FLUIDDA

Respiratory solutions
for better patient care

Disease Characterization & Therapy Analysis

Describe your patients' lungs comprehensively.
Characterize disease progression accurately.
Analyze and monitor treatment or therapy efficiency in a fast and cost-beneficial way.
Allow our state-of-the-art approach to bring your clinical trials into the twenty-first century.

SENSITIVE

CLINICALLY RELEVANT

EARLY INSIGHTS

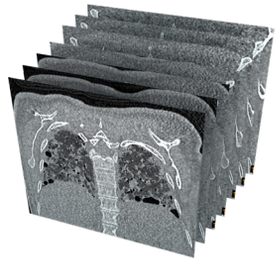
www.FLUIDDA.com

FRI

Functional Respiratory Imaging

Functional Respiratory Imaging (FRI) is a clinically meaningful and non-invasive measurement of the patient-specific respiratory system. A set of distinct biomarkers analyzes *exposure, structure and function* of the lungs and airways in any respiratory disease.

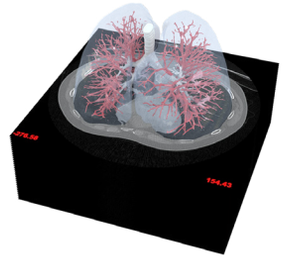
The usage of FRI biomarkers as endpoints in therapy development is scalable and easy to implement:



1

Image acquisition

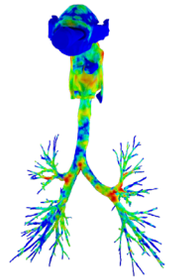
The process starts with the acquisition of low dose, high-resolution computed tomography (HRCT) scans of the patient's thorax



2

Structure segmentation

Measurements are performed on the segmented 3-dimensional geometries from these scans



3

Flow simulation

Computational fluid dynamics (CFD) is used to quantify airflow and exposure to inhaled particles

OVERCOME

challenges posed by the often unclear link between labelled dose and pharmacokinetic (PK) values

the high variance of conventional efficacy endpoints, which lead to large, long and expensive trials to demonstrate pharmacodynamic effects

the difficulty of obtaining conclusive results in a highly variable, less controllable real-life situation

the difficulty of detecting clinically relevant differences between therapies

THROUGH THE USE OF FRI IN

Safety

Phase I and Phase II to support dose finding

Efficacy

Phase I to support early therapy activity
Phase II to understand therapy activity
Phase III to lower the risk of bringing a drug to market
Phase IV to improve value proposition

Effectiveness

Observational studies to demonstrate therapy performance
Phase IV to improve value proposition

Therapy comparison

Preclinical to investigate device differences
Phase I to support early hypothesis
Phase II to understand comparison
Phase III to complement the registration filing
Phase IV to improve value proposition

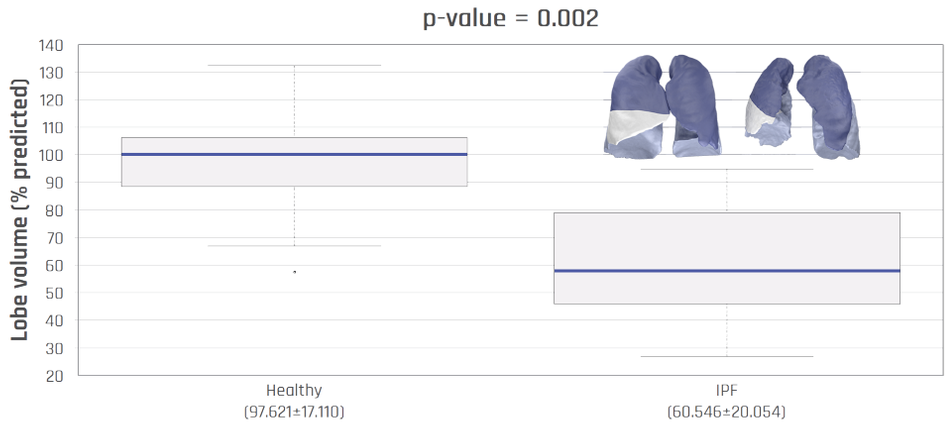
OVERCOME

the challenge of defining sensitive parameters that describe disease progression, predict patient outcomes, or determine disease phenotypes

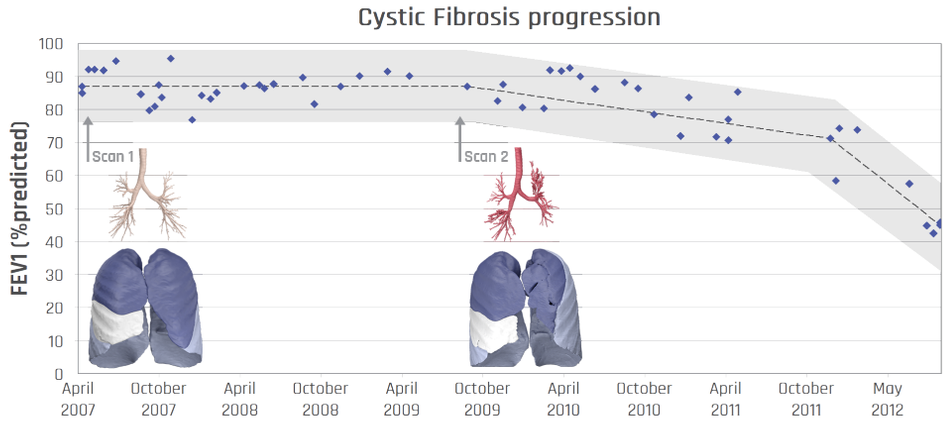
THROUGH THE USE OF FRI IN

Respiratory disease characterization

- **Understand your target disease better** with equally clinically relevant endpoints but much more sensitive than interventional trials' parameters
- Conduct **research prior to, or in parallel with, your interventional trials** to increase confidence in your therapy in your target population
- Keep your longitudinal or cross-sectional trials short and small by **identifying your target population**
- **Use FLUIDDA's expertise** to choose FRI endpoints that best describe the target disease
- **Combine the power of machine learning and FRI** to predict disease prognosis more accurately (e.g. exacerbation, lung rejection)



FRI results showing that there is a significant reduction in lobe volume in idiopathic pulmonary fibrosis (IPF) as compared to a healthy population (lobe volume expressed as percentage predicted) *Vos, W. et al., ATS 2015*



Forced expiratory volume in 1 second (FEV1) expressed as % predicted over the course of 3 years in a cystic fibrosis patient. FRI was performed twice and showed a clear deterioration (bronchiectasis and decreased lobar volumes) before FEV1 detected disease progression.

85% accuracy

in predicting Bronchiolitis Obliterans Syndrome (BOS) developers at baseline

Barbosa et al., 2018

CLIENT EXPERIENCE

I just about fell out of my chair looking at these FRI results on how wildfire is affecting the respiratory system. It's unbelievable. I'm so glad that we had your team work on this!

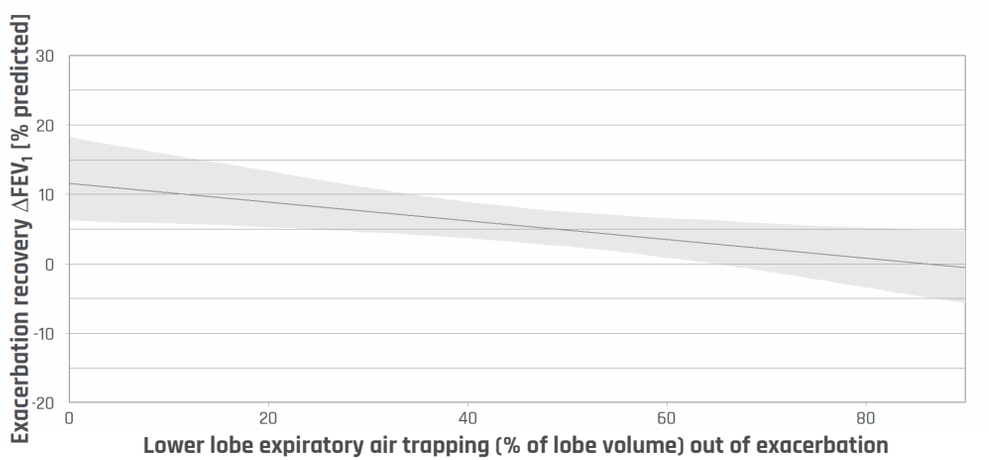
Lisa A. Miller, Ph.D.
Respiratory Diseases Unit
Unit Leader Inhalation Exposure Core
Lead Professor, Dept. of Anatomy, Physiology, & Cell Biology, UC Davis School of Veterinary Medicine

CASE STUDY

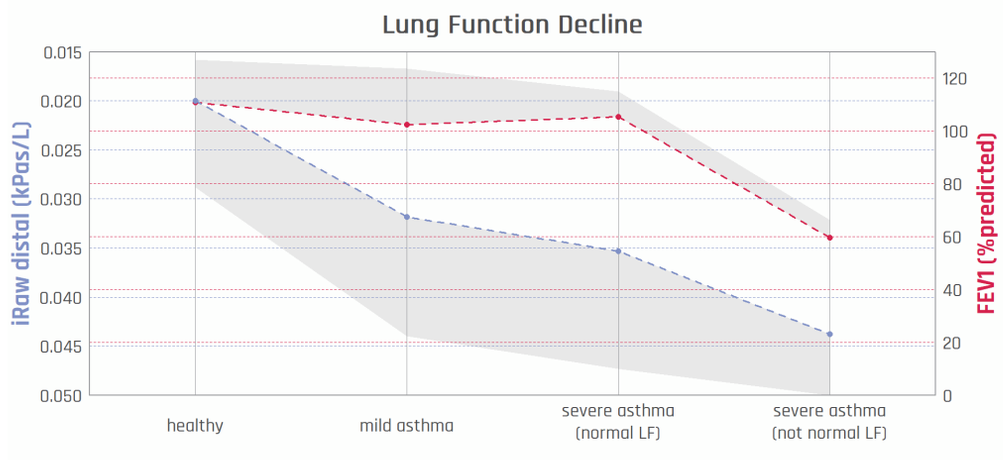
Regional assessment is indispensable in predicting COPD exacerbation recovery rate

Patients with evidence of expiratory air trapping in the lower lobes (outside of an exacerbation) have a worse recovery (expressed as change in FEV1) from acute COPD exacerbation. This demonstrates the importance of obtaining regional information about disease expression in COPD patients in a clinical setting.

Abstract **Vos, W. et al.**,
ERS 2015 - GSK supported

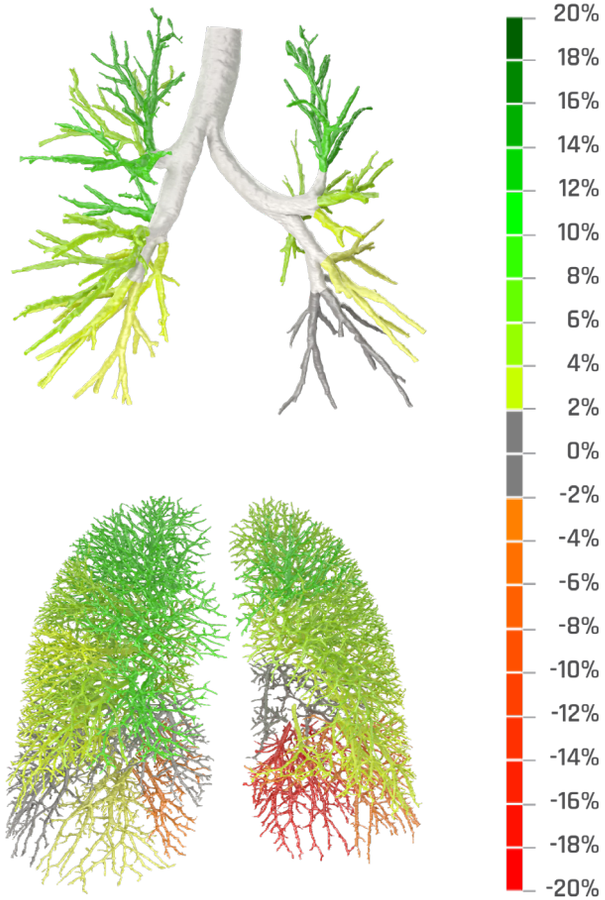


LUNG FUNCTION DECLINE



Forced expiratory volume in 1 second (FEV1) and image based airway resistance (iRaw) measured in asthma patients with different levels of severity. FEV1 has a step-wise decline versus iRaw declining gradually with increasing severity.
Data from Airprom Consortium; Principal Investigator: Prof C. Brightling

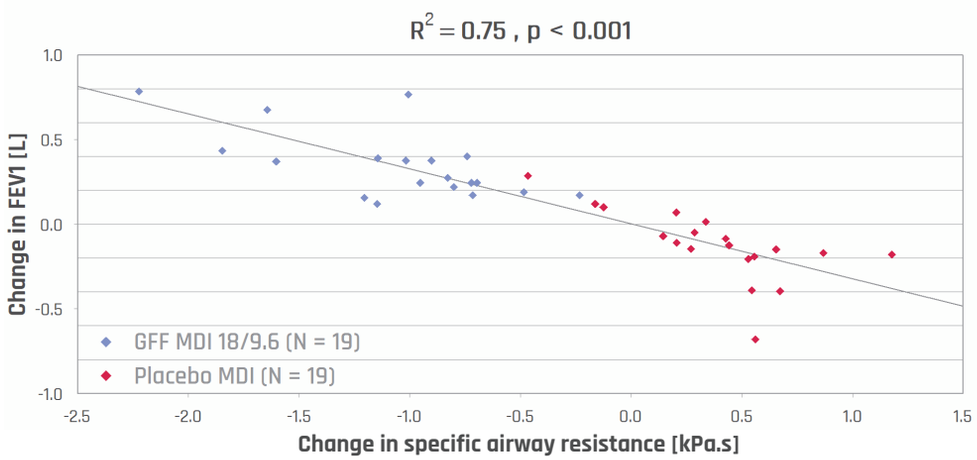
SAFETY > **EFFICACY >** **EFFECTIVENESS >** **THERAPY COMPARISON >**



Changes **(green = improvement, red = worsening)** of the image based airway volumes caused by an inhaled bronchodilator (top image) and of the image based blood vessel volumes caused by a systemic vasodilator (bottom image)

- Efficiently assess treatment efficacy with **highly sensitive endpoints**, detecting the smallest changes
- **Reduce your sample size** to assess pharmacodynamics (PD) with FRI endpoints
  Lanclus, M. et al., 2017
- Assess the **true regional PD effect and link it to regional aerosol deposition**
- Extensively **validated against clinically relevant parameters**
  De Backer, J. et al., 2008 – FEV1
  De Backer, W. et al., 2018 – FEV1
  Hajian et al., 2017 – 6MWT
  Vos, W. et al., 2013 – ACS
- Assess **which safe lung dosage allows maximum efficacy** by linking blood safety measures to proper dosage (without the need of a full-on PK trial)
- Combine safety and efficacy in your trial to **gain maximum confidence and time savings** when advancing to further clinical development stages
- Use **state-of-the-art technology** to assess quality characteristics and to determine:
  - **Superiority**
  - **Bioequivalence**

CASE STUDY >



FRI correlates well with clinically relevant improvements

- The figure shows the correlation between the change in FEV1 and the change in airway resistance for 19 COPD patients who were treated with a bronchodilator and placebo (cross-over).
- Treatment with GFF MDI resulted in a 71% decrease in airway resistance vs. placebo MDI while FEV1 only showed a 28% increase of GFF versus placebo (>2.5 times larger signal with FRI).

De Backer, W. et al., 2018

DISEASES ANALYZED WITH FRI

- **Asthma**
- **Chronic obstructive pulmonary disease (COPD)**
- **Alpha 1 antitrypsin deficiency (A1AD)**
- **Cystic fibrosis (CF)**
- **Idiopathic pulmonary fibrosis (IPF)**
- **Bronchiolitis obliterans syndrome (BOS)**
- **Bronchopulmonary dysplasia (BPD)**
- **Idiopathic diaphragmatic paralysis (IDP)**
- **Sleep apnea**
- **Sinusitis**
- **Acute respiratory distress syndrome (ARDS)**
- **Scleroderma**
- **Non-CF bronchiectasis**
- **Chronic bronchitis**

Up to 16 times less

patient enrolment needed to establish significant results with FRI when compared to FEV1 or FVC as endpoint

Lanclus, M. et al., 2017
Vos, W. et al., 2013
De Backer, L.A. et al., 2012

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CLIENT EXPERIENCE

The application of Functional Respiratory Imaging in early clinical development can be done with relatively few patients per treatment arm and results in clear and detectable differences.
It will be exciting to determine how FRI parameters correlate with more known and established outcomes, such as exacerbations or patient-reported outcomes in the respiratory field.

Dr. Edith M Hessel
Vice President, Respiratory Therapy Area Unit at GSK

The insights provided by the FRI technology have been extremely useful for the understanding of regional lung deposition, to differentiate potentially similar products beyond in vitro and to design appropriate clinical investigations. I strongly endorse this innovative approach and look forward to use it also in the future.

Giovanni Caponetti
Managing Director at Eratech

OUR EXPERIENCE SINCE 2005

- **40+** Clinical centers trained worldwide
- **90+** Clinical studies in Disease characterization & Therapy analysis

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for better patient care

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