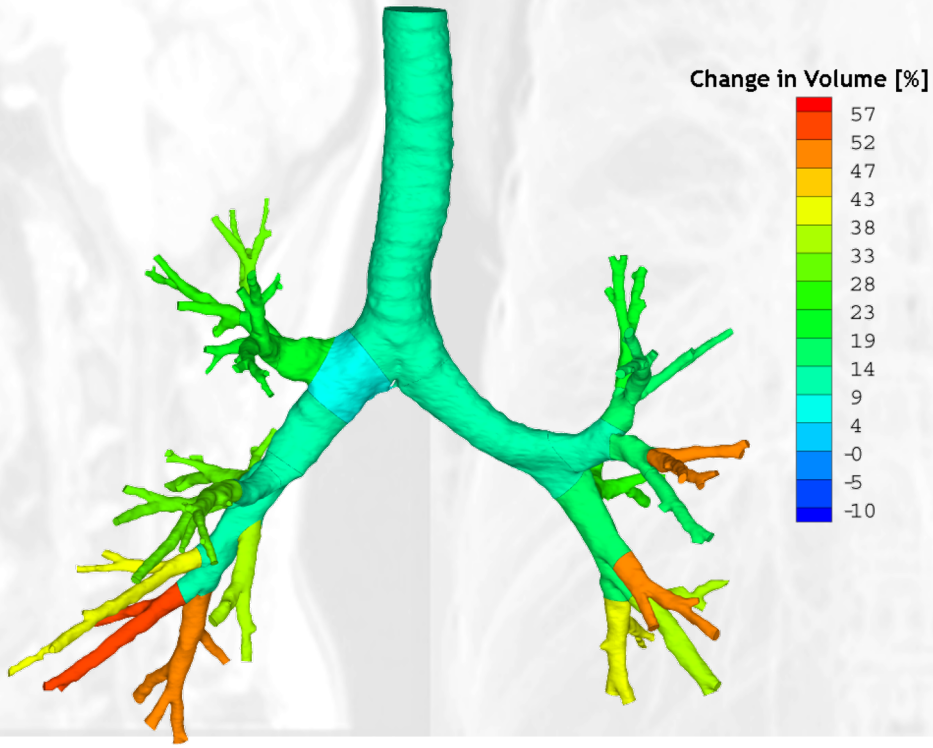
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FRI: IMAGE-BASED AIRWAY VOLUME CHANGE

ASTHMA CASE: Acute Bronchodilation (4hr) compared to Baseline

FEV1 pre = 121 %p FEV1 post = 120 %p

Change in Airway Volume (iVaw)



Reference: **Journal of Biomechanics 41 (2008) 106-113**

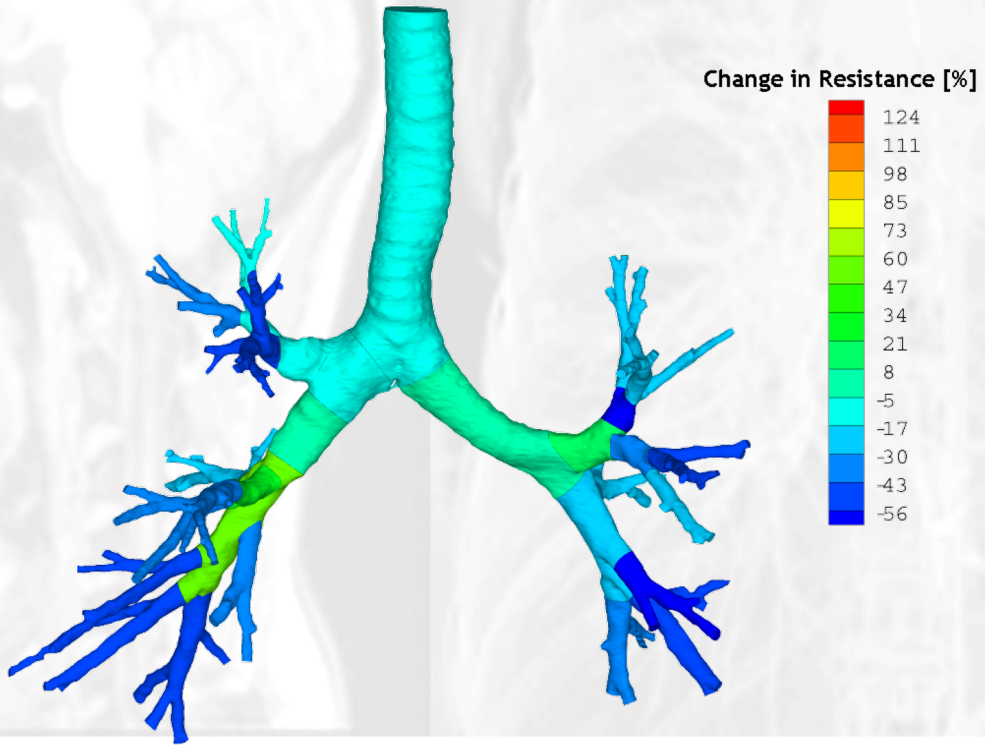
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ASTHMA CASE: Acute Bronchodilation (4hr) compared to Baseline

FEV1 pre = 121 %p FEV1 post = 120 %p

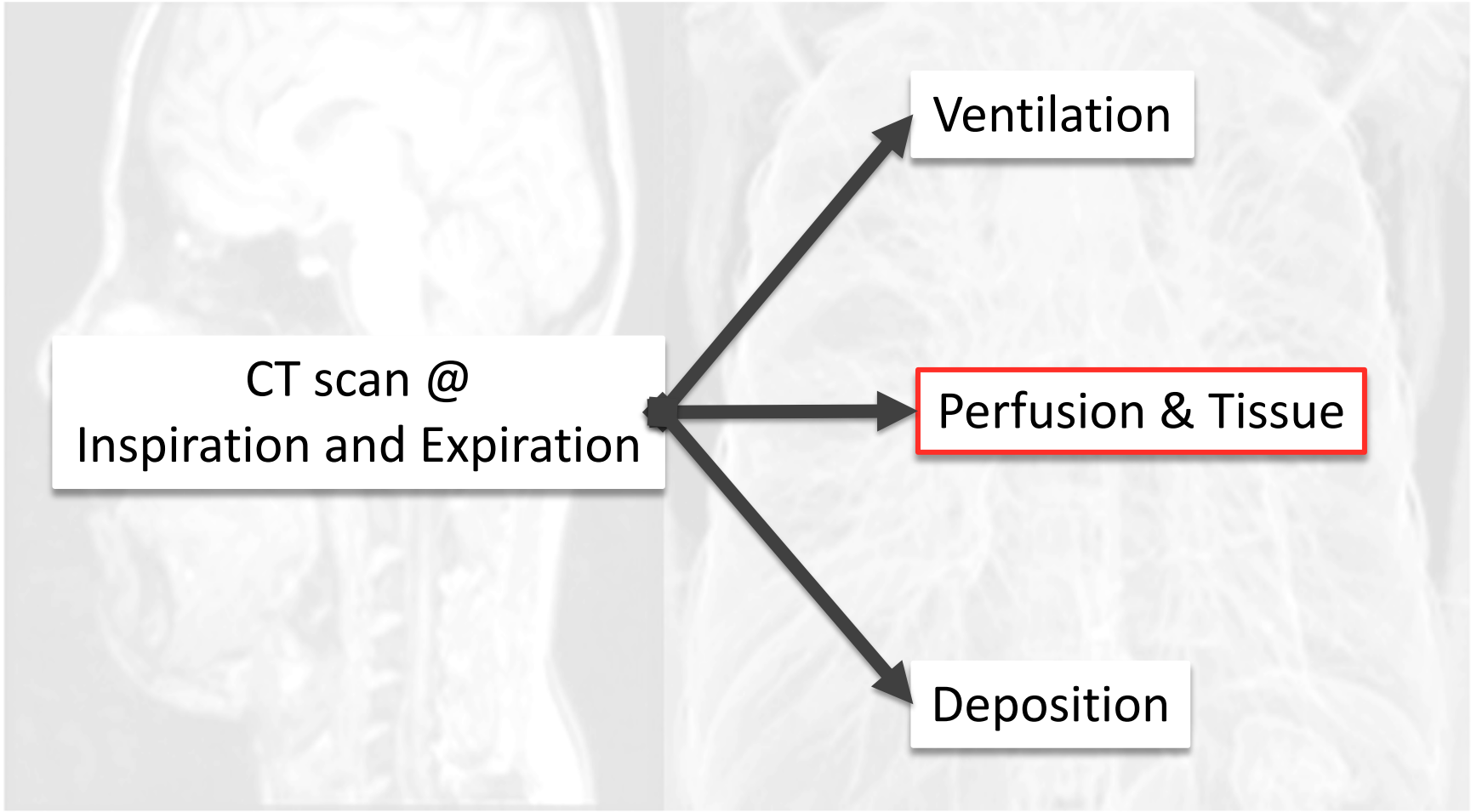
Change in Resistance (iRaw)



Reference: **Journal of Biomechanics 41 (2008) 106-113**

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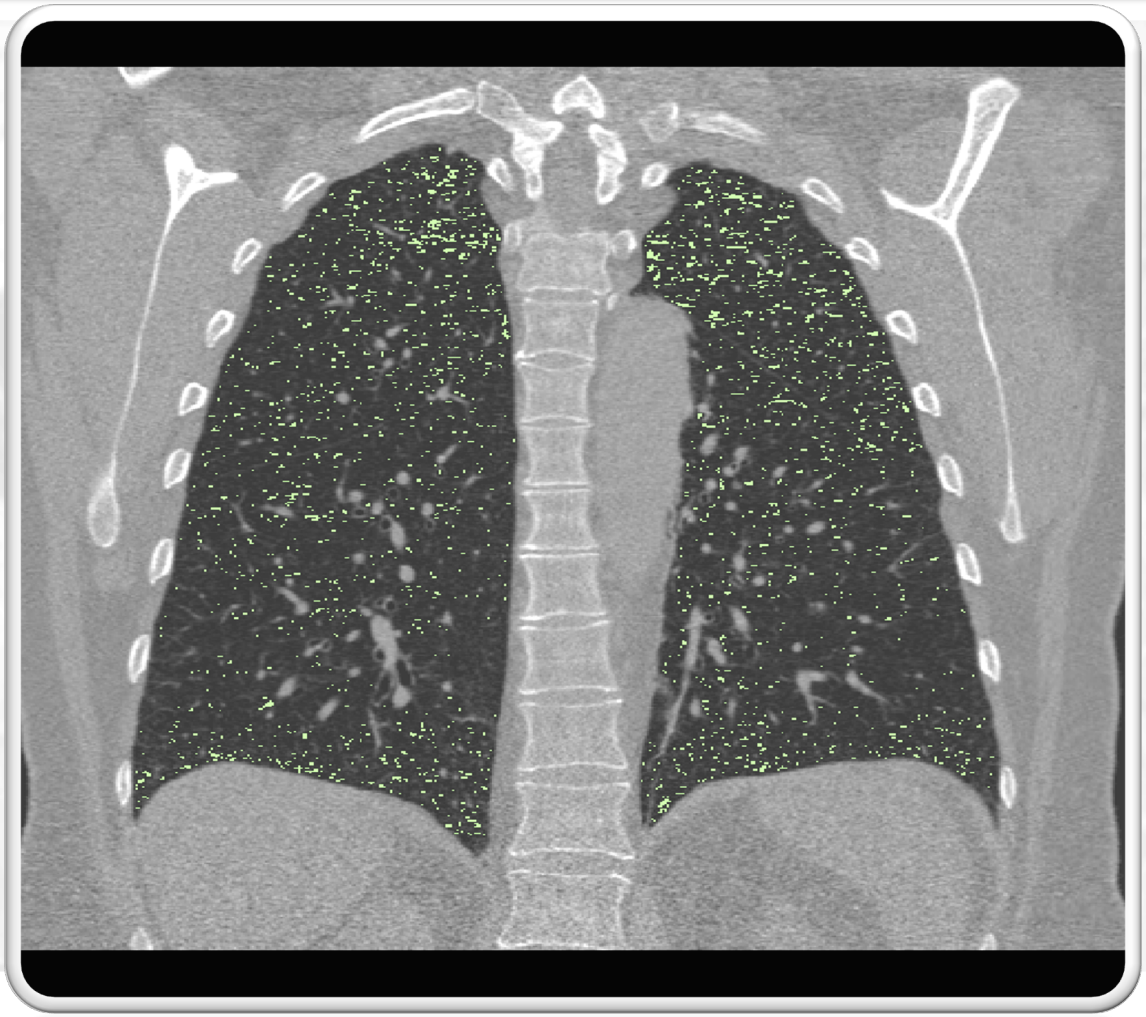


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FRI: PERFUSION & TISSUE

EMPHYSEMA: % on Lobar Level



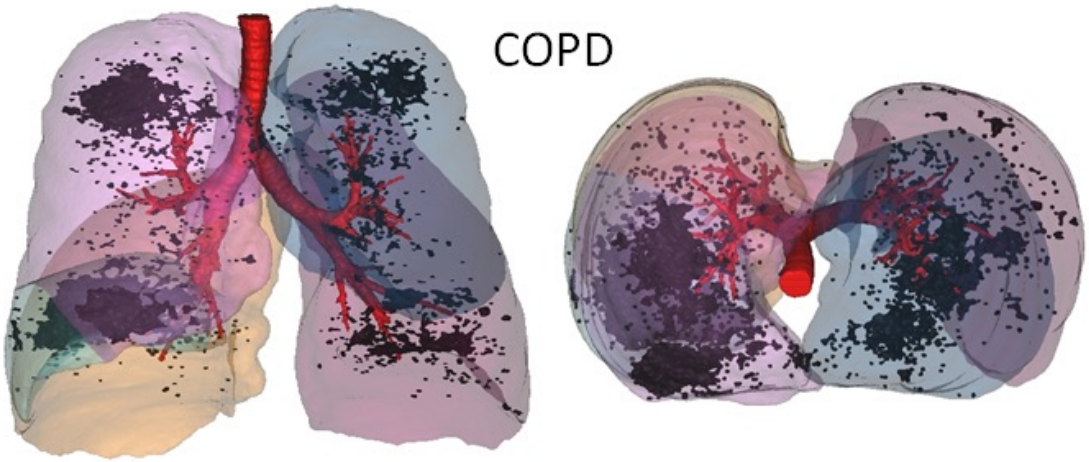
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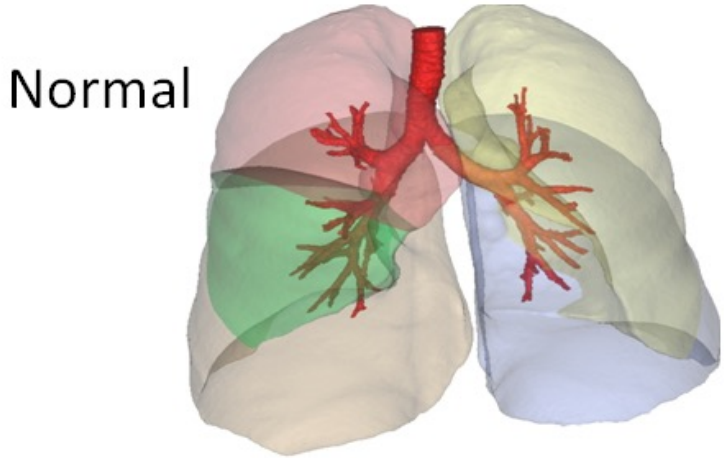
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FRI: PERFUSION & TISSUE

EMPHYSEMA : % on Lobar Level





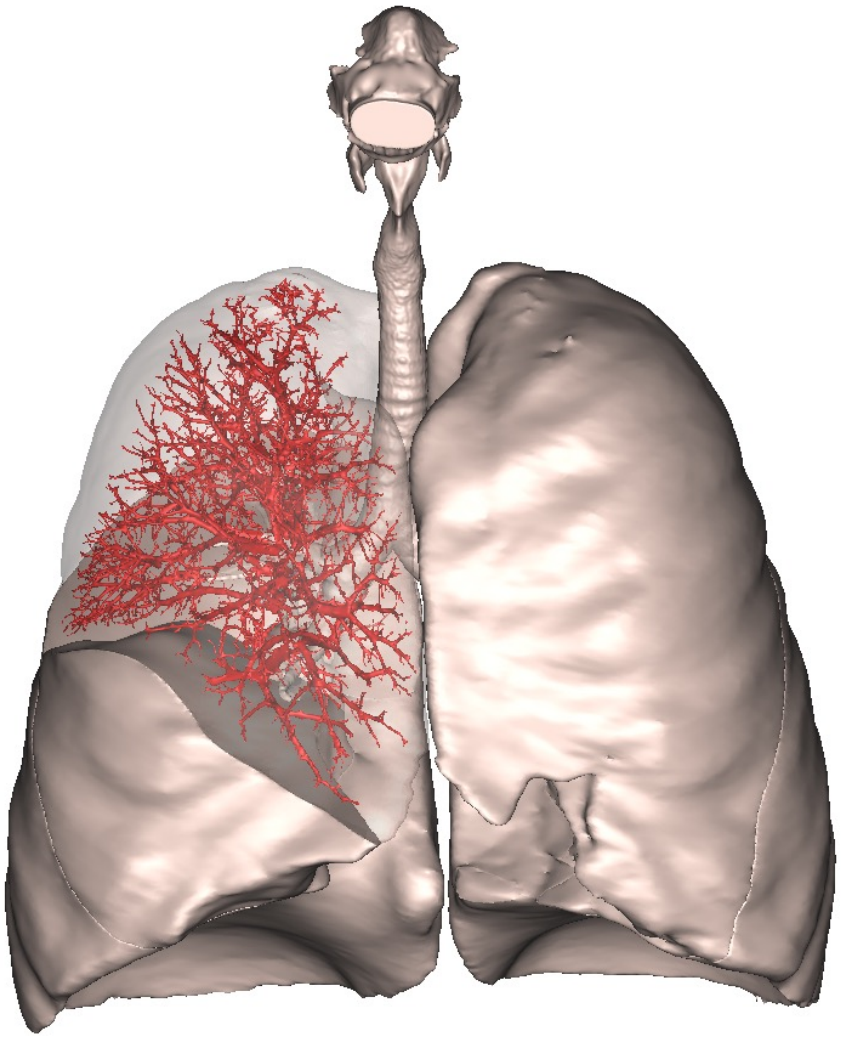
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FRI: PERFUSION & TISSUE

BLOOD VESSELS: : % on Lobar Level



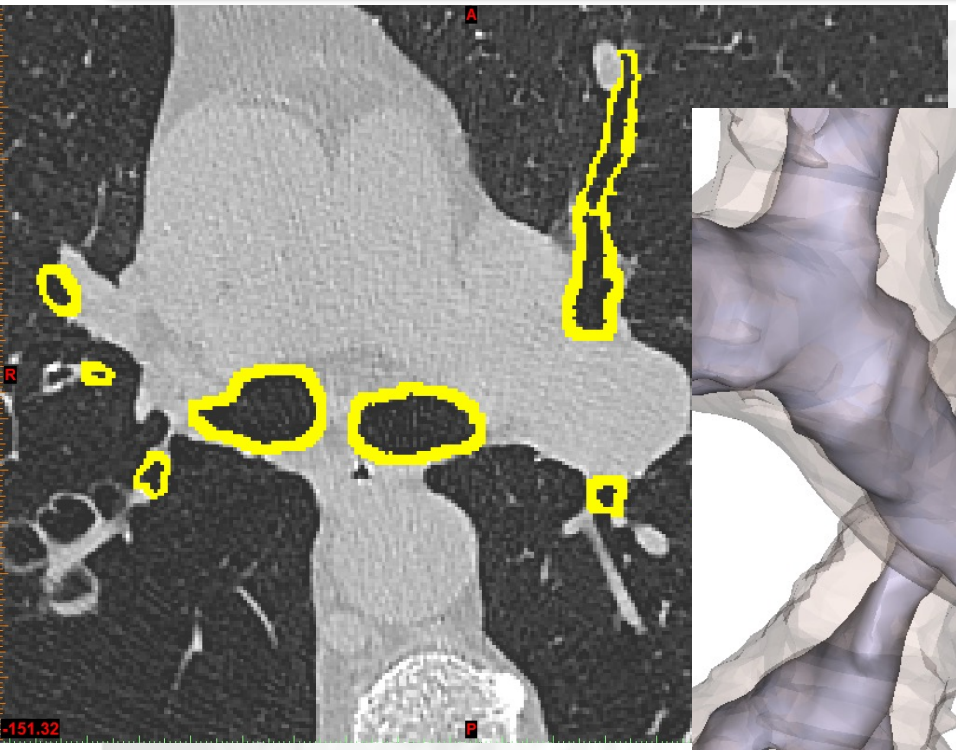
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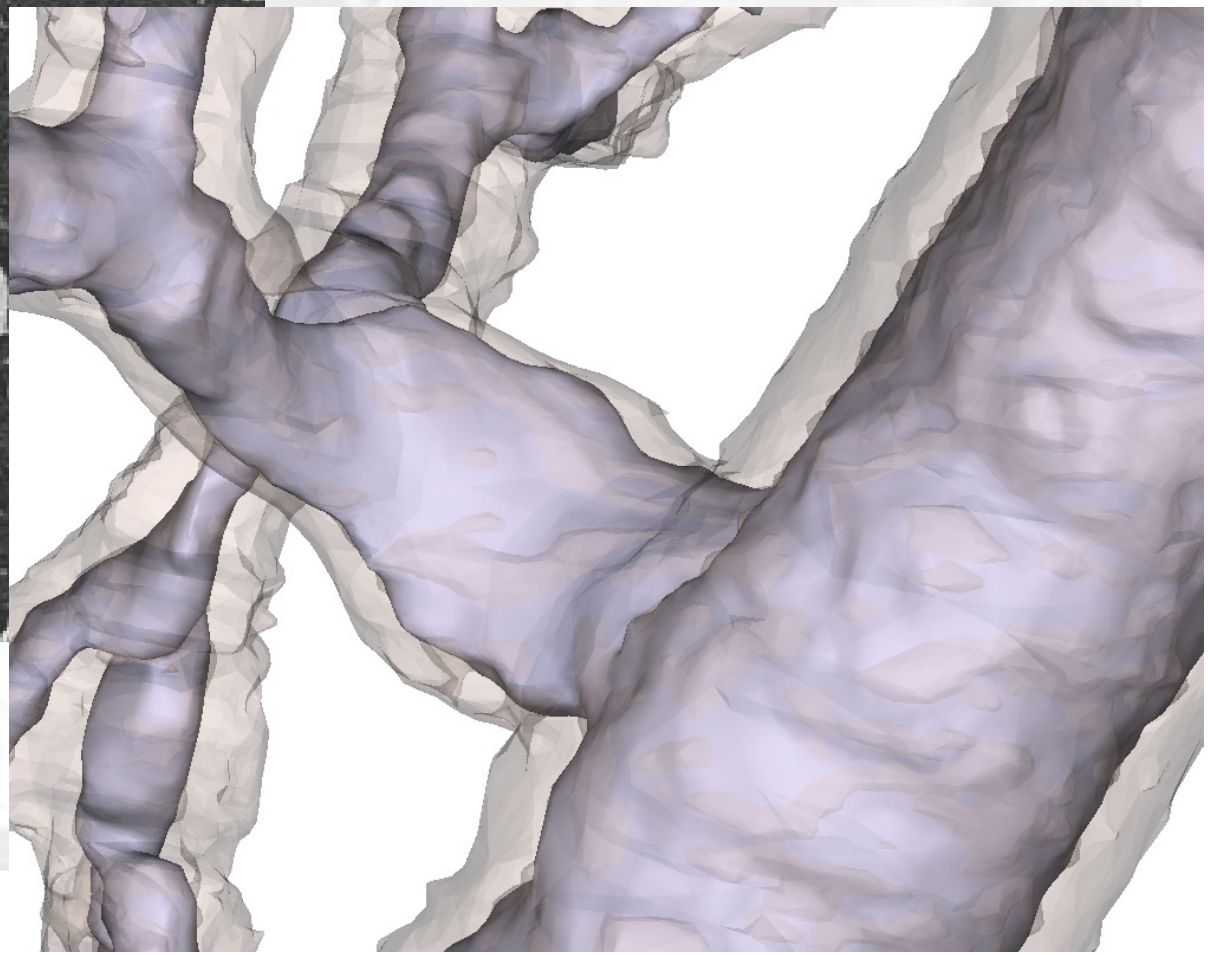
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FRI: PERFUSION & TISSUE

AIRWAY WALL THICKNESS

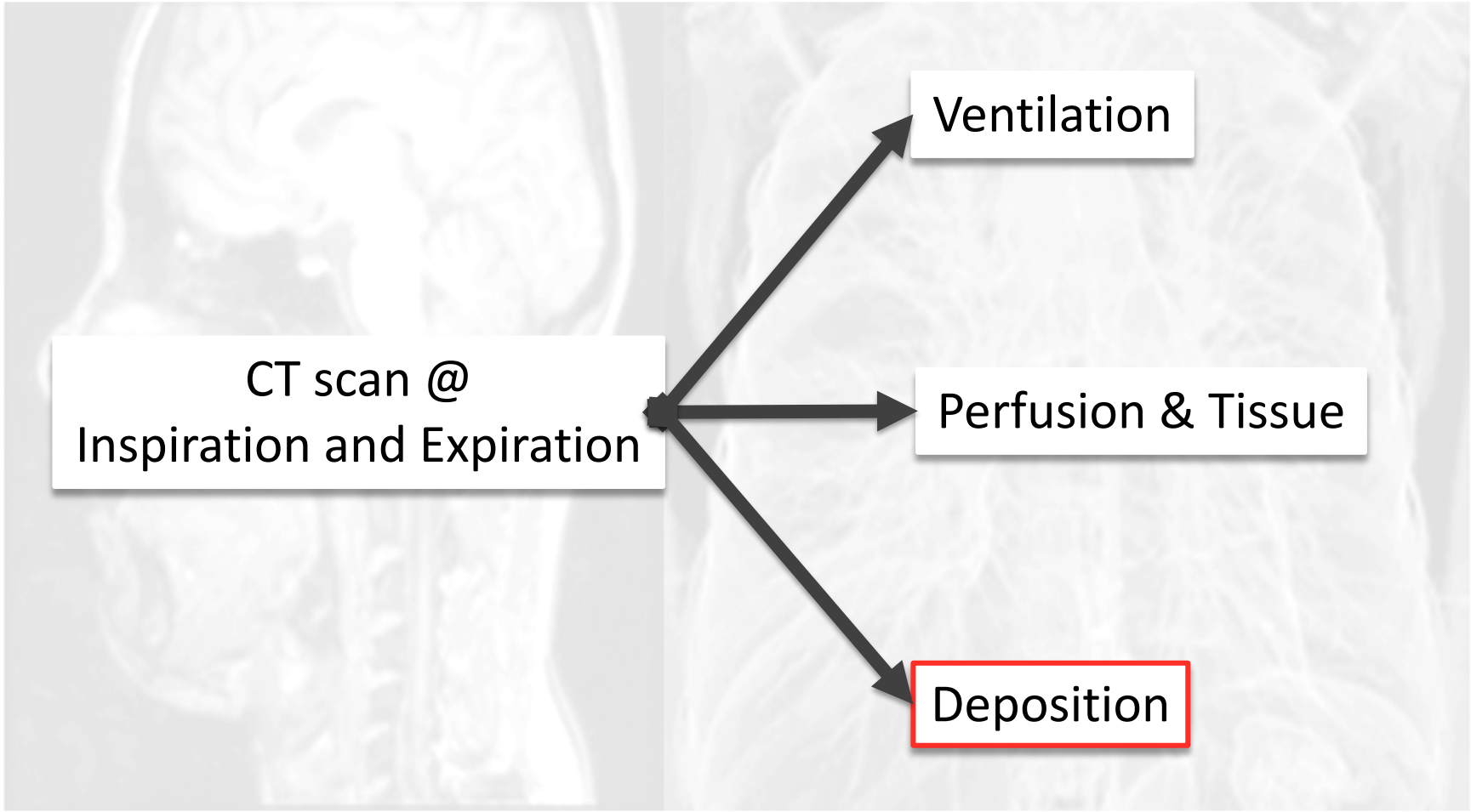




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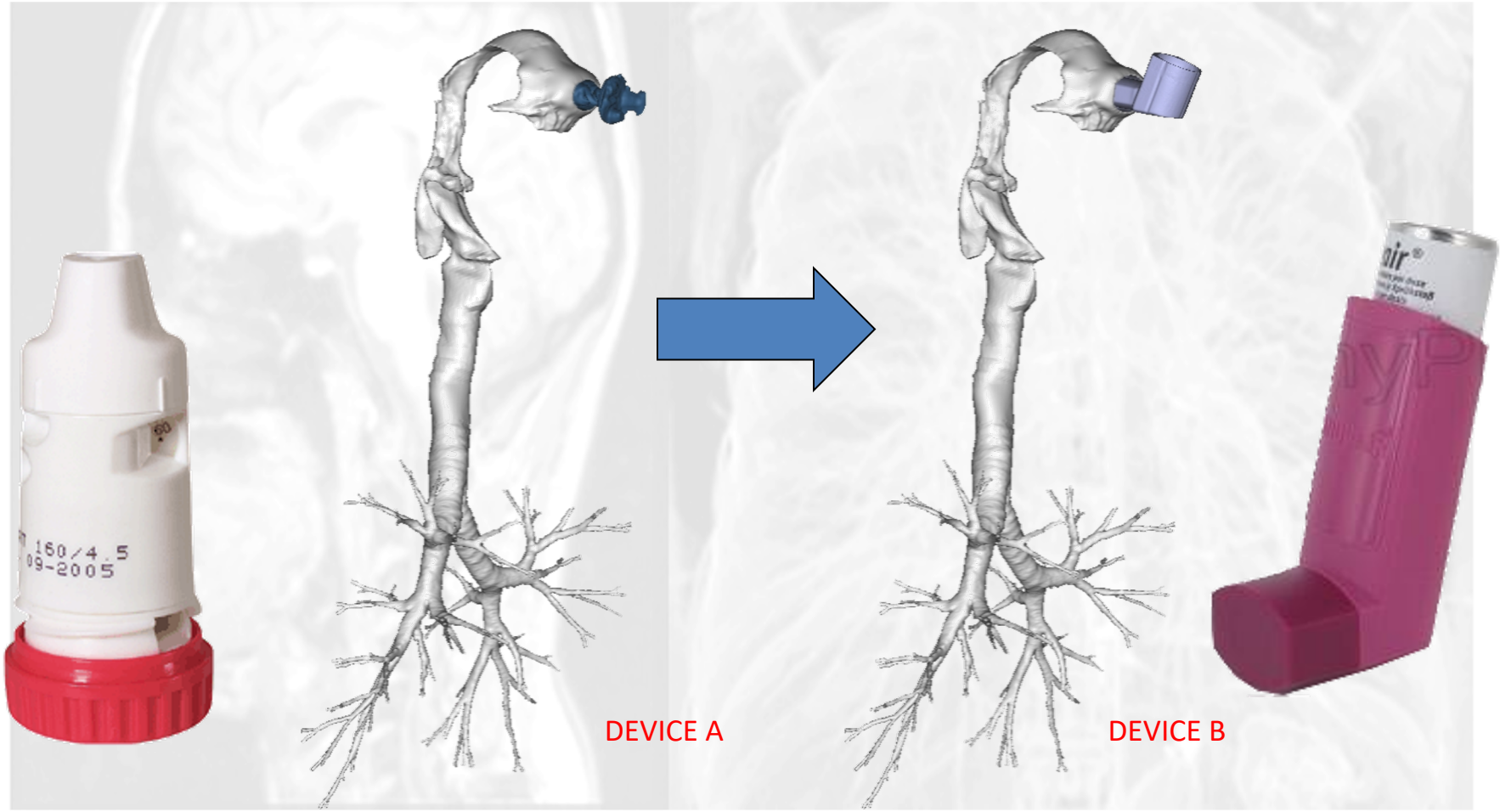


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FRI: DEPOSITION

Patient-specific model coupled with different inhalers

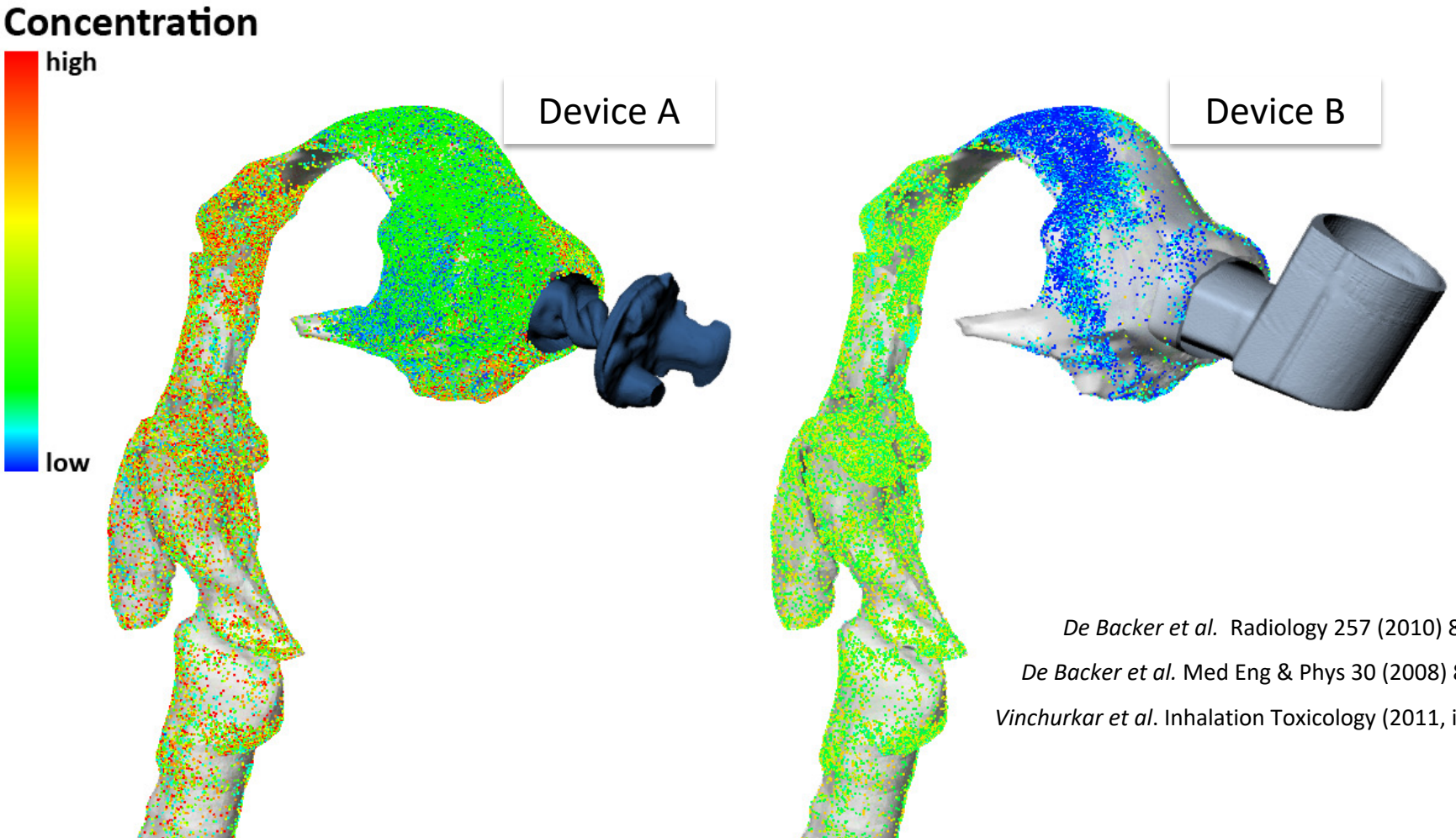


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FRI: DEPOSITION

Difference in upper airway deposition for 2 different inhalers and formulations



De Backer et al. Radiology 257 (2010) 854–862

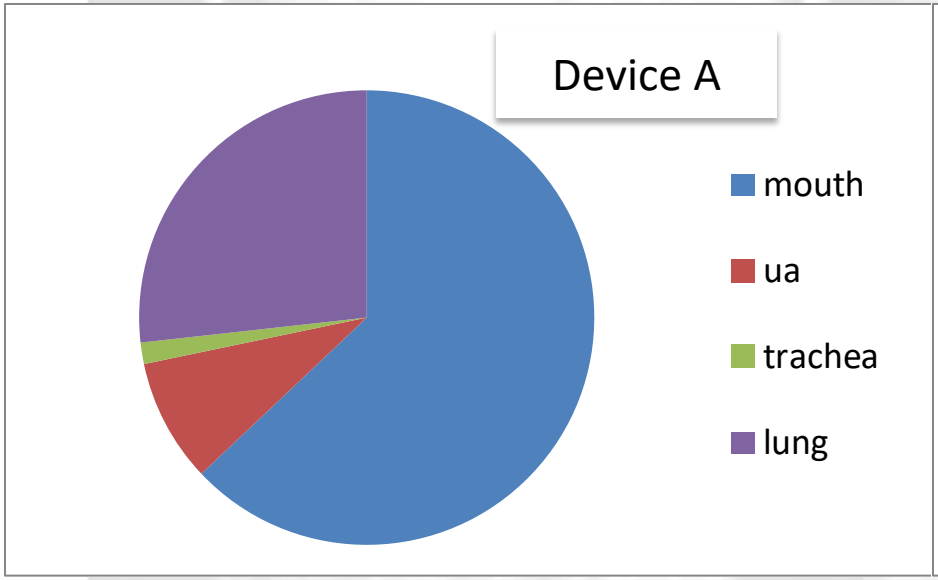
De Backer et al. Med Eng & Phys 30 (2008) 872-879

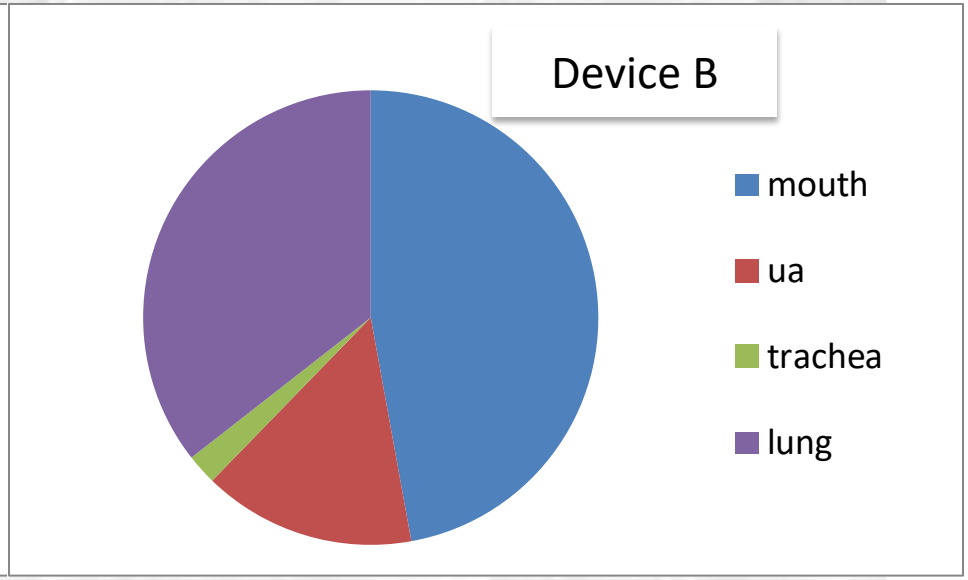
Vinchurkar et al. Inhalation Toxicology (2011, in press)

FRI: DEPOSITION

Patient-specific effective lung dose for 2 different inhalers and formulations

- Lung deposition increases by 9%



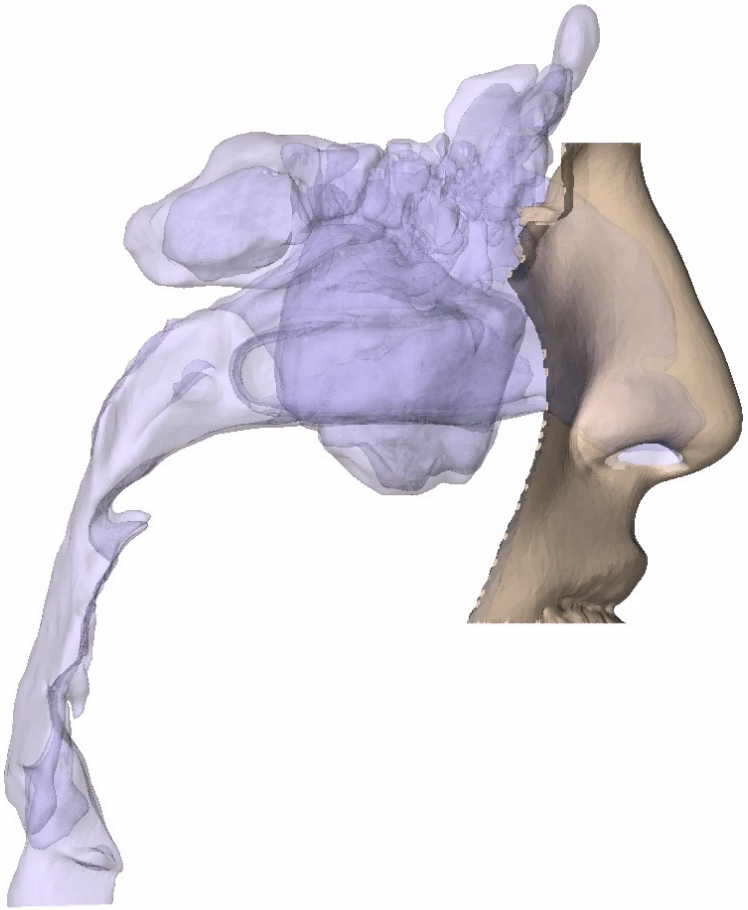


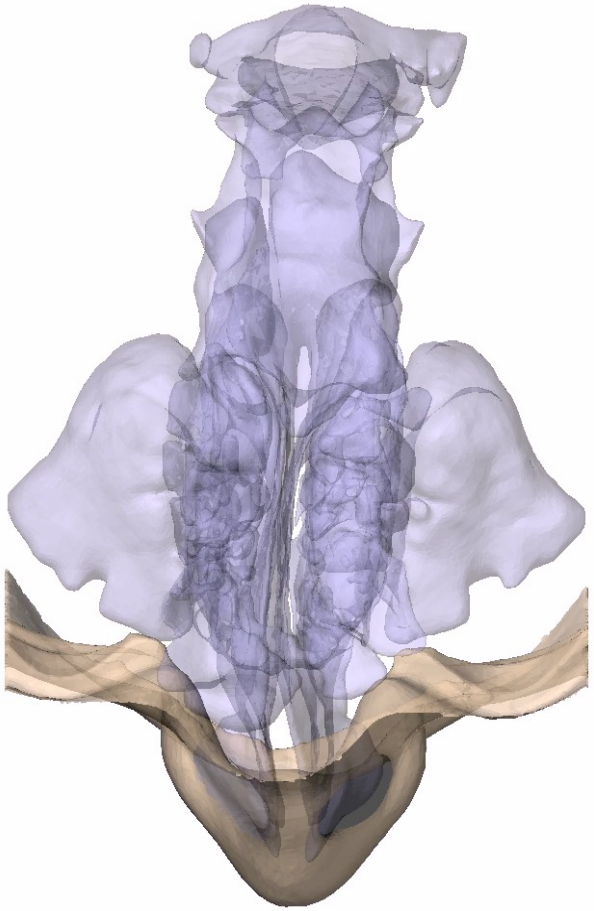
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FRI: DEPOSITION

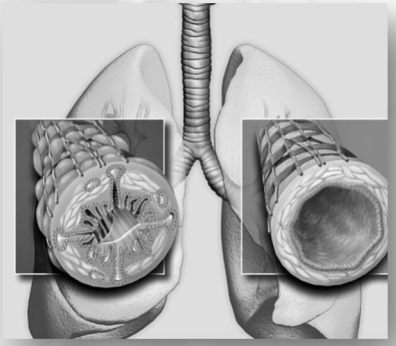
Patient-specific nasal deposition

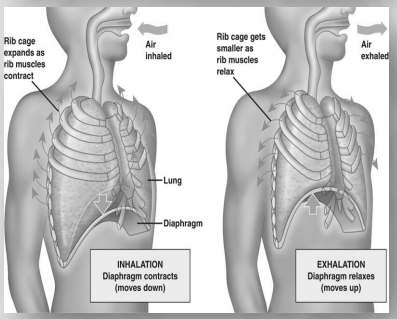


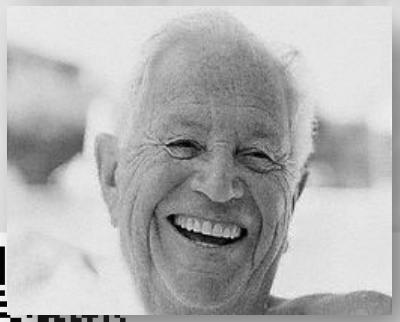


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FROM MODE OF ACTION TO CLINICAL BENEFIT



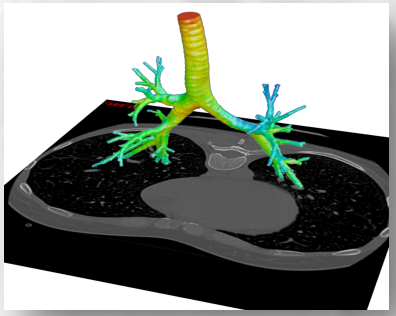




GEOMETRY

PULMONARY FUNCTION

PATIENT'S QUALITY OF LIFE

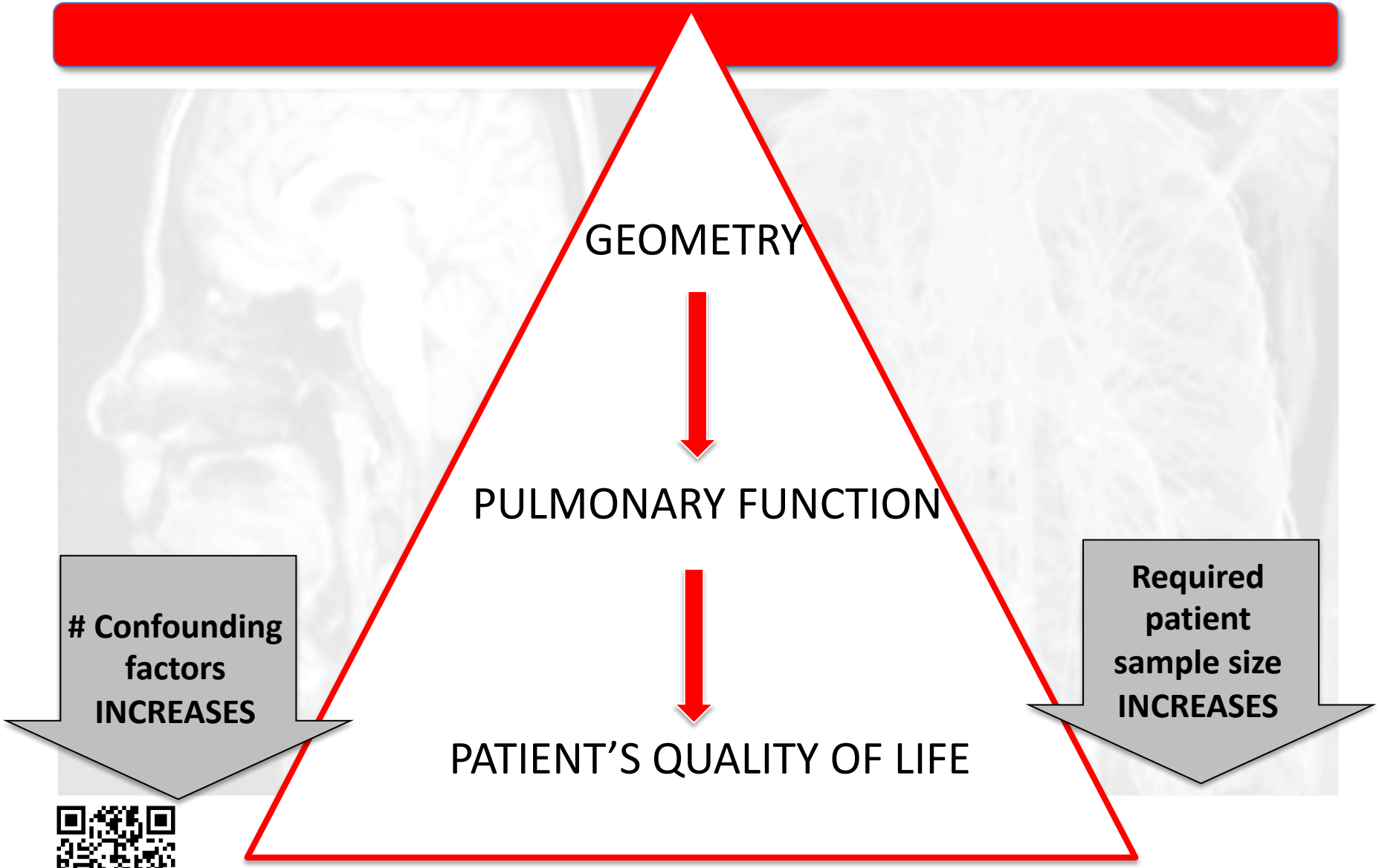






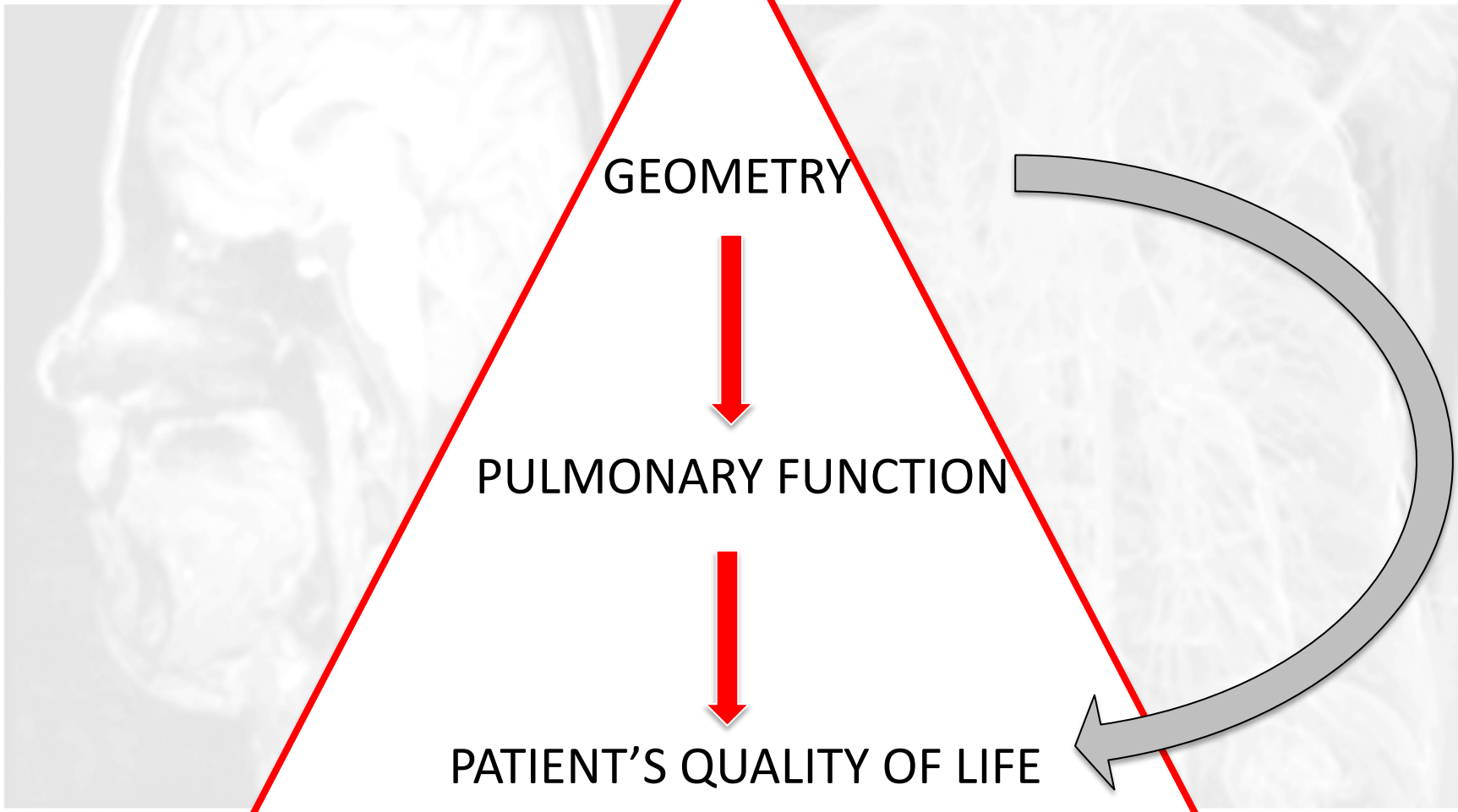
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BENEFIT OF MORE SENSITIVE ENDPOINTS



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CORRELATION BETWEEN GEOMETRY AND QOL

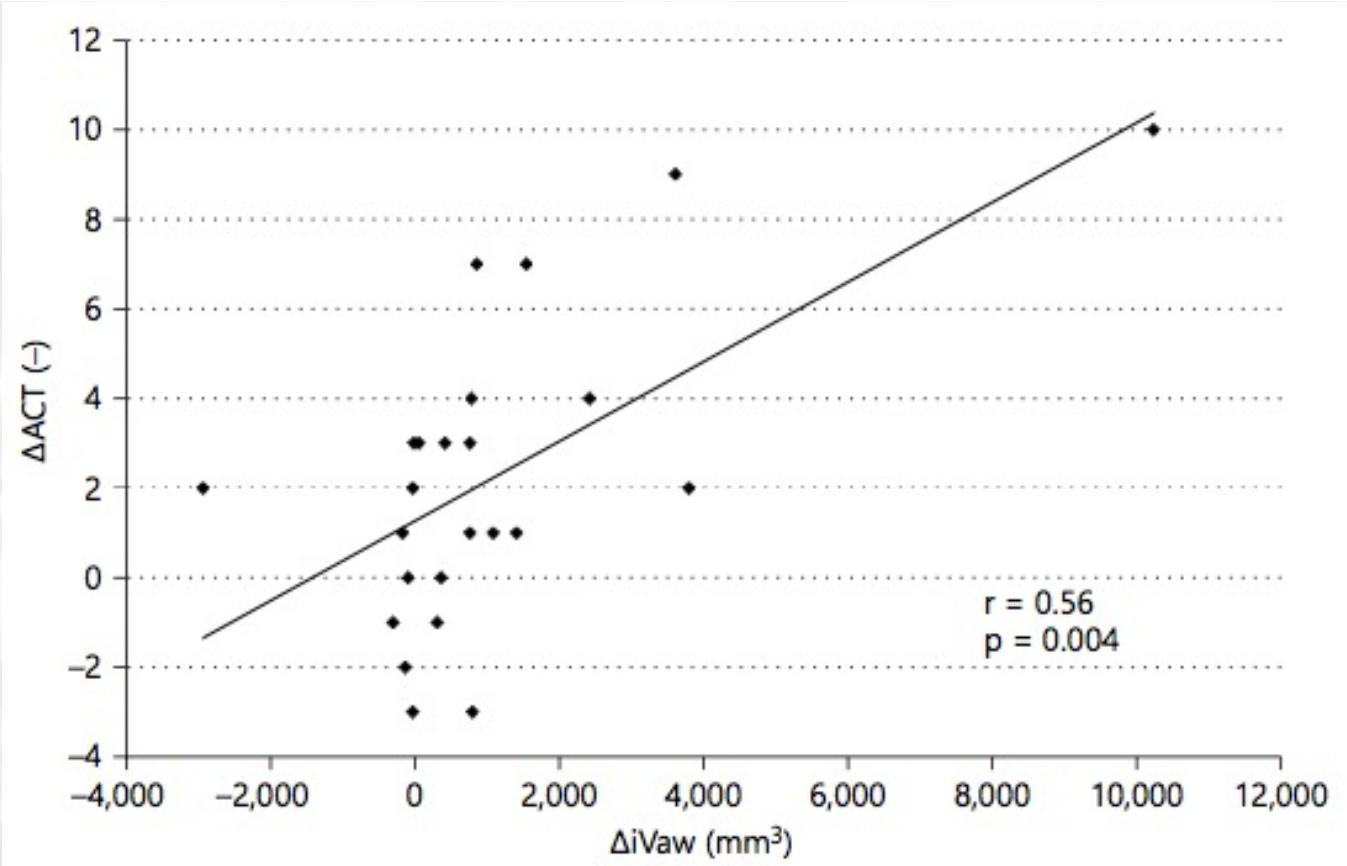


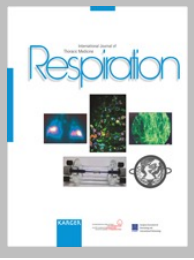
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CORRELATION FRI – PRO

Delta iVaw (image-based airway Volume) vs. Delta ACT (Asthma Control Test)



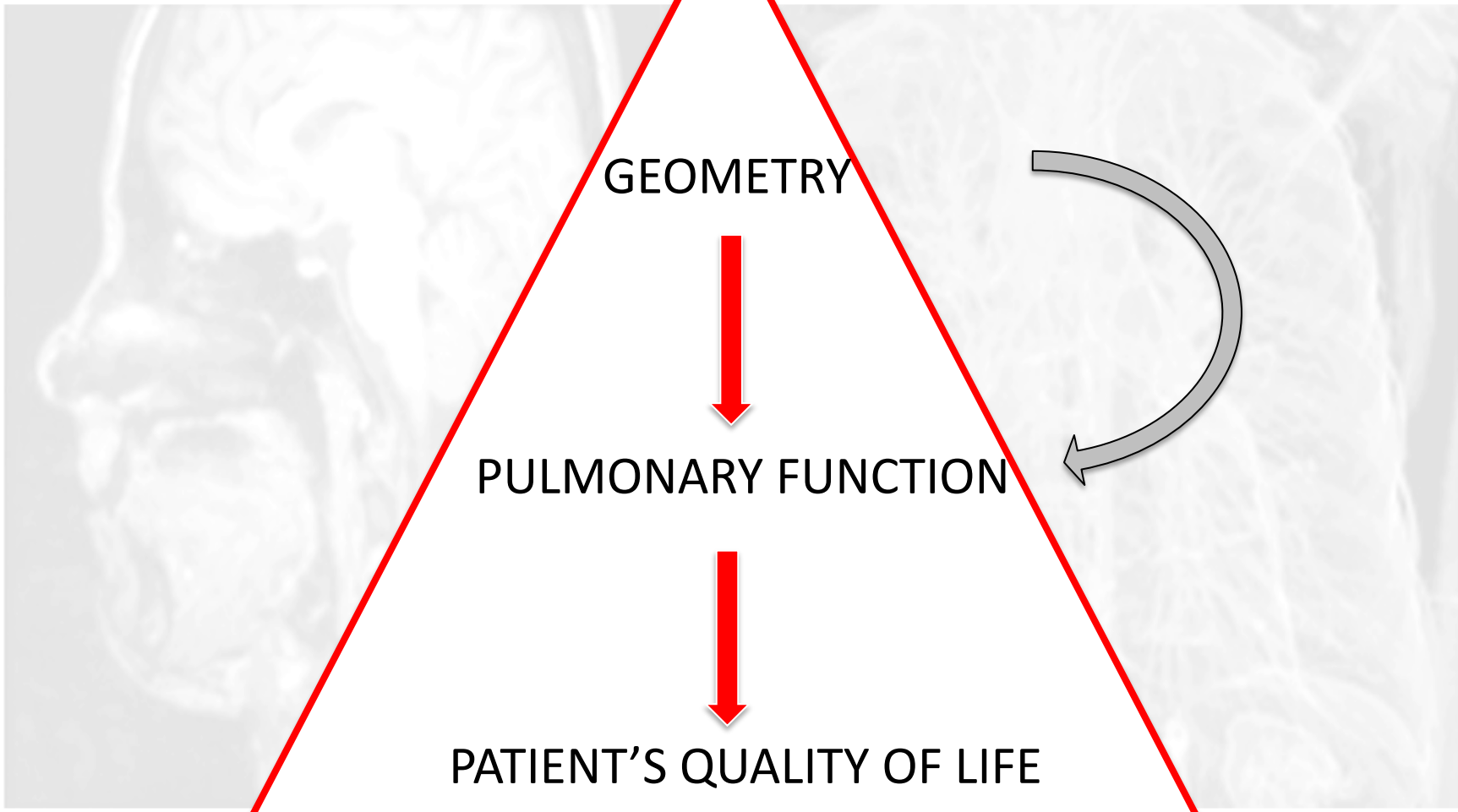


Wim Vos, Jan De Backer, Gianluigi Poli, Annick De Volder, Liesbeth Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer

Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013

CORRELATION BETWEEN GEOMETRY AND PFT



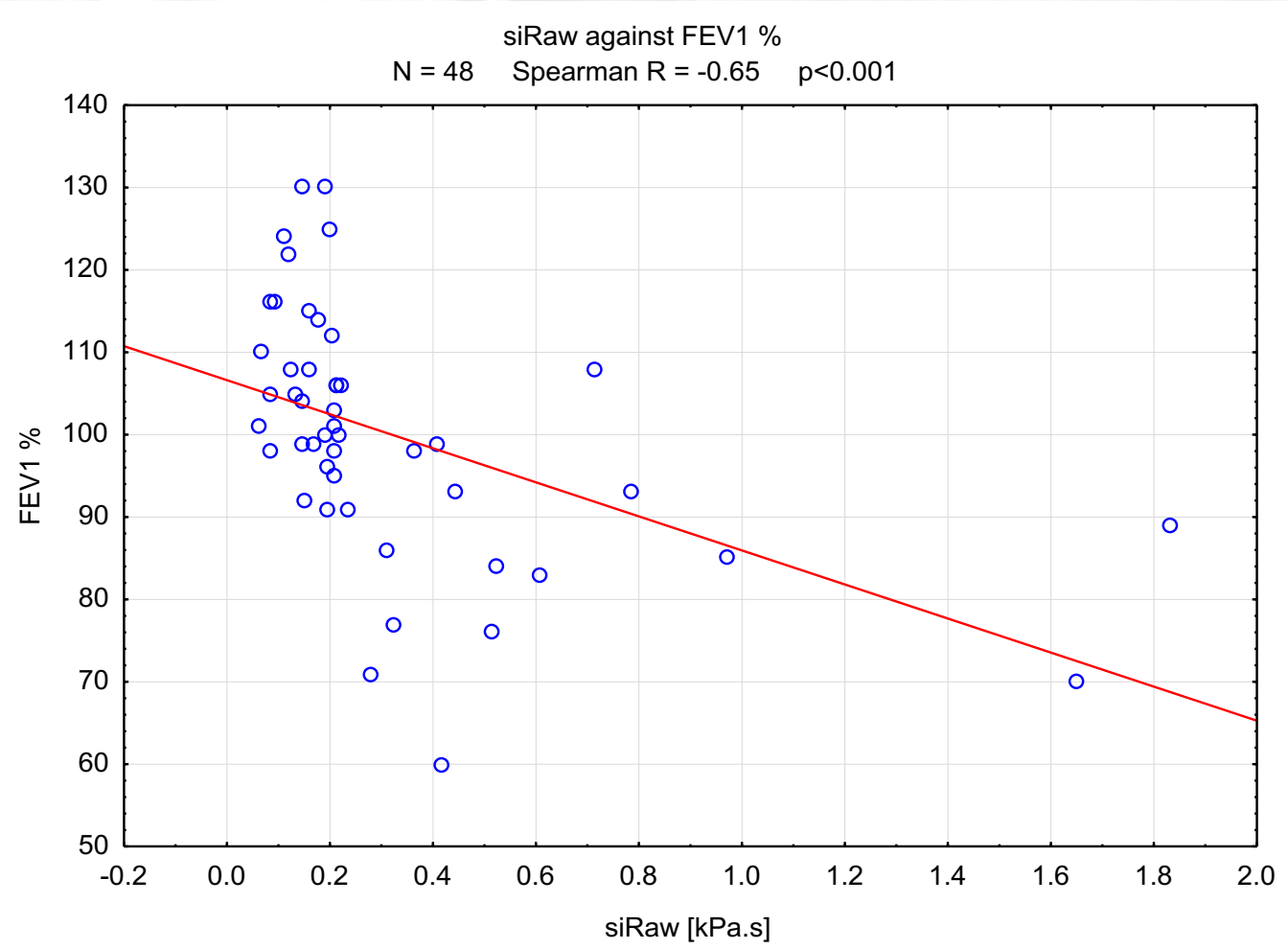
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CORRELATION FRI – FEV1

siRaw (specific image-based airway Resistance) vs. FEV1%

- Pooled data – ASTHMA patients



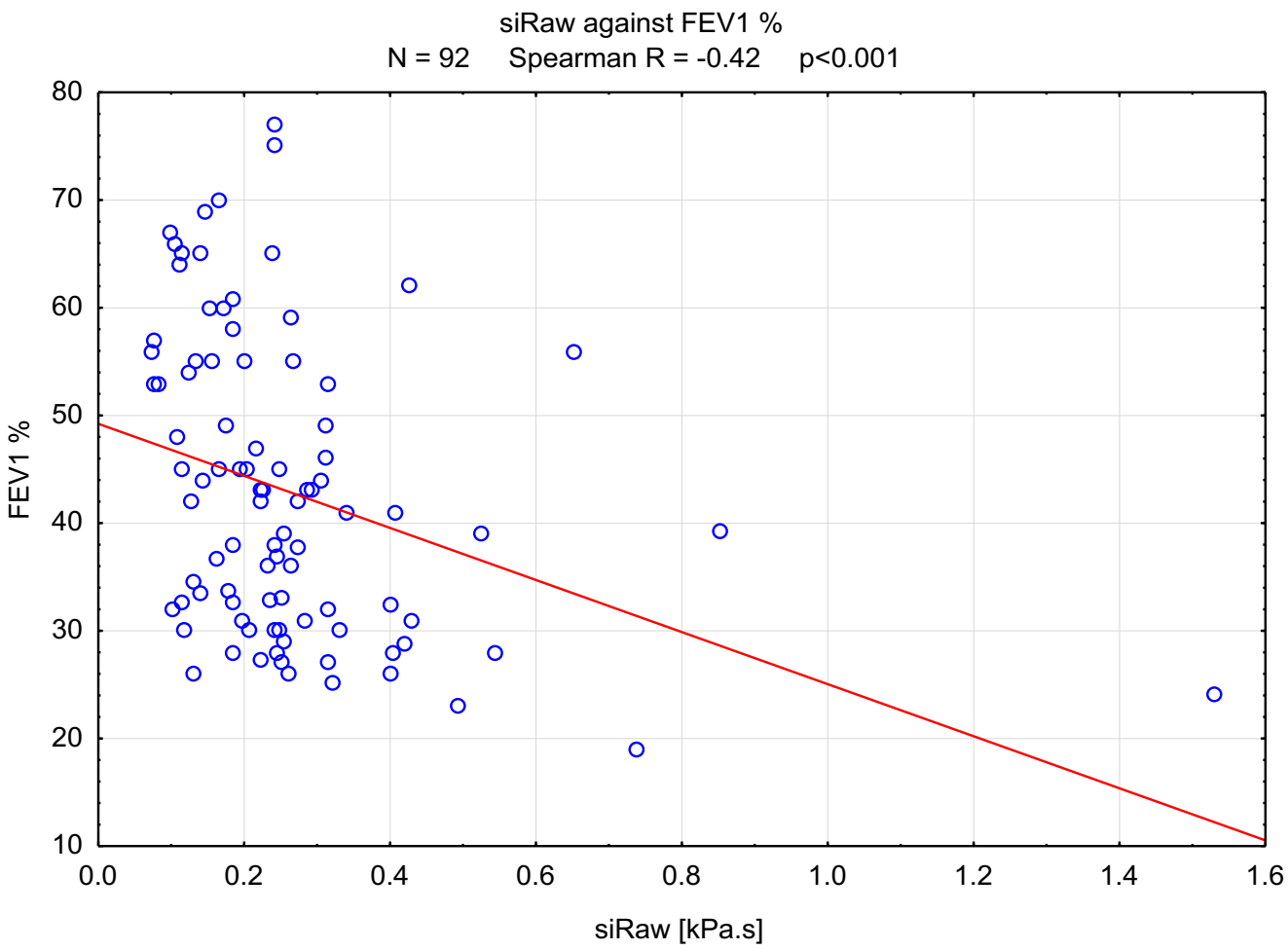
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CORRELATION FRI – FEV1

siRaw (specific image-based airway Resistance) vs. FEV1%

- Pooled data – COPD patients

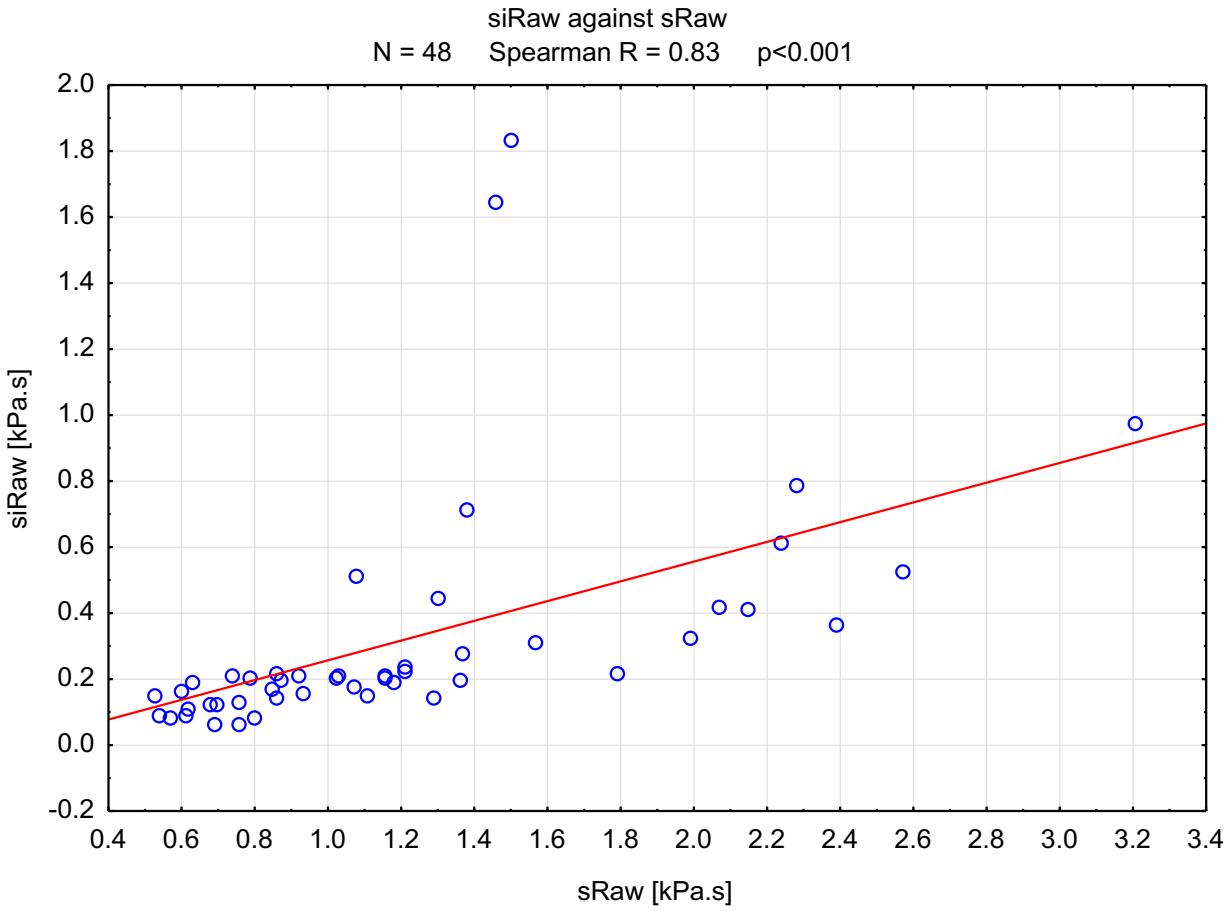


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CORRELATION FRI – BODY BOX

sRaw vs. siRaw (specific image-based airway Resistance)

- Pooled data – ASTHMA patients

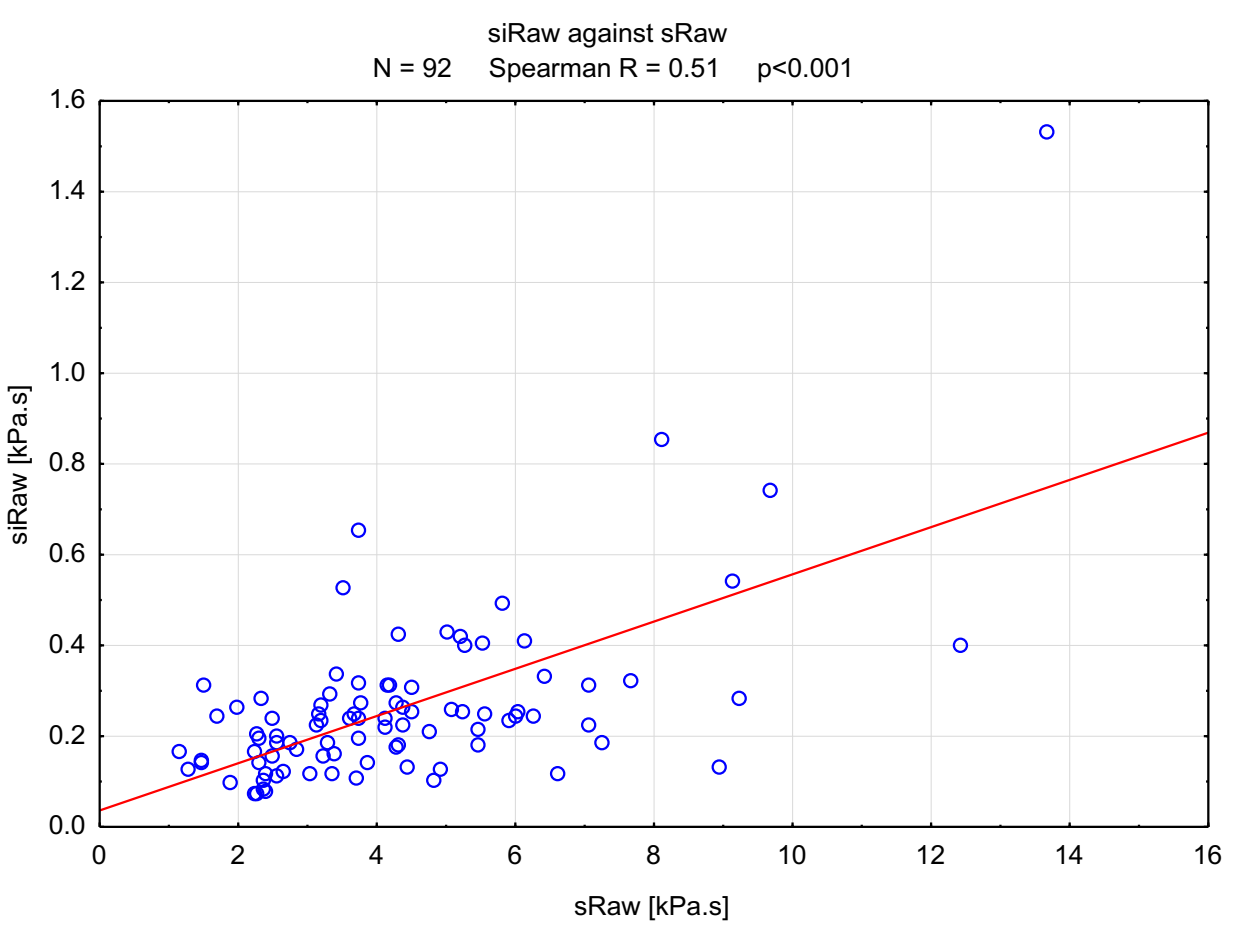


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CORRELATION FRI – BODY BOX

sRaw vs. siRaw (specific image-based airway Resistance)

- Pooled data – COPD patients

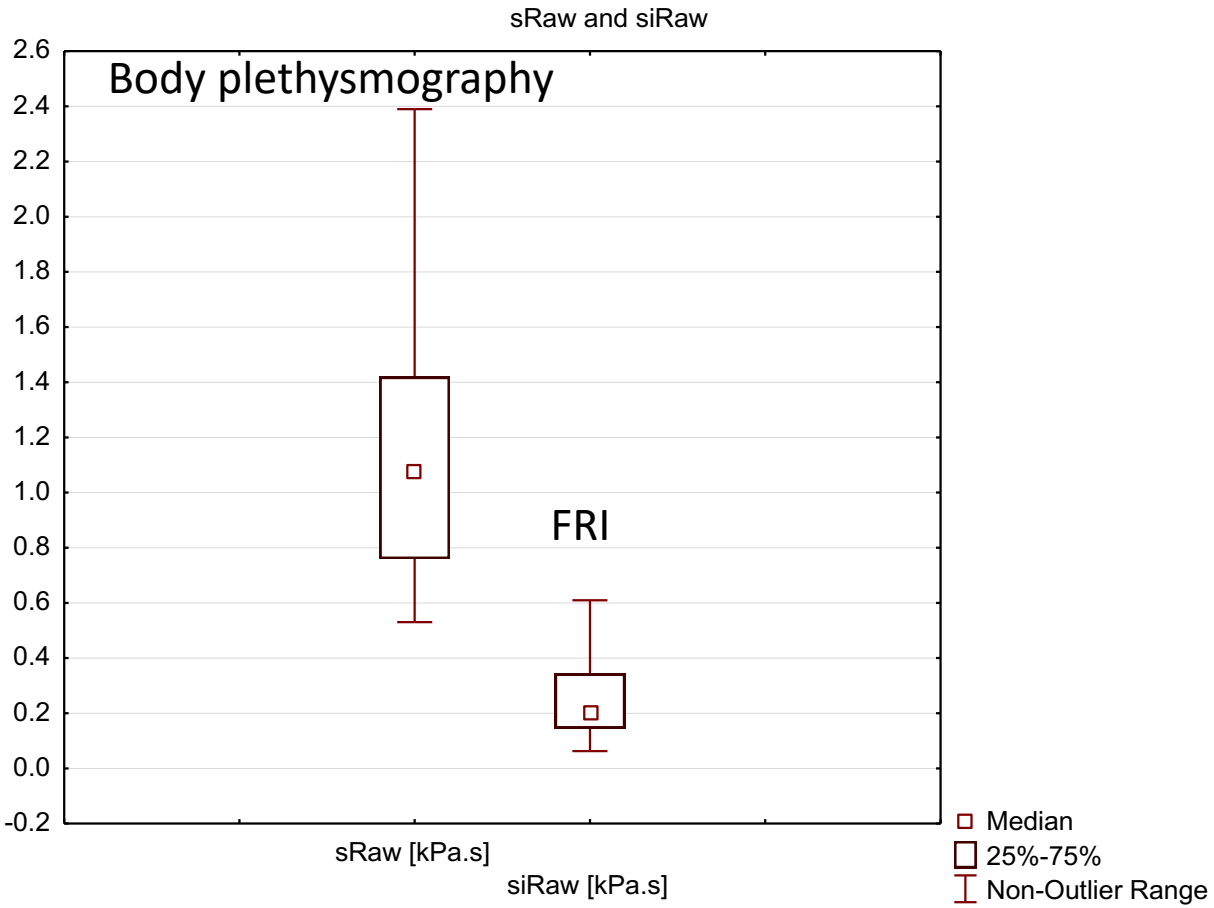


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CORRELATION FRI – BODY BOX

Improved signal-to-noise ratio with FRI

- Pooled data – ASTHMA patients

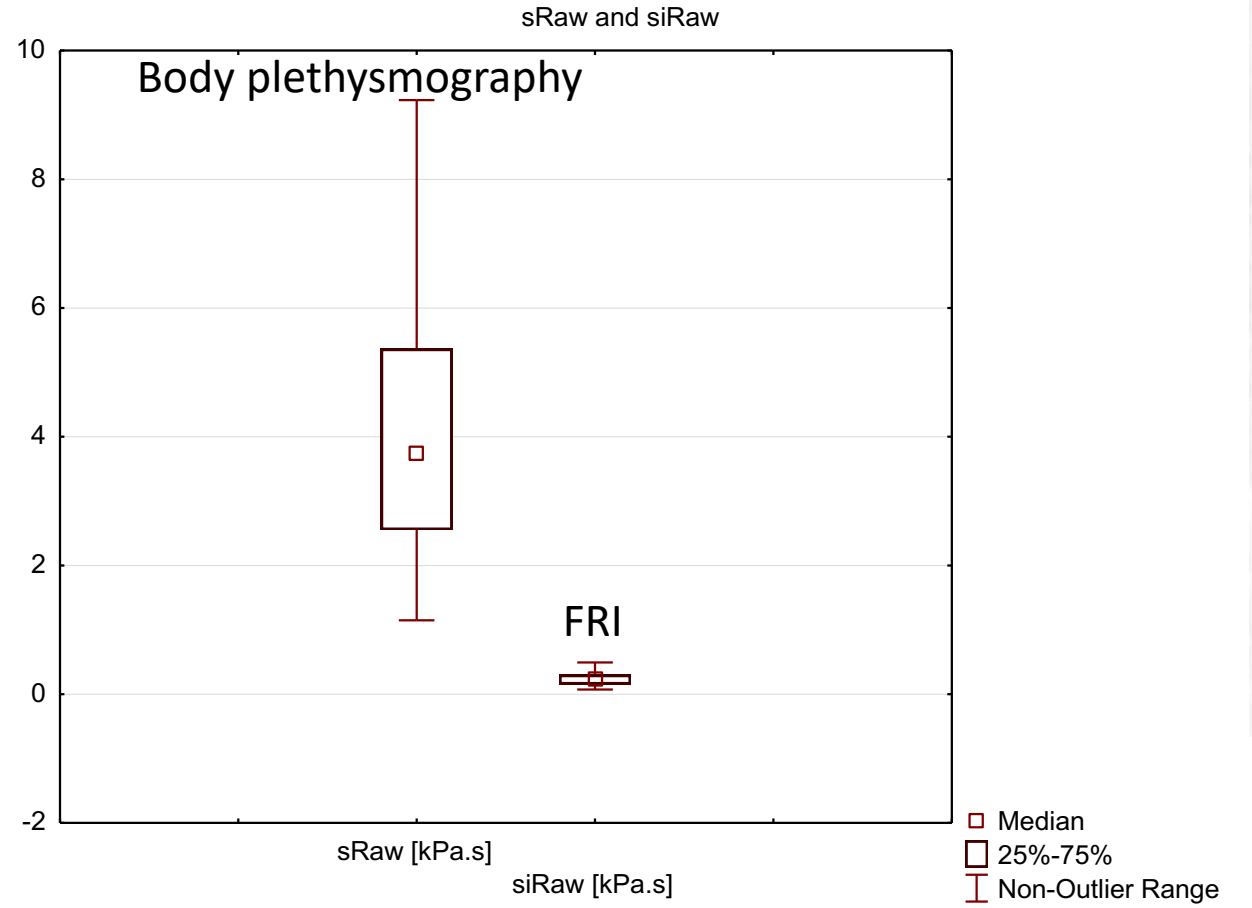


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CORRELATION FRI – BODY BOX

Improved signal-to-noise ratio with FRI

- Pooled data – COPD

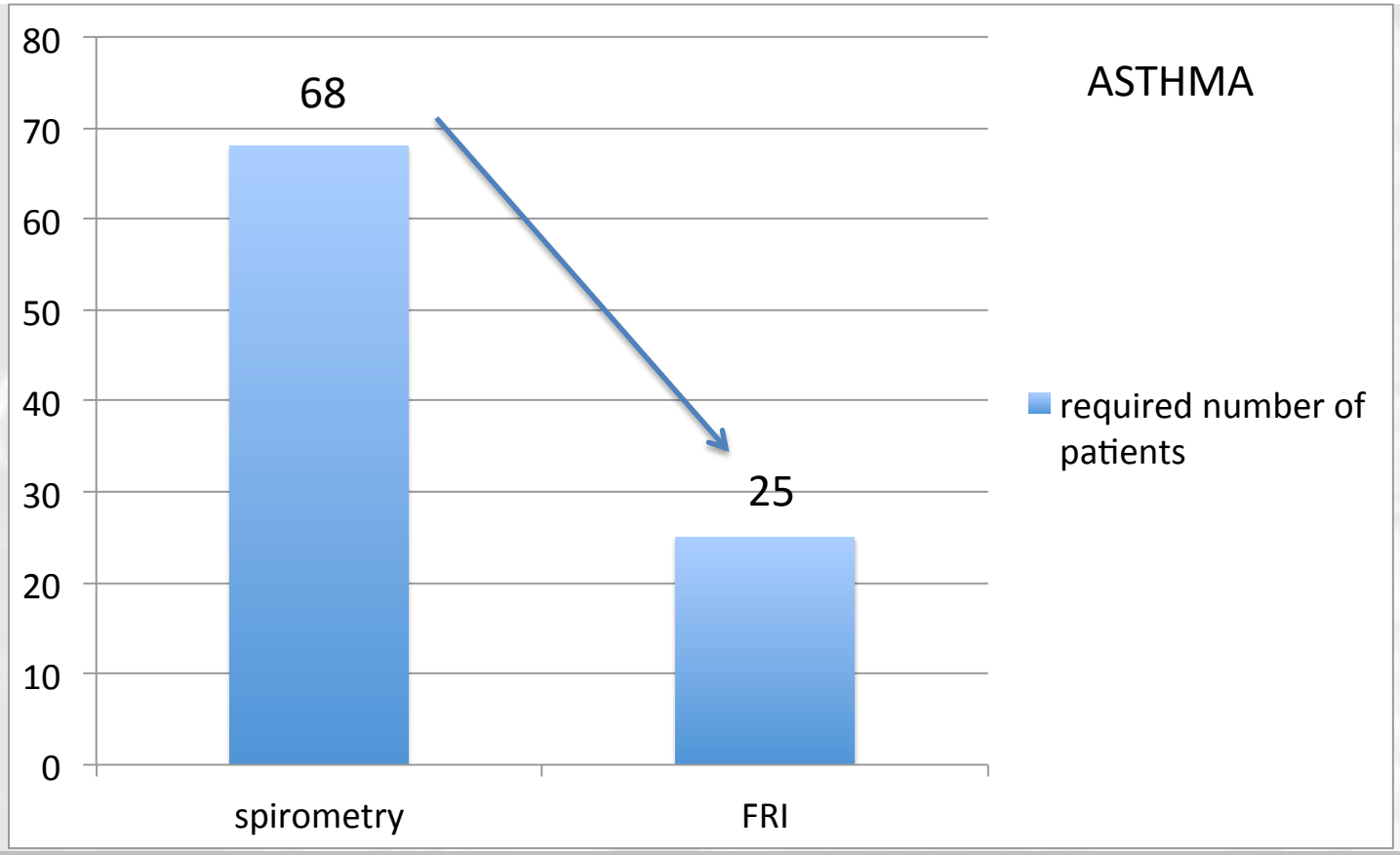


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SAMPLE SIZE CALCULATION

Improved signal-to-noise ratio results in lower required number of patients





Wim Vos, Jan De Backer, Gianluigi Poli, Annick De Volder, Liesbeth Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer

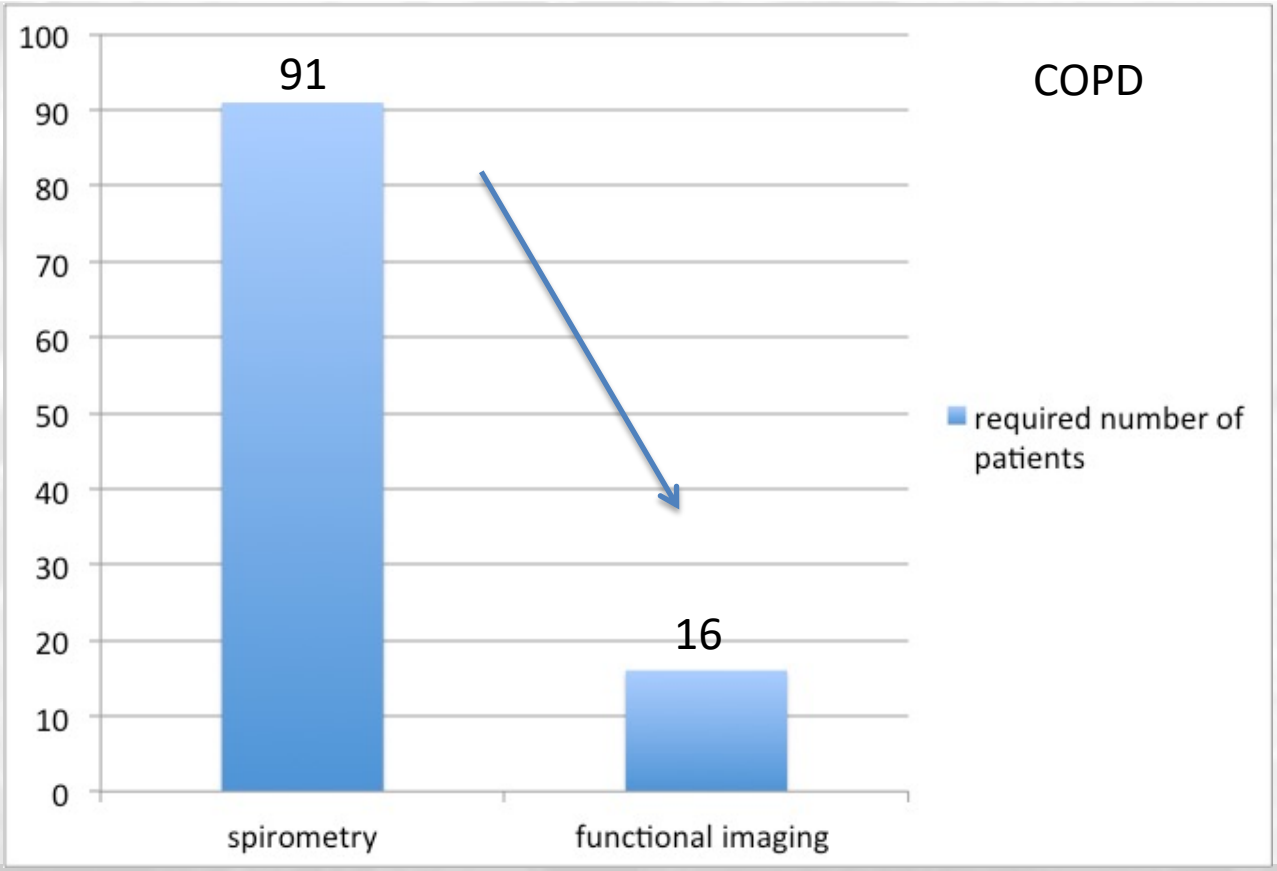
Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013

FluidDA

SAMPLE SIZE CALCULATION

Improved signal-to-noise ratio results in lower required number of patients





Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

Eur Respir J 2012; 40: 298-305

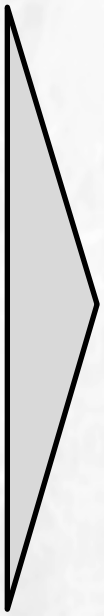
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FRI de-risks Phase III by focusing on Mode of Action research in Phase I/II

Advantages of implementing FRI in early clinical research

- **More sensitive outcome parameters than standard Pulmonary Function Tests:** e.g. FEV1 test is effort-dependant and therefore has inherent higher inter -and intra-variability
- **Smaller trials (fewer patients)**
- **Early insight in Method of Action of novel therapies:** focusing on functional and physiological parameters such as small airway geometry, resistance,...
- **Adaptive clinical trial design:**

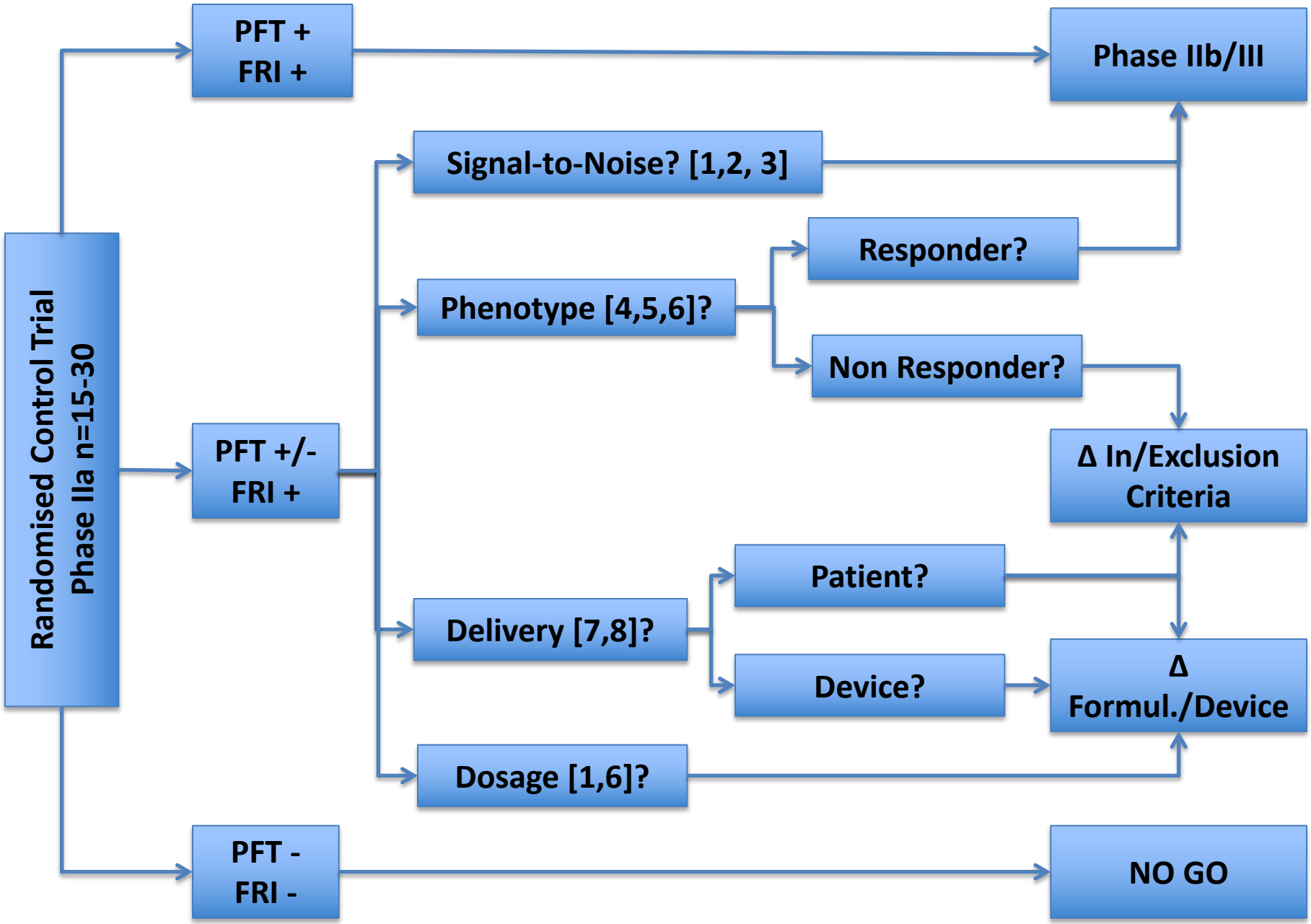
  "Fail fast – Fail early – Fail often"



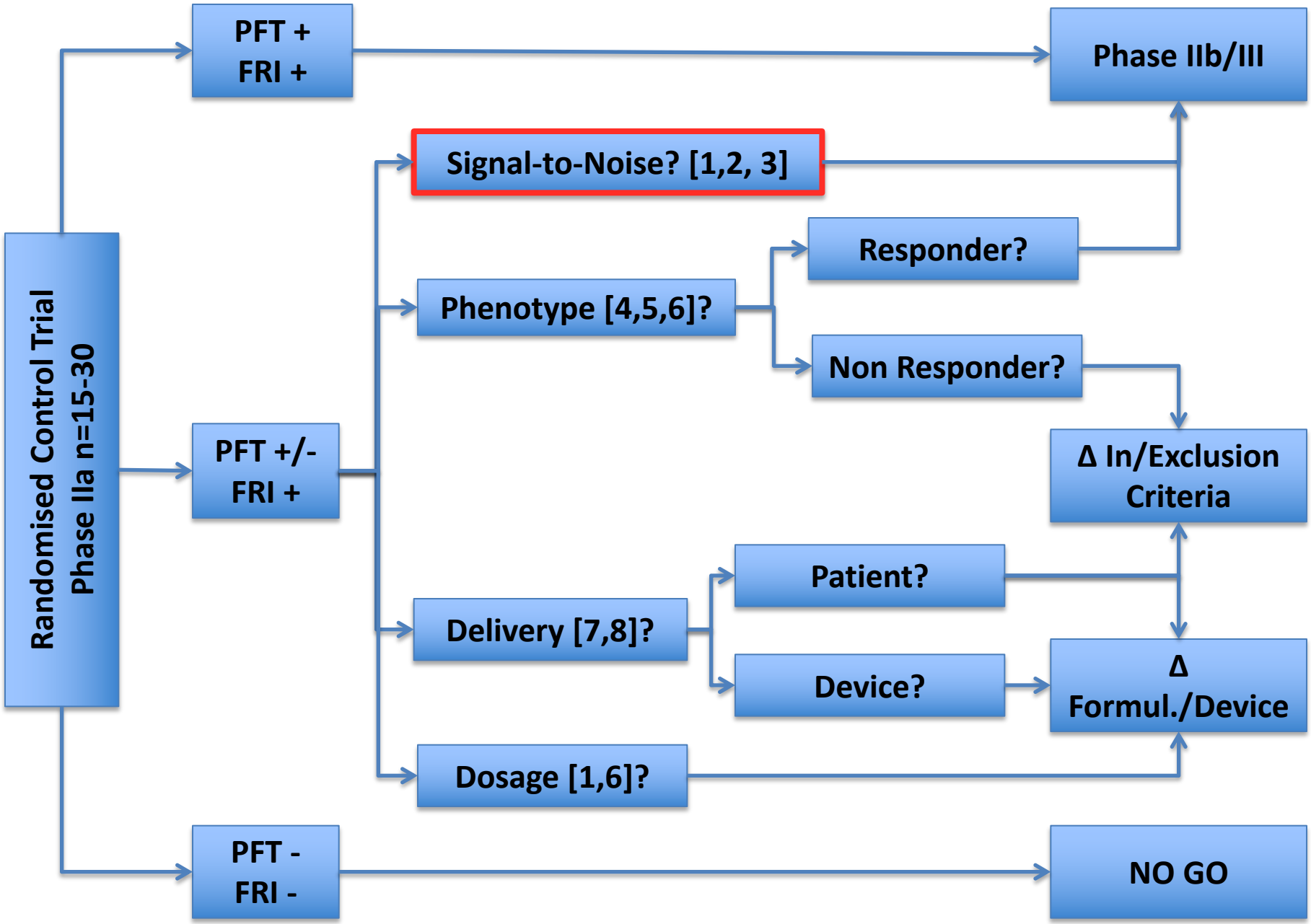
Substantial risk mitigation with minimal additional investment in Phase II

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DECISION TREE - Mode of Action

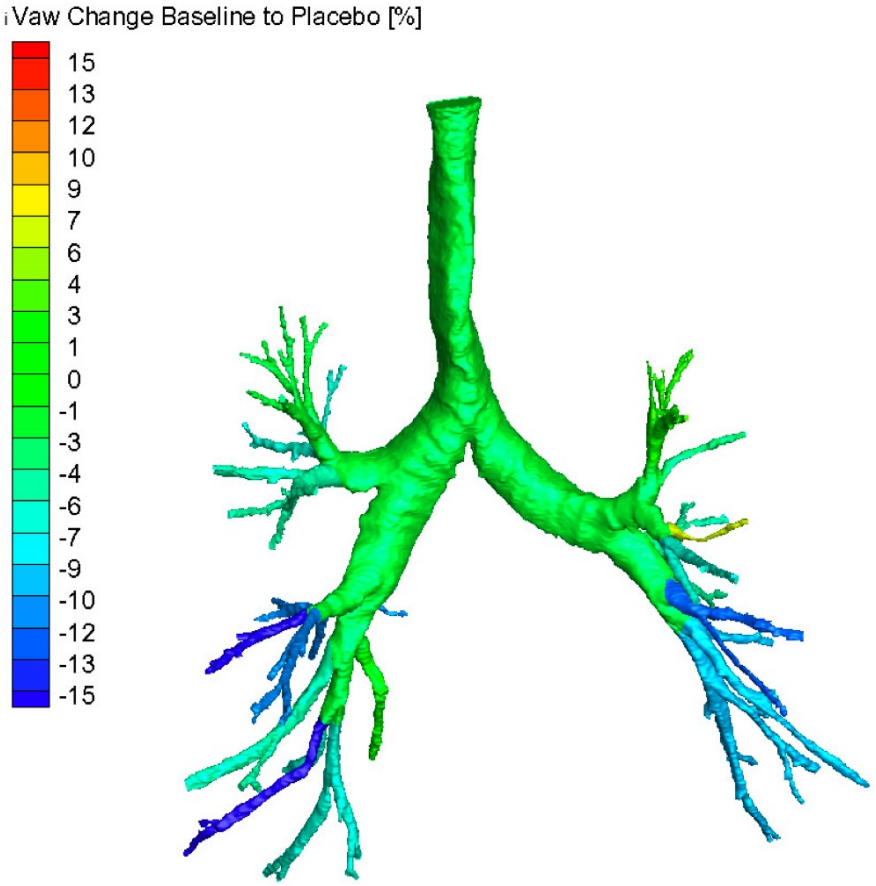


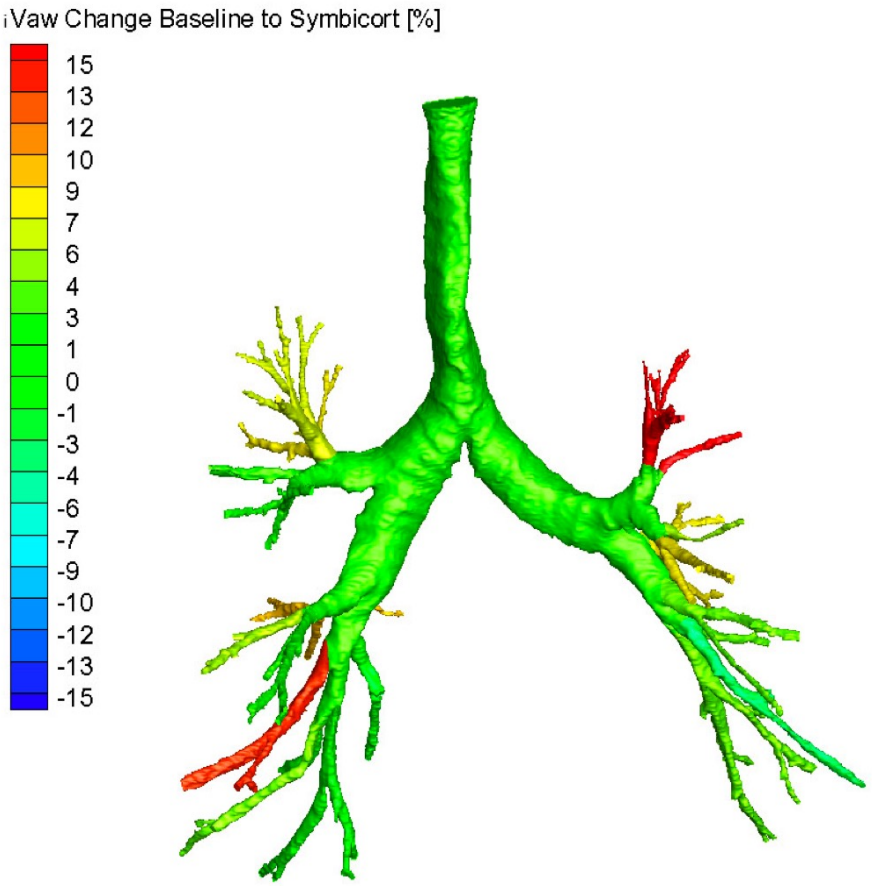
DECISION TREE - Mode of Action



SCENARIO 1: SIGNAL TO NOISE

Airway volume (iVaw) change after Placebo and Symbicort





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SCENARIO 1: SIGNAL TO NOISE

PFT vs. FRI parameters change after Placebo and Symbicort treatment

	symbicort			placebo		
	pre	post	p	pre	post	p
iVaw (cm3)	9.6±4.67	10.14±4.81	0.011	9.6±4.67	9.16±4.37	0.025
iRaw (kPs/L)	0.051±0.021	0.043±0.019	0.047	0.051±0.021	0.06±0.03	0.047
FEV1 (L)	0.95±0.33	0.98±0.33	0.34	0.96±0.31	0.93±0.33	0.07
FEV1 (%p)	34.8±7.69	35.9±7.89	0.34	34.9±6.71	33.7±7.24	0.09
FEV1/VC	34.32±6.99	34.72±6.67	0.51	33.68±7.36	33.89±6.8	0.74
PEF (L/s)	3±1.26	3.12±1.22	0.71	3.07±0.95	2.77±1.03	0.025
Raw (kPas/L)	1±0.5	0.92±0.45	0.20	0.94±0.46	1.01±0.43	0.07
sRaw (kPas)	5±2.87	4.65±2.29	0.14	4.89±2.72	5.33±2.48	0.026

Larger studies will most likely result in conclusive PFT

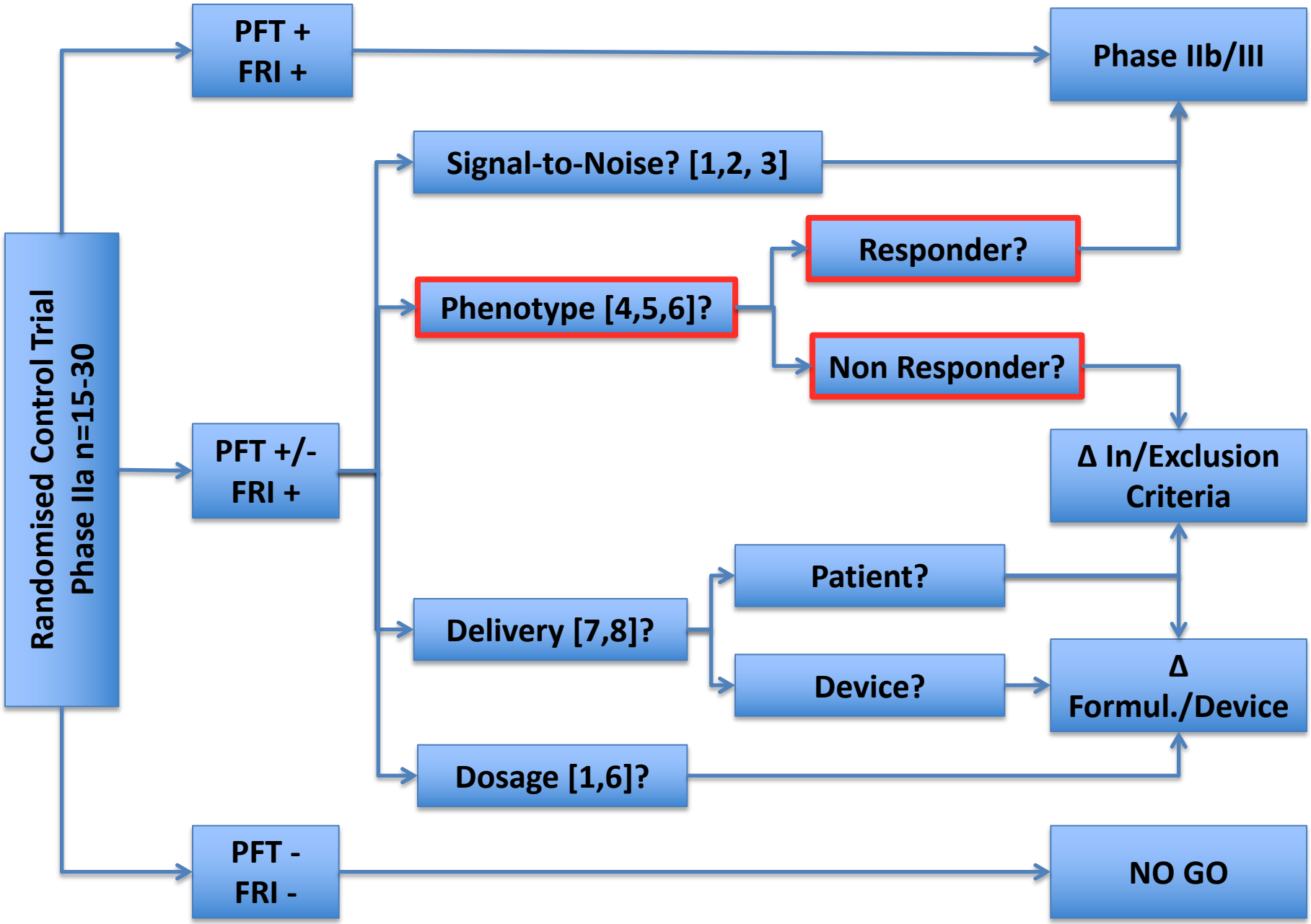


Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

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DECISION TREE - Mode of Action

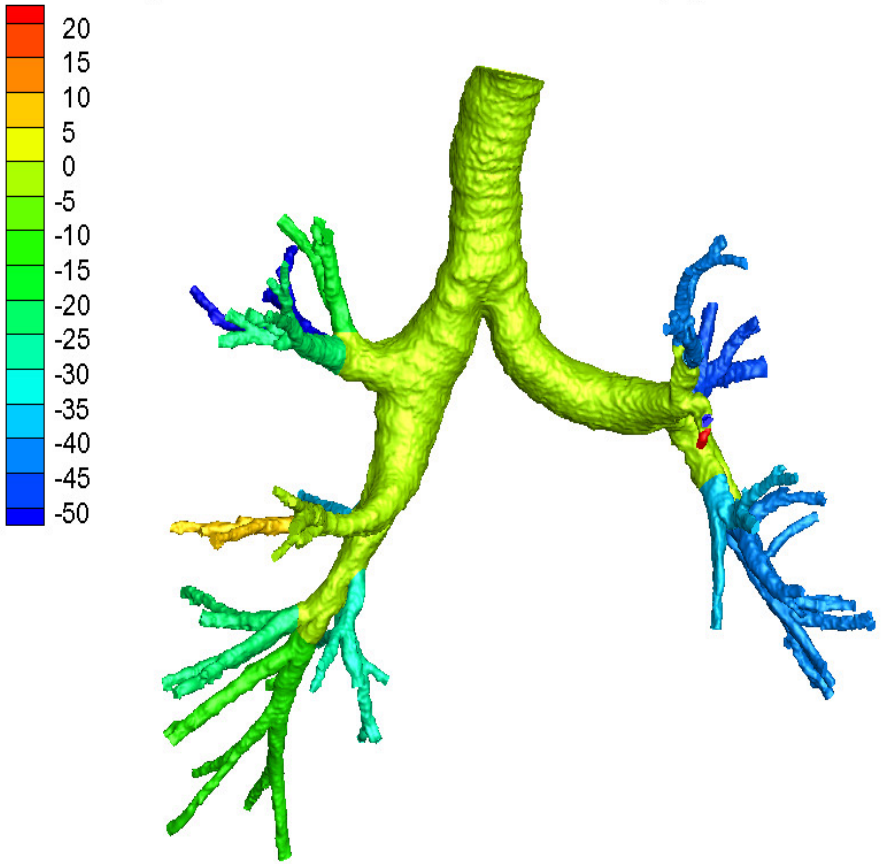


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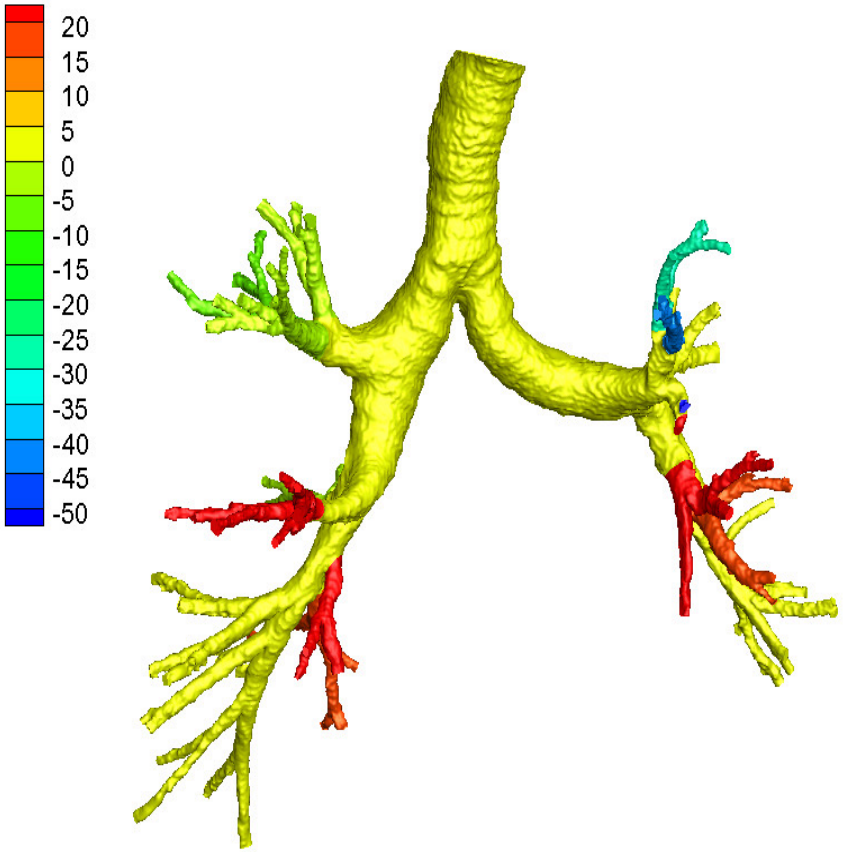
SCENARIO 2: PHENOTYPING

COPD responder after treatment with n-Acetyl Cysteine

iRaw changes after 3 months of NAC treatment [%]



iRaw changes after 3 months of placebo treatment [%]



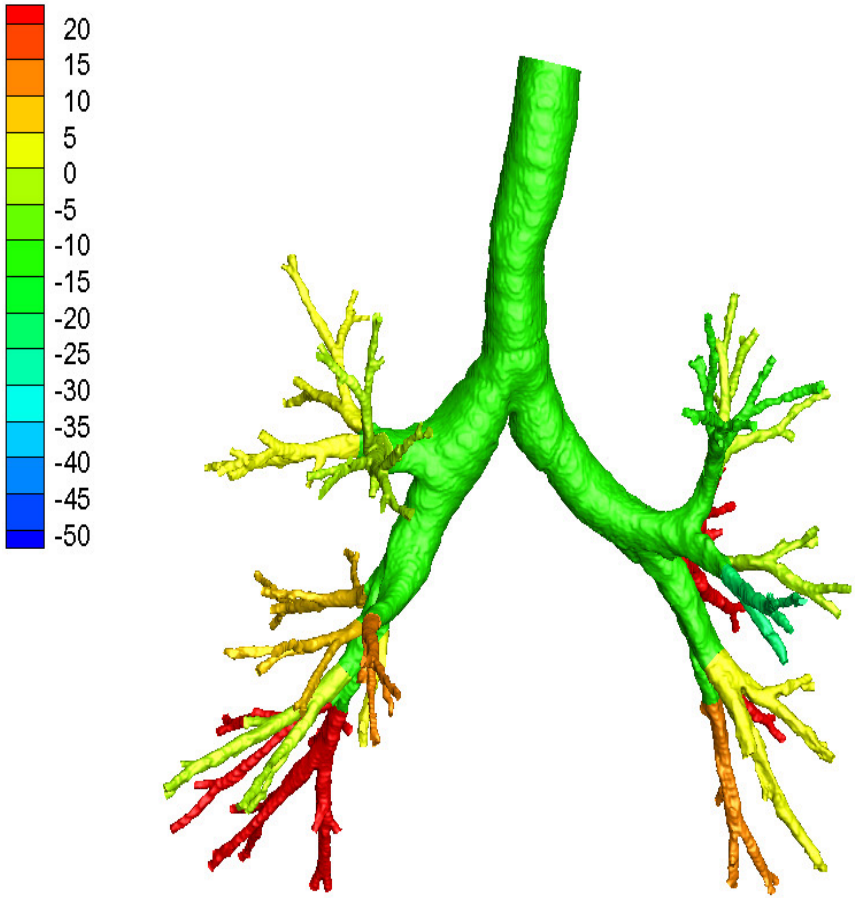
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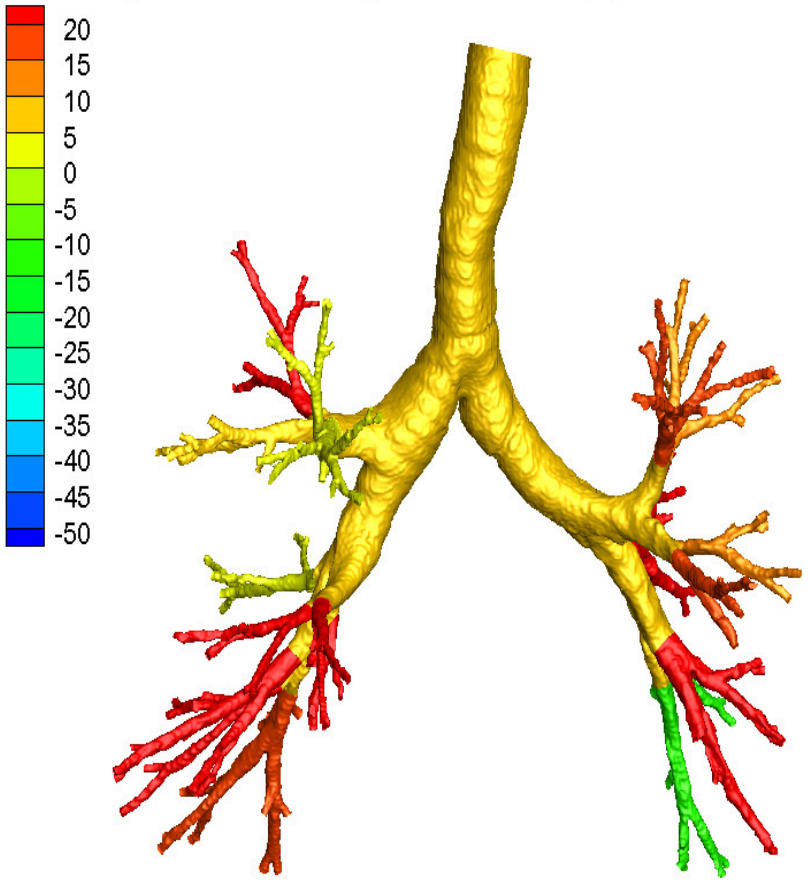
SCENARIO 2: PHENOTYPING

COPD non-responder after treatment with n-Acetyl Cysteine

iRaw Changes after 3 months of NAC treatment [%]



iRaw Changes after 3 months of placebo treatment [%]

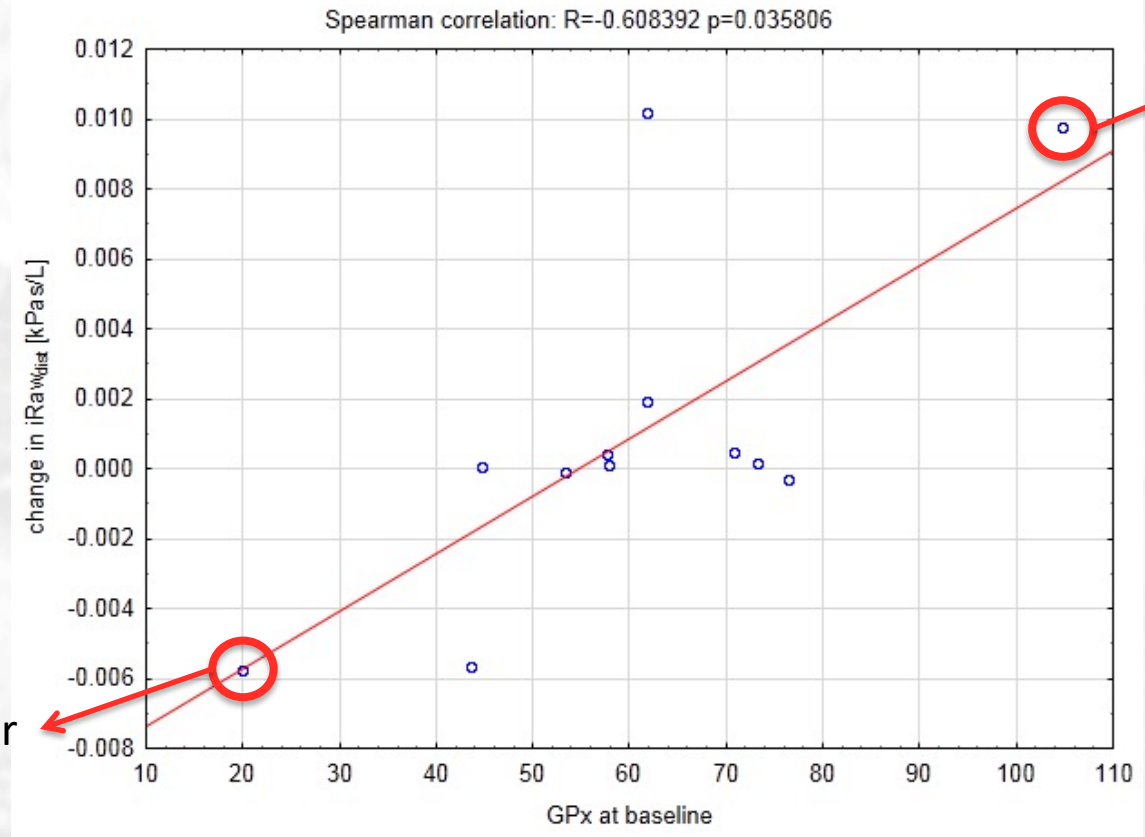


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SCENARIO 2: PHENOTYPING

COPD responder vs. non-responder based upon change in iRaw of distal airways



Non - Responder

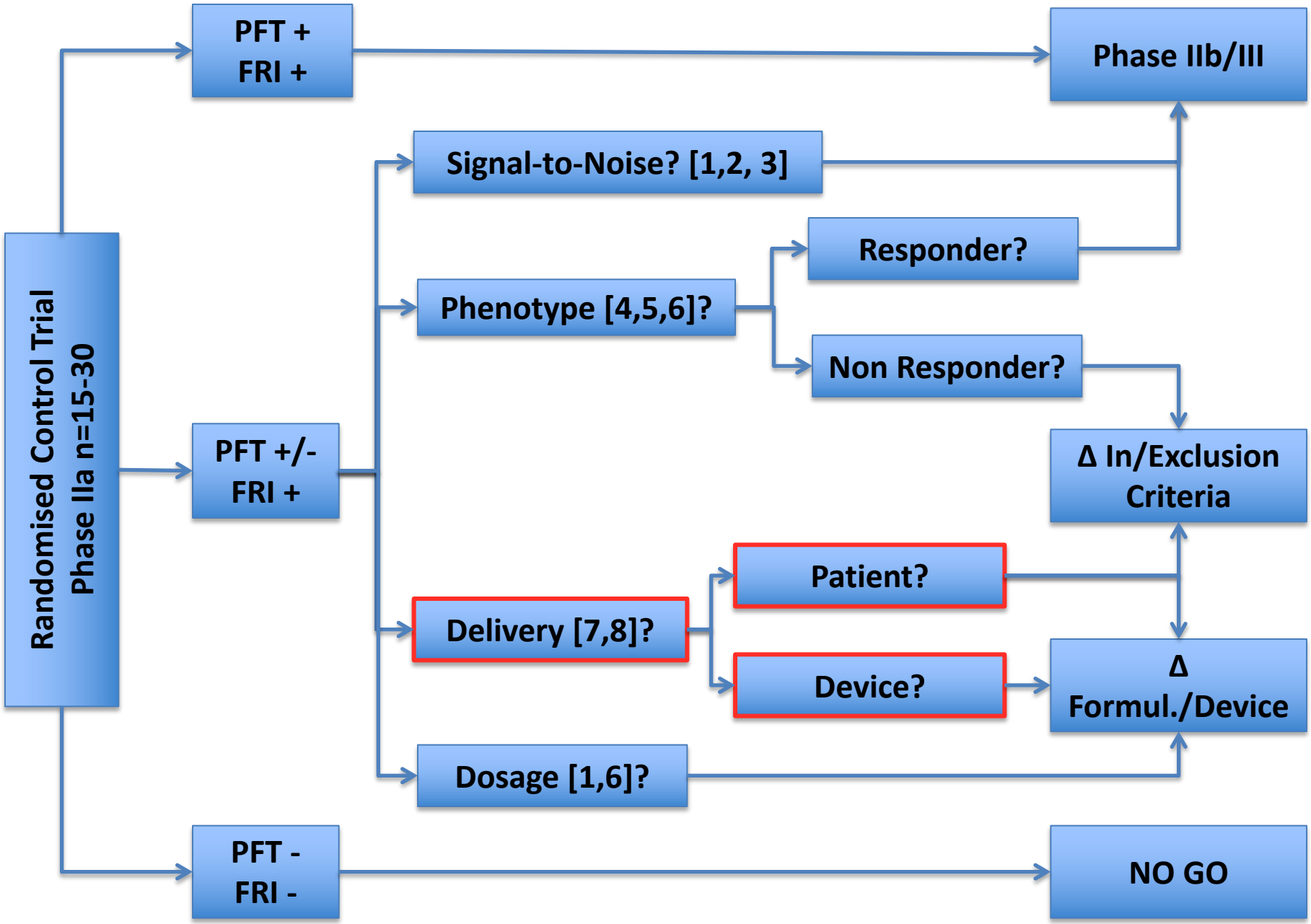
Responder

Jan De Backer, Wim Vos, Cedric Van Holsbeke, Samir Vinchurkar, Rita Claes, Paul Parizel, Wilfried De Backer

The effect of high dose N acetylcysteine on airway geometry, inflammation and oxidative stress in COPD patients

(submitted)

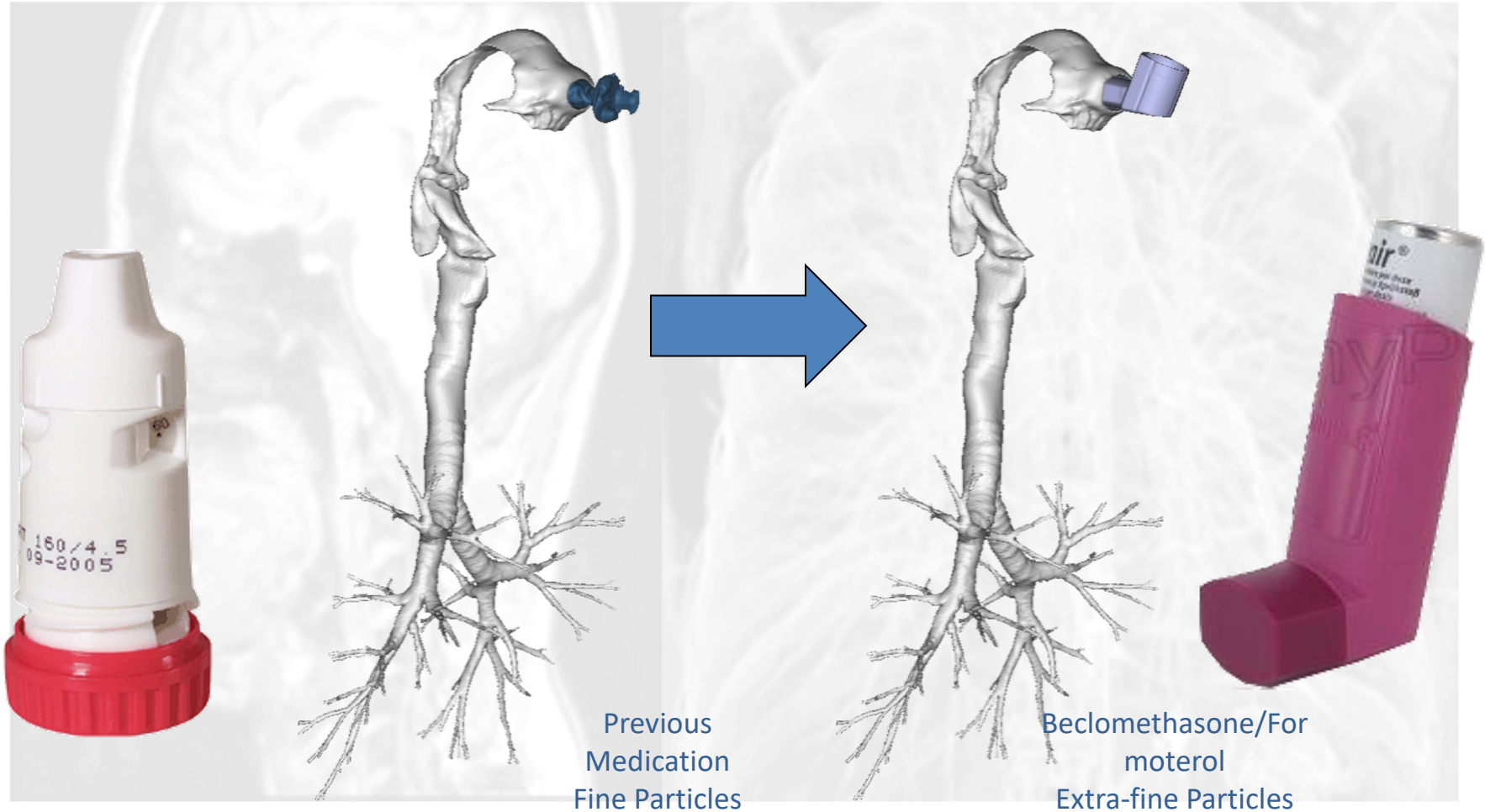
DECISION TREE - Mode of Action



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SCENARIO 3: DELIVERY

Patient-specific model coupled with different inhalers



Previous Medication Fine Particles

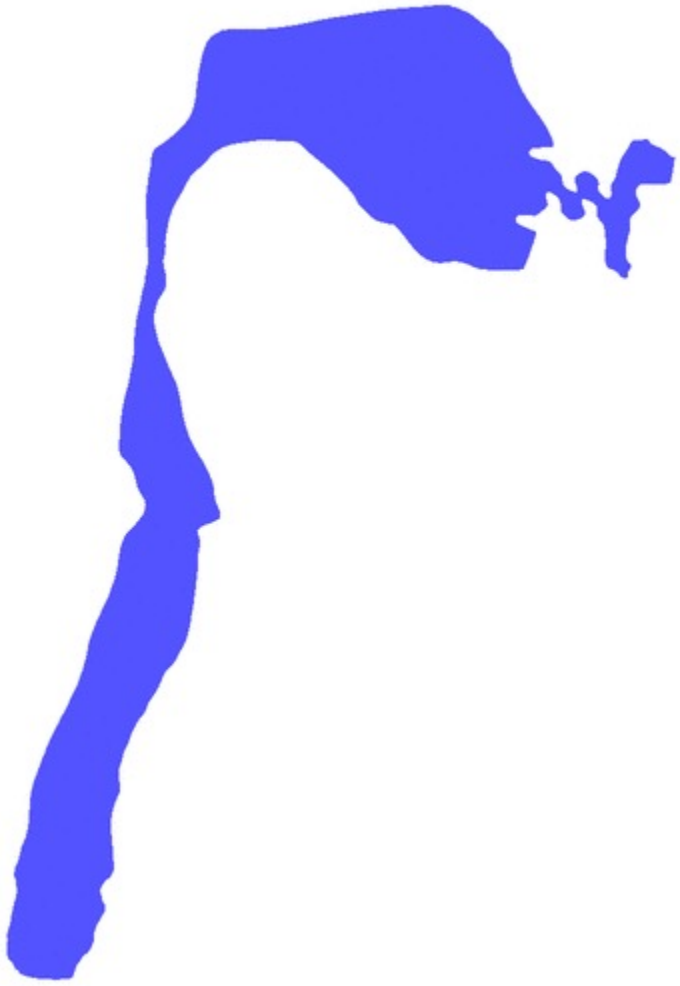
Beclomethasone/Formoterol Extra-fine Particles

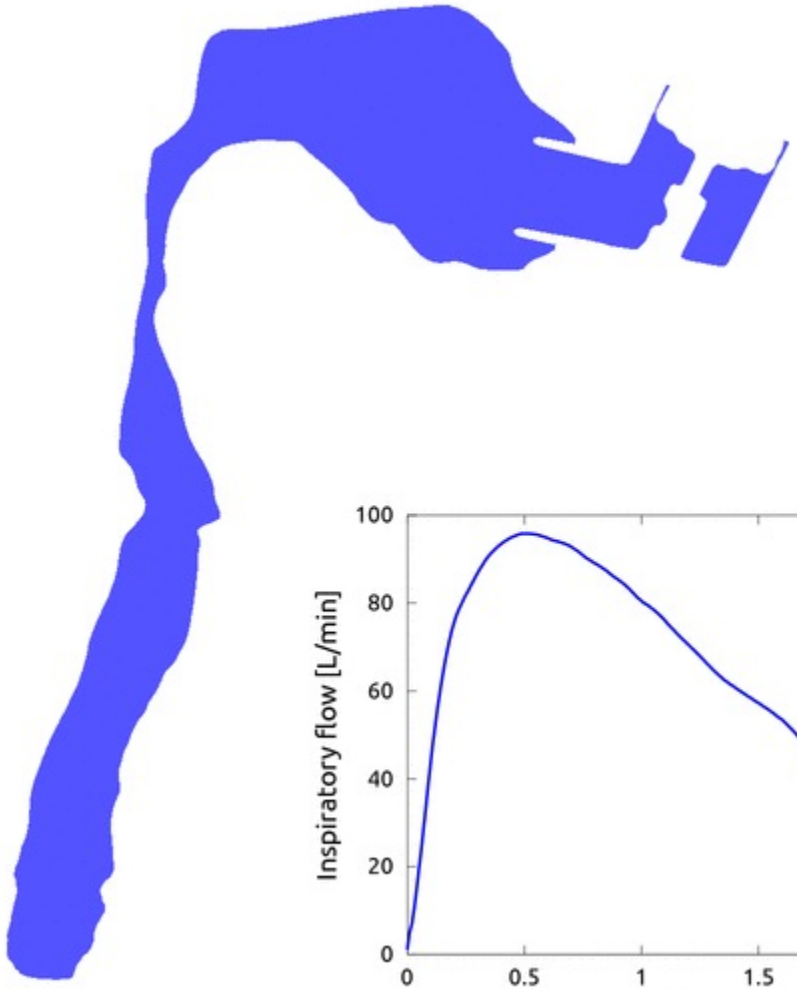
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SCENARIO 3: DELIVERY

Patient-specific model coupled with different inhalers: flow simulations



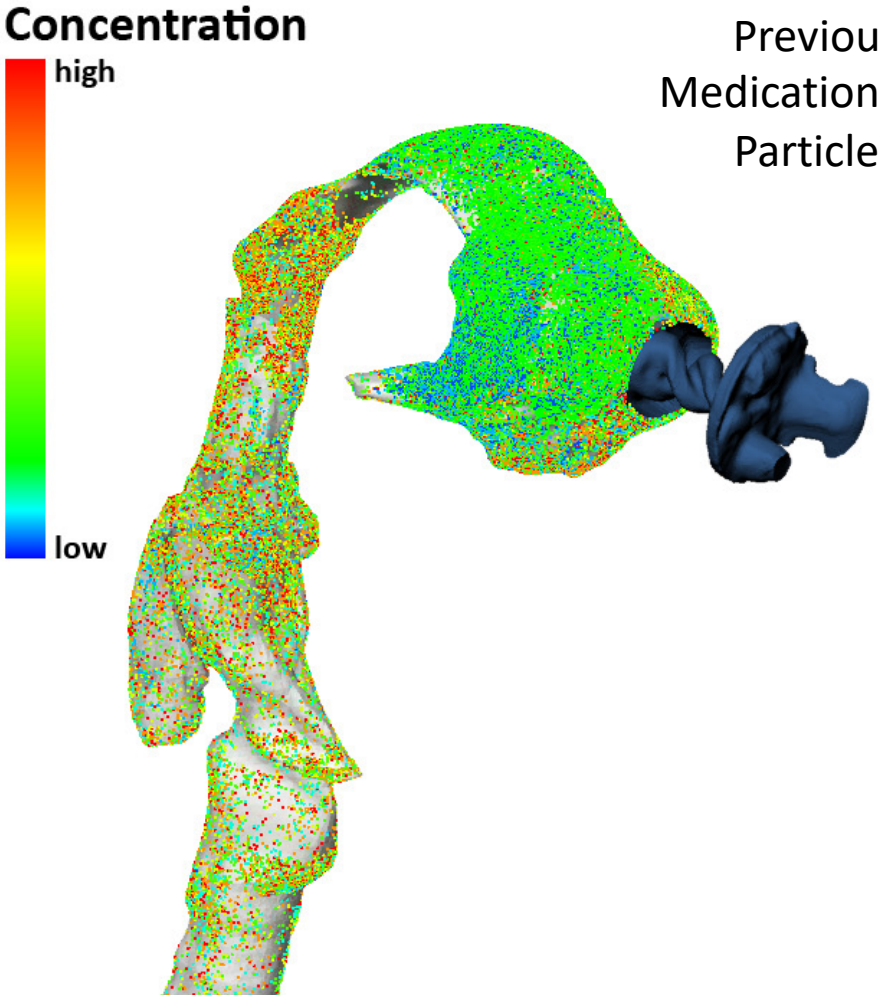


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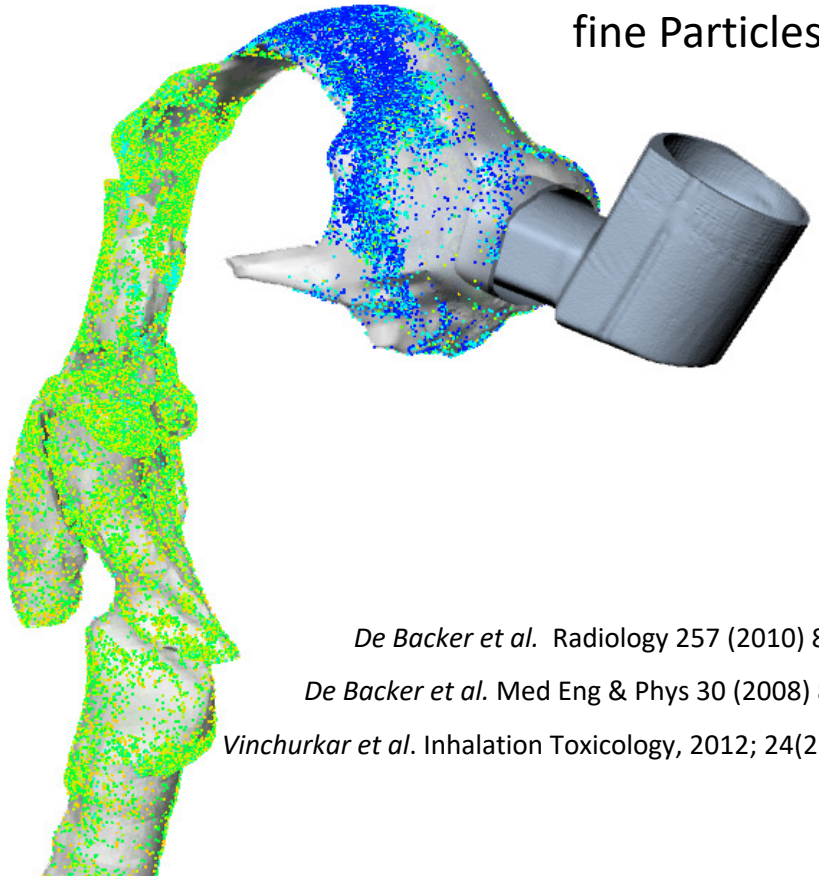
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SCENARIO 3: DELIVERY

Difference in upper airway deposition for 2 different inhalers and formulations



Previous Medication Fine Particles



Beclomethasone/Formoterol Extra-fine Particles

De Backer et al. Radiology 257 (2010) 854–862

De Backer et al. Med Eng & Phys 30 (2008) 872-879

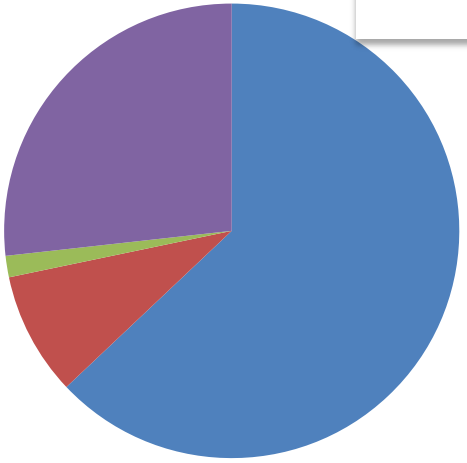
Vinchurkar et al. Inhalation Toxicology, 2012; 24(2): 81–88

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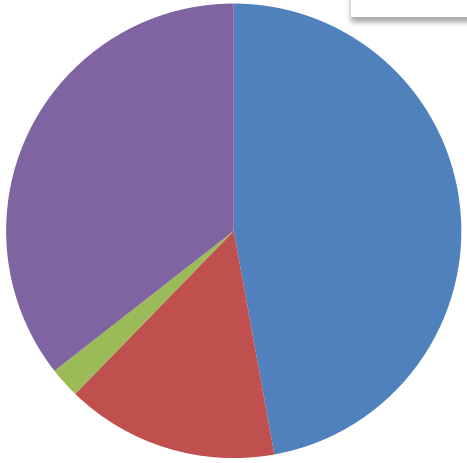
SCENARIO 3: DELIVERY

Patient-specific effective lung dose for 2 different inhalers and formulations

Previous Medication Fine Particles



Beclomethasone/Formoterol Extra-fine Particles

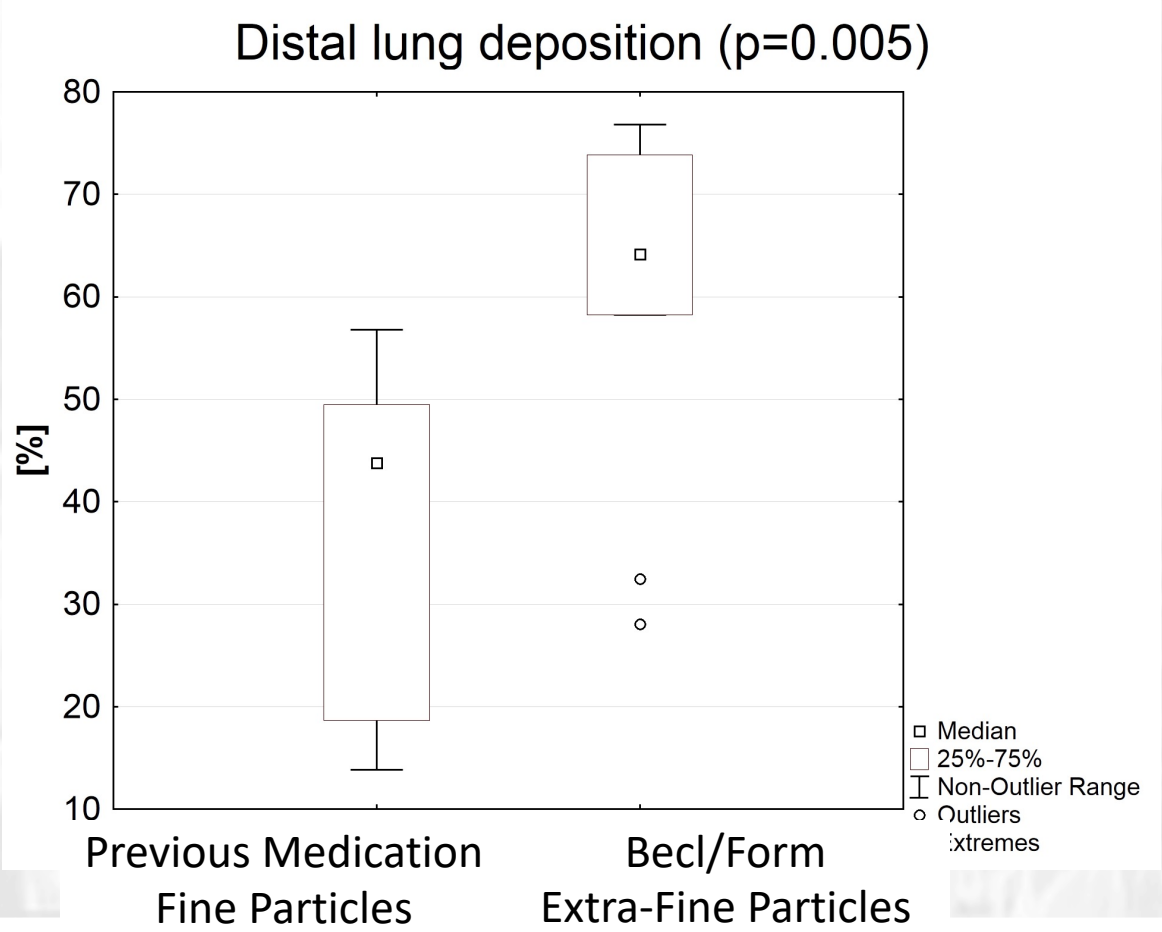


Lung deposition increases by 9%

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SCENARIO 3: DELIVERY

% Distal lung deposition: Fine particles vs. Extra-Fine particles

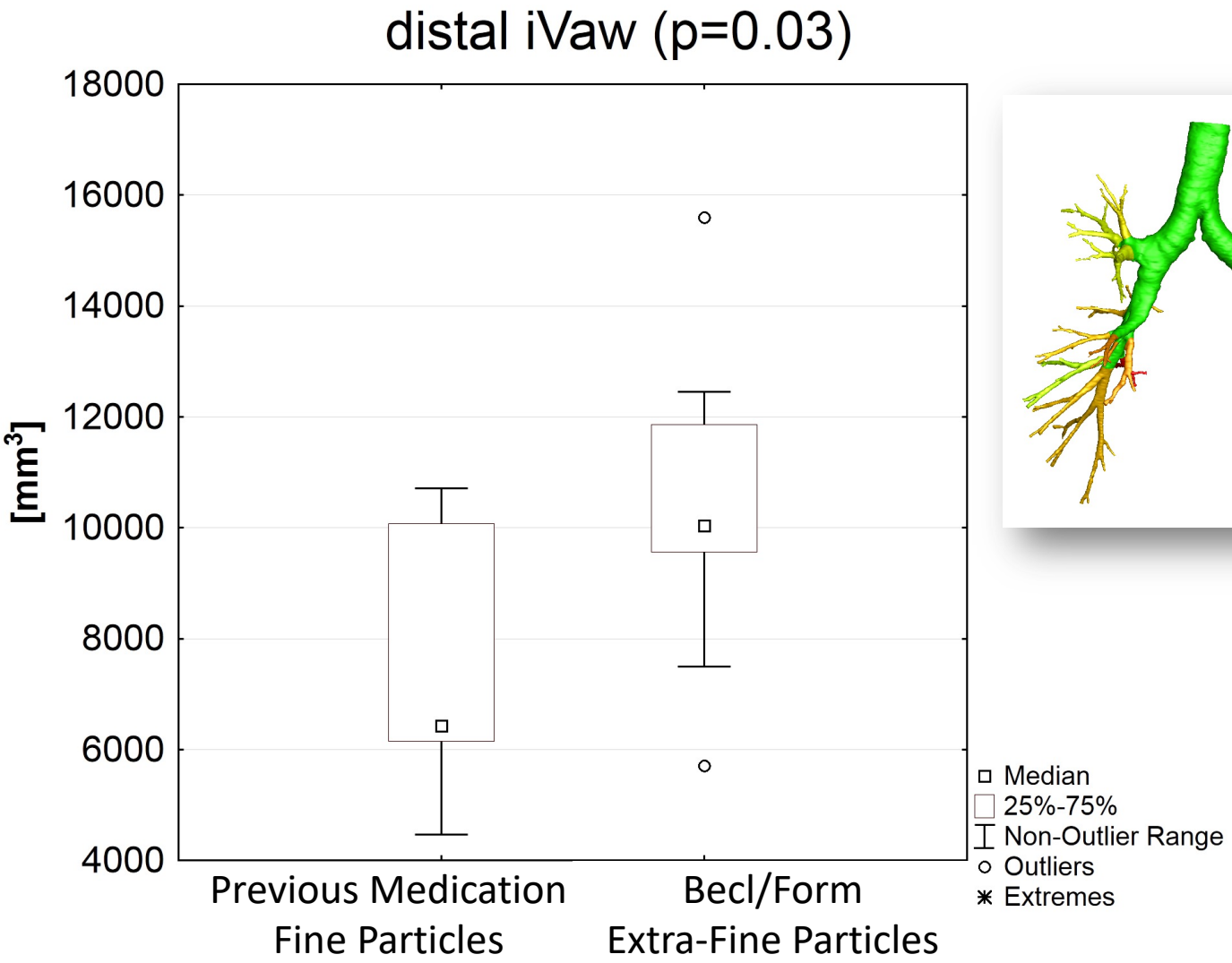


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SCENARIO 3: DELIVERY

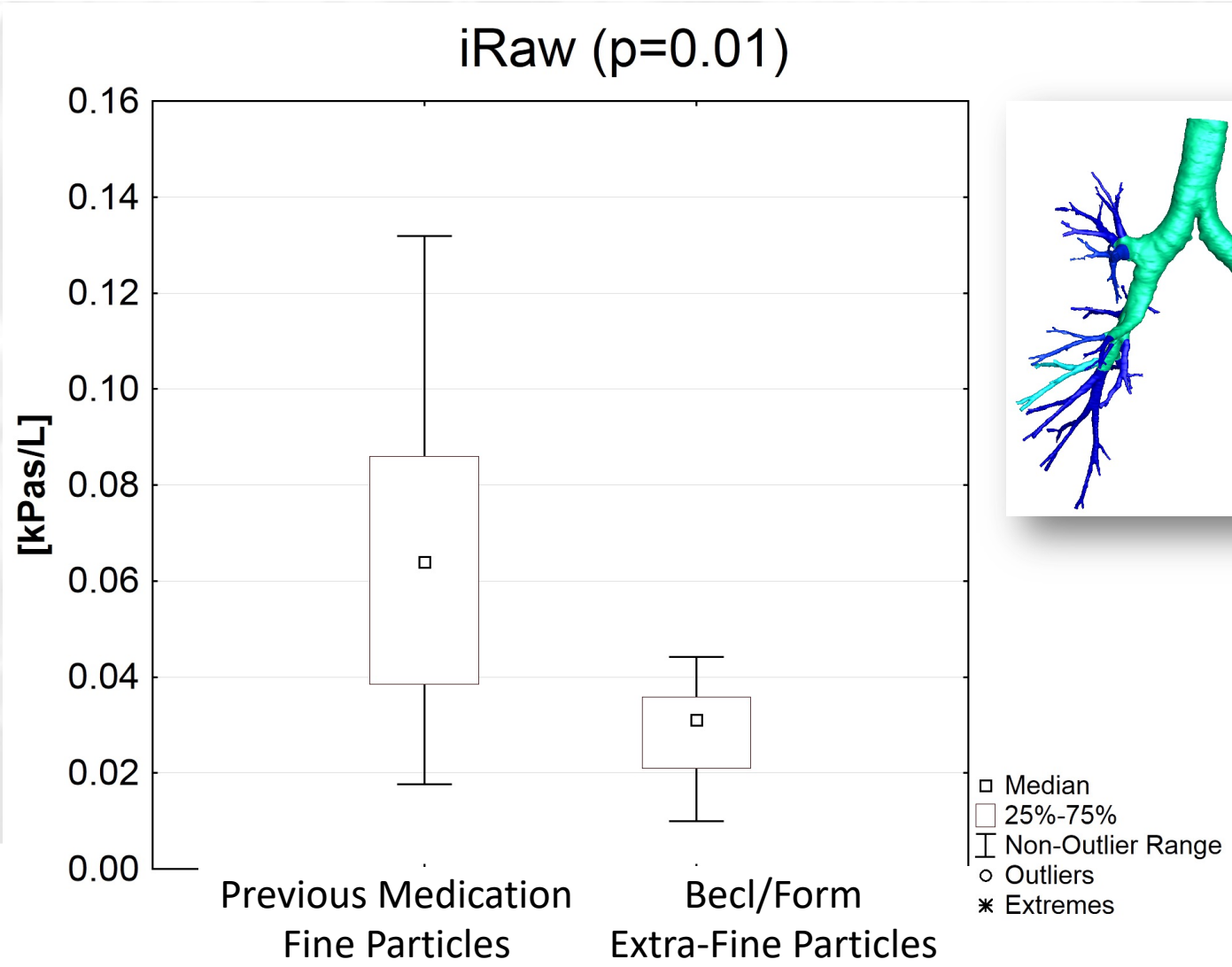
Therapeutic effect due to % Distal lung deposition: Fine vs. Extra-Fine particles



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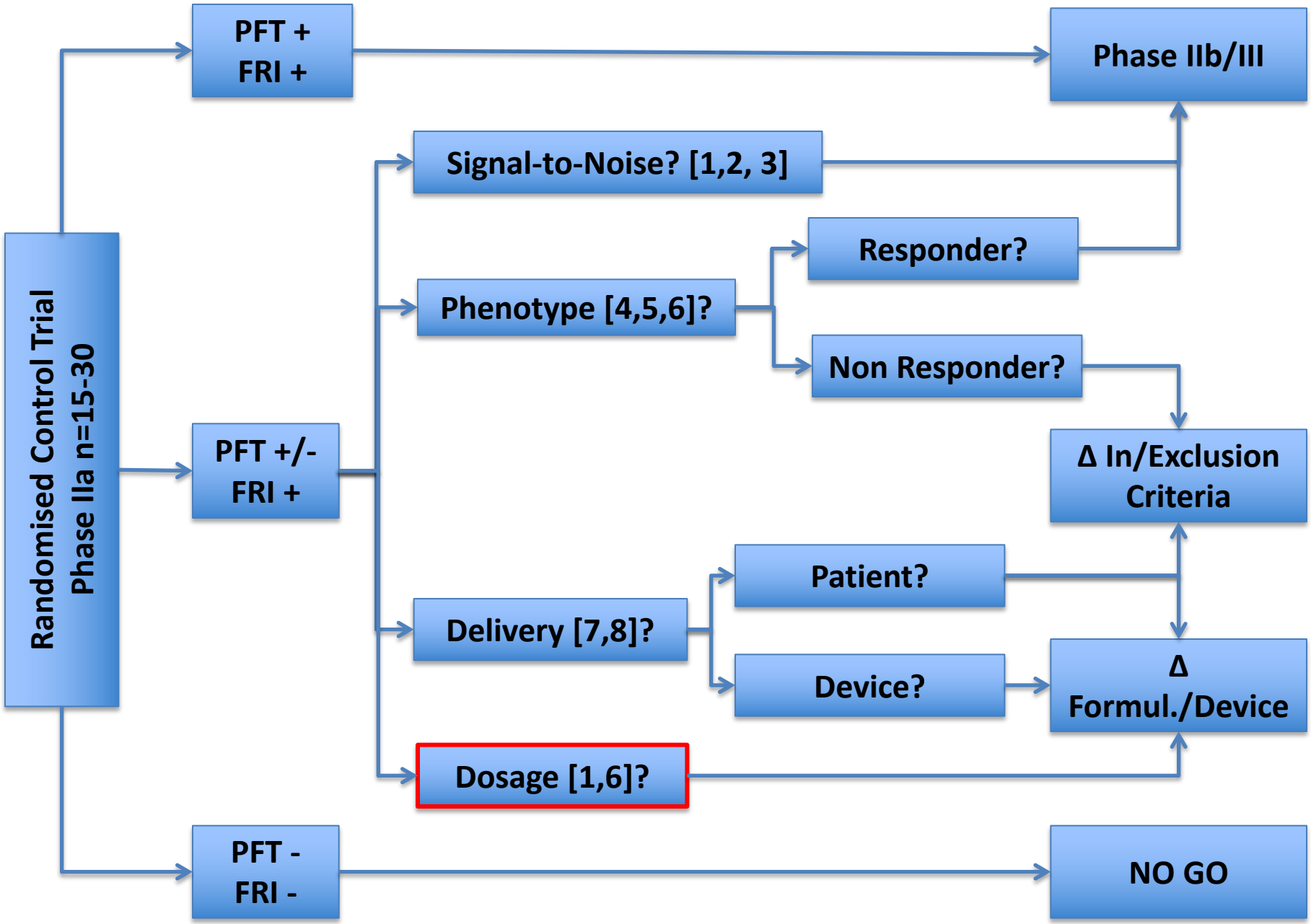
SCENARIO 3: DELIVERY

Therapeutic effect due to % Distal lung deposition: Fine vs. Extra-Fine particles



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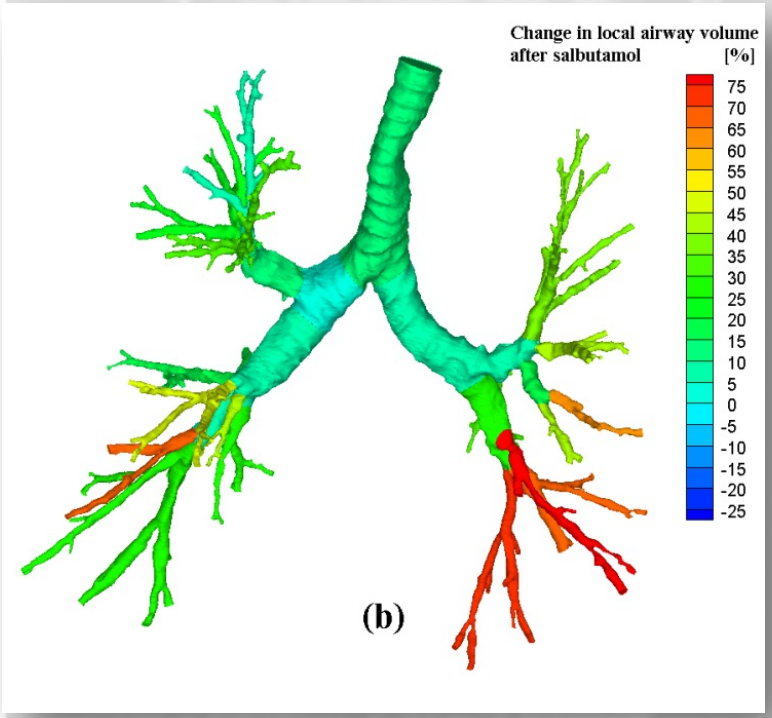
DECISION TREE - Mode of Action



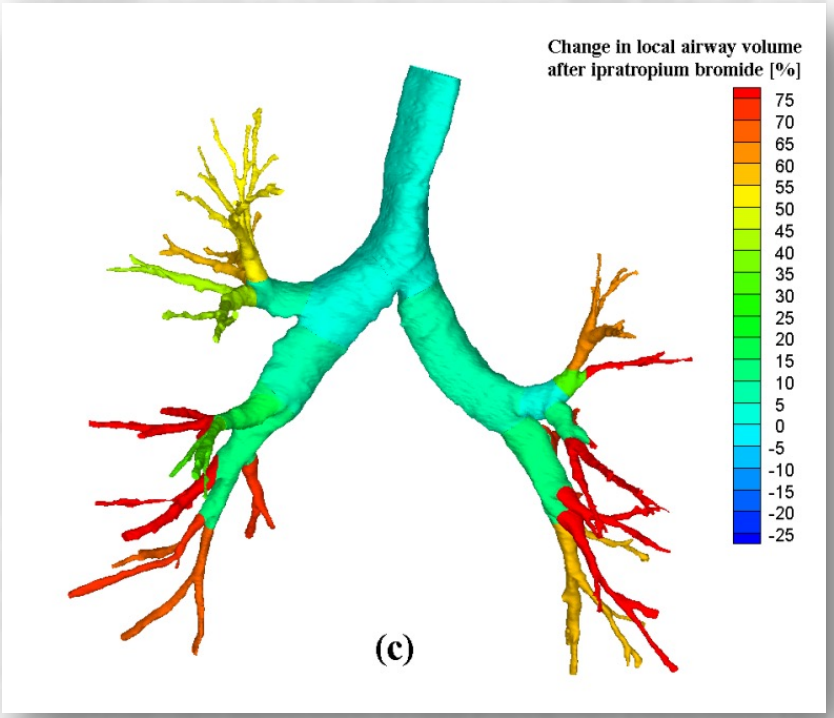
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SCENARIO 4: DOSAGE

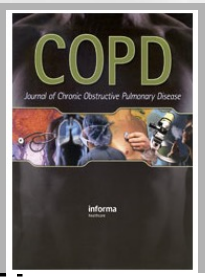
HIGH DOSE



400 microgram Salbutamol



80 microgram Ipratropium Bromide



De Backer LA, Vos WG, De Backer JW, Devolder A, Verhulst SL, Claes R, Salgado R, Germonpré PR, De Backer WA

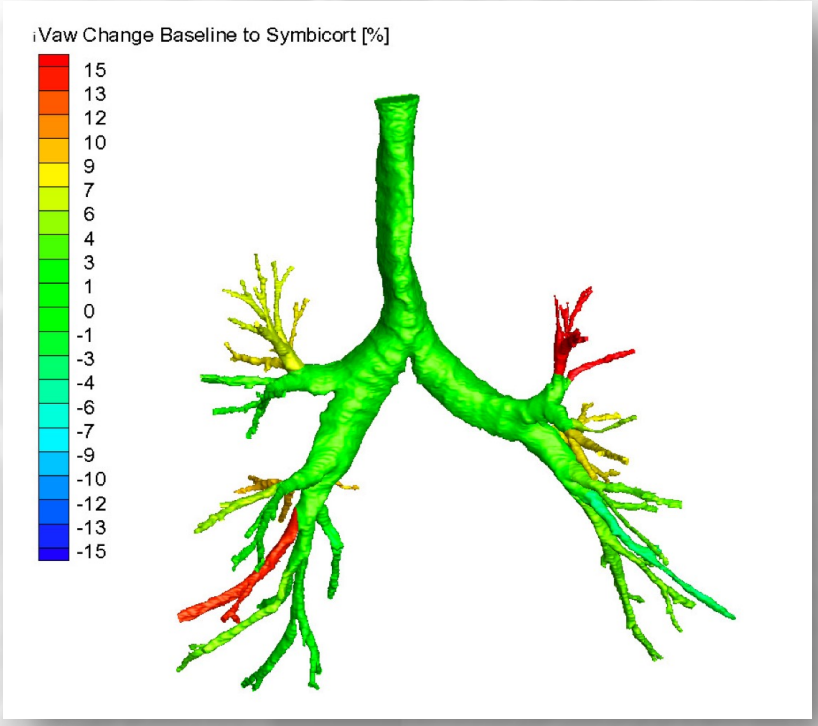
The effect of salbutamol in comparison with ipratropium bromide on central and peripheral airways in COPD

Int J Chron Obstruct Pulmon Dis. 2011;6:637-46.

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SCENARIO 4: DOSAGE

NORMAL DOSE



4.5/160 microgram Formoterol/Budesonide



Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

Eur Respir J 2012; 40: 298-305

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REFERENCES

Non-comprehensive publication list

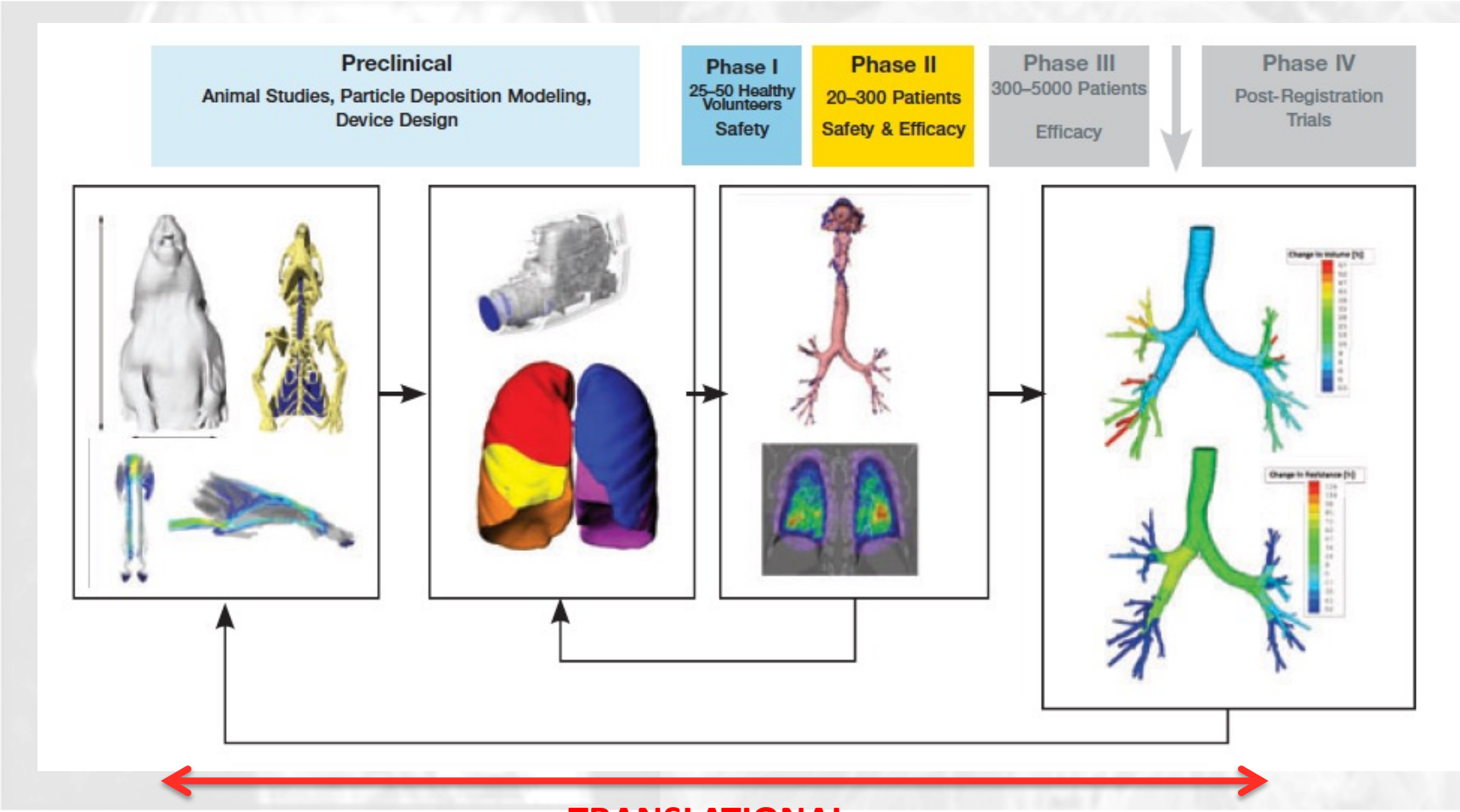
1. Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests. De Backer LA, Vos W, De Backer J, Van Holsbeke C, Vinchurkar S, De Backer W. European Respiratory Journal 2012;40:298-305.
2. Novel Functional Imaging Of Changes In Small Airways Of Patients Treated With Extrafine Beclomethasone/Formoterol Wim Vos, Jan De Backer, Gianluigi Poli, Annick Devolder, Liesbet Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer Respiration 2013 (published ahead of print: doi:10.1159/000347120)
3. The effects of extra-fine beclometasone/formoterol (BDP/F) on lung function, dyspnea, hyperinflation and airway geometry in COPD patients J. De Backer, W. Vos, S. Vinchurkar, C. Van Holsbeke, G. Poli, R. Claes, W. D'Hondt, R. Salgado, W. De Backer (under review)
4. The effect of high dose N acetylcysteine on airway geometry, inflammation and oxidative stress in COPD patients Jan De Backer, Wim Vos, Cedric Van Holsbeke, Samir Vinchurkar, Rita Claes, Paul Parizel, Wilfried De Backer (under review)
5. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study L De Backer, W Vos, B Dieriks, D Daems, S Verhulst, S Vinchurkar, K Ides, J De Backer, P Germonpre,W De Backer International Journal of COPD 2011;6:615–624
6. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD LA De Backer, R Salgado, WG Vos, JW De Backer, A Devolder, SL Verhulst, AS Verstraeten, R Claes, PR Germonpre, WA De Backer International Journal of COPD 2011;6:637–646
7. A case series on lung deposition analysis of inhaled medication using functional imaging based computational fluid dynamics in asthmatic patients: effect of upper airway morphology and comparison with in vivo data. Vinchurkar S, De Backer L, Vos W, Van Holsbeke C, De Backer J, De Backer W. Inhalation Toxicology 2012 Jan;24(2):81–8.
8. Validation of computational fluid dynamics (CFD) in CT-based airway models using single photon computed tomography (SPECT). De BackerJW, Vos WG, Vinchurkar S, Claes R, Drollmann A, Wulfrank D, Parizel P, Germonpre P, De Backer W. Radiology 2010; 257:854-862

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FRI AS DRUG DESIGN TOOL

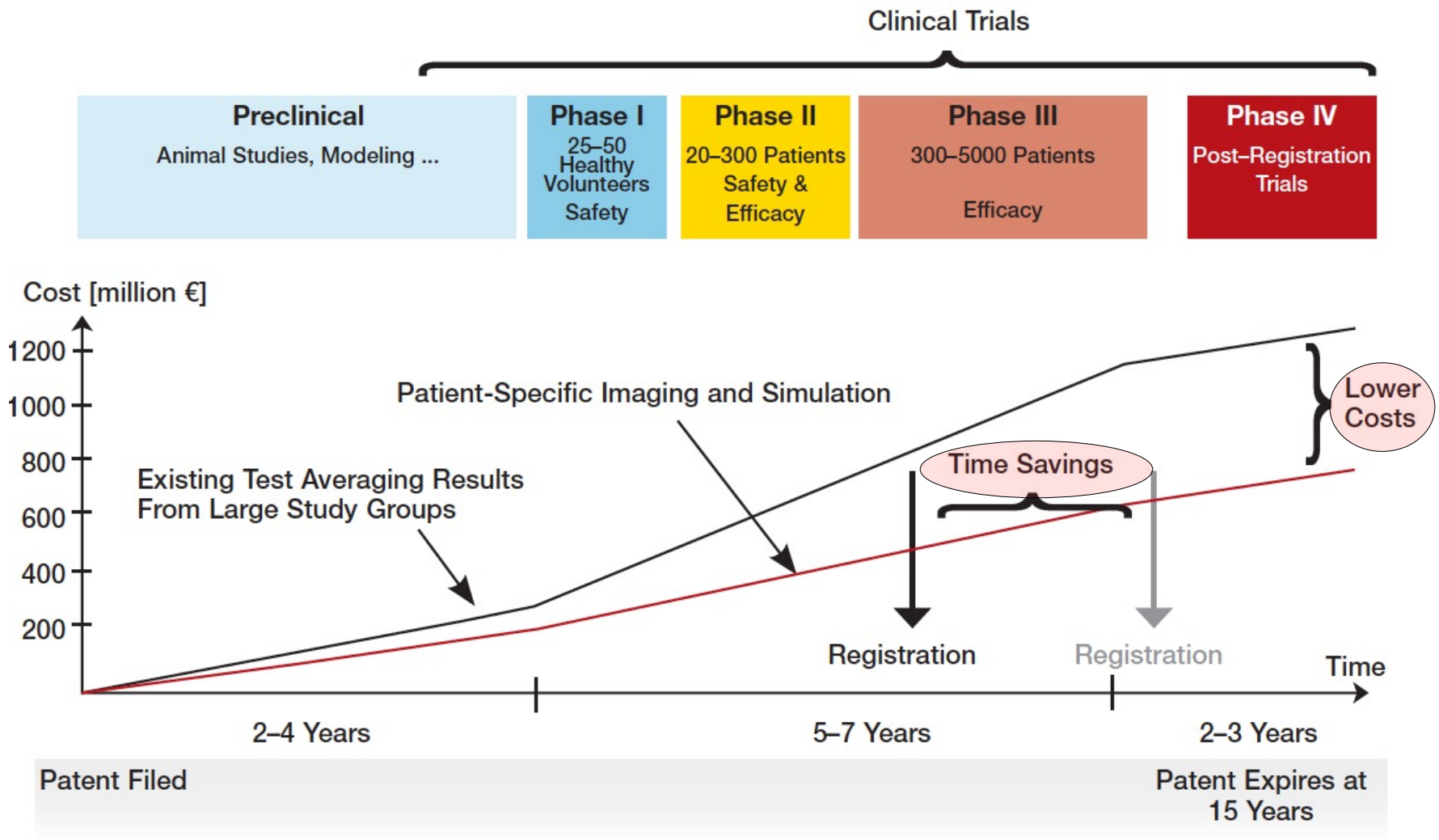
Focus on pre-clinical/clinical studies facilitating translational approach



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FRI – ADDED VALUE

Focus on Mode of Action in Phase I and II will derisk Phase III



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CONCLUSIONS

- FRI is more sensitivity compare to standard PFT
- Reduction in # patients required for clinical trials aimed to understand Mode of Action
- Use clinical trials as a design tool in phase I and II
  - To de-risk phase III

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NEXT STEPS FOR FRI

- Broader implementation of FRI in phase I and II clinical studies
- FRI as surrogate endpoint for (rare) lung diseases
  - Idiopathic pulmonary fibrosis
  - Cystic Fibrosis
  - Alpha 1 antitrypsin deficiency
  - Lung transplantation
  - Bronchiolitis obliterans
- FRI as surrogate endpoint for all lung diseases

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DAXAS® STUDY AIM

- The primary objective of this study is to evaluate the possible use of CT based functional respiratory imaging (FRI) on the phenotyping of severe COPD patients after a 6 month treatment with Daxas®

- Secondary outcome variables are health related quality of life, lung function tests and exercise tolerance.

→ Daxas® on top of triple therapy (ICS/LABA/LAMA)

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DAXAS® STUDY AIM

- Double blind placebo controlled design
- Block randomization
  - 3 Daxas®/ 1 placebo
- Inclusion period: ±10 months (jan-oct 2012)

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DAXAS® STUDY AIM

- Inclusion criteria
  1. Male or female patient ≥ 30 years old
  2. Patient with BMI ≥ 20
  3. Written informed consent obtained
  4. Female patient of childbearing potential who confirm that a contraception method was used at least 14 days before visit 1 and will continue to use a contraception method during the study.
  5. Patient should be treated according to GOLD guidelines
  6. COPD patient with GOLD stages III until IV
  7. Patient with smoking history of at least 10 pack-years
  8. Patient takes Spiriva® and a fixed combination of inhaled steroids and LABA at least 6 weeks before visit 1
  9. Patient must be able to understand and complete to protocol requirements, instructions, questionnaires and protocol-stated restrictions.

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DAXAS® STUDY AIM

- Exclusion criteria
  1. Pregnant or lactating females
  2. Patient with severe immunological diseases and/ or severe acute infectious diseases.
  3. Patient with heart failure
  4. Patient with diagnosis of cancer (except basal cell carcinoma)
  5. Patient with a history of depression associated with suicidal ideation or behaviour
  6. Patient with moderate or severe hepatic impairment.
  7. Patient with lactose intolerance
  8. Patient is unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study.
  9. Patient who received any investigational new drug within the last 4 weeks prior to the baseline visit or twice the duration of the biological effect of any drug (whichever is longer).

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DAXAS® STUDY AIM

	Baseline*	3 months*	6 months*
Functional Respiratory Imaging	X		X
Spirometry	X	X	X
Body Plethysmography	X	X	X
Diffusion	X		X
FOT	X		X
6MWT	X		X
PRO	X		X

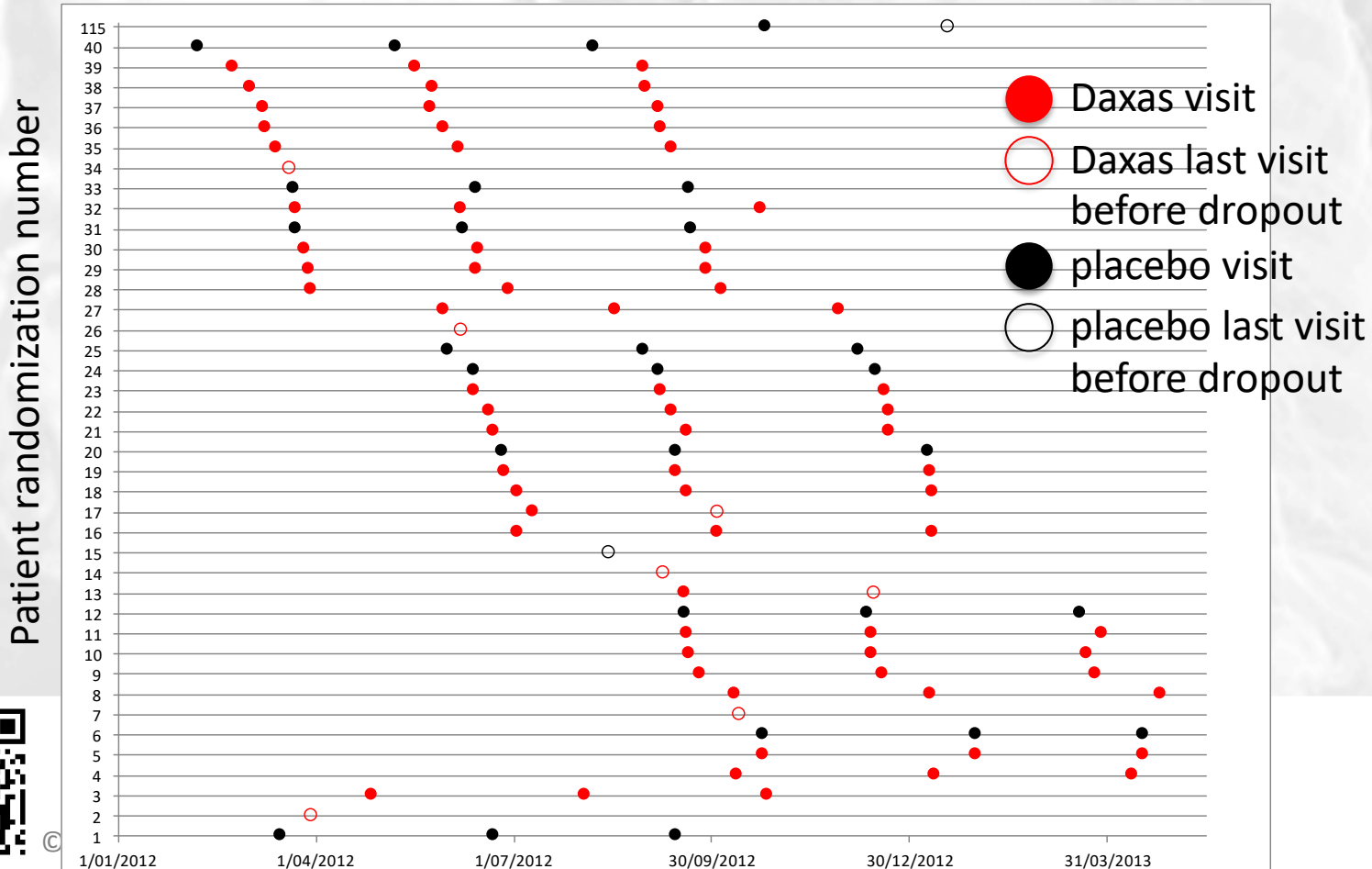
*All tests were performed post bronchodilation

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PATIENT POPULATION

- 41 included COPD GOLD III and IV patients
  - 9 drop-outs / 32 evaluable patients



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PATIENT POPULATION

- Dropouts
  - 7 treated with Daxas® on top of ICS/LABA/LAMA
  - 2 treated with placebo on top of ICS/LABA/LAMA

	Non-dropout	dropout
Length (cm)	167.28±7.83	171.83±9.41
Packyears (years)	53.61±33.69	42.63±20.18
Age (years)	65.41±7.68	68.89±6.66
Weight (kg)	86.53±27.79	78.19±18.31
FVC (%pred)	79.82±19.02	95.29±16.25
FEV1 (%pred)	42.98±12.04	45.49±9.96
FEV1/FVC (%)	43.66±12.02	38.18±8.93
RV (%pred)	164.3±34.94	173.63±27.61
TLC (%pred)	112.13±19.24	122.88±14.56
FRC (%pred)	142.64±32	157.38±18.3
Raw (kPas/L)	0.74±0.31	0.69±0.16
sRaw (kPas)	3.7±1.83	3.84±1.2
LCI (-)	8.96±1.5	8.84±0.84
N2 washout time (min)	4.87±2.36	4.76±1.91
6MWT (m)	371.26±109.73	373.38±66.63

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PATIENT POPULATION

- 32 evaluable patients
  - 23 treated with Daxas® on top of ICS/LABA/LAMA
  - 9 treated with placebo on top of ICS/LABA/LAMA

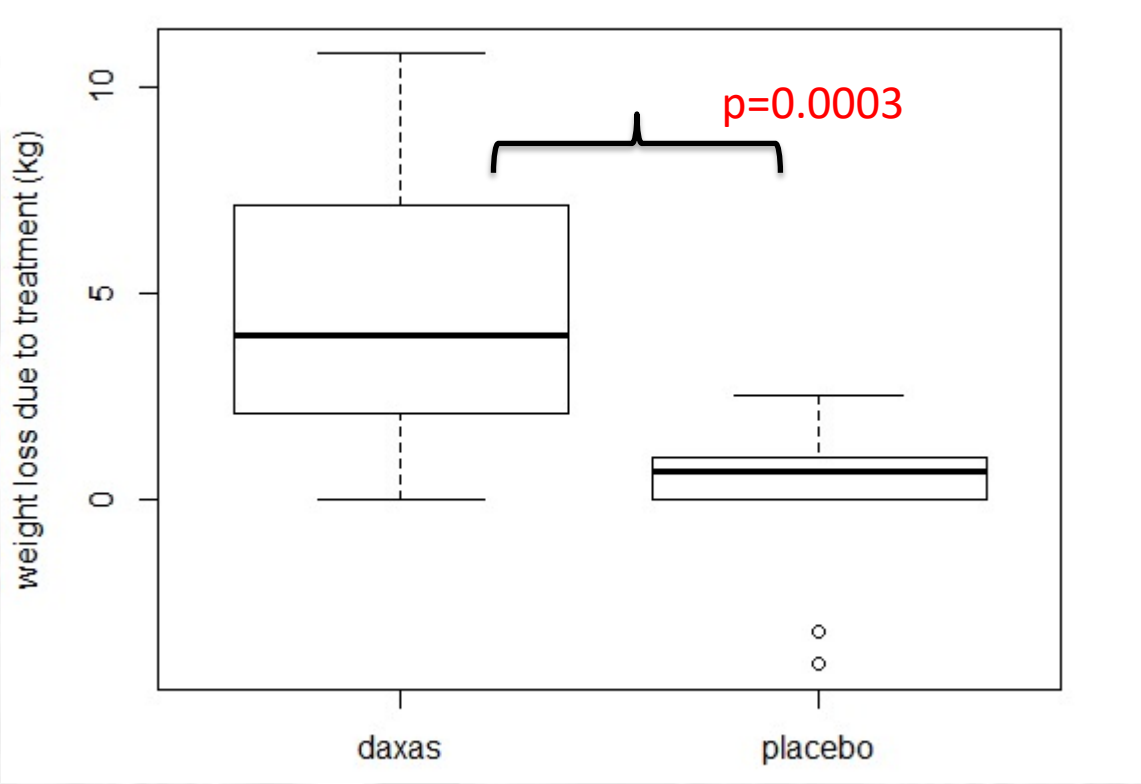
	Daxas®	placebo
Length (cm)	166.2±6.44	170.06±10.56
Packyears (years)	53.13±35.57	54.83±30.24
Age (years)	63.61±7.38	70±6.76
Weight (kg)	84.08±28.58	92.81±26.18
FVC (%pred)	79.76±21.08	79.97±13.43
FEV1 (%pred)	41.3±12.17	47.28±11.19
FEV1/FVC (%)	42.5±12.62	46.61±10.41
RV (%pred)	171.32±35.31	146.36±28.26
TLC (%pred)	114.44±21.39	106.22±11.02
FRC (%pred)	147.22±33.72	130.94±25.07
Raw (kPas/L)	0.77±0.3	0.67±0.35
sRaw (kPas)	3.97±1.96	3±1.26
LCI (-)	8.87±1.33	9.16±1.94
N2 washout time (min)	5.48±2.51	3.46±1.16
6MWT (m)	357.53±90.02	403.88±148.84

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WEIGHT LOSS

- Significant weight loss in Daxas® treated patients

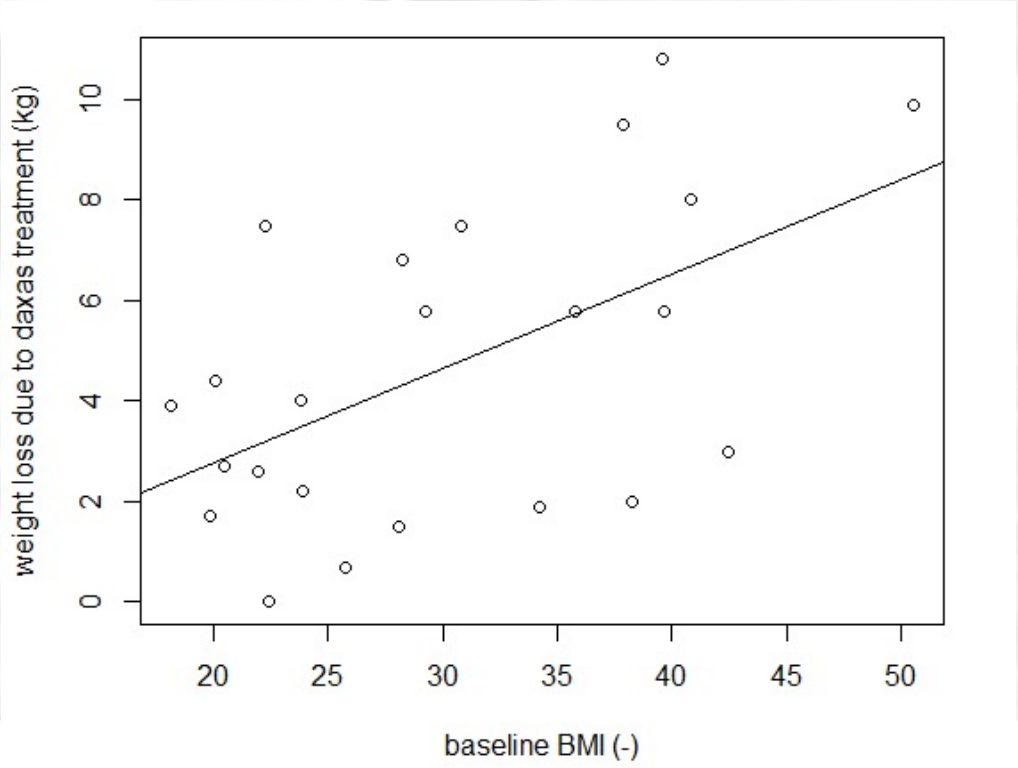


p<0.0001 p=0.73

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WEIGHT LOSS

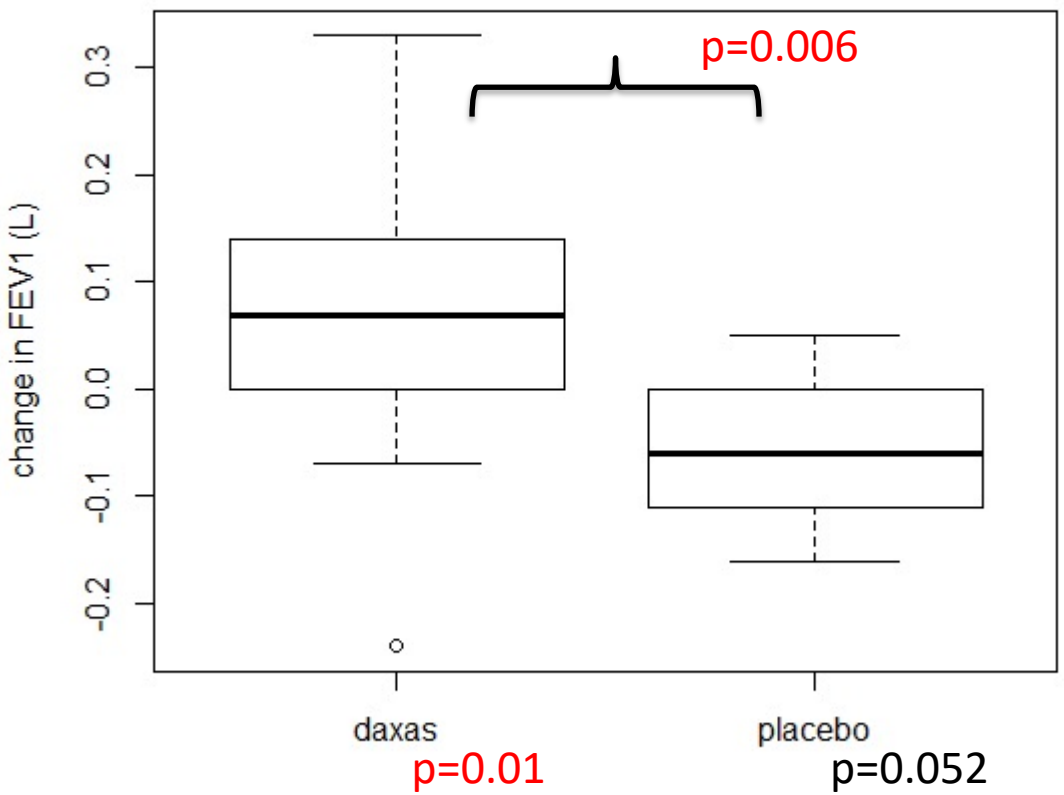
- Larger weight loss after Daxas® treatment in more obese patients (Spearman R=0.46, p=0.025)



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CHANGE IN FEV 1

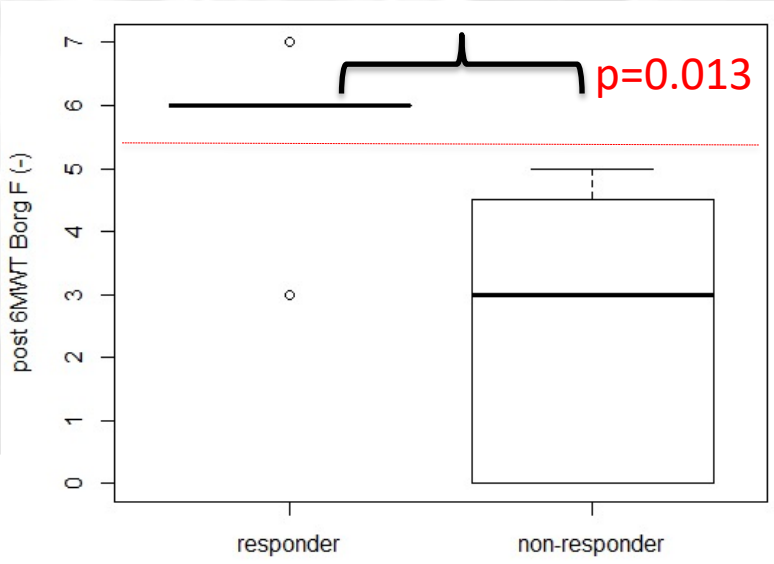
- Significant improvement in FEV1 in Daxas® group (+66ml) compared to drop in placebo (-59ml)



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DAXAS® RESPONDERS IN TERMS OF FEV 1

- 8 patients (35%) in the Daxas® group have a FEV1 response > 120ml* (+ 186 ml on average)
- Responders are the patients who feel at baseline significantly worse after 6MWT compared to non-responders in terms of Borg score



*Quality and reproducibility of spirometry in COPD patients in a randomized trial (UPLIFT). Janssens W et al. Respir Med. 2013 May 25.

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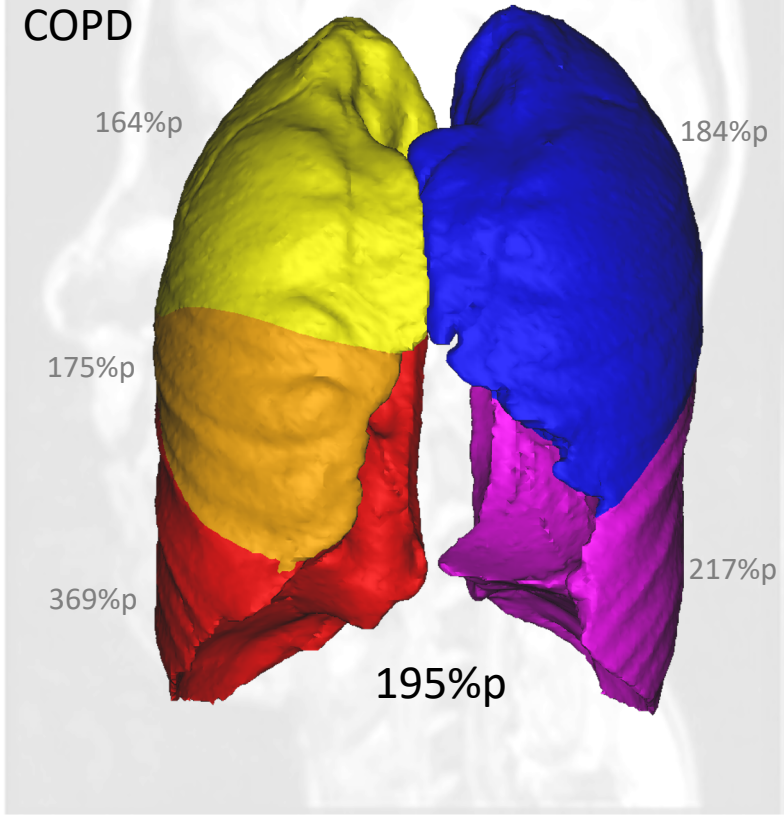
HYPOTHESIS 1

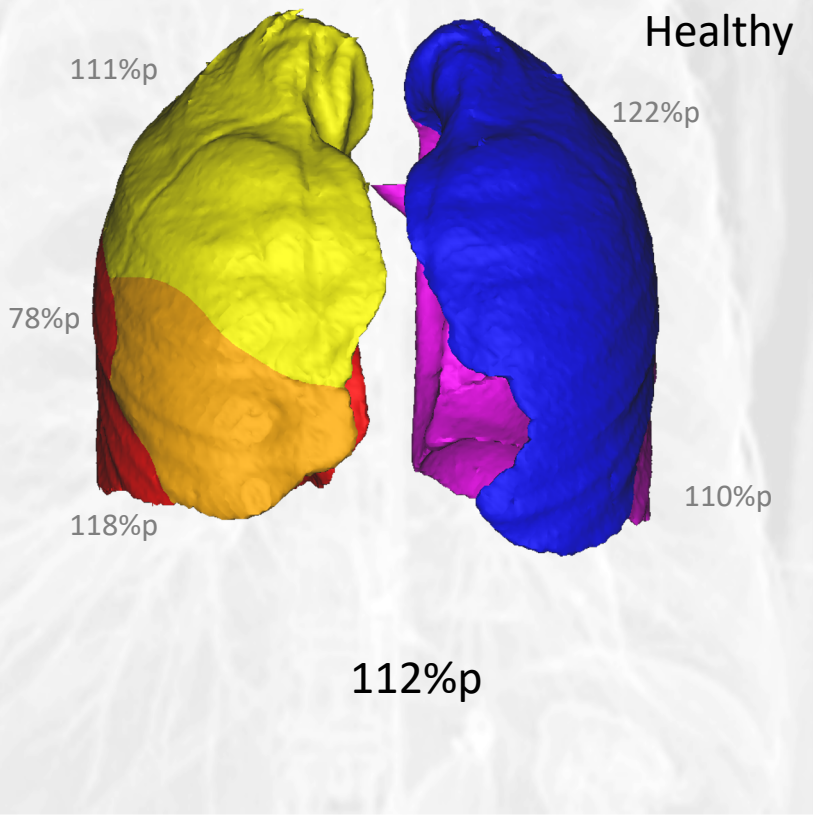
Daxas® reduces regional hyperinflation in responders

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DAXAS® RESPONDERS IN TERMS OF HYPERINFLATION

- Regional hyperinflation @ FRC



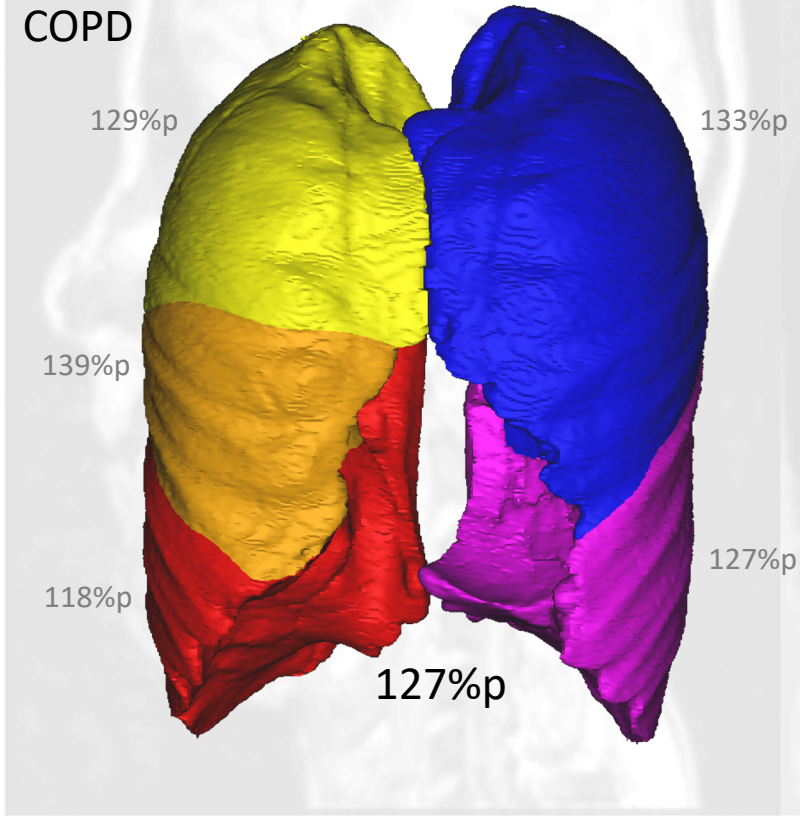


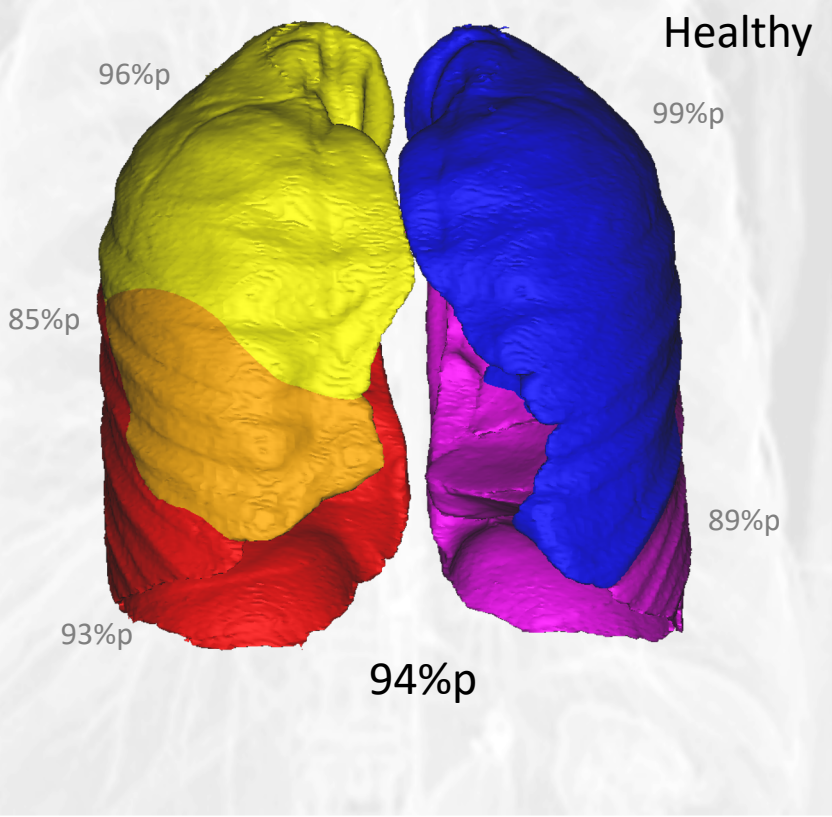
Both subjects are female, 1.70m

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DAXAS® RESPONDERS IN TERMS OF HYPERINFLATION

- Regional hyperinflation @ TLC



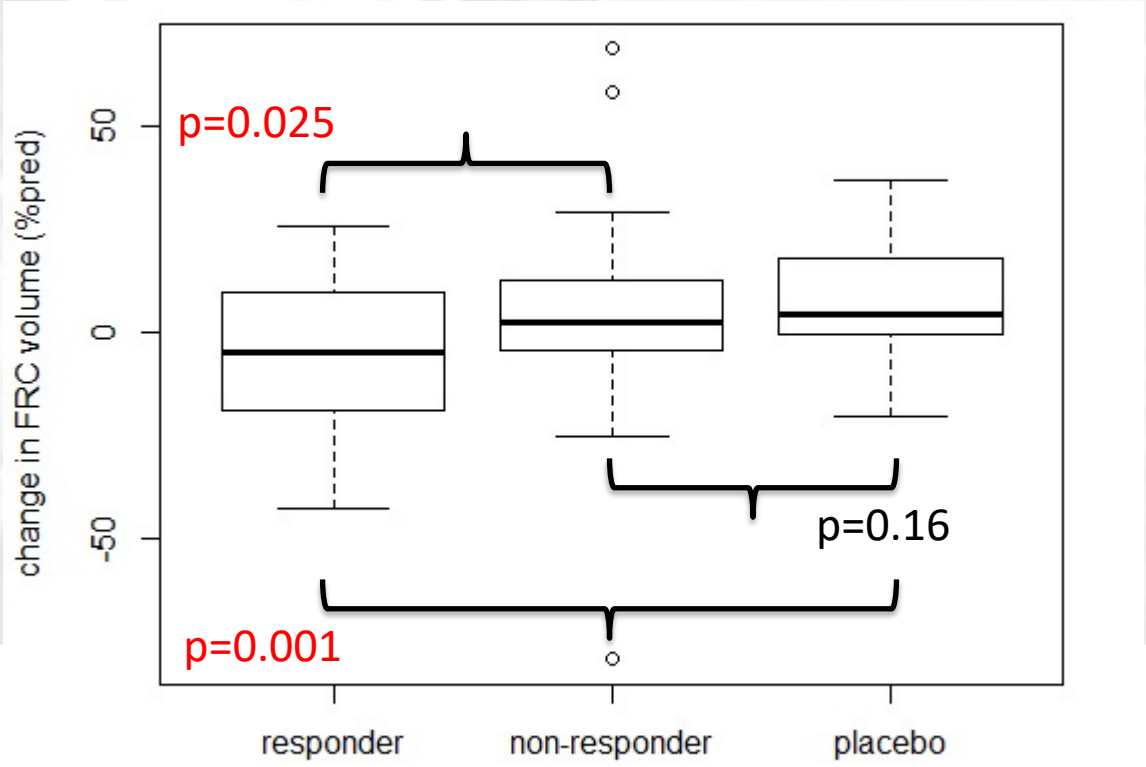


Both subjects are female, 1.70m

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DAXAS® RESPONDERS IN TERMS OF HYPERINFLATION

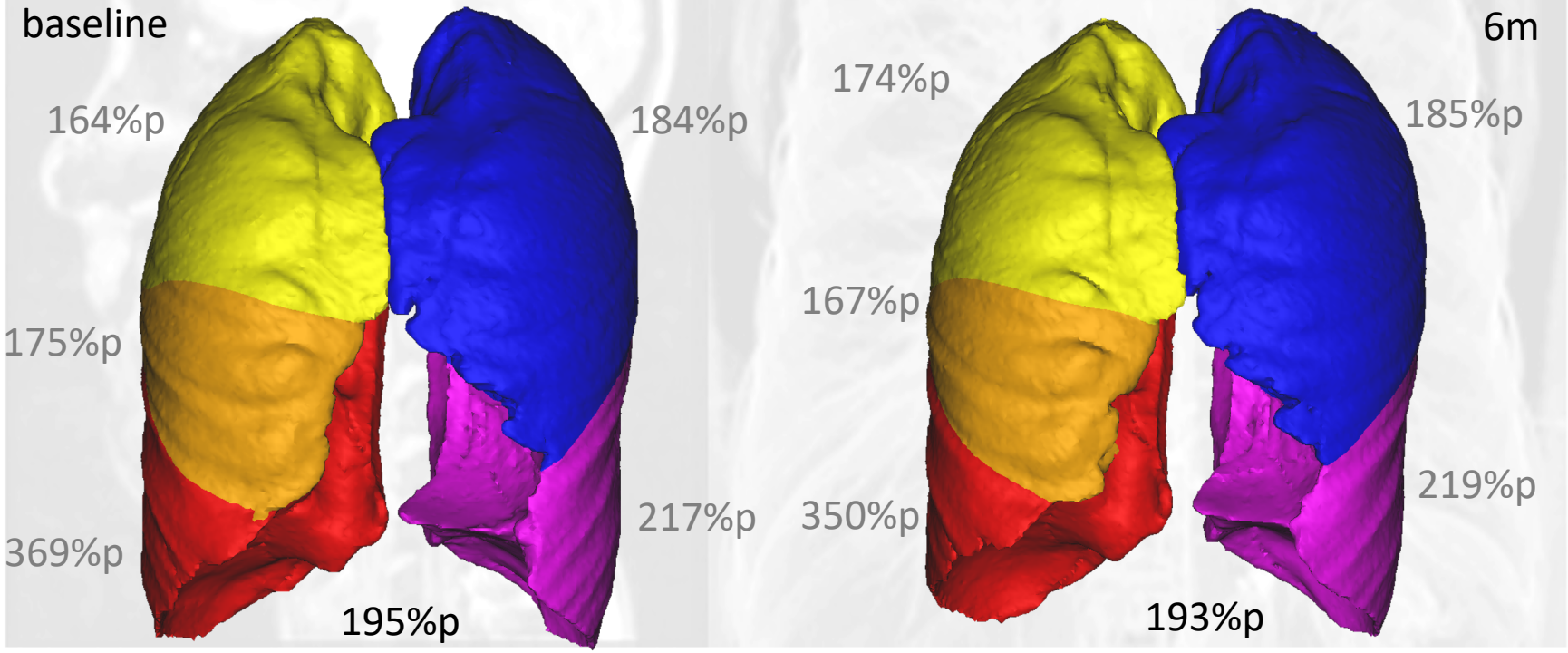
- FRC lobes reduce significantly in volume for the Daxas responders (-4.88 %p) as compared to the non-responders (+3.47 %p) and placebo (+8.28 %p)



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DAXAS® RESPONDERS IN TERMS OF HYPERINFLATION

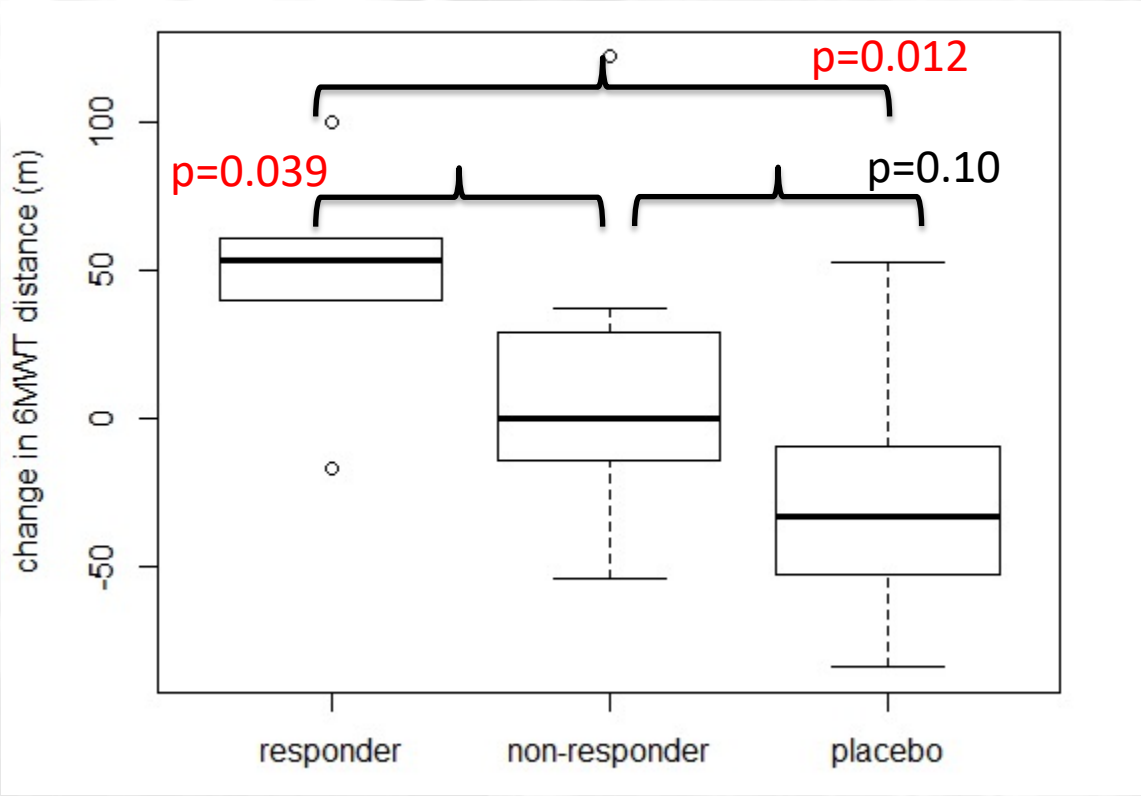
- Regional hyperinflation change @ FRC in Daxas® responder



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DAXAS® RESPONDERS IN TERMS OF HYPERINFLATION

- Daxas® responders improve 6MWT distance (+53.5 m)



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HYPOTHESIS 2

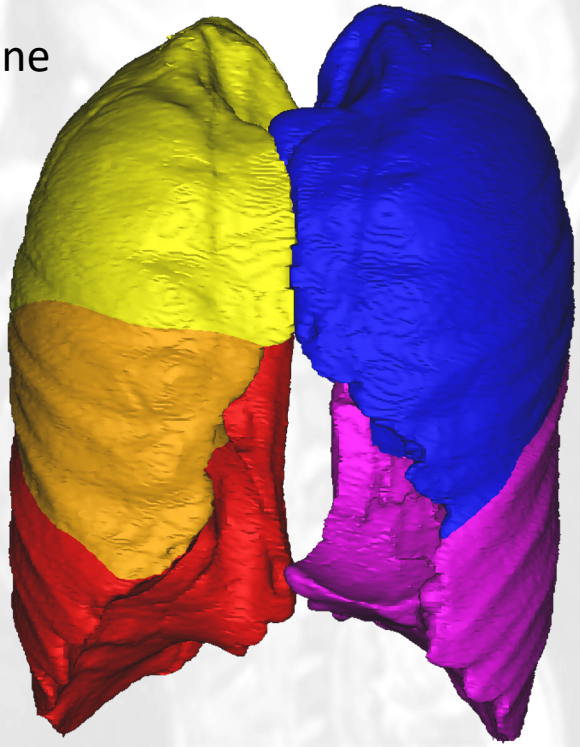
Daxas® improves efficacy of ICS/LABA/LAMA in responders

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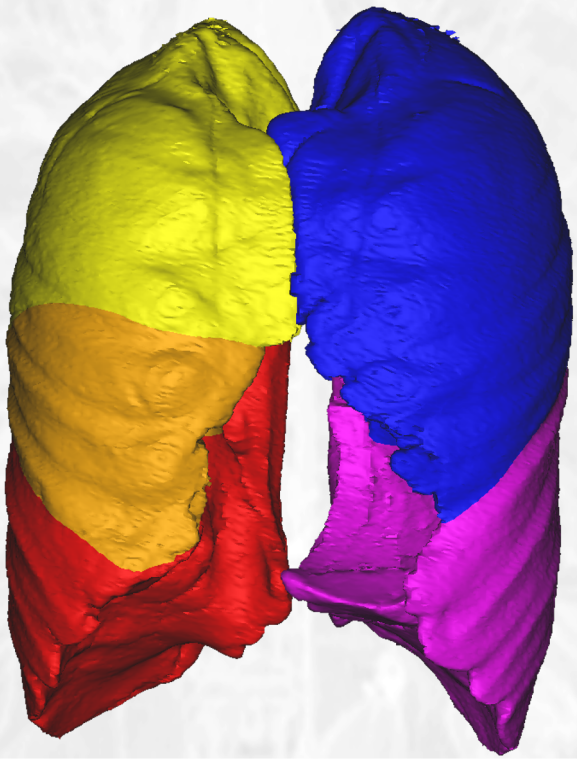
DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

- Daxas® changes internal airflow distribution and deposition efficacy of ICS/LABA/LAMA

baseline



6m



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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

Lobes FRC				
	Volume[L]	Volume[% Total]	Volume[% Predicted]	Comment
RUL	0,967	17,55	164,17	HH
RML	0,452	8,19	174,97	HH
RLL	1,515	27,49	218,54	HH
LUL	1,233	22,37	183,96	HH
LLL	1,346	24,41	217,40	HH

Lobes TLC				
	Volume[L]	Volume[% Total]	Volume[% Predicted]	Comment
RUL	1,215	18,06	128,60	HH
RML	0,537	7,99	138,15	H
RLL	1,767	26,27	118,55	HH
LUL	1,484	22,06	133,45	HH
LLL	1,724	25,62	126,60	HH

baseline

	Distribution[% Total]	Normal range[% Total]	Comment
RUL	20,39	[10,79;19,07]	HH
RML	7,05	[2,95;8,67]	N
RLL	20,76	[26,66;36,70]	LL
LUL	20,65	[13,75;22,93]	N
LLL	31,16	[24,87;33,61]	N

Lobes FRC				
	Volume[L]	Volume[% Total]	Volume[% Predicted]	Comment
RUL	1,025	18,69	173,90	HH
RML	0,429	7,83	166,18	HH
RLL	1,435	26,17	206,86	HH
LUL	1,238	22,58	184,60	HH
LLL	1,356	24,73	219,01	HH

Lobes TLC				
	Volume[L]	Volume[% Total]	Volume[% Predicted]	Comment
RUL	1,210	17,86	128,07	HH
RML	0,491	7,25	126,25	H
RLL	1,851	27,34	124,18	HH
LUL	1,463	21,61	131,60	HH
LLL	1,757	25,94	129,02	HH

post

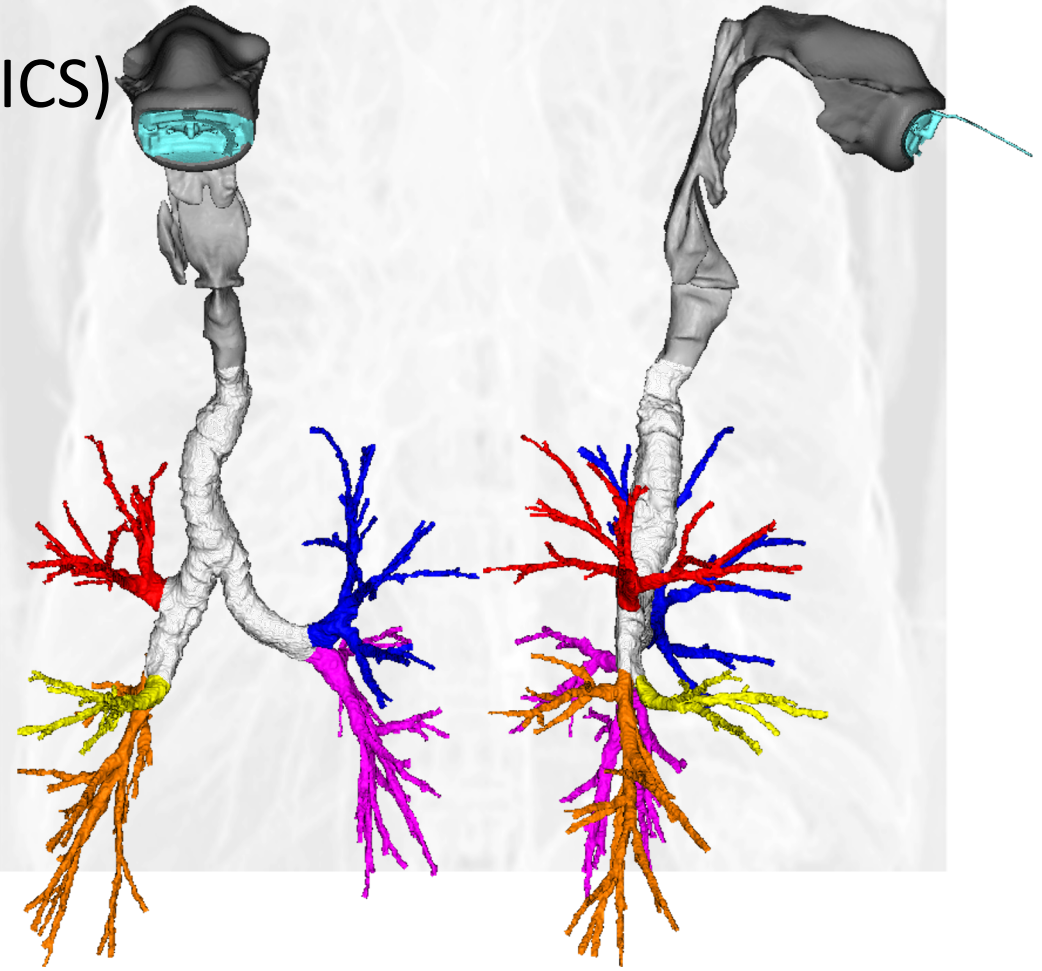
	Distribution[% Total]	Normal range[% Total]	Comment
RUL	14,33	[10,79;19,07]	N
RML	4,80	[2,95;8,67]	N
RLL	32,31	[26,66;36,70]	N
LUL	17,48	[13,75;22,93]	N
LLL	31,08	[24,87;33,61]	N

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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

Daxas® responder

- Seretide Diskus (LABA/ICS)
  - 8% more deep lung deposition
  - 38% more deposition in the lower lobes

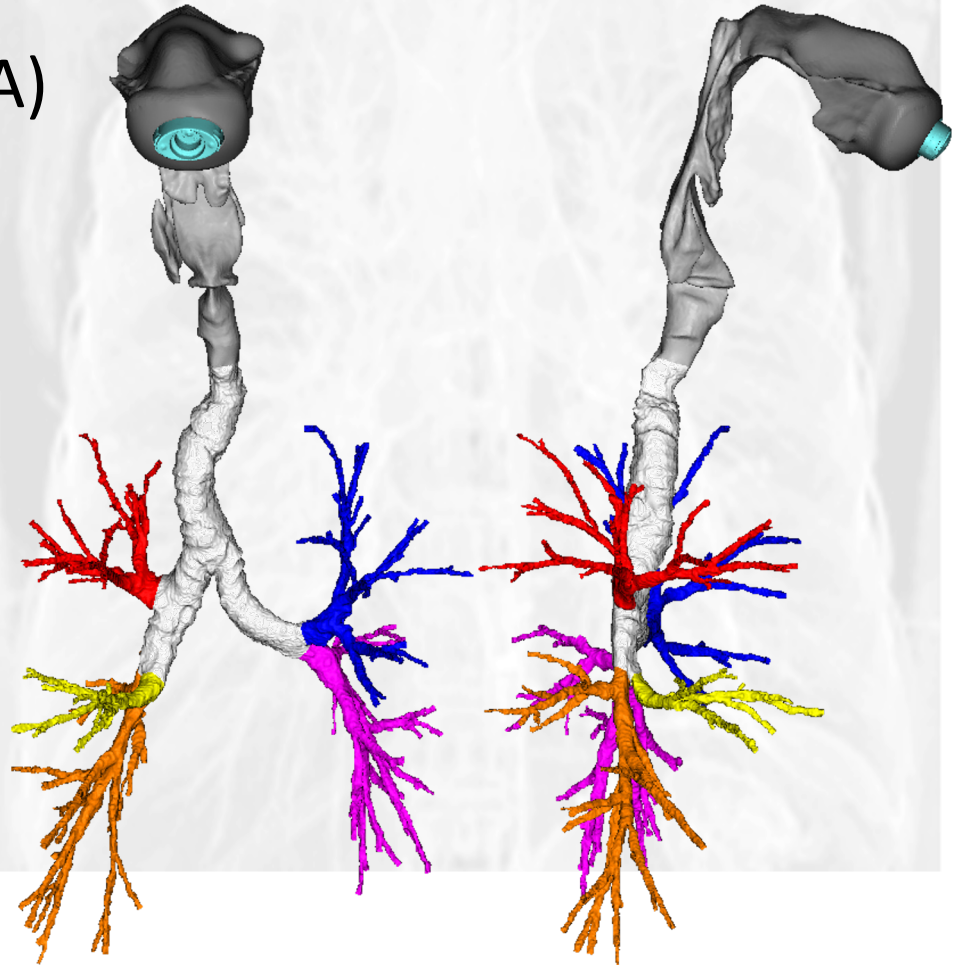


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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

Daxas® responder

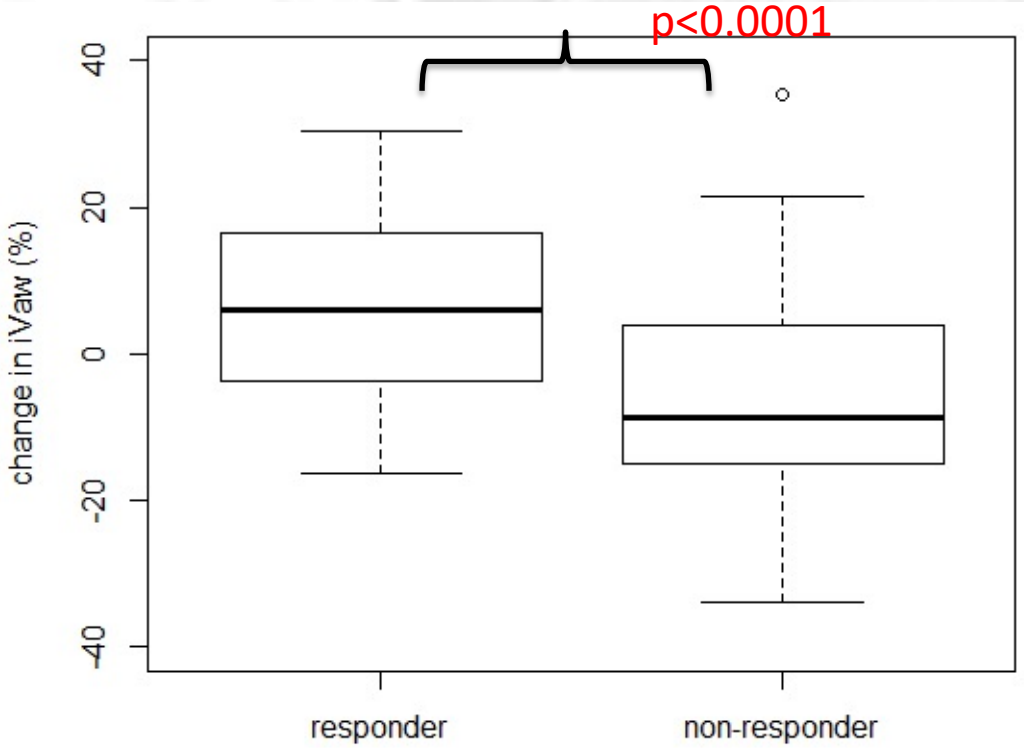
- Spiriva Respimat (LAMA)
  - 6 % more deep lung deposition
  - 37% more deposition in the lower lobes



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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

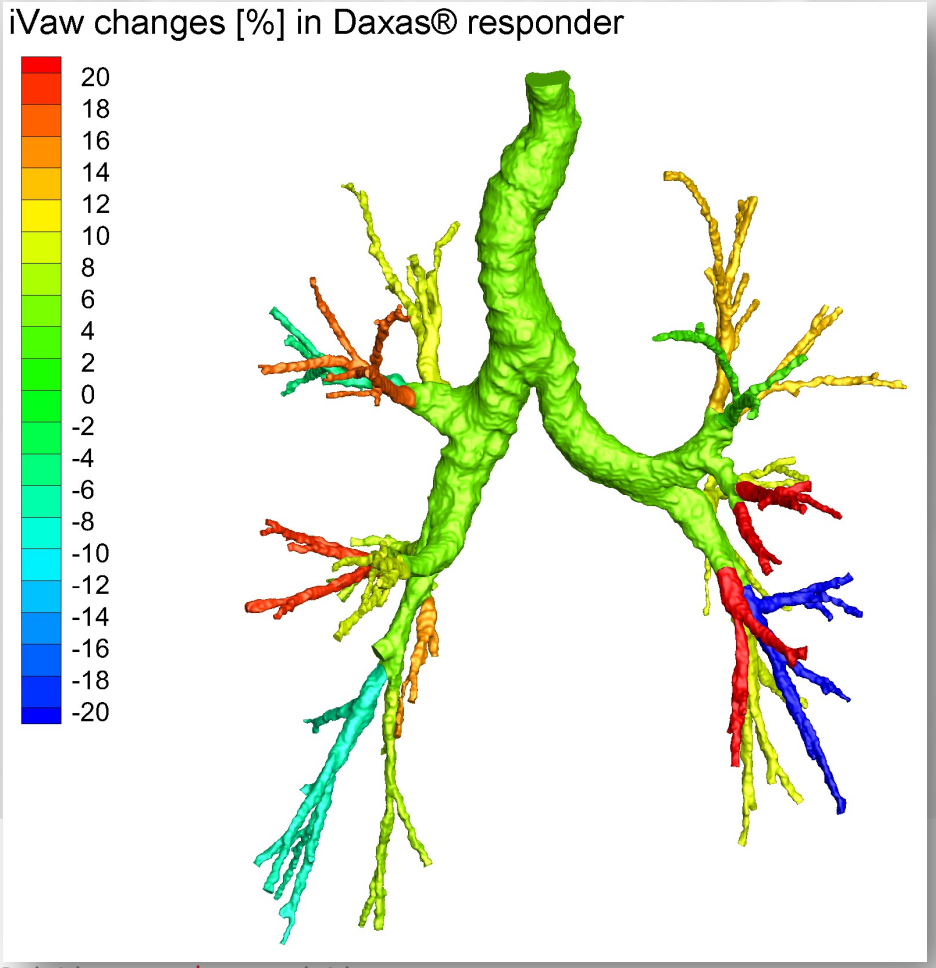
- Significant improvement in iVaw for the Daxas® responders (+8.5%)



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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

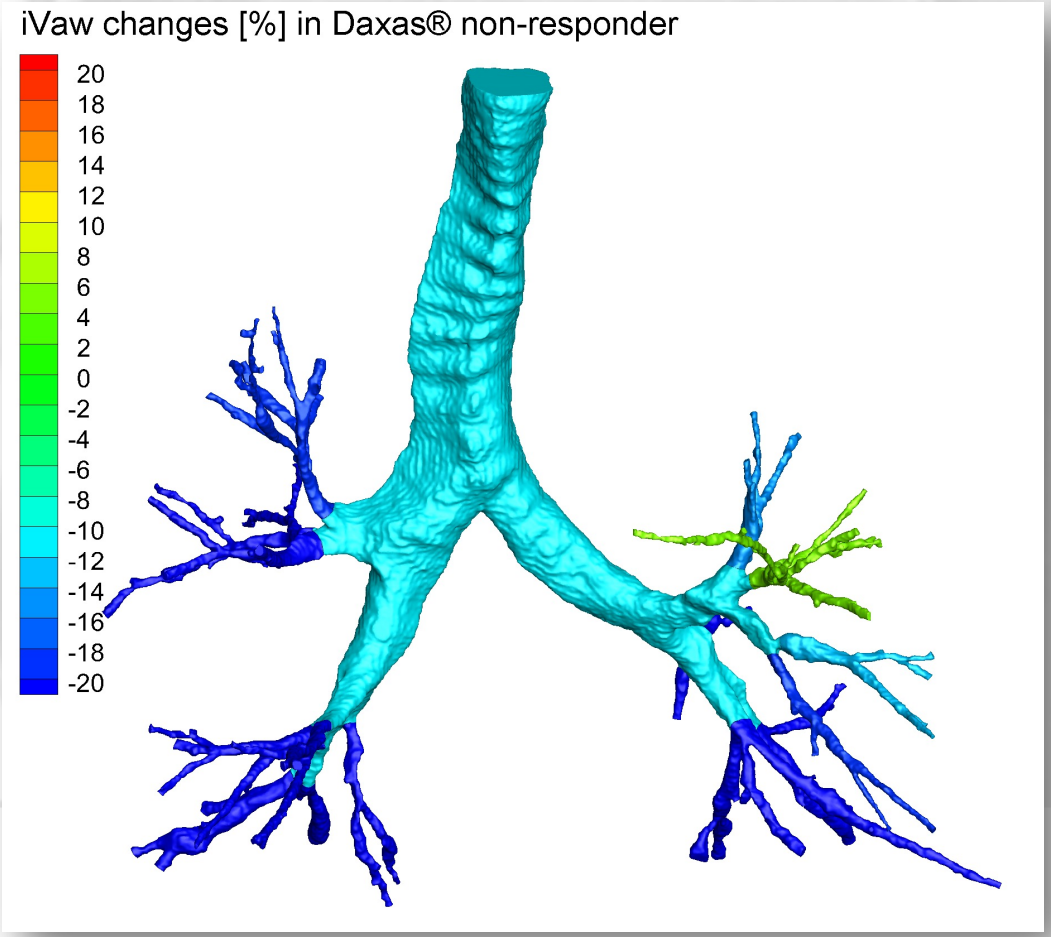
- Significant improvement in iVaw for the Daxas® responders



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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

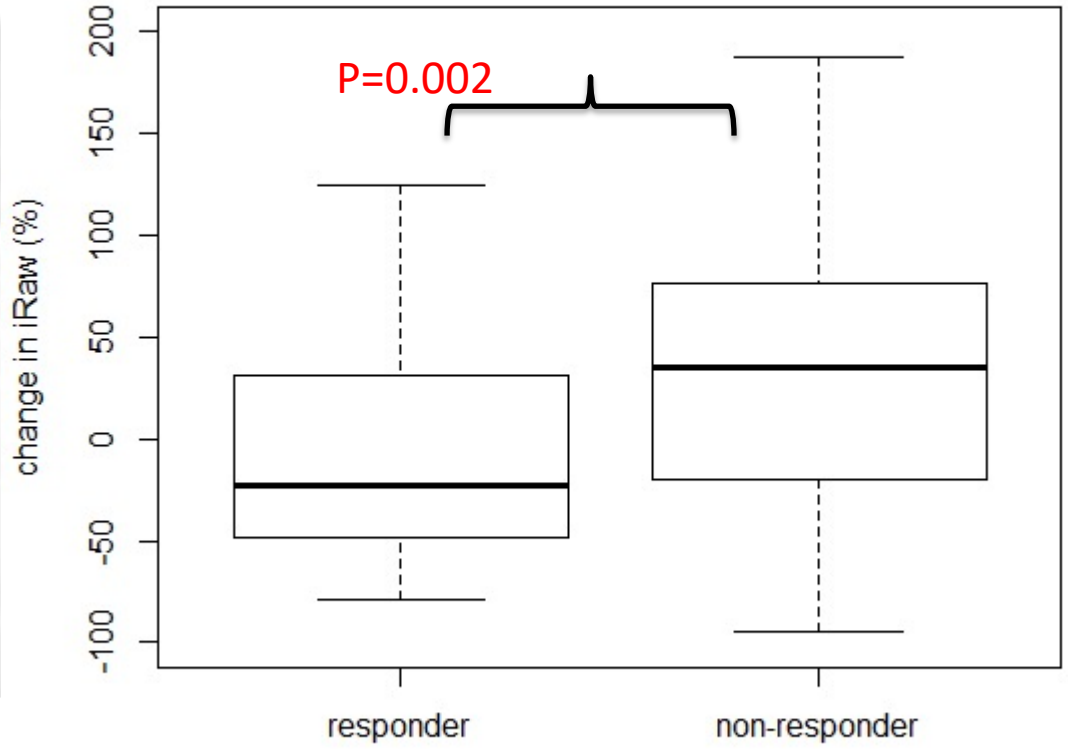
- No improvement in iVaw for the Daxas® non-responders



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DAXAS® RESPONDERS IN TERMS OF BRONCHODILATION

- Significant improvement in iRaw for the Daxas® responders (-30%)



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CONCLUSIONS

- Daxas improves the patient compared to placebo
- Daxas group has responders and non-responders
- Study provided hypothesis for the mode of action of response and for the phenotype of the responders
- Hypothesis were supported by the data (statistically significant)

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NEXT STEPS

Additional analyses using novel imaging endpoints on existing data:

- What is the relation between response and
  - Emphysema
  - Blood vessel density
  - Deposition

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NEXT STEPS

Clinical study with selection criteria

- What is the average clinical benefit (PFT, PRO, FRI) in patients pre-selected based on dynamic hyperinflation characteristics

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Roflumilast in asthma

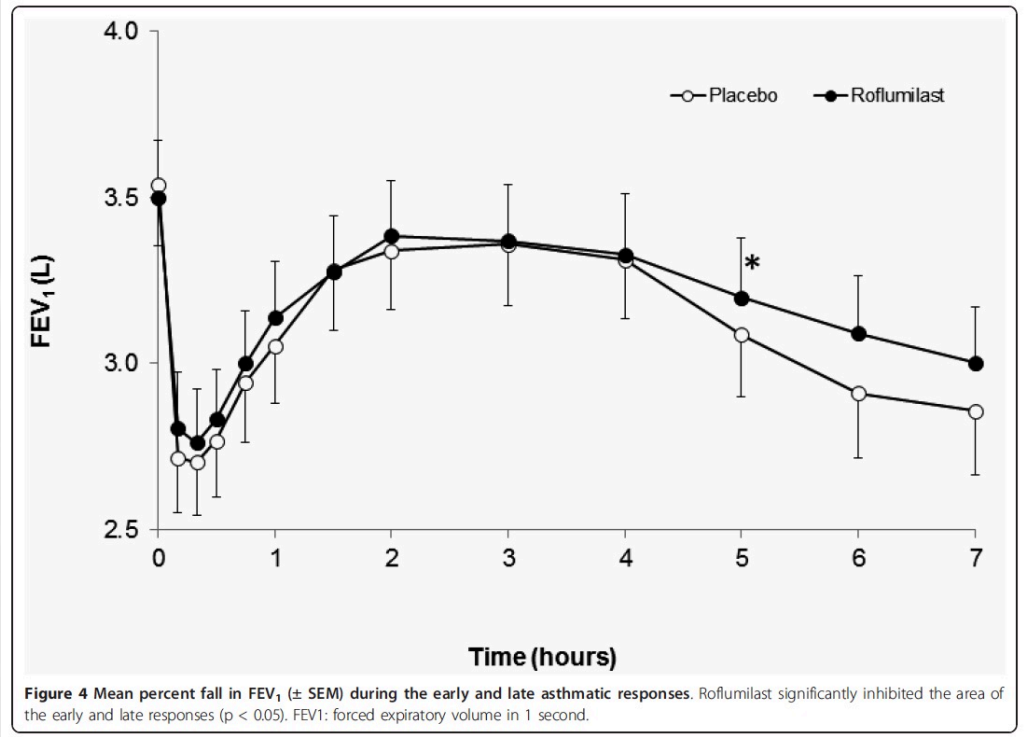


Figure 4 Mean percent fall in FEV_1 (± SEM) during the early and late asthmatic responses. Roflumilast significantly inhibited the area of the early and late responses ($p < 0.05$). FEV1: forced expiratory volume in 1 second.

Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects
Gauvreau et al. Respiratory Research 2011, 12:140

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NEXT STEPS

Roflumilast in asthma

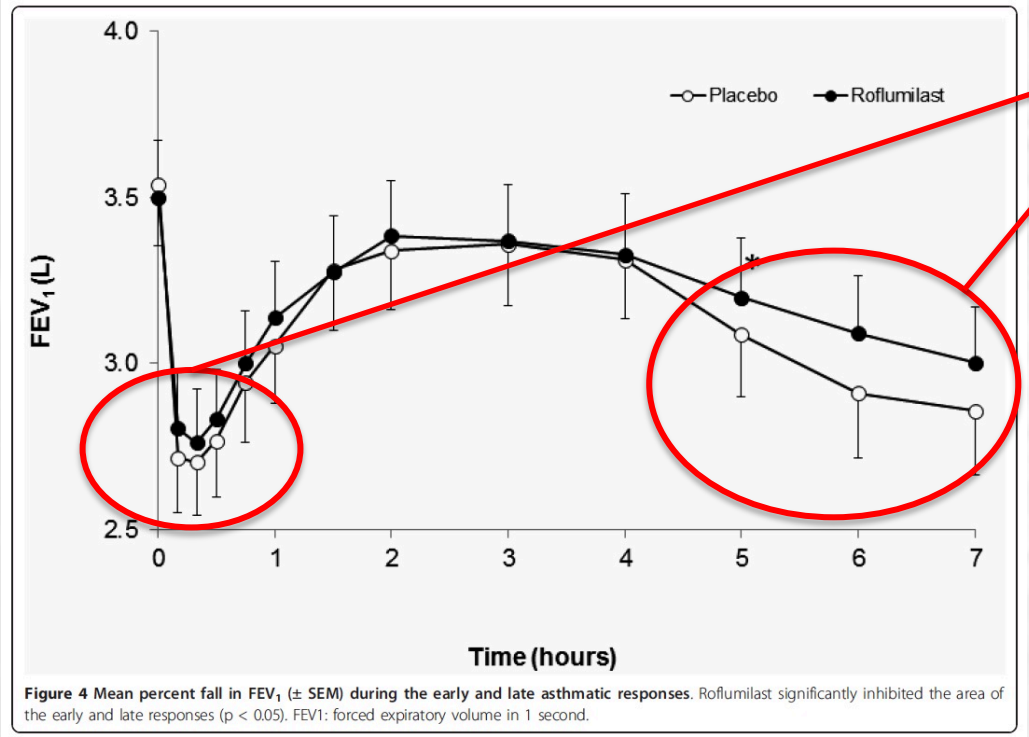


Figure 4 Mean percent fall in FEV_1 (± SEM) during the early and late asthmatic responses. Roflumilast significantly inhibited the area of the early and late responses ($p < 0.05$). FEV1: forced expiratory volume in 1 second.

- What is the mode of action in these regions?
- What is the responder phenotype?
- How does Roflumilast relate to ICS?

FRI can be used to answer these questions in small clinical trials

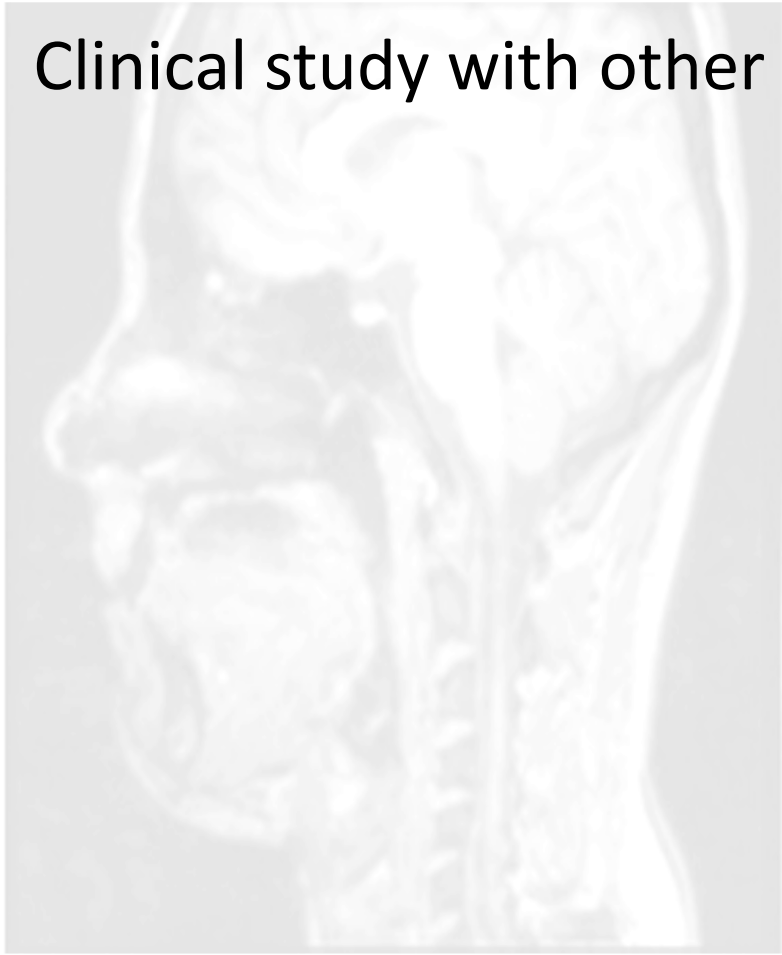
Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects
Gauvreau et al. Respiratory Research 2011, 12:140

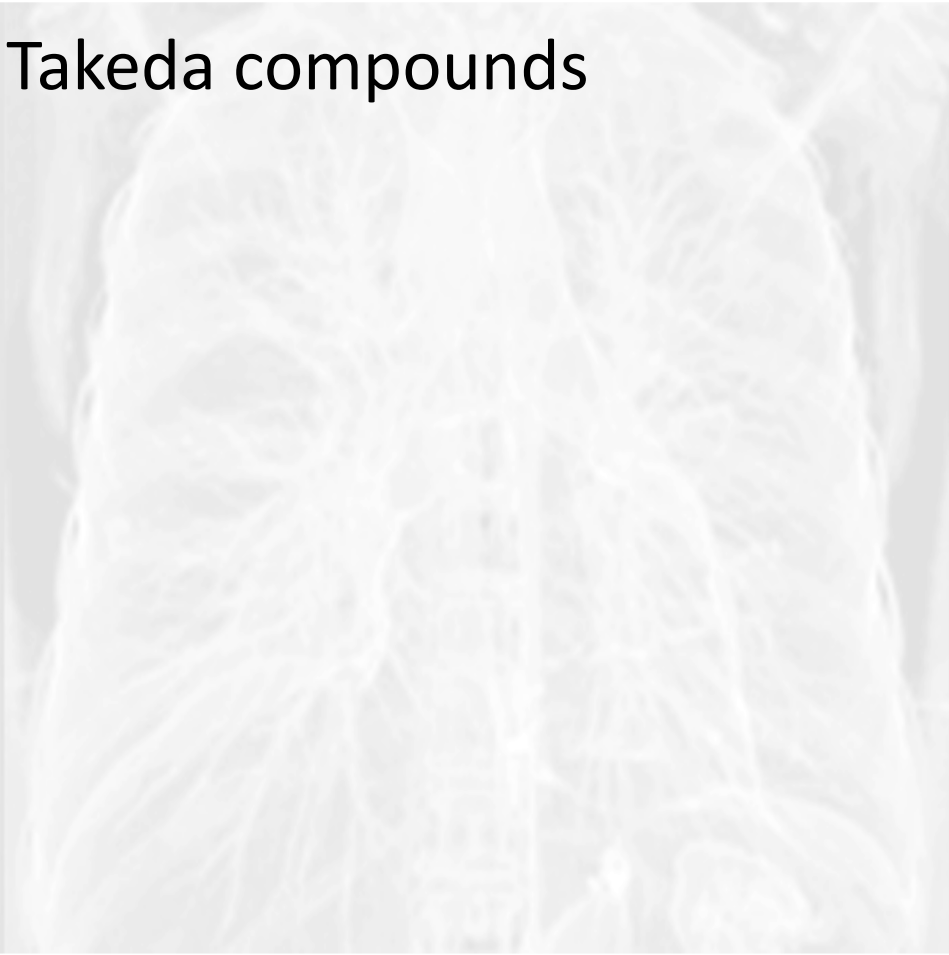
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NEXT STEPS

Clinical study with other Takeda compounds





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