FLUIDDA

PATIENT-SPECIFIC AEROSOL DEPOSITION ASSESSMENT

TECHNOLOGY & VALIDATION


IN-SILICO METHODS
& DIGITAL TWINS

IN-SILICO METHODS & DIGITAL TWINS FOR OINDP

FLUIDDA

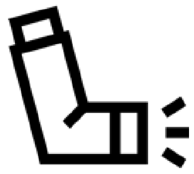
In order for in-silico models and digital twins to be dependable and accurate, they must effectively capture and replicate the essential parameters of the physical processes they are simulating.

Computational Fluid Dynamics (CFD) can simulate in-silico deposition in digital patients by solving the equations that describe flow behavior (Navier-Stokes equations)

The precision of Computational Fluid Dynamics (CFD) depends on the input parameters being as similar as possible to the actual clinical scenario.

KEY PARAMETERS FOR DEPOSITION OF OINPD

FLUIDDA



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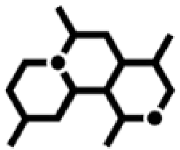
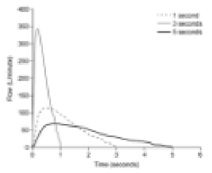


DRUG FORMULATION



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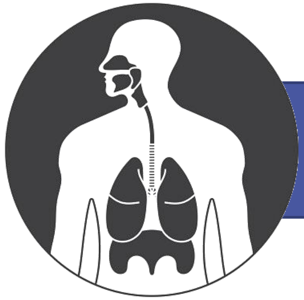
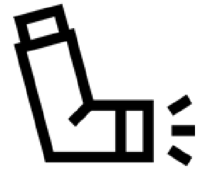


LUNG STRUCTURE & FUNCTION

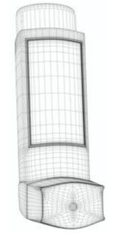
KEY PARAMETERS FOR DEPOSITION OF OINPD

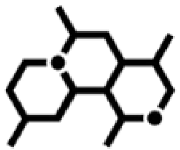
FLUIDDA



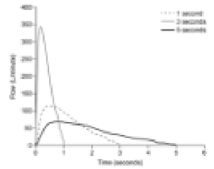
DEVICE

COMPUTER GEOMETRY DEVICE





DRUG FORMULATION



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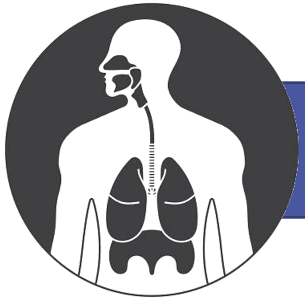


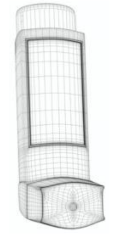
LUNG STRUCTURE & FUNCTION

KEY PARAMETERS FOR DEPOSITION OF OINPD

FLUIDDA

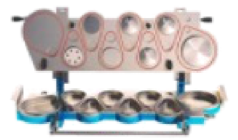
DEVICE

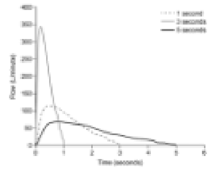
COMPUTER GEOMETRY DEVICE



DRUG FORMULATION

IN-VITRO CHARACTERIZATION





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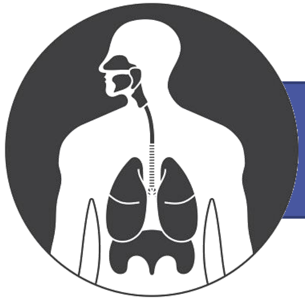


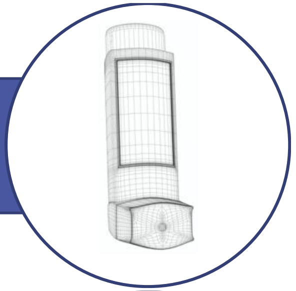
LUNG STRUCTURE & FUNCTION

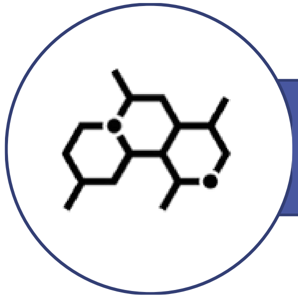
KEY PARAMETERS FOR DEPOSITION OF OINPD

FLUIDDA

DEVICE

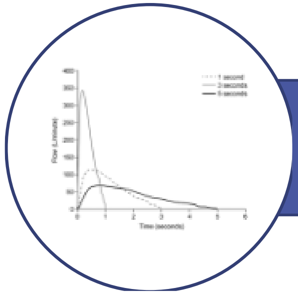
COMPUTER GEOMETRY DEVICE





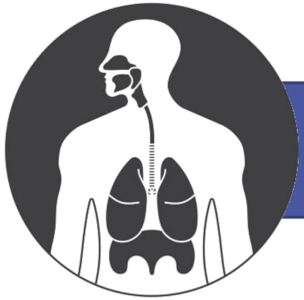
DRUG FORMULATION

IN-VITRO CHARACTERIZATION



INHALATION PROFILE

IN-VIVO MEASUREMENT



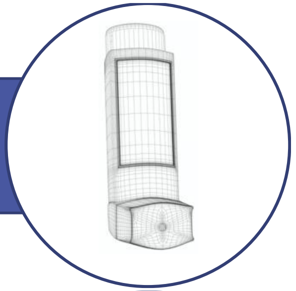
LUNG STRUCTURE & FUNCTION

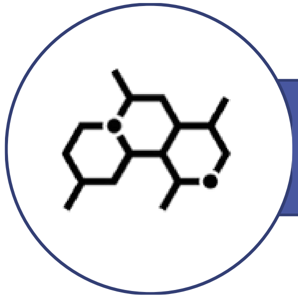
KEY PARAMETERS FOR DEPOSITION OF OINPD

FLUIDDA

DEVICE

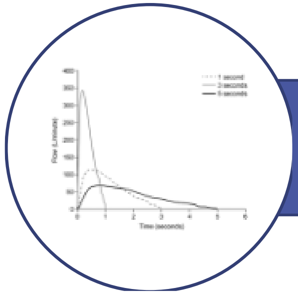
COMPUTER GEOMETRY DEVICE





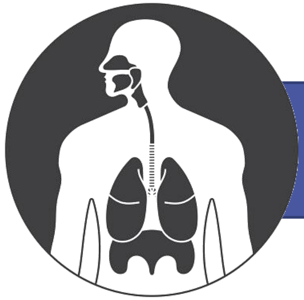
DRUG FORMULATION

IN-VITRO CHARACTERIZATION



INHALATION PROFILE

IN-VIVO MEASUREMENT



LUNG STRUCTURE & FUNCTION

FUNCTIONAL RESPIRATORY IMAGING

FUNCTIONAL RESPIRATORY IMAGING

1. CT SCAN

2. VISUAL READ

CONVENTIONAL CT ANALYSES

FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

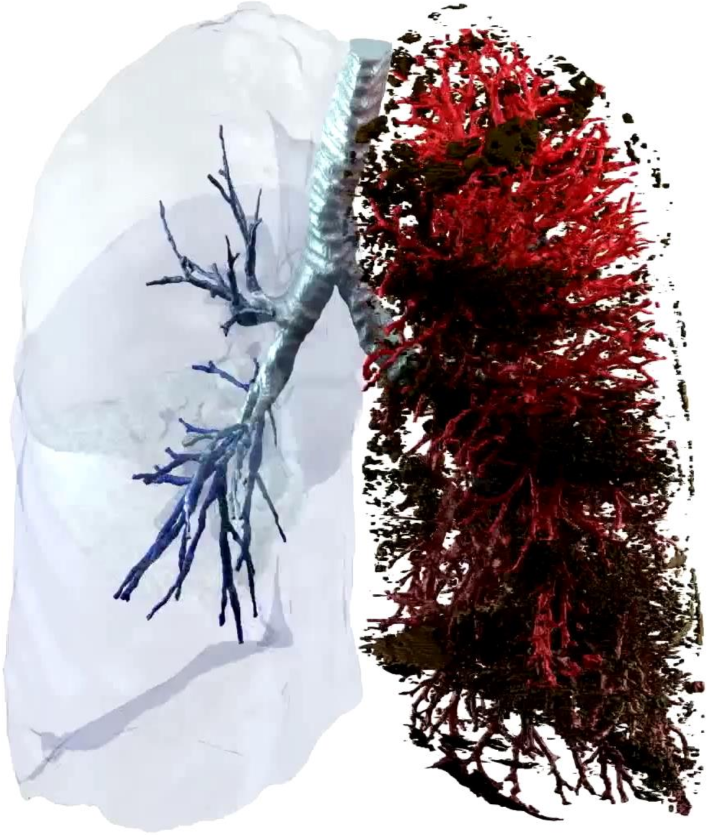
1. CT SCAN

2. CLOUD UPLOAD

3. REPORTS

20min

FUNCTIONAL RESPIRATORY IMAGING (FRI)



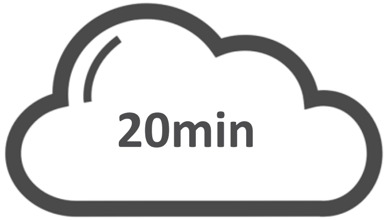
FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

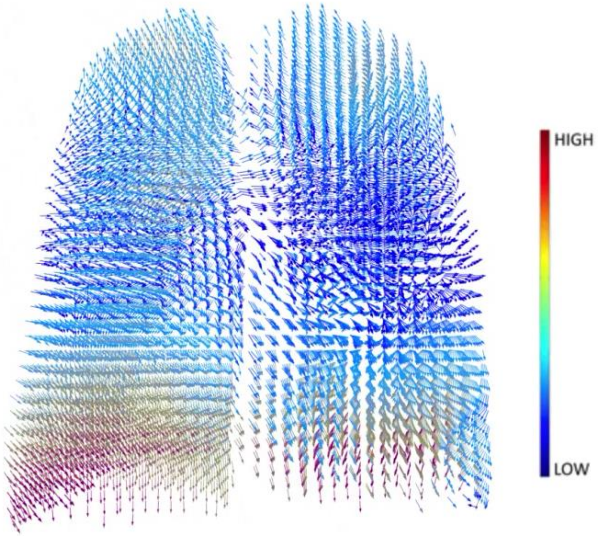
1. CT SCAN

2. CLOUD UPLOAD

3. REPORTS

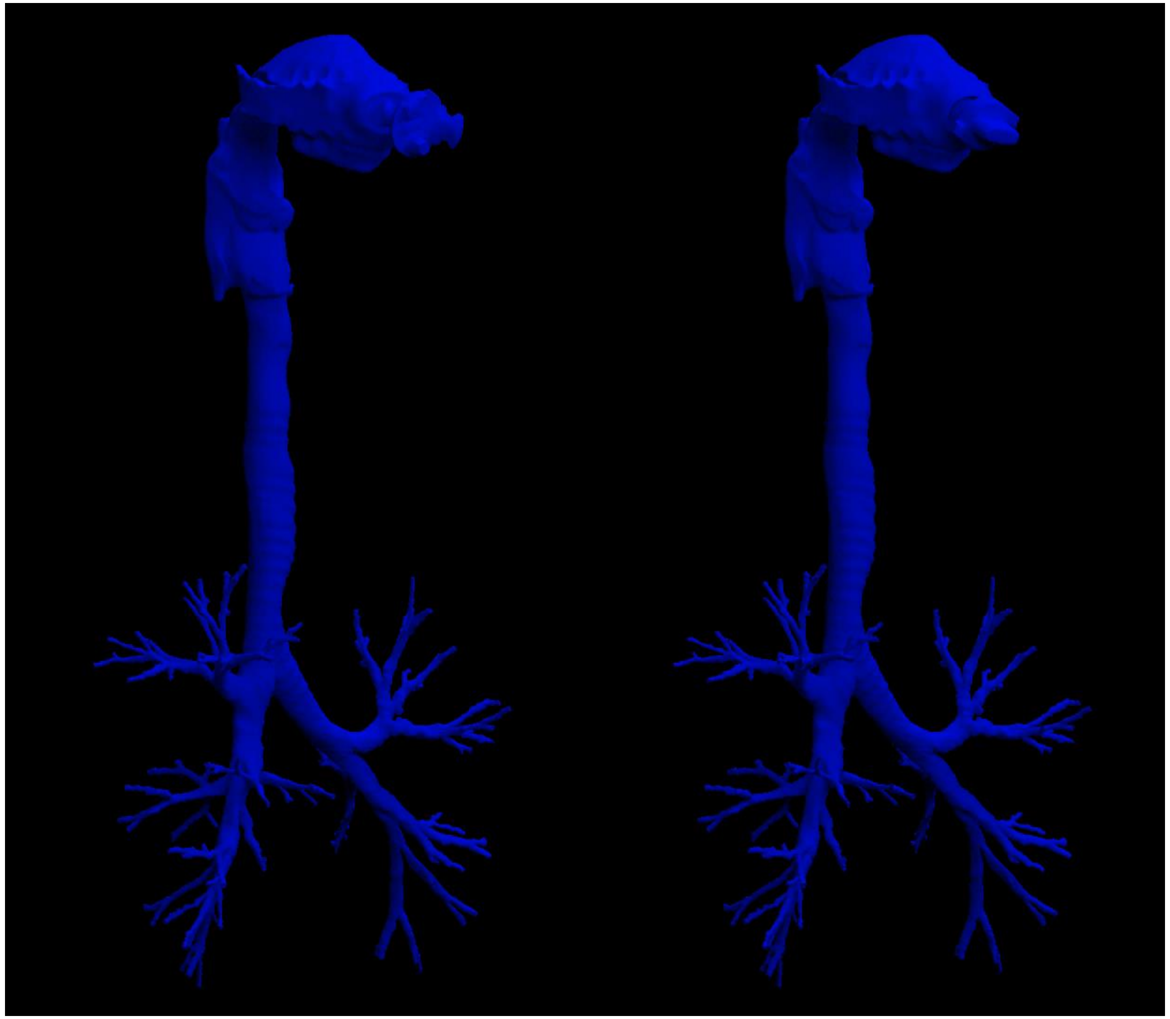


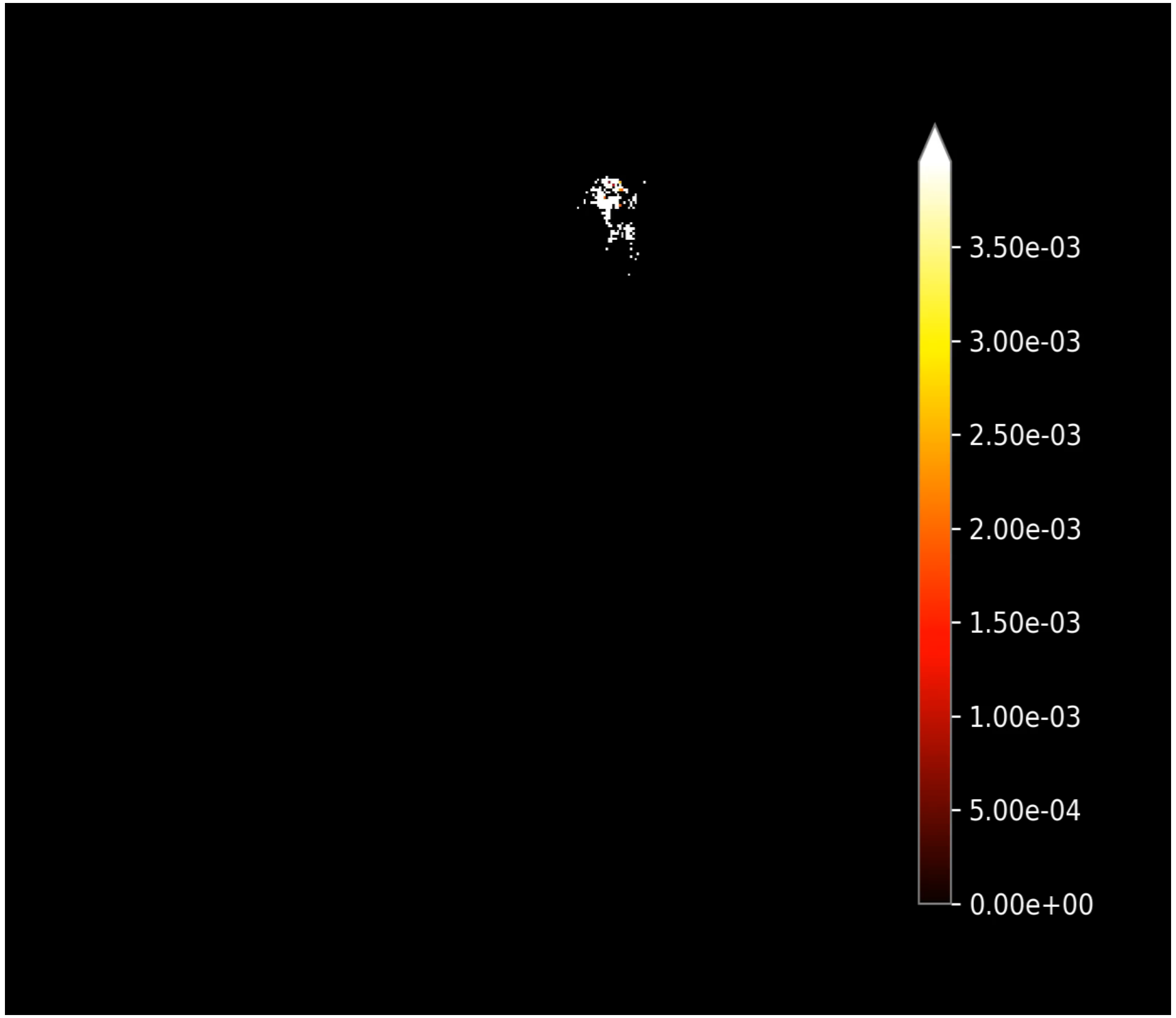
FUNCTIONAL RESPIRATORY IMAGING (FRI)



AEROSOL DEPOSITION

FRI yields drug deposition without the need for radiolabeling





COMPARISON FRI VS SCINTIGRAPHY

FLUIDDA

Product	FRI [%Lung Dose]	Scintigraphy [%Lung Dose]
Foster® in COPD	28 [1]	31-34 [2,3]
Flutiform® in Asthma	42 [4]	41 [5]
Symbicort® in Asthma	23 [4]	22 [6]
Qvar® in Asthma	54 [*]	53 [7]
I-neb® nebulization	45 [8]	42 [9]
eFlow® nebulization	18 [8]	17 [10]
LC Sprint® nebulization	9 [11]	10-15 [12]
AKITA® nebulization	34 [11]	31 [12,13]

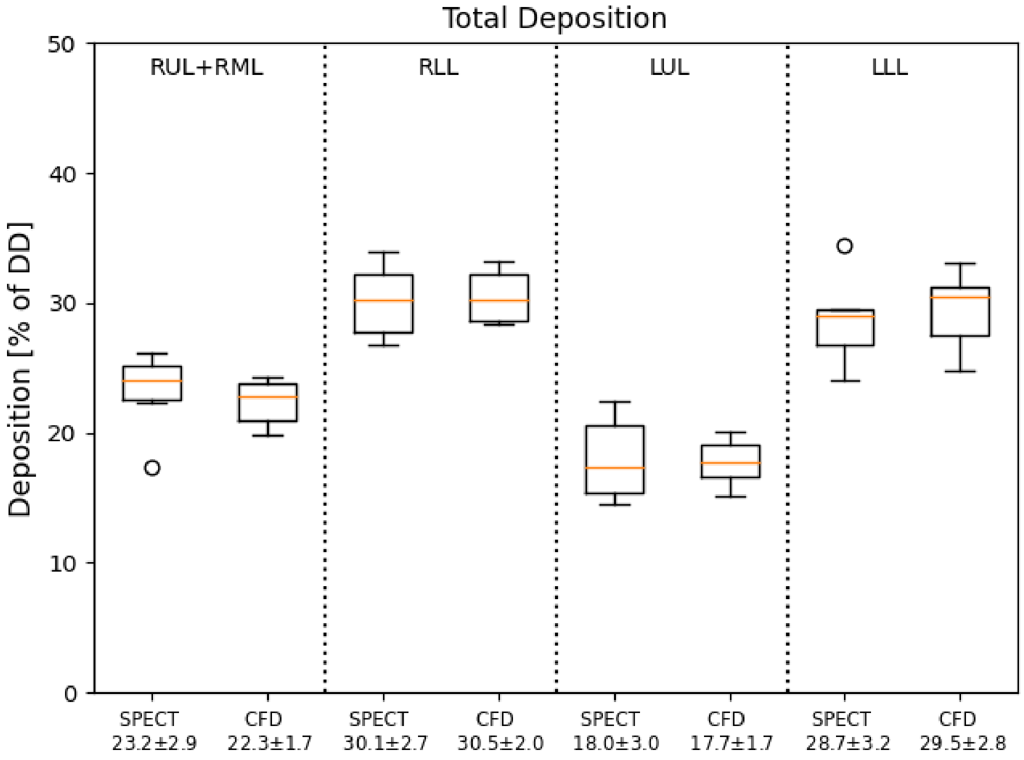
1. Usmani O et al. Proc 28th Int Congr Eur Respir Soc. 2018 Sep.
2. De Maria R et al. Comb Prod Ther. 2014 Feb 1;4.
3. De Backer W et al. J Aerosol Med Pulm Drug Deliv. 2010 Jun;23(3):137–48.
4. Iwanaga T et al. Pulm Ther. 2017;3(1):219–231.
5. Kappeler D et al. Eur Respiratory Soc; 2017.
6. Hirst PH et al. Respir Med. 2001;95(9):720–727.
7. Leach CL et al. J Aerosol Med Pulm Drug Deliv. 2016;29(2):127–133.
8. Hull D et al. J Cyst Fibros. 2018 Jun 1;17:S26.
9. Nikander K et al. J Aerosol Med Pulm Drug Deliv. 2010;23(S1):S–37.
10. Lenney W et al. J Cyst Fibros. 2011;10(1):9–14.
11. Munro S et al. Drug Deliv Lungs. 2017;
12. Fischer A et al. Eur J Med Res. 2009;14(4):71.
13. Müllinger B et al. J Cyst Fibros. 2005 Jan 1;4:S53.

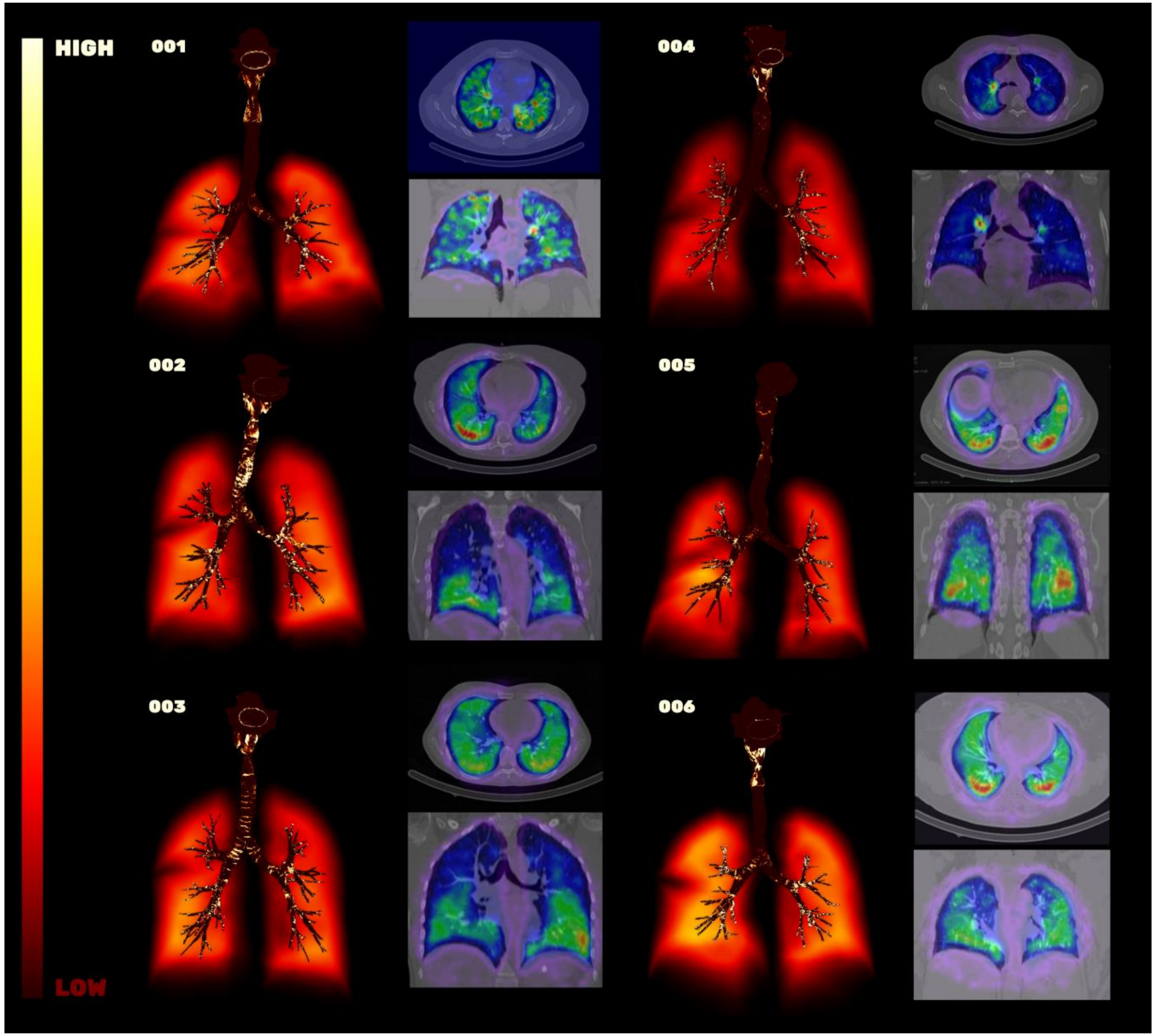
*. Data on file

COMPARISON FRI VS SPECT

FLUIDDA

- 6 patients (3F/3M) with mild asthma
- Average age = 46 years ± 17

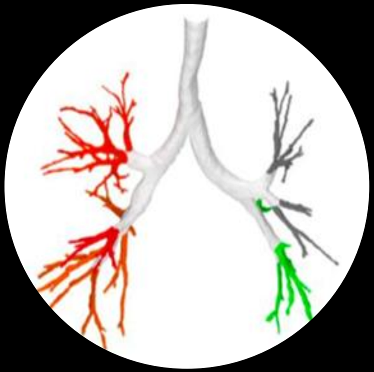




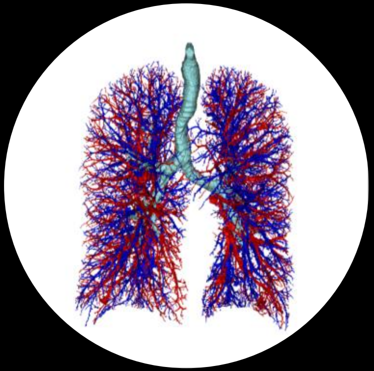
De Backer et al. Radiology 2010

FRI PROVIDES COMPREHENSIVE SET OF QUANTITATIVE OUTCOME PARAMETERS

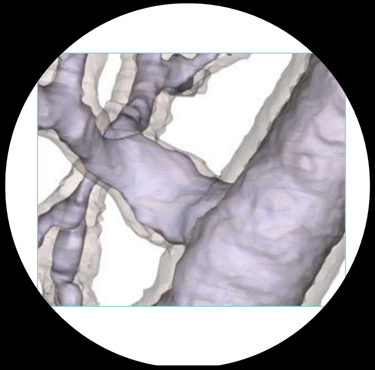
Lung Volumes



Airway Volumes



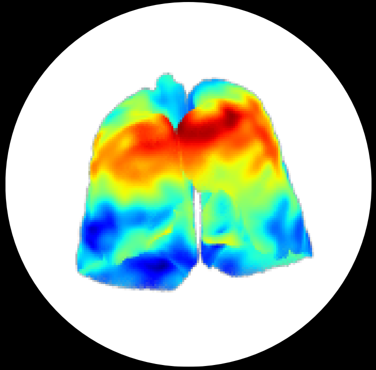
Arteries/Veins Volumes



Airway Wall Volumes

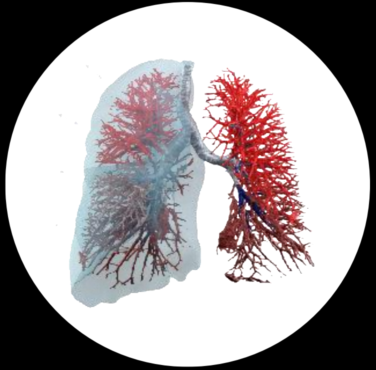
Nodules

Emphysema

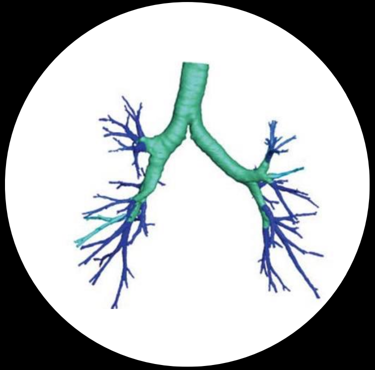


Ventilation

Air Trapping

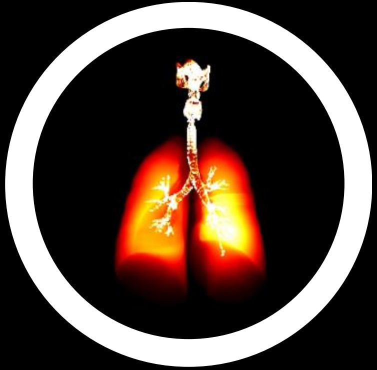


Ventilation/ Perfusion



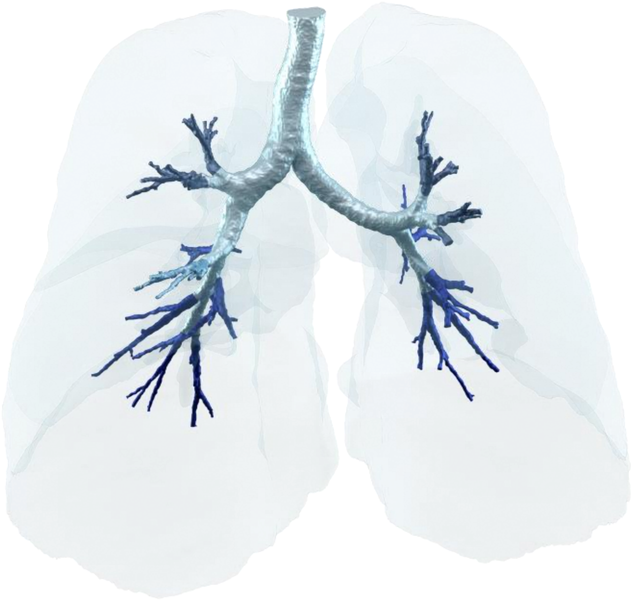
Airway Resistance

Fibrosis

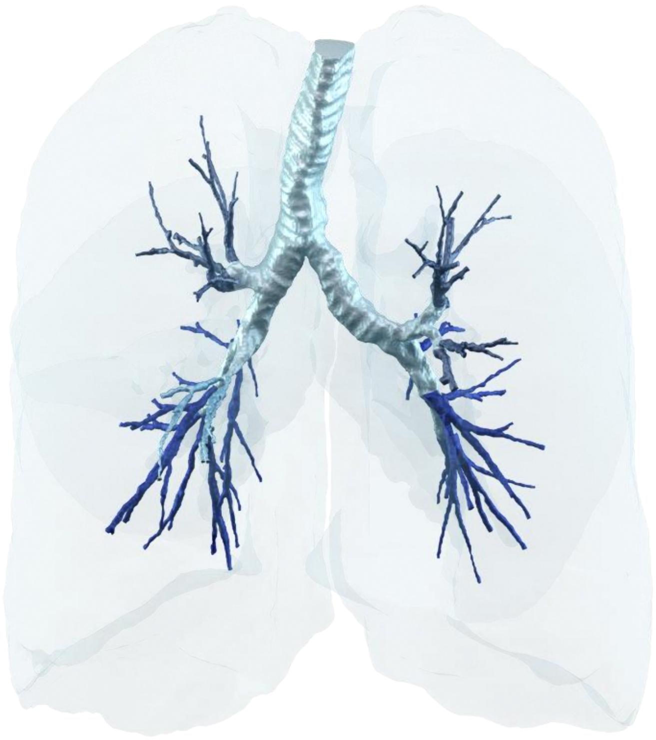


Aerosol Deposition

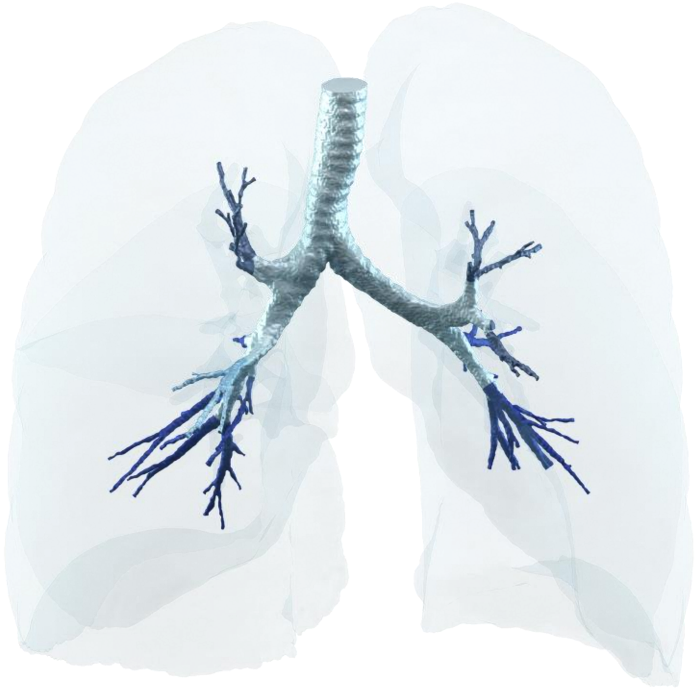
IMPORTANCE OF CAPTURING DISEASED AIRWAYS



Healthy
FEV1 = 108%p



COPD
FEV1 = 52%p



asthma
FEV1 = 72%p

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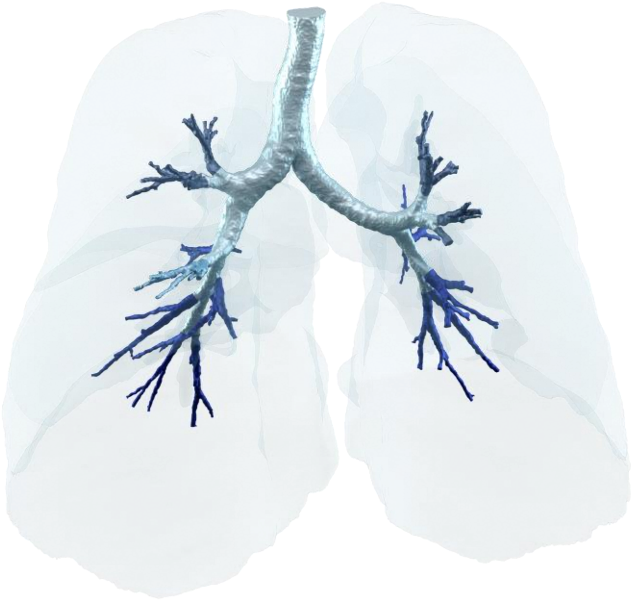
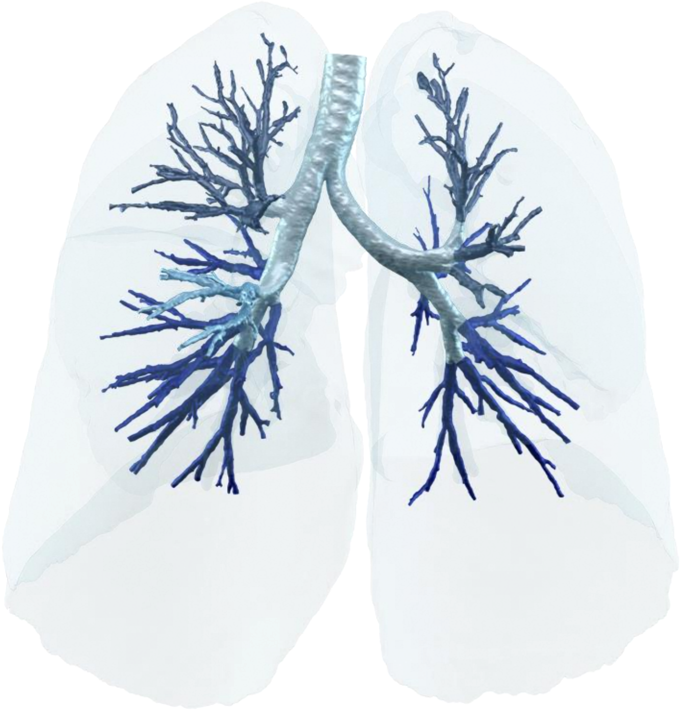
IMPORTANCE OF CAPTURING DISEASED AIRWAYS

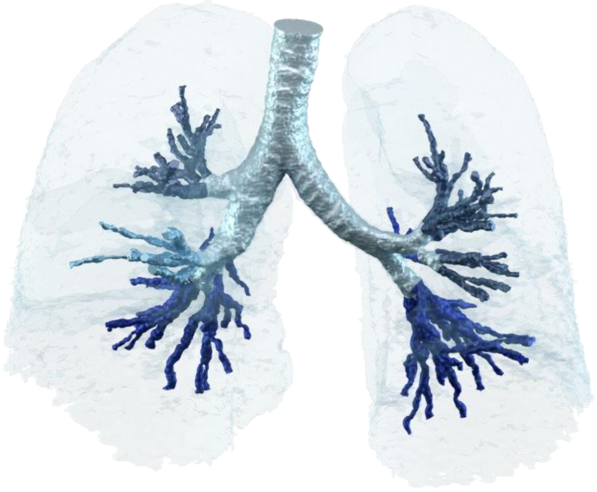
FLUIDDA



Healthy
FEV1 = 108%p



Cystic Fibrosis (CF)
FEV1 = 57%p



Idiopathic Pulmonary Fibrosis (IPF)
FVC = 42%p

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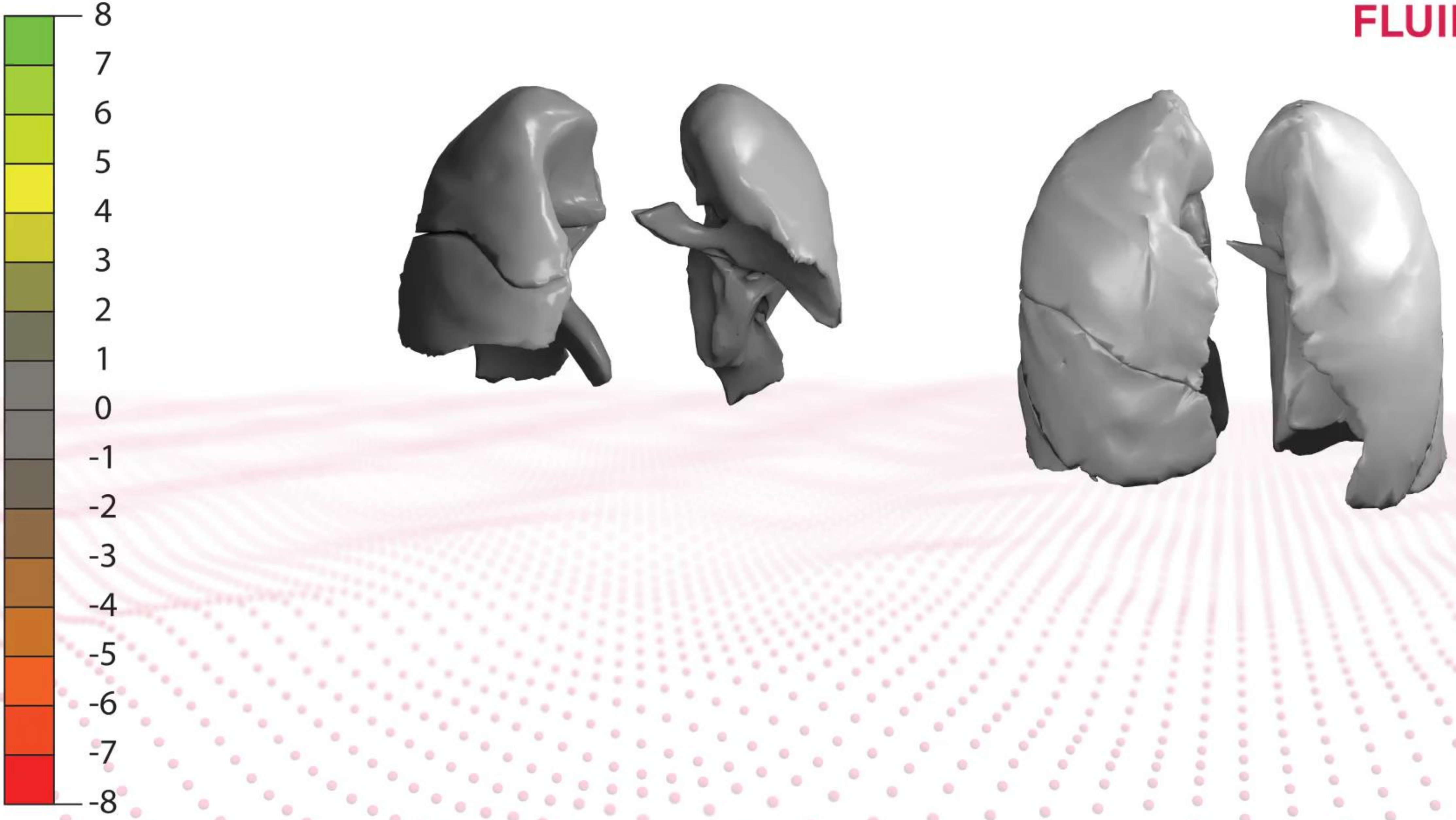
Difference in Lobar Ventilation between IPF and Healthy



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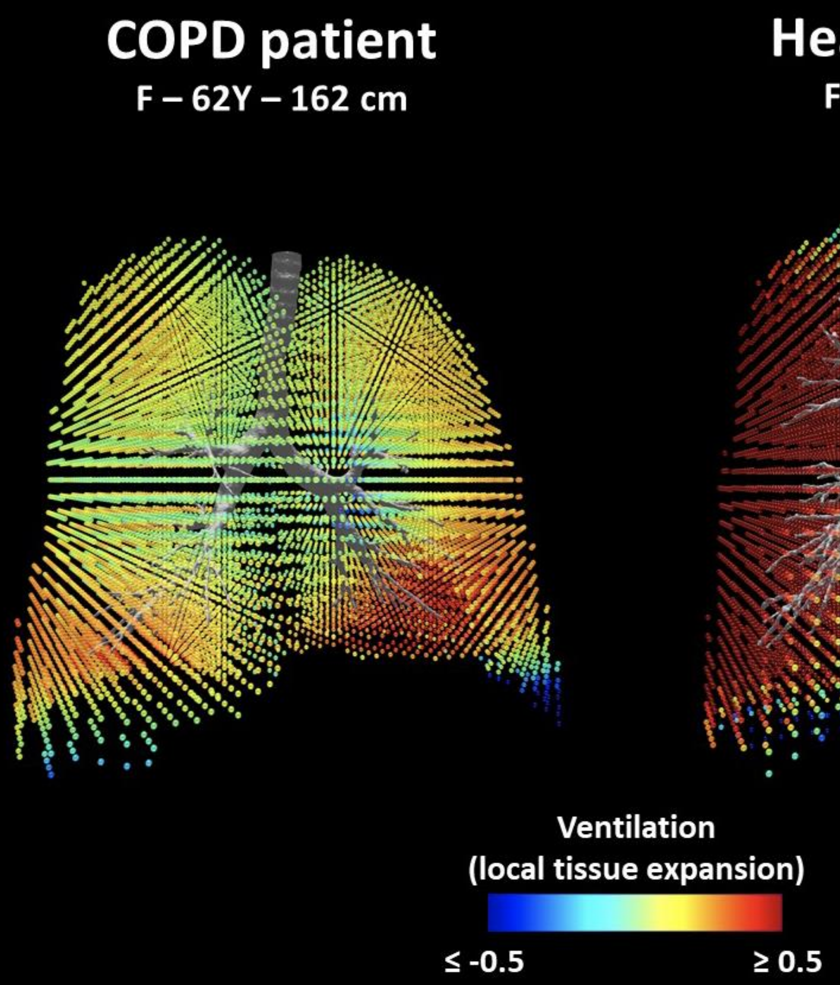
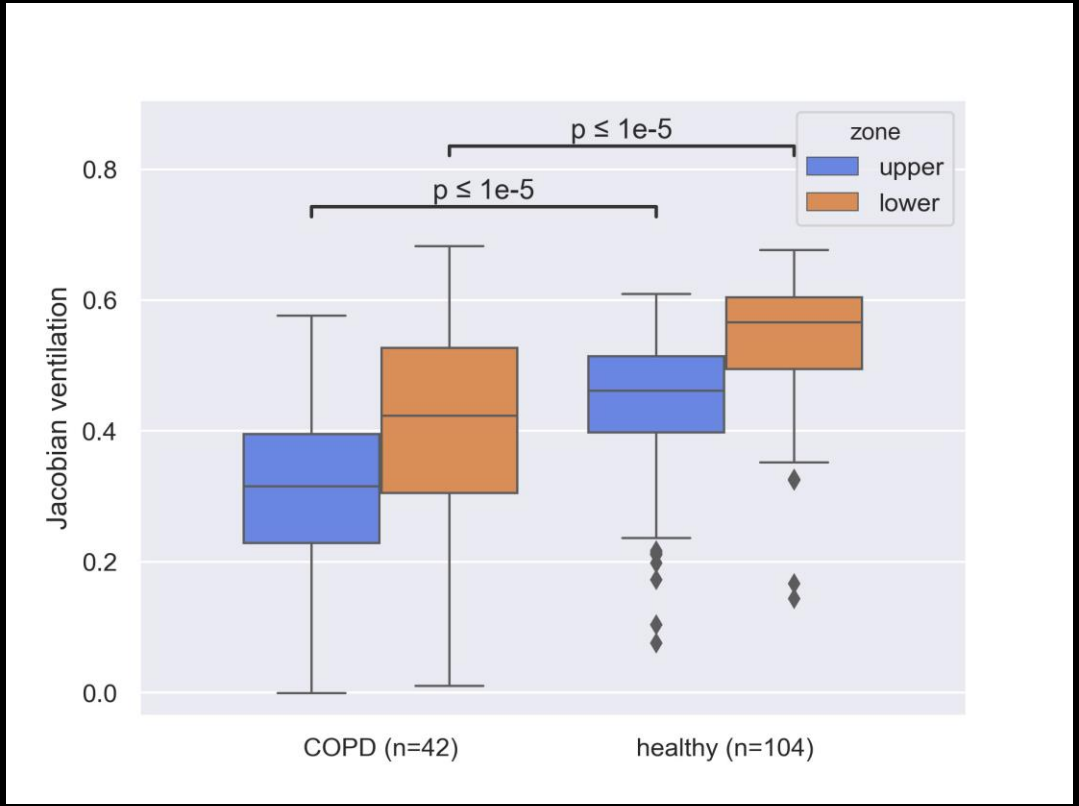
VENTILATION DEFECTS IN COPD





Bonte et al. ATS 2021

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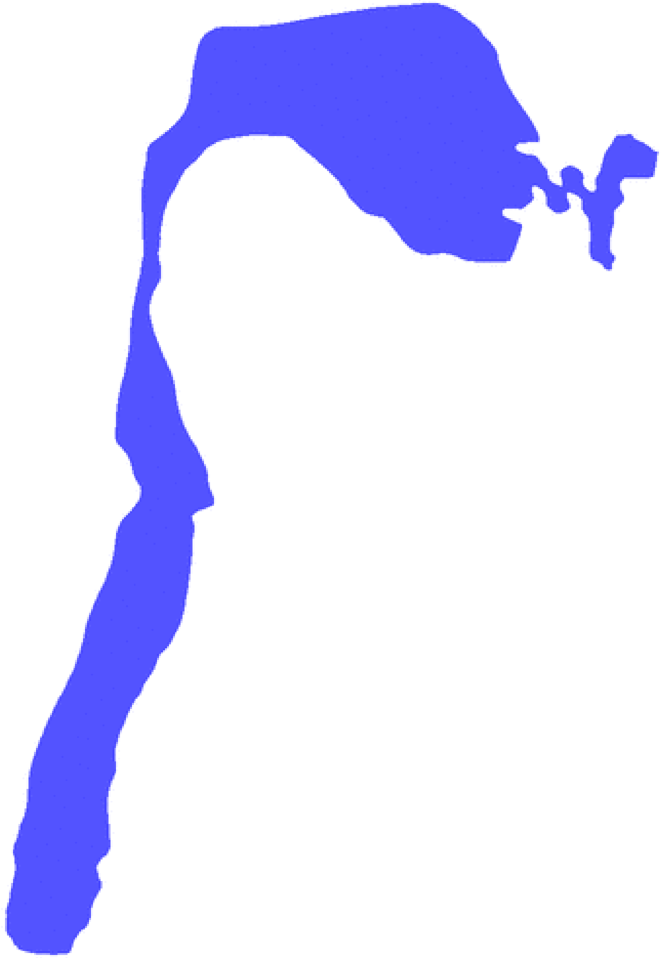
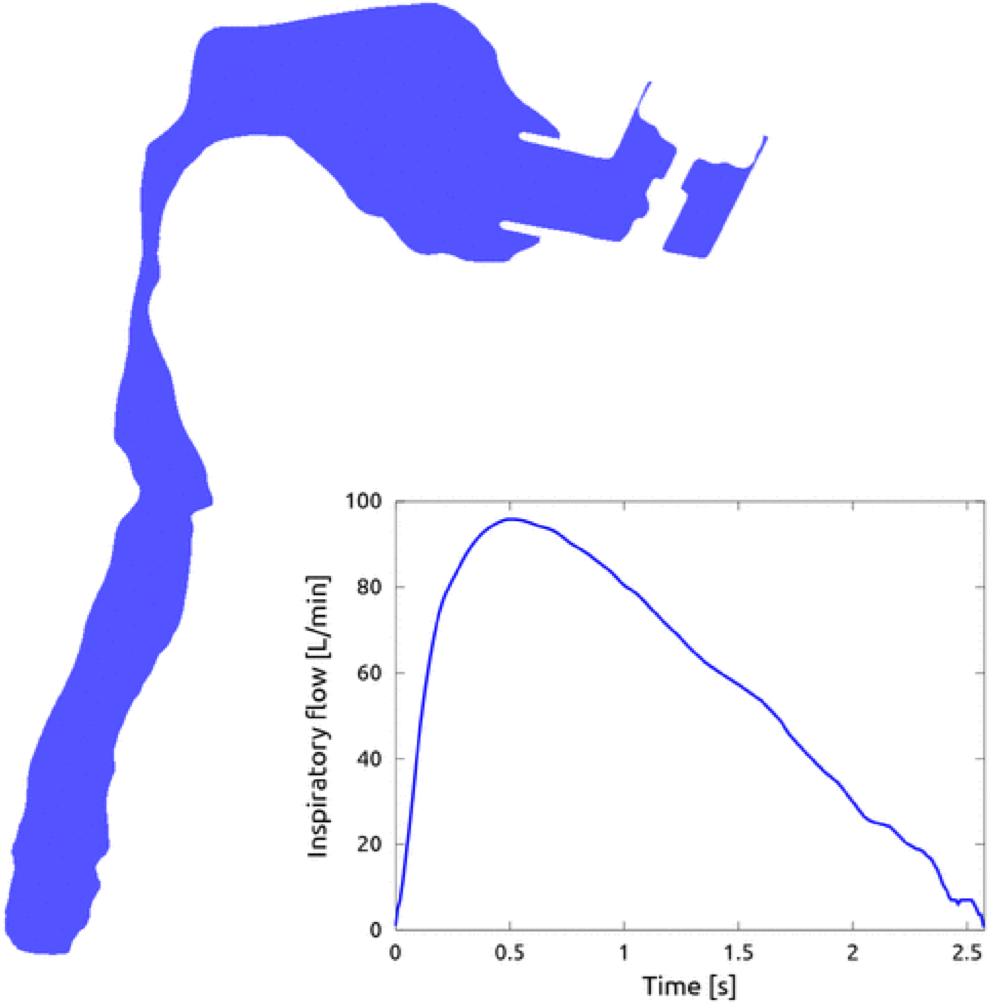
IMPORTANCE OF INCLUDING THE DEVICE

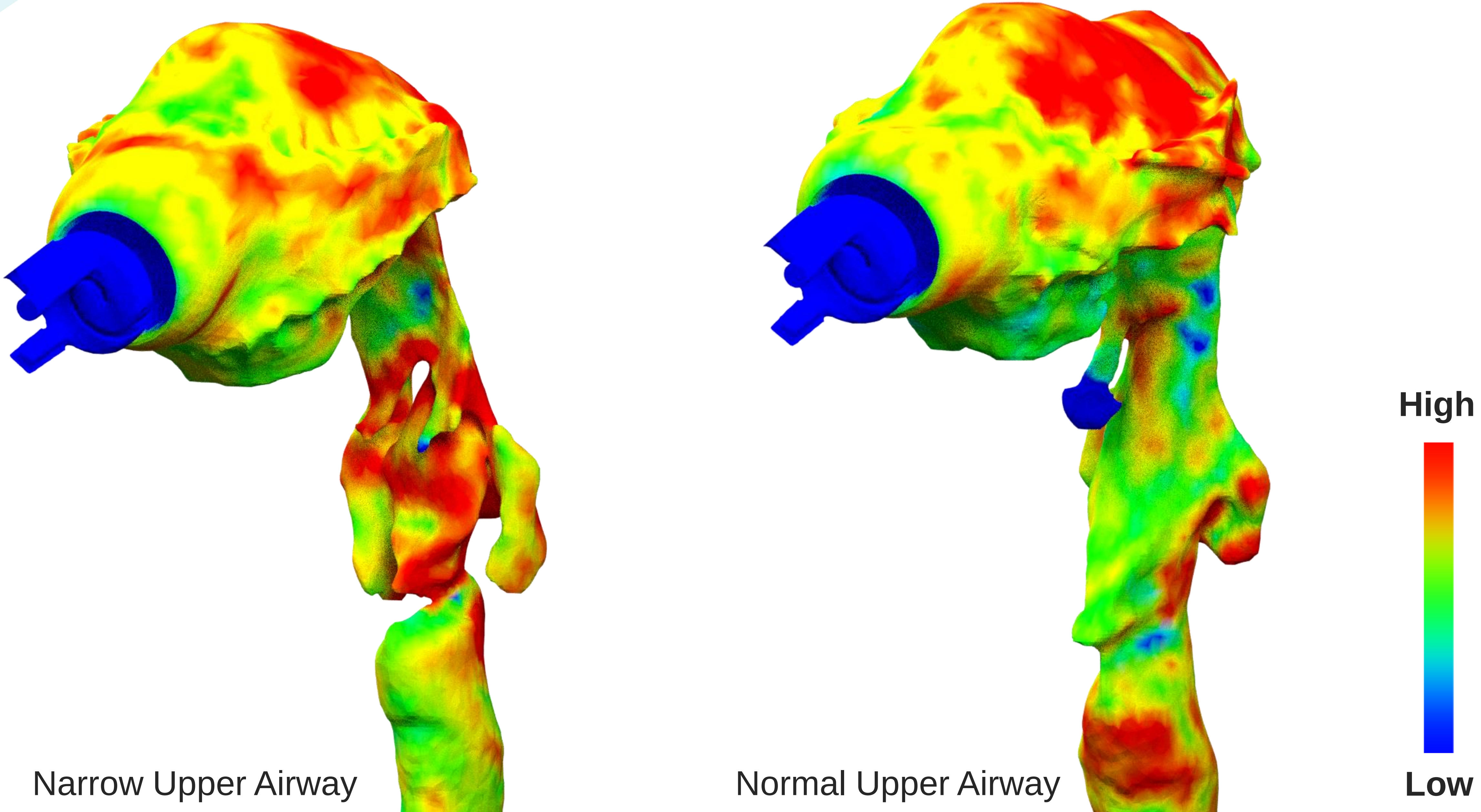
FLUIDDA





IMPORTANCE OF UPPER AIRWAYS

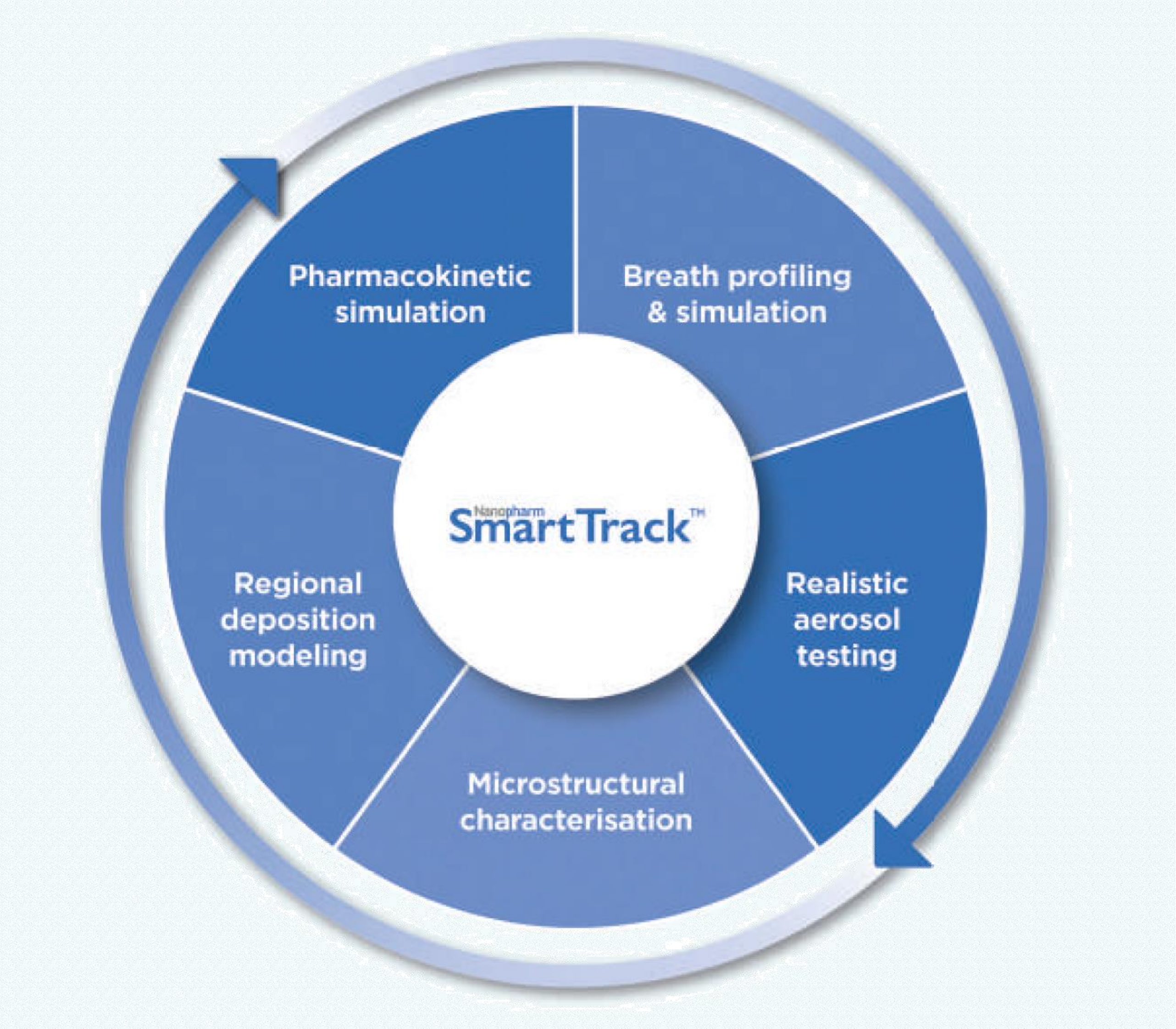
FLUIDDA



Narrow Upper Airway

Normal Upper Airway

BRINGING IT ALL TOGETHER



EXAMPLE: DEPOSITION OF TRIMBOW AND TRELEGY

FLUIDDA

Nanopharm
an Aptar pharma company

TRIMBOW pMDI
(BDP/FF/GB)

TRELEGY DPI
(FluF/VI/UMEC)

Usmani et al. International Journal of Chronic Obstructive Pulmonary Disease 2020:15

TRIMBOW VS TRELEGY

FLUIDDA

Study design

- HRCT scans of 20 COPD patients
- Post bronchodilator FEV1 range: 19.3%p – 66.0%p

Flow rate (based on recommendations for use):

- for pMDI: 16 to 68 l/min
- for DPI: 30 to 90 l/min

Table 1 Characteristics of Patients Providing HRCT Scan Data

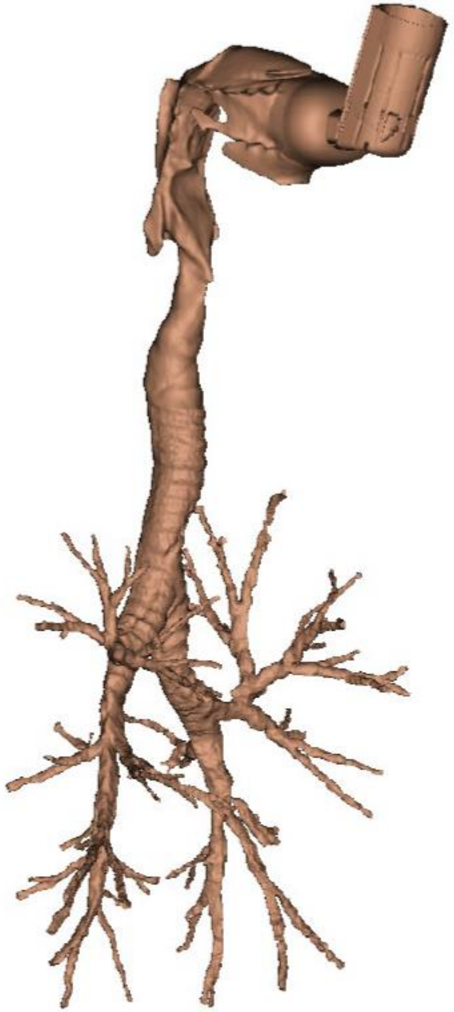
Parameter	**Patients (N=20)**
Male, n (%)	15 (75.0)
Age, years	64.0±7.68 (44–77)
Height, cm	168.9±8.40 (158–188)
Smoking history, pack-years	51.3±29.5 (25–110)
Post-bronchodilator FEV_1 predicted	42.3±14.8 (19.3–66.0)
50–80%, n (%)	7 (35.0)
30–50%, n (%)	8 (40.0)
<30%, n (%)	5 (25.0)
Post-bronchodilator FEV_1 to FVC ratio	0.41±0.14 (0.17–0.62)

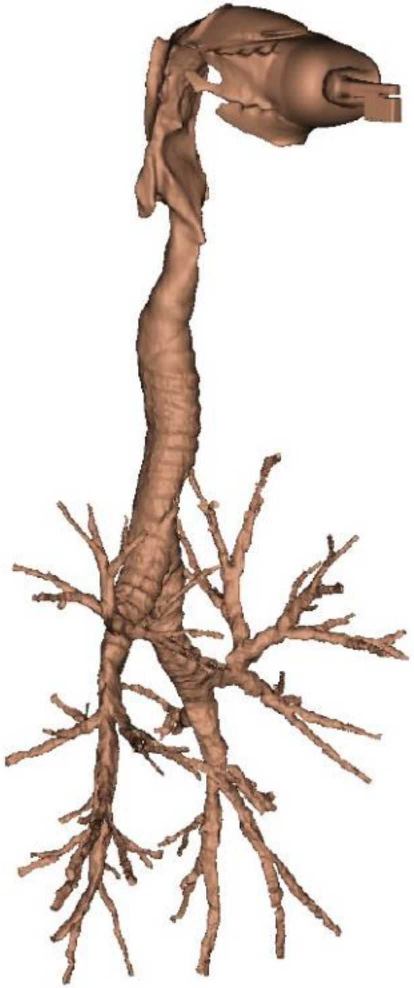
Note: Data are mean±SD (range) unless specified otherwise.
Abbreviations: FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Usmani et al. International Journal of Chronic Obstructive Pulmonary Disease 2020:15

TRIMBOW VS TRELEGY

Device coupling





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TRIMBOW VS TRELEGY

FLUIDDA

Aerosol Particle Size Distributions

Flow rate	40 L/min			60 L/min			93 L/min		
API	BDP	For	GB	BDP	For	GB	BDP	For	GB
MMAD [µm]	1.9	1.9	2.4	1.8	1.8	2.3	1.7	1.8	2.2
GSD	2.0	1.7	1.9	2.0	1.8	1.9	2.0	1.8	2.0
DD [µg]	174.10	10.28	21.37	172.70	10.18	21.05	173.82	10.40	21.97
FPF [%]	36.21	38.77	33.84	40.46	43.54	36.68	47.15	50.02	39.36

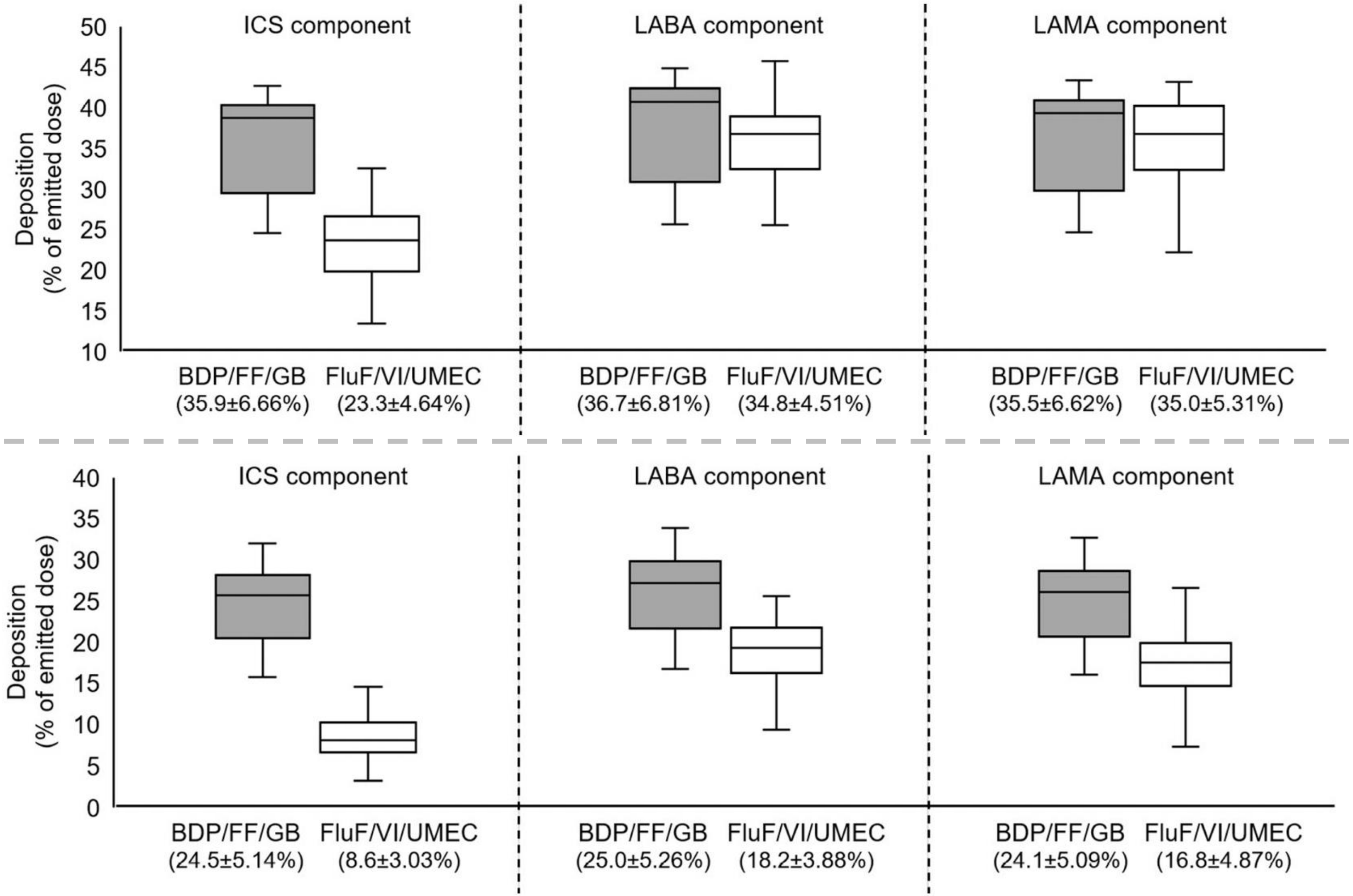
Flow rate	40 L/min			60 L/min			74 L/min		
API	FF	Vil	Ume	FF	Vil	Ume	FF	Vil	Ume
MMAD [µm]	4.4	2.2	3.0	4.2	2.1	2.9	4.0	1.9	2.7
GSD	2.0	2.2	2.0	2.2	2.3	2.1	2.2	2.1	2.0
DD [µg]	96.19	20.47	51.71	99.54	22.40	56.34	103.17	20.70	54.25
FPF [%]	24.36	42.60	46.67	27.10	45.50	48.55	31.77	50.07	47.53

TRIMBOW VS TRELEGY

FLUIDDA

intrathoracic deposition

peripheral deposition



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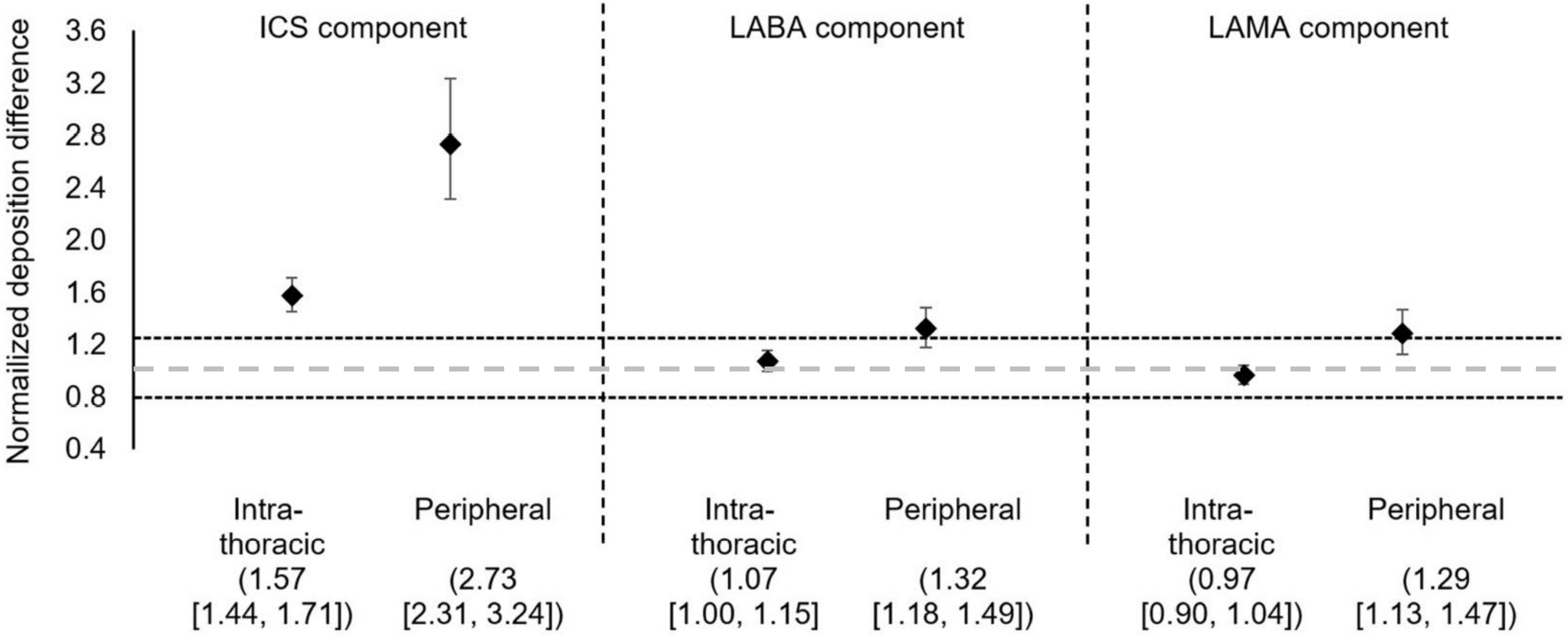
TRIMBOW VS TRELEGY



favors Trimbow

favors Trelegy

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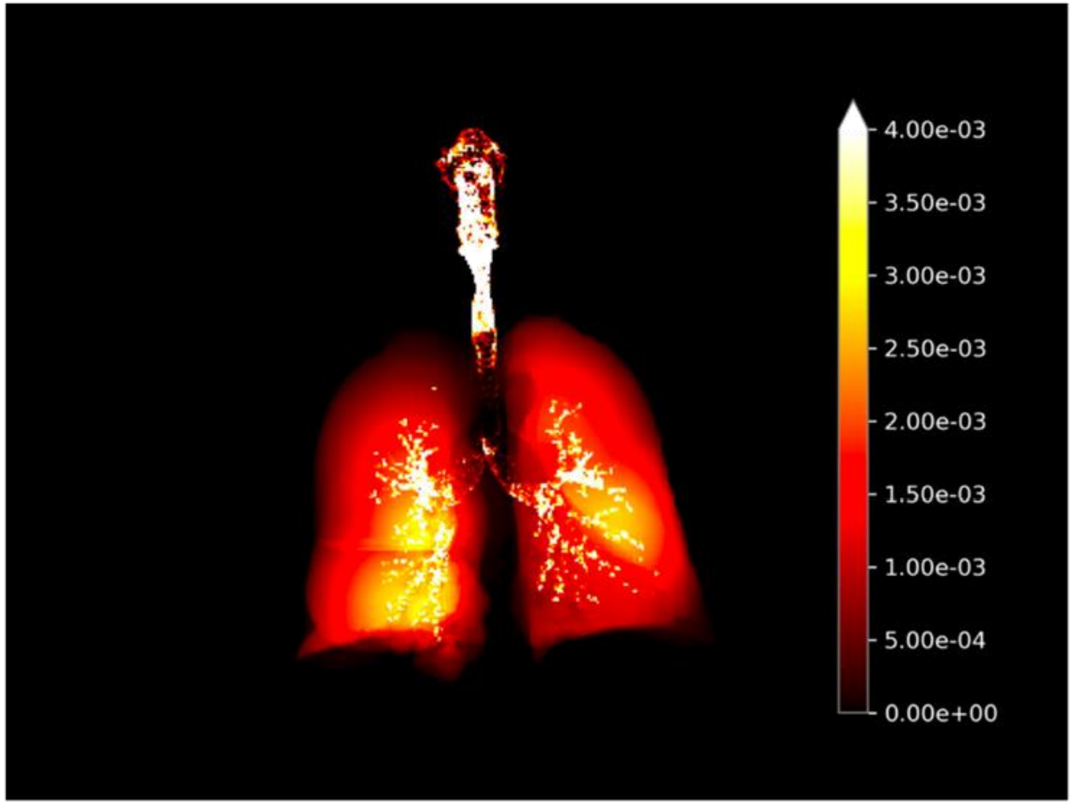
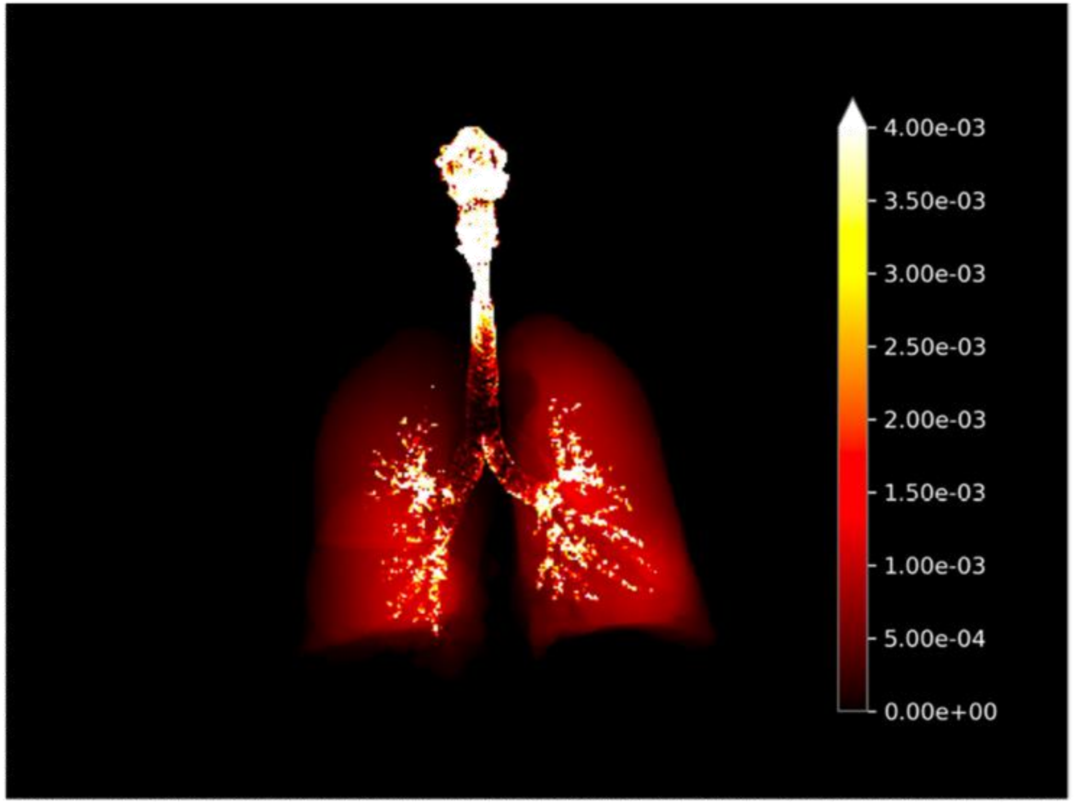
TRIMBOW VS TRELEGY

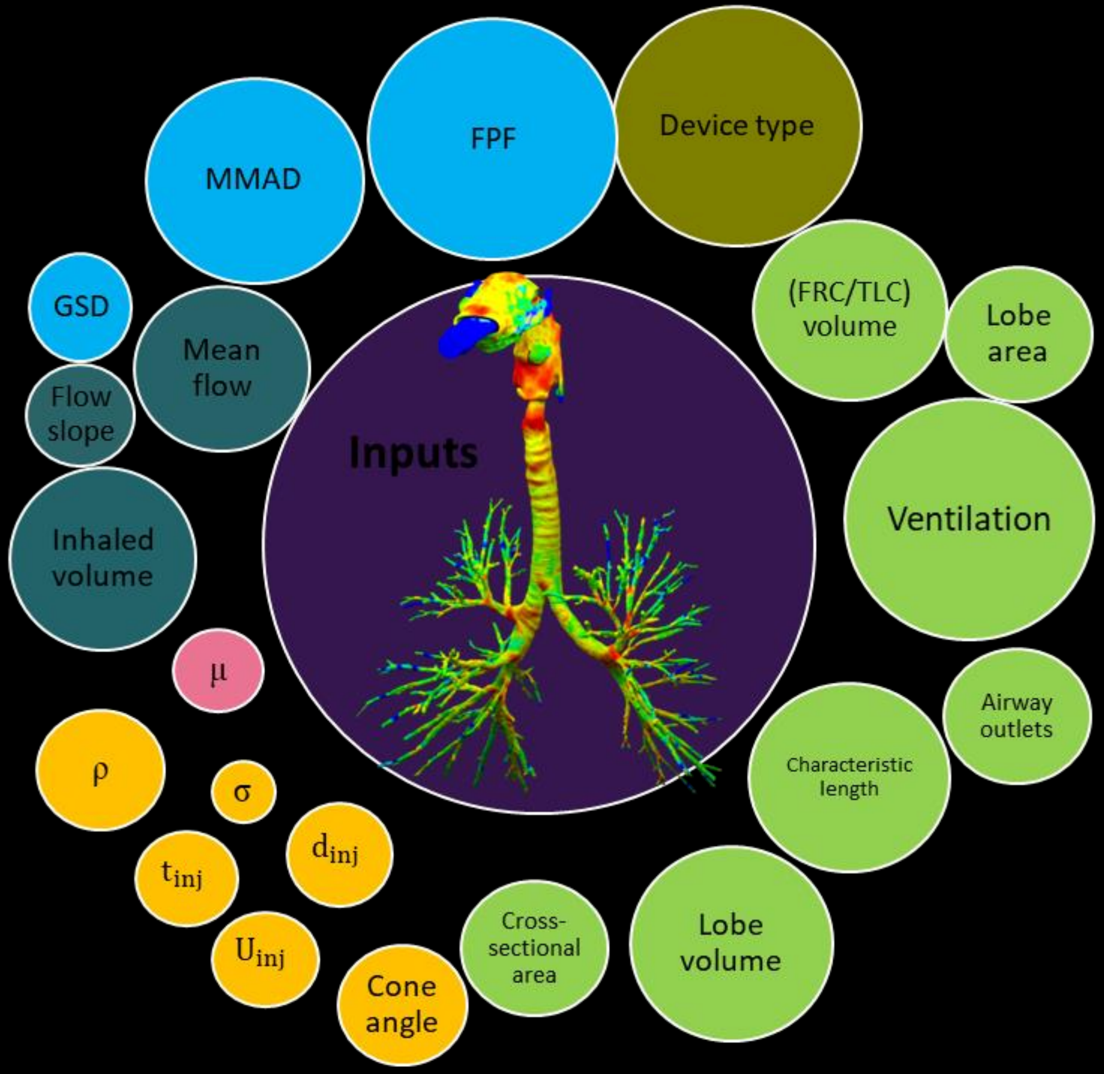
Visualization of average deposition of all components for all flow rates





Usmani et al. International Journal of Chronic Obstructive Pulmonary Disease 2020:15

RAPID DEPOSITION ANALYSIS (RDA)



AI-BASED

RDA is trained using >10,000 CT scans, including virtually all lung diseases, and >2,500 CFD simulations

FLUIDDA

Patent pending

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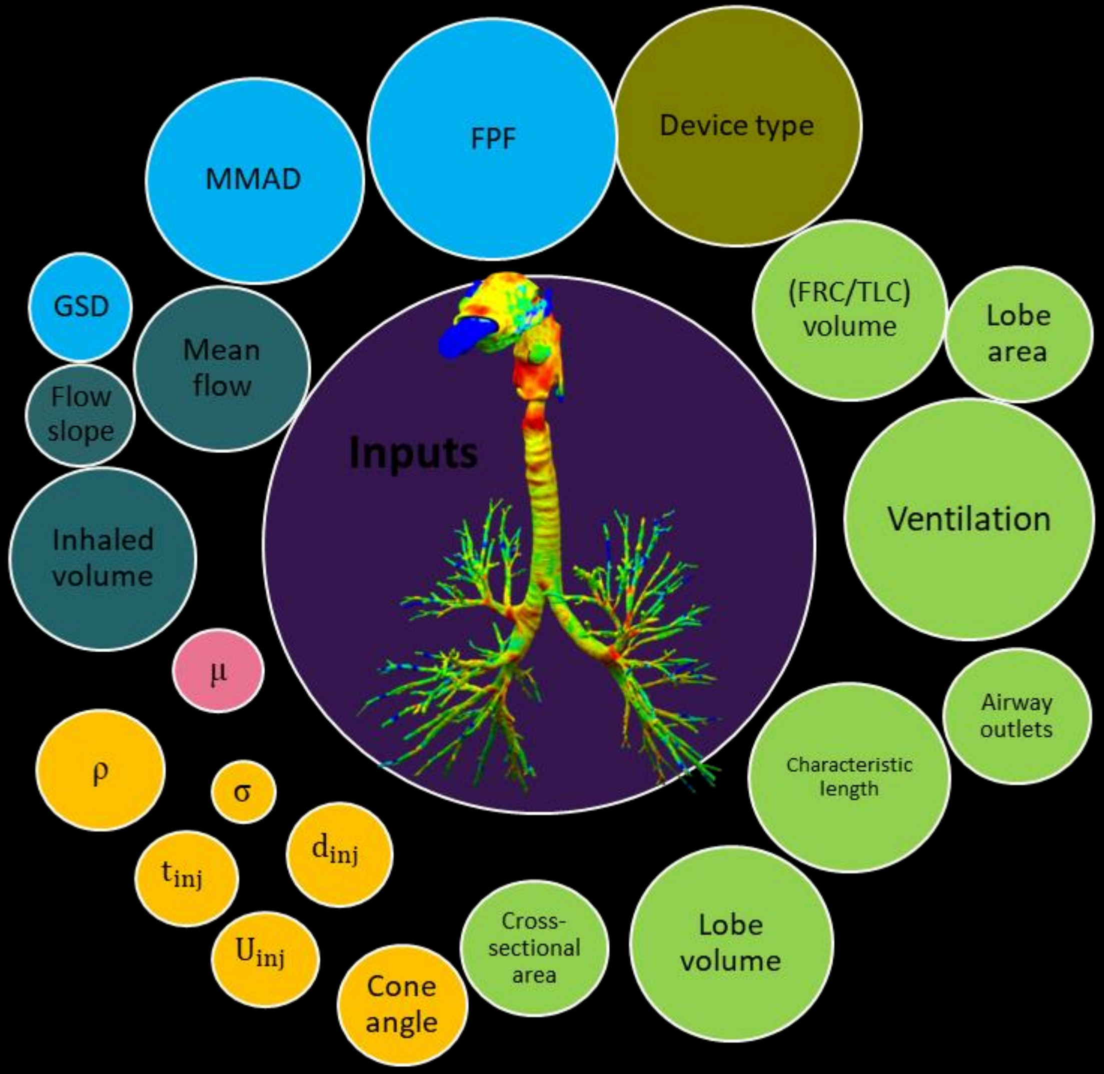

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RDA includes patient specific disease elements and is applicable to all inhaler types on the market including DPI, pMDI and nebulizers

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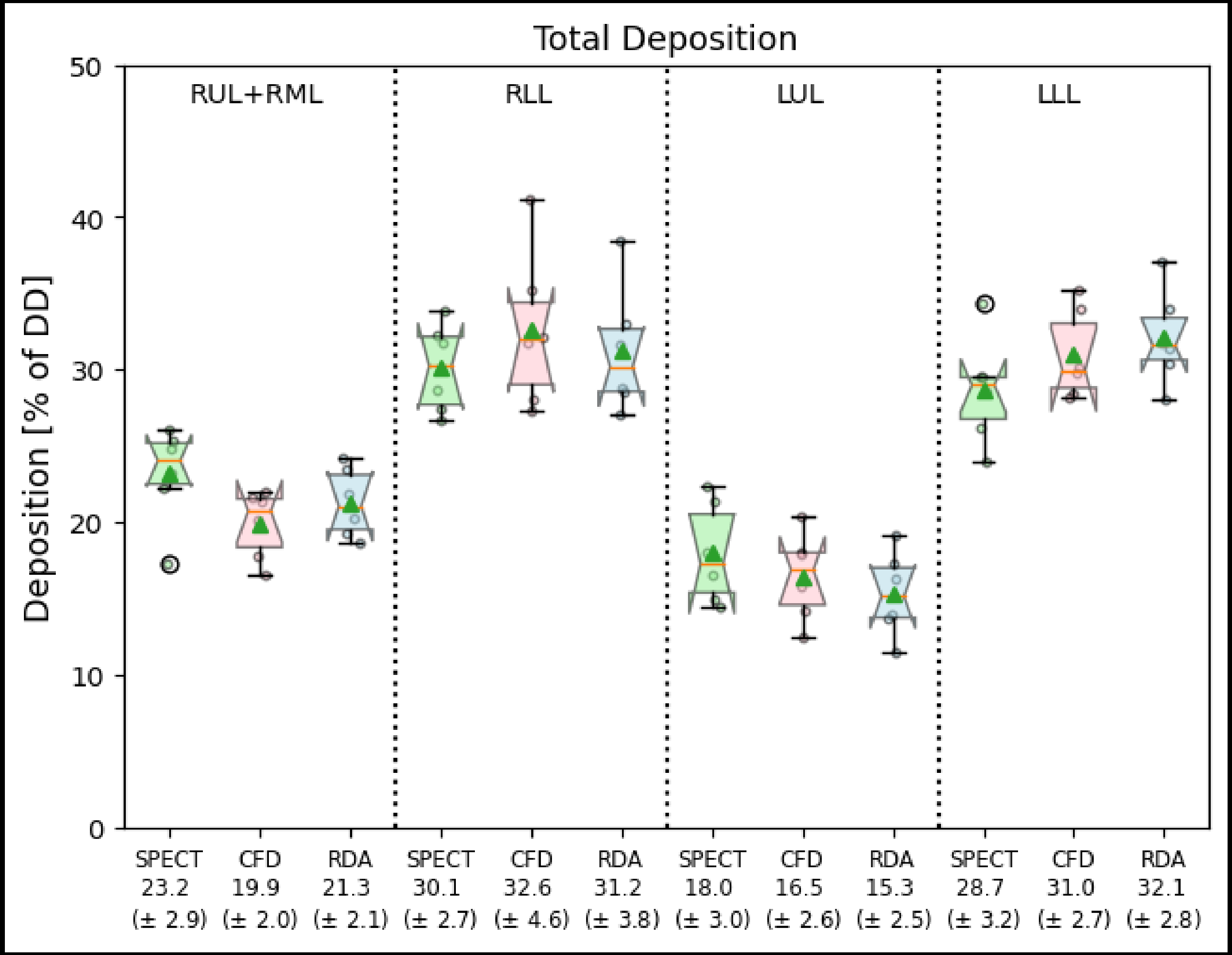

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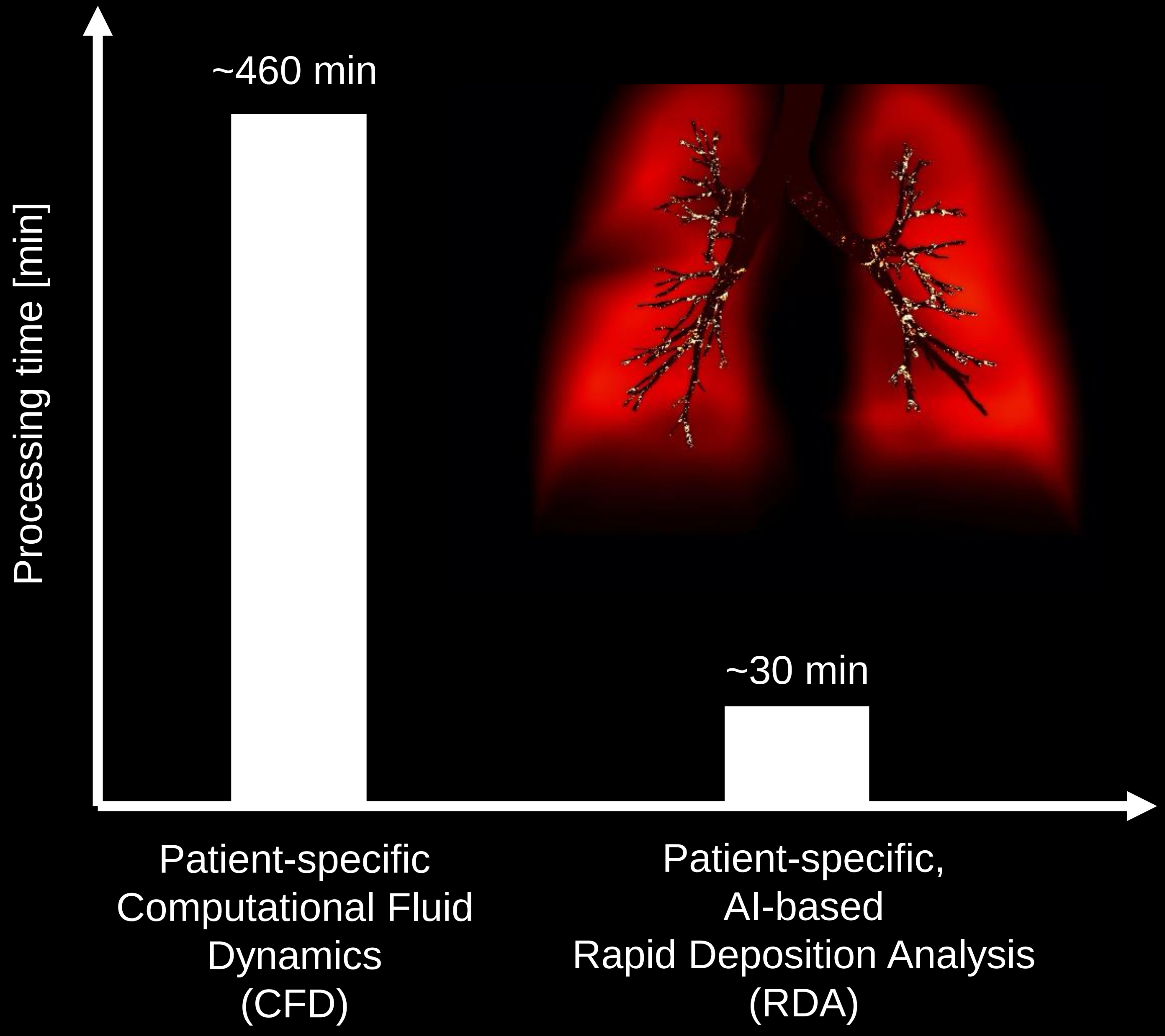

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PROCESSING TIME VS CFD: -94%

RDA reduces the time to determine patient specific lung deposition patterns by 94% compared to CFD

Patent pending

FLUIDDA

RAPID DEPOSITION ANALYSIS (RDA)

>1000 RDA iterations including variability in formulation, inhalation profile and patient's disease severity

RAPID DEPOSITION ANALYSIS (RDA)

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Sample Size Calculation

RAPID DEPOSITION ANALYSIS (RDA)

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Sample Size Calculation

COMPUTATIONAL FLUID DYNAMICS (CFD)

100-200 highly accurate CFD runs in representative sample

CONCLUSIONS

FLUIDDA

- The key drivers for deposition of inhaled drug products include
  - Device characteristics
  - Drug formulation
  - Inhalation profile
  - Lung structure & Function
- Key drivers can be adequately included into an in-silico approach through a combination of in-vitro tests and a database of relevant in-vivo data (eg HRCT)
- High-resolution but time consuming CFD simulations can be complemented with AI-based RDA to extrapolate CFD results to a larger study population level allowing for in-silico trials to reflect in-vivo trials in sample size and likely surpass in-vivo trials in accuracy

- The digital twin model used for bio-equivalence could become a valuable tool for the development of NCE