FLUIDDA'S

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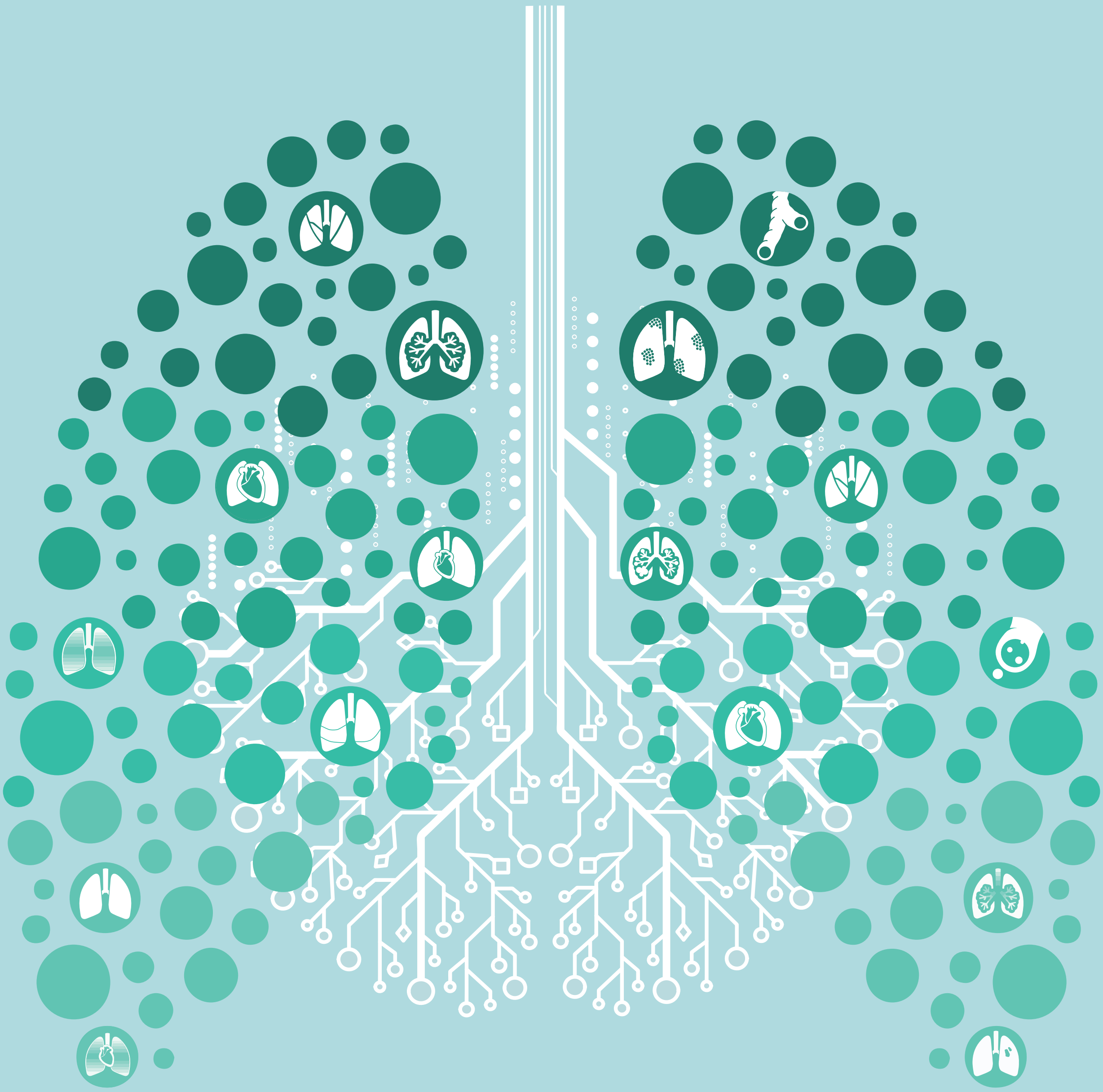
Respiratory solutions for better patient care

Magazine on Functional Respiratory Imaging

#3-2022



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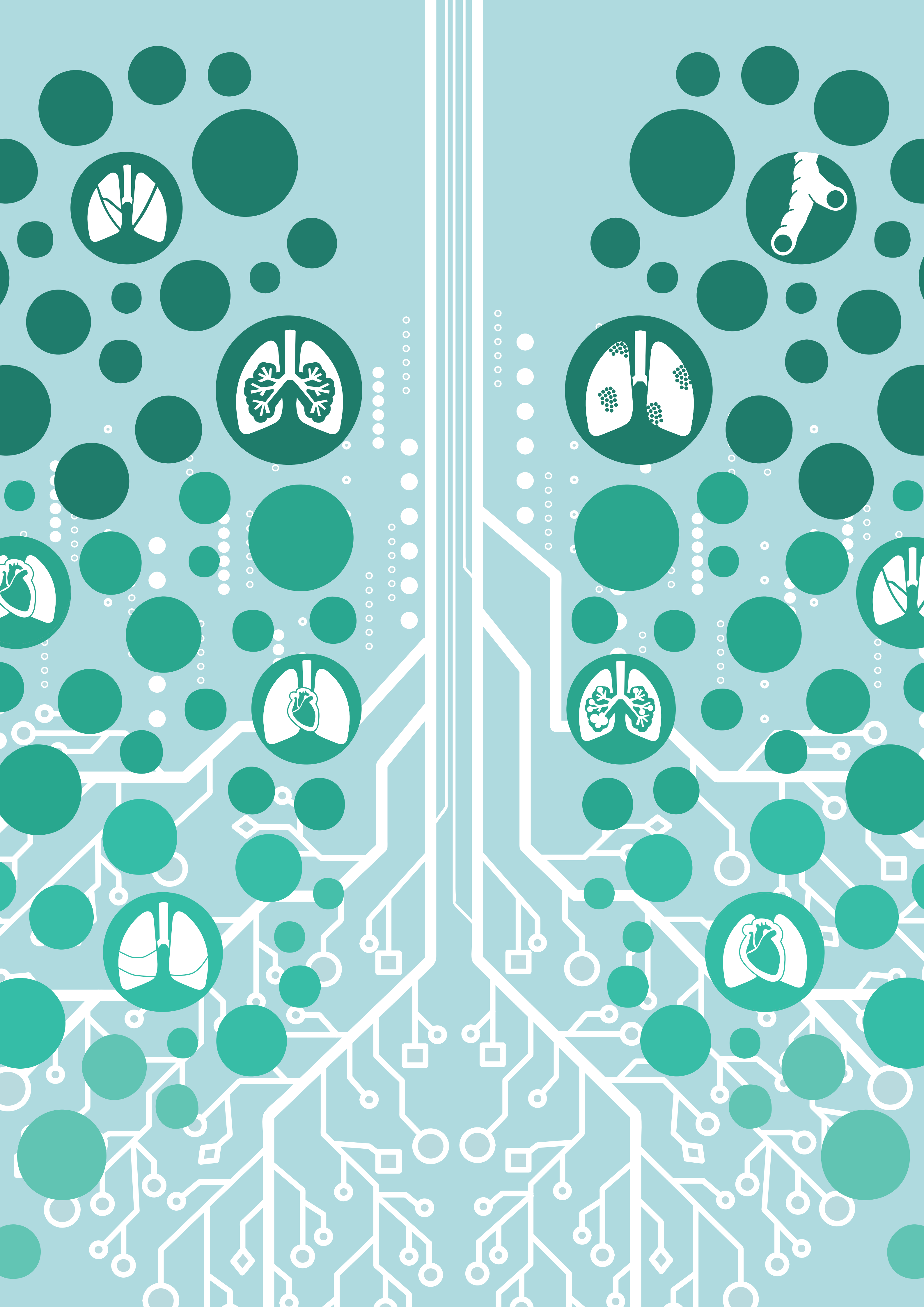

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Dear reader,

We are pleased to present to you the third issue of the Fluidda Magazine on FRI technology!

With over 17 years of experience in applying our imaging technology in respiratory clinical research, we are pleased to see that Functional Respiratory Imaging (FRI) is now routinely used in clinical trials to assess treatments across a range of respiratory indications. With its consortium of endpoints, FRI creates a wealth of information around the mode of action of compounds and indications.

Over the last few years, we at FLUIDDA have broadened the reach and extent of our collaborations with academic instituti-ons all over the world. As a result, FRI is emerging as the imaging research tool of choice in a wide variety of therapeutic areas including COPD, pulmonary vascular disease, interstitial lung disease, asthma, and COVID-19. These collaborations continue to yield valuable insights and mounting evidence of the value of quantitative imaging in clinical management of pulmonary disease.

With our platform Broncholab, Fluidda is paving the way for FRI in clinical care settings. Broncholab offers emphysema and fibrosis scoring, lobe volumes, fissure integrity, and vascular volume analysis all from a single chest CT scan, with turnaround times of under 24 hours.

In this edition we speak with physician-scientists using FRI in their research, and ask them to share their thoughts on the potential role of FRI in clinical practice, the challenges, and future of the technology. We hope these interviews will inspire you to explore the potential of FRI in your own practice and wish you happy reading!

On behalf of Fluidda,
Charles Mussche
VP Clinical applications

Colophon

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Fluidda/FRI technology:
Fluidda N.V.
Groeningenlei 132
2550 Kontich
Belgium
info@fluidda.com

Publisher:
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Jackie L. Johnson
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A full list of publications related to scientific research with Fluidda's FRI technology can be found at: www.fluidda.com

Functional Respiratory Imaging: improving healthcare in a post-pandemic world

JAN DE BACKER

Jan De Backer is CEO of Fluidda. Dr. De Backer graduated from Delft University of Technology, The Netherlands as an aerospace engineer. He attained an MSc degree in aerodynamics and specialized in applied biomedical computational fluid dynamics leading to a PhD from the University of Antwerp, Belgium. He is an alumnus of the MBA programs at London Business School, London and Columbia Business School, New York. Dr. De Backer has received several awards for his innovative research in the field of airway modelling in respiratory and sleep medicine. His work has been published in international journals. Dr. De Backer founded FLUIDDA in 2005 and he has held the position of Chief Executive Officer since 2007.

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The COVID-19 pandemic accelerated the incidence and severity of lung disease, serving as a catalyst to search for more personalized and precise approaches for managing these patients. As an imaging technology that has been in the respiratory space for over 15 years and has FDA approval, Functional Respiratory Imaging (FRI) can serve as a pivotal tool to better inform disease diagnoses, treatment decisions, and clinical research discoveries.

Even before the COVID-19 pandemic, there were a considerable number of respiratory patients receiving suboptimal treatments. "I think one of the reasons why the pandemic was so severe, especially the first waves, is that we probably didn't take care of these patients optimally," says Dr. Jan De Backer, CEO of Fluidda. "As the world gets ready to evaluate the lessons learned from the past two years, it is our responsibility to look back and ask: *What happened? Can we do better?*"

NEW TECHNOLOGIES IN RESPIRATORY MEDICINE

"In the respiratory space, the use of technology is still at a fairly low level," says De Backer. "The gold standard is still spirometry. I think it's time to reassess and see if we can use technology in a way that really improves the lives of patients." With that aim, Fluidda's FRI technology reconstructs a 3D map of the lungs from CT scans, which can inform physicians on disease states, efficacy of medications, and more.

FRI entered the respiratory space in 2005, used mainly as an imaging tool for exploratory endpoints in clinical trials. Unlike spirometry, which can take up to six months to demonstrate changes in lung function, FRI can show changes in a matter of weeks. In recent years, Fluidda's technology has taken center-stage as a source of primary endpoints of clinical trials. New treatments are being tested for severe asthma patients, and FRI is being used as a primary endpoint to examine efficacy of those medications. "Fluidda has become the go-to party for pharmaceutical companies to study these new drugs" explains De Backer. "These large clinical trials are giving clinicians more exposure to the technology and building on the current evidence."

FROM CLINICAL TRIALS TO CLINICAL PRACTICE

In 2020, the FDA approved FRI as a diagnostic support tool, under the name *Broncholab*. This approval has opened the door for bringing the technology into clinical practice. De Backer explains, "Fluidda is currently the company that has been doing clinical trials with interventions the longest in the imaging space. We have a pretty good idea about what the typical drugs and devices are doing in terms of changing airways, blood vessels, ventilation, etc. This puts us in a position where we can use the technology to start linking the knowledge from those clinical trials to the application in clinical practice." The number of physicians who recognize the potential of new diagnostic technologies like Broncholab also increased during the pandemic, making this the ideal time for technology-based approaches to enter routine clinical practice.

> **When you think about the future of cardiorespiratory medicine, especially in a post-pandemic world, pulmonary rehabilitation will play an important role.**

CARDIOPULMONARY REHABILITATION

FRI has the potential to facilitate new approaches in cardiopulmonary rehabilitation. "When you think about the future of cardiorespiratory medicine, especially in a post-pandemic world, rehabilitation will play an important role," explains De Backer. "Research has shown that rehabilitating respiratory patients has resulted in a considerable improvement in respective clinical outcomes." Currently, this approach is highly under-utilized because it involves putting the patient in a rehabilitation center, giving them an exercise regimen, and then following-up with them periodically. Although effective, these treatments face scrutiny and are rarely adequately reimbursed by insurance companies. "As the number of long-COVID patients compounds the burden from respiratory patients receiving sub-optimal treatment before the pandemic, the demand for new therapeutic approaches in the respiratory space will increase. We believe that currently the only thing that works for them is a rehabilitation program based on technology and better diagnostics, like FRI," explains De Backer. "A tailor-made program that promotes the best possible condition is the goal."

Schematic Workflow Broncholab

FDA APPROVED

PACS

CLIENT uploads DICOMS from its PACS system into a GATEWAY , installed on CLIENT-side.

1. DICOM

The GATEWAY will remove most personal data (partial anonymization). The limited personal data processed, needed to re-identify the subject data will be encrypted. The encryption keys resides on the GATEWAY CLIENT-side.

CLOUD-TRANSFER

Transfer of the data via Ambra Health company , a third-party cloud provider.

2. DATASET

The DICOMs partially anonymized expect for the encrypted pre-defined personal tag.

FLUIDDA

Fluidda will analyze the DATASET and return the processed DATASET, in the format of a REPORT.

3. REPORT

FLUIDDA analysis containing the encrypted pre-defined personal tags.

4. REPORT

GATEWAY on CLIENT-side will decrypt pre-defined personal tags contained on the REPORT and match the REPORT to the correct subject in the PACS.

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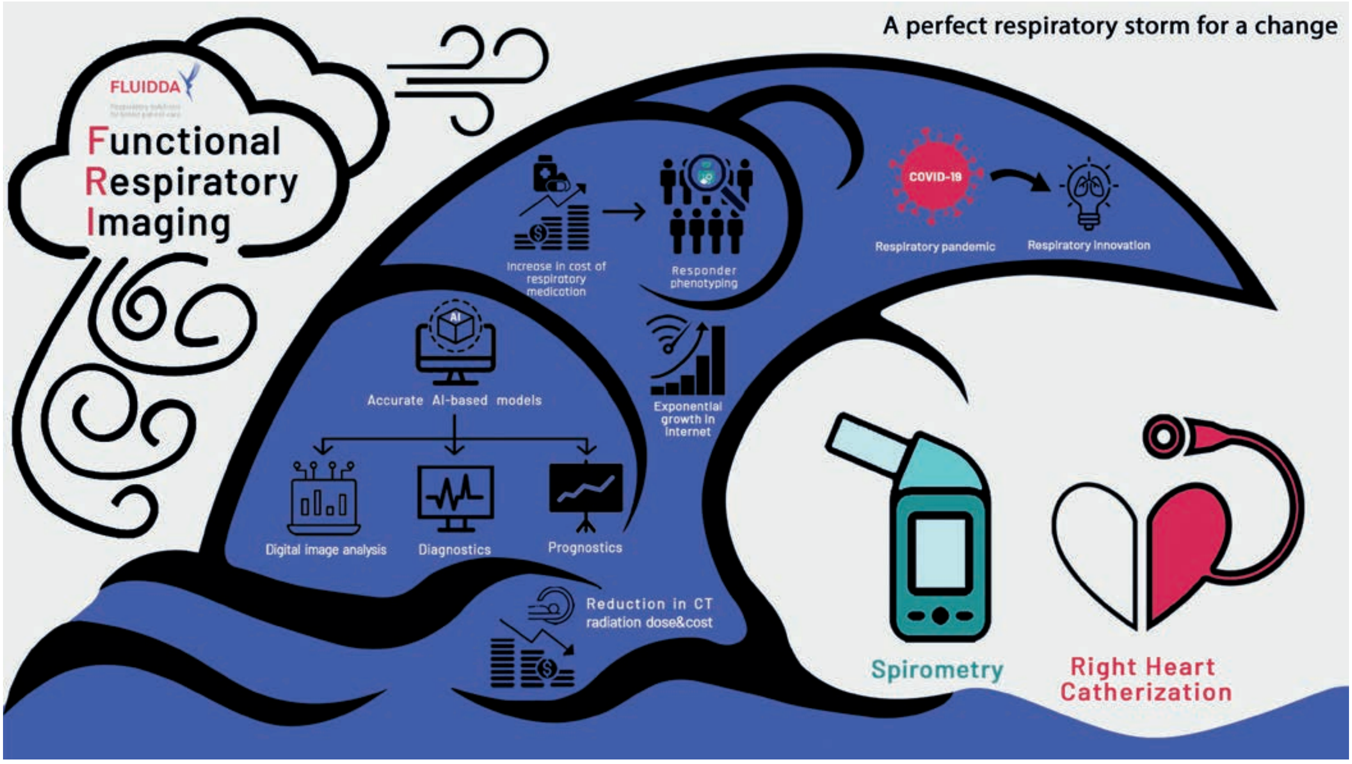


> It's time to reassess and see if we can use technology in a way that really improves the lives of patients.

A HEALTH-WEARABLE APPROACH FOR RESPIRATORY HEALTHCARE?

Health-wearables and associated apps linked with exercise equipment read-outs could potentially serve the unmet needs of healthcare. Currently, medical interventions are unlikely to be informed by these tools, but it is possible to use these innovative technologies to improve health. De Backer explains a possible scenario, "Starting with a baseline health-assessment using a Broncholab analysis, physicians could then use the information gathered from clinical trials and clinical practice to predict the best course of action. Once the assessment is done, a regimen could be assigned that includes wearables to monitor things like heart-rate, oxygenation level, etc."

Optimizing rehabilitation centers' infrastructure to manage patients' wearables-data would allow patients to gain access to a more personalized approach to health. "Coming out of a pandemic where even young, healthy, non-smoking people were affected gives us an opportunity to use technology to bring these worlds closer together to create value for all patients," concludes De Backer.

FRI in critical care: challenges and opportunities

Functional Respiratory Imaging (FRI) did not have a place in critical care before the COVID-19 pandemic, but as healthcare systems were overloaded with an unprecedented number of patients, new technologies and solutions became more desirable. Dr. Daniel Salerno, a pulmonologist specialized in critical care at Temple University, highlights that as new FRI data become available, this technology could play a more significant role in critical care of respiratory patients, both with COVID-19 infections and beyond.

DANIEL SALERNO

Dr. Daniel Salerno is a pulmonology and critical care specialist at Temple University Hospital and the Director of Critical Care Services. One of his areas of research interest is the development of biomarkers for critical care.

> We are yet to employ FRI in critical care; however, this doesn't mean that there is no place for FRI in critical care.

Though most patients with COVID-19 exhibit mild symptoms, approximately 5% become critically ill and need intensive care treatment [1]. At the peak of the pandemic, hospitals across the globe were overwhelmed, with ICUs swamped by the influx of patients, requiring critical care management to accommodate the surge rapidly and dramatically. Among the ICU-admitted patients, 50–85% of them developed hypoxemia or respiratory exhaustion [2]. Timely and effective respiratory support strategies and effective patient care were therefore paramount. Functional Respiratory Imaging (FRI) has emerged as a unique computational workflow in which functional data complement respiratory images [3]. Among other novel tools, FRI holds the potential to provide new insights in critical care settings [4].

IMPACT OF THE PANDEMIC ON CRITICAL CARE

At the beginning of 2020, when the number of COVID-19 cases started to increase, pulmonary centers like the one in Temple University Hospital started to prepare for the worst. They implemented logistic adjustments, such as making more ICU beds available to ensure they could take care of the number of patients who were going to arrive. Clinical researchers also shifted their interests, with some taking a new direction to study the phenotypes associated with this new disease and its complications. Regarding CT scans, Salerno says, "Our center is unique because we did an initial CT scan for all of our patients with COVID-19, whereas many other places in the USA or other parts of the world didn't take this approach. It allowed us to access a lot of data for our COVID-19 admissions." This policy also resulted in a large data resource for future retrospective studies.

Notably, even while managing the hefty COVID-19 volumes in Philadelphia, Temple's medical team has achieved survival rates better than the national and regional averages. The death rate for patients with COVID at Temple was 15% lower than other hospitals in Pennsylvania and 28% lower than the national average [6].

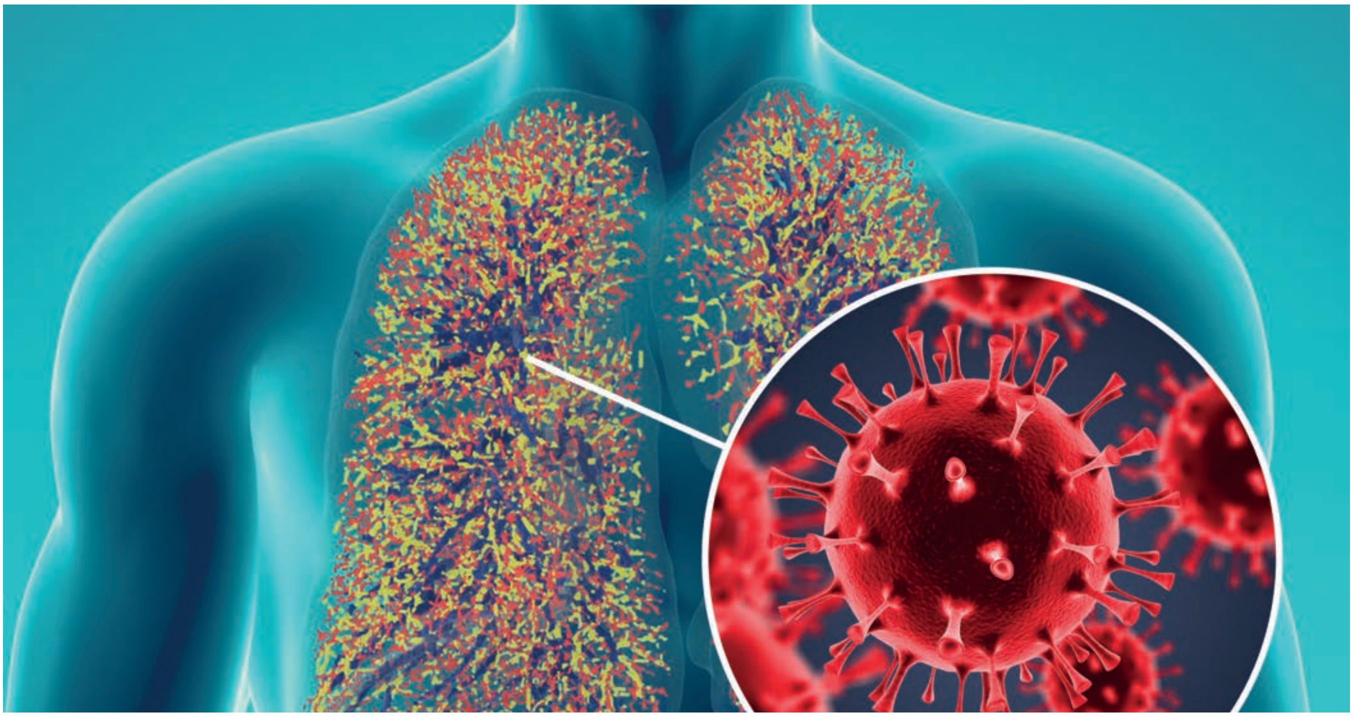
USING FRI TO ASSESS LUNG ABNORMALITIES AFTER COVID-19

Having access to this data resource has allowed Salerno and colleagues to perform retrospective studies. One such study hypothesized that CT scan parameters from the time of infection could predict abnormal lung function after COVID-19 infection [7]. The team used FRI to analyze the volume of pulmonary blood vessels in patients with COVID-19 who were hospitalized due to COVID-19-related pneumonia.

The study found that patients who had pulmonary vascular abnormalities at the time of hospitalization with COVID-19, especially in the medium and large vessels, were at higher risk of having abnormally low diffusion capacity of carbon monoxide (DLCO, a measure of lung function) even three months after discharge. "Using technologies like FRI allows you to see more than what radiologists could see and to have a quantitative approach, which allows you to do more objective determinations," says Salerno.

Recent studies from Salerno and others aim to identify the long-term effects of COVID-19 (called *long COVID*), which is the manifestation of symptoms that continue for weeks to months beyond the initial illness [8]. Salerno shared the relevance of FRI, "We can and should use FRI and other imaging approaches to do new studies regarding the chronic and long-term effects of COVID-19, especially given the amount of data that we gathered during the pandemic. There is a group in the United Kingdom that is also using imaging approaches to gather more information about people who have had COVID-19, and what they argue is that there are many parameters that can guide treatment and that are difficult or impossible to see with a plain image, but it becomes apparent when you use more sophisticated technologies. This could eventually help in discovering treatments. I think this shows the potential of the field, creating ample opportunities to execute novel research."

According to Salerno, the application of FRI is not limited to COVID-19 infections: it can also inform the treatment of other lung diseases, for example, in acute respiratory distress syndrome (ARDS). ARDS is a life-threatening ailment where the lungs are unable to provide enough oxygen to the body's vital organs [9]. "In ARDS, there are issues with blood perfusion that are difficult to evaluate in a regular CT scan. Analyses like FRI could help explain why oxygenation is more difficult in some of the individuals with ARDS."



TECHNICAL CHALLENGES OF USING FUNCTIONAL RESPIRATORY IMAGING IN CRITICAL CARE

Prior to the COVID-19 pandemic, FRI had never been used to manage critically ill patients; even now, its application to this area of medicine has only been in retrospective studies. This might be partly because many procedures that are routine in other settings are not frequently performed in critical care patients due to technical or logistic challenges. Transporting critically ill patients out of ICU alone could increase the risk of adverse events [5]. "If you want to move a patient who is in the ICU, cables can come out, mechanical ventilation settings can be changed, and that can have dramatic consequences," says Salerno. "Therefore, experienced clinicians tend to be reluctant to order CT scans to critically ill patients, unless they have a clear idea of how the information gathered from that intervention will change patient management."

The FRI technique starts with two CT scans, the first taken after deep inspiration and the second taken after normal expiration. Salerno explains, "If you have a patient who is not moving, things like holding a breath are much more difficult than what you would encounter in the non-critical care or outpatient care settings."

Salerno adds, "We are yet to employ FRI in critical care; however, this doesn't mean that there is no place for FRI in critical care. I work in a large pulmonary center with advanced critical care units with extensive lung-transplant populations that require this sophisticated tool." Salerno further illuminates the potential of FRI, "There are still cases where we could take CT scans of critically ill patients and then have additional information: the FRI analysis can be useful." He expects that as more FRI data become available, the technology will play a bigger role in critical care.

THE FUTURE OF FRI IN CRITICAL CARE

The COVID-19 pandemic has brought big changes to healthcare systems. Critical care management in particular went through some adjustments, explains Salerno. "The pandemic has changed our approach to critical care. We are taking a more aggressive approach in doing interventions on our patients now than we were doing before COVID-19." This opens the door for technologies like FRI to play a more prominent role in guiding the management of critical care patients with lung diseases. More data are needed that could better inform management and ease clinical decision-making.

Salerno describes a possible scenario, "Let us assume that we know that ARDS patients can present different phenotypes based on blood markers, categorized as hyper- or hypo-inflammatory in nature. The recommended therapeutic interventions for each state might be different. If clinicians could use FRI to recognize the different phenotypes, one can argue patients with ARDS in the ICU would need a CT scan. This is the same that we did with patients with COVID-19." In this case, the benefits of performing the scan would outweigh the risks of taking the patient out of the ICU.

Weighing the prospects of FRI in the critical care setting, Salerno concludes, "In the end, it will depend on how much research we do and how much we can prove that doing this type of image analysis can impact what we find in patients and how we treat them. If new parameters become available, it makes sense to think that FRI might become a routine procedure in critical care for pulmonary patients."

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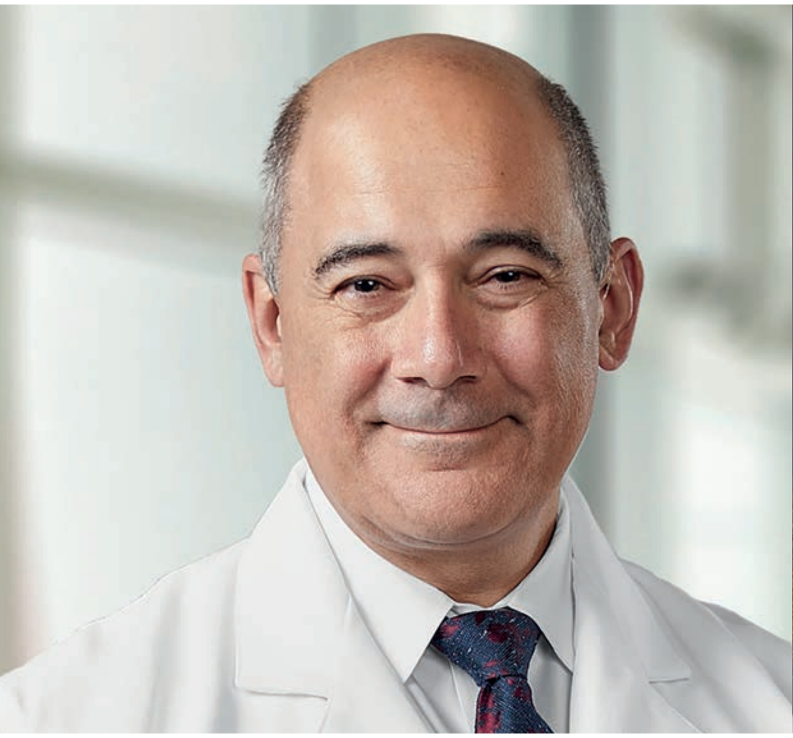

FRI is the missing link for pulmonary vascular disease

RAYMOND L BENZA, MD
Dr. Raymond Benza is a cardiologist at The Ohio State University Wexner Medical Center with more than 30 years of experience in clinical medicine. He serves as the Bob and Corrine Frick Endowed Chair in Heart Failure in the Division of Cardiovascular Medicine.

MARDI GOMBERG-MAITLAND, MD
Dr. Mardi Gomberg is a cardiologist and Professor of Medicine at the George Washington University School of Medicine & Health Sciences. She also serves as the Medical Director of the MFA/GWUH Pulmonary Hypertension Program.

> **Lung biopsies can be risky, and FRI might be the first virtual imaging biopsy.**
>
> MARDI GOMBERG-MAITLAND, MD

Novel imaging technologies to identify and monitor patients with pulmonary vascular disease (PVD) are needed. Clinical researchers and cardiologists, Dr. Raymond L Benza of The Ohio State University and Dr. Mardi Gomberg-Maitland of George Washington University, share their expertise on PVD, highlighting their collaborations with Fluidda. Functional Respiratory Imaging (FRI) creates an image of the minute details of lung vasculature, which can serve as a surrogate readout of what's happening in the hearts of patients with PVD. In the context of PVD, FRI may be a useful tool throughout the patient journey – for early identification of disease, as a diagnostic instrument, and as a monitoring tool during treatment. Taken together, FRI has the potential to be a true imaging technique to monitor disease-modification for PVD.

As a clinical researcher in the field of PVD, Dr. Raymond Benza's major interest lies in developing risk stratification tools to predict pulmonary hypertension (PH). Benza says, "In my vascular biology lab, along with genomic studies, we employ machine learning and artificial intelligence to develop tools to limit clinical worsening of the disease."

A fellow researcher and collaborator, Dr. Mardi Gomberg adds, "I am particularly interested in drug development. What intrigues me about PVD is that it is a cardio-pulmonary disease and – being cardiologists – we offer a unique perspective."

LUNG IMAGING FOR PVD

Pulmonary hypertension, a type of PVD, is characterized by high blood pressure in the vessels of the lung which stresses the heart and leads inevitably to heart failure. Imaging plays an important role in the screening and monitoring of PH to evaluate the structural changes of the heart and lungs over time, but current routine clinical protocols still have their shortcomings. In the case of PVD, researchers have an unmet need when it comes to imaging the veins in addition to the arterioles; previous imaging technologies haven't had high enough resolution to monitor the veins of the pulmonary vasculature. Benza states, "In the past, we only had indirect tools, such as invasive hemodynamic monitoring. But now with FRI, we can create images of the lung vasculature affected by the disease."

Gomberg adds, "We initially asked, in the patients with PH, how do we evaluate the veins early enough and potentially target the PVD? Now, FRI helps us to image not only the arterioles but also the venules of the lungs."

Now, employing the uniqueness of FRI, Benza and Gomberg are designing a clinical trial that treats patients with Group 2 PH. Benza explains, "In the most prevalent form of PH, the prior lack of imaging technology to visualize the veins affected the therapeutic interventions. If a drug is designed to target lung arteries but not the veins, it could result in pulmonary edema – the Achilles heel in treating patients with Group 2 PH." Gomberg explains the role of FRI in the trial: "We are incorporating FRI – with a probable intention to use it as an endpoint to understand the precise effects in the lung vasculature. Establishing this system would help future therapeutic interventions."

FROM CLINICAL TRIALS TO CLINICAL PRACTICE

When discussing the potential of FRI in clinical practice, Benza states, "FRI is applicable to clinical practice. Dr. Gomberg and I are both developing risk prediction tools, but those are restricted to final phases of disease manifestations. FRI functions at a step ahead: you could actually see in advance what you are remodeling and predict the treatment route." He adds, "It could be periodically applied throughout the course of a patient's clinical journey to see whether a treatment alteration is needed."

Gomberg reflects on the utility of FRI, "It supplements existing tools like CT scans, which are often done as a part of routine clinical protocol, making FRI more accessible." She adds, "In PVD, although MRI is a useful tool both for heart and lungs, it is not available in every center. CT scanners are widely available, which highlights how FRI could be even more important." Some centers may have repositories of historical patient data, including CT scans. "We can go back in time and use old CT scans and apply FRI for retrospective investigations as well."

Benza reconfirms the need for FRI, "We couldn't image the lungs due to the incapability of current technologies, except for the diffusing capacity of the lungs for carbon monoxide (DLCO). But now we can image the lungs as well as the heart, and this could help identify the secondary effects of PVD and other diseases." Gomberg concurs, "Lung biopsies can be risky, and this might be the first virtual imaging biopsy using FRI." she adds, "The more researchers would understand the technique and see how it can help, the more it may become the standard of care."

APPLICABILITY OF FRI IN A POST-COVID-19 WORLD

The COVID-19 pandemic brought new challenges, not only for researchers in pulmonary medicine, but also for healthcare systems and management. Benza discusses the changes in organizing clinical trials: "COVID-19 impacted clinical trial management, particularly earlier in the pandemic. However, the pandemic is showing us, we have the potential to run clinical trials distantly. We never tried that before, but it worked. Using technologies that can remotely help assess patients without going to a crowded hospital is appreciated by most patients. Technologies can certainly alter the ways that trials are designed in the future and reduce expenses."

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Gomberg explains her clinical experience from the recent past: "We could not conduct some tests (e.g., ventilation/perfusion scans) due to the chances of higher COVID-19 exposure. Comparably, CT scans are much faster, and once FRI is widely available, we can assess everything that the older testing methods could not do during the pandemic. During the pandemic, we saw many patients with PVD and varied risk status. To meet this problem, FRI could help detect individuals with or without pulmonary pneumonia – to screen the risk level." Both Gomberg and Benza are interested in research on long-hauler COVID and the associated attrition of the pulmonary vasculature, which causes long-term breathlessness and fatigue. Several preliminary studies suggest that this attrition could be measured by FRI. To this end, research on the topic is ongoing.

Other diseases could also benefit from a widespread adaptation of FRI. Benza explains, "Nearly 60% of patients with scleroderma could develop Group 1 PAH. With FRI, we could detect the effects in their blood vessels." Benza suggests further that patients with heritable PH experience changes in their lungs before symptoms develop, and that imaging changes to the blood vessels would be highly beneficial. HIV is another example – people living with HIV have a five-fold higher risk of developing PH than the general population. Using screening tools like FRI, PH could be detected in at-risk patients earlier in the course of the disease.

POTENTIAL CHALLENGES FOR FRI IMPLEMENTATION

As with any new technology, there are challenges to acceptance and use, including competing technologies. Benza discusses his experience with a Xenon-based MRI imaging technique, "It involves cardiac MRI, which is far less practical than the CT scans. Not to forget, CT scans have their own negative implications in terms of radiation (1 CT scan = ~ 50 X-rays). But FRI uses a minor amount of radiation compared to a standard CT scan."

Gomberg raises another significant challenge: reimbursement of imaging techniques from payers. "In the USA, refund of imaging techniques could be challenging and works on a case-to-case basis. Radiologists are particularly concerned about new technologies from an operational standpoint."

THE FUTURE OF FRI

"The USA FDA is looking for disease-modifying outcomes in clinical studies, and FRI could be one of the first technologies that can actually be described as a disease-modifying endpoint," explains Benza. In his view, FRI may serve as a tripartite tool: for early diagnosis and screening of at-risk individuals, to track disease progression and manage patient expectations, and to stratify patients into different treatment groups based on their disease state. Benza explains, "Using FRI, we could track the effects of treatments, and learn which would be effective to stabilize patients in an early stage without needing a transplant." Gomberg supports Benza and concludes, "We are also excited about FRI because of its capacity not only in Group 1 but also in Groups 2 and 3 PH. Imaging the small vasculature is going to make a big difference."

FRI advances the patient care journey in pulmonary hypertension

Innovative technologies are necessary to improve diagnosis and treatments in patients with pulmonary hypertension (PH). As a non-invasive tool that gives detailed information about the smallest blood vessels of the lungs, Functional Respiratory Imaging (FRI) could become a pivotal tool to evaluate novel disease-modifying therapies in clinical trials and to improve early diagnosis of this disease. Dr. Roham Zamanian, Associate Professor of Medicine at Stanford University School of Medicine and the director of the Adult Pulmonary Hypertension Service at the Vera Moulton Wall Center for Pulmonary Vascular Disease, explains how his current collaborations with the Fluidda team have convinced him that FRI could revolutionize the way that PH is diagnosed and treated.

ROHAM ZAMANIAN

Roham Zamanian, MD, is associate professor of medicine (pulmonary and critical care medicine) at Stanford Hospital and Clinics. Dr. Roham Zamanian specializes in the treatment of pulmonary hypertension, right heart failure, and pulmonary embolism. He has more than 19 years of sub-specialty experience in pulmonary vascular diseases. Zamanian is considered one of the leading national experts in clinical trials and drug development for pulmonary hypertension.

PH is a chronic and progressive disease associated with high blood pressure in the vessels of the lungs which causes symptoms like shortness of breath and fatigue. Currently, there is no cure for PH and the standard of care consists of vasodilators, which relieve symptoms but cannot halt disease progression.

Zamanian explains why the current strategies for patient care are not satisfactory, “PH is not only a vasoconstrictive disease, which is what vasodilators treat, but an angio-proliferative disease in which a certain lineage of cells present cancer-like proliferation and create vascular occlusion and vessel dropouts, which in time cause severe damage to the lung vasculature. We need new therapies that can have a more lasting impact by addressing the underlying mechanisms of the disease and the vascular changes that occur in PH.”

THE SEARCH FOR DISEASE MODIFYING THERAPIES IN PULMONARY HYPERTENSION

Researchers have studied the damage to the vasculature that occurs in PH by looking at the explanted lungs of patients who have received a transplant to save their lives. "The pathology of these end stage organs was very advanced with vascular occlusion and lesions," explains Zamanian. "This shows that while vasodilators cause physiologic improvement there is no reverse remodeling and the disease keeps progressing even when the patient gets treatment. We currently have approximately 14 advanced therapies that can improve vascular constriction, but these cannot prevent the damage to the lungs, and most only offer temporary relief."

Over the past five years, there has been an increasing interest in making new therapies that can have long lasting effects available to PH patients. "Unlike vasodilators, these therapies would be disease modifying. This means that they could effectively slow disease progression and even revert lung damage over time," explains Zamanian. "Some of the genetic and molecular mechanisms responsible for the damage in the vasculature of the lungs of PH patients have been identified. So, we have a starting point to develop therapies that can address the angio-proliferative aspect and prevent lung damage, but we need a technology that will allow us to evaluate whether a drug is indeed disease modifying, and I think this is where FRI may play a relevant role."

FRI AS A TOOL TO ASSESS DISEASE MODIFYING THERAPIES FOR PH

The damage to the pulmonary vasculature of PH patients starts in the smaller blood vessels of the lungs. To evaluate the potential of an experimental therapy in a clinical trial, researchers require a technology that can accurately assess subtle changes in these vessels over time. Currently, it is possible to measure how a therapy alters general processes like blood flow patterns or ventricular function, but these approaches cannot reach the level of detail required for new PH therapies. It is also possible to examine changes in the small vasculature through lung biopsies, but this approach is invasive and poorly tolerated by patients who may already be quite sick. FRI allows clinicians to study changes in blood vessels with a diameter of one millimeter or more and relies on CT scans, which are non-invasive procedures, making it an ideal tool to assess new PH therapies in clinical trials.

"If FRI has the capacity to accurately define small vascular changes – and I think it has a high potential to do so – it could become the first surrogate marker of distal vascular changes in pulmonary arterial hypertension. This would be extremely important for the field," explains Zamanian. "FRI by itself will not be enough, but in combination with the right drug acting on the right mechanism and the right clinical trial design, it could be the technology that helps us convince ourselves and the regulatory agencies that an experimental therapy is indeed disease modifying."

IMPROVING PH DIAGNOSIS AND MANAGEMENT

PH is a rapidly progressing disease and even small increases in pulmonary artery pressure have a substantial impact on long term morbidity and mortality, so ensuring early diagnosis is as important as developing new disease modifying therapies. Currently, clinicians rely on invasive pressure measurements in the pulmonary artery to diagnose PH. The threshold for high pulmonary artery pressure was recently decreased from 25 mm Hg to 20 mm Hg to improve the chances of early diagnosis. However, it would be ideal to have a non-invasive approach, such as FRI, to detect early disease.

"We need to gather more data and answer some questions before we can implement FRI for early diagnosis of PH," says Zamanian. "For example, what exactly is normal and abnormal, what are meaningful clinically incremental changes over a period of time, and what is a normal BV5% [1]. In the future, these parameters could become adequate markers for early disease."

FRI could also play a role in evaluating disease progression and overall patient state once PH has been diagnosed. Follow up currently relies on the results of several exams such as CT scans, MRIs, and exercise tests. According to Zamanian, combining these approaches and taking advantages of new technologies could give a better picture of the state of a patient, informing the clinical course of action. "I would like to see if FRI could be combined with what we consider provocative maneuvers for the diagnosis of earlier disease. In our lab, we perform re-catheterization with exercise plus incremental resistances. Currently, it is plausible to obtain adequate CT images of a person at different exercise stages and identify

> **FRI could become the first surrogate marker of distal vascular changes in pulmonary arterial hypertension.**

the overall vascular conditions for each exercise state. If we can use FRI data to determine what early PH looks like under these conditions, that would be a tool for patient follow up. There is already research showing that you can do these kind of exercise challenges with cardiac MRI. I think it is possible to put together a similar protocol using CT and FRI."

GATHERING THE MISSING DATA

The Fluidda team has a strong interest in establishing academic collaborations to better understand pulmonary vascular disease and help generate the data that would allow FRI to become a relevant tool in clinical trials and in clinical practice. "The culture of the Fluidda team is one of discovery and advancement," says Zamanian. "As an academic, it was easy to connect with them and have a conversation about what can be done, what are the hurdles, and what is the missing information that needs to be generated by research. This is not very common in collaborations between academia and industry."

In collaboration with the Fluidda team, Zamanian and other researchers are studying a large cohort of patients with PH and well-established phenotypes. CT scans are assessed using FRI to understand how changes in BV5 relate to clinical changes and responses to medication. These data could help predict clinical outcomes and guide patient management in the future. In a second collaboration, researchers use a combination of FRI and molecular imaging data to characterize hidden phenotypes of PH and refine molecular clusters that were previously identified as relevant for long term outcomes.

Zamanian is also collaborating with Fluidda in a clinical trial that is assessing the impact of a novel therapeutic for COVID-19 in non-hospitalized patients with mild symptoms. They are using FRI to evaluate the impact of the disease on the patients' vasculature, and to determine whether treatment with the investigational drug alters this process.

THE FUTURE OF FRI

FRI is reaching the tipping point where it could stop being just a research tool and enter the clinical space. "Once we establish the normal and abnormal thresholds and clinically meaningful incremental differences that FRI can show us, the clinical applicability of this technology will become increasingly apparent," says Zamanian. "I can think of scenarios where clinicians could use FRI to evaluate if a therapy is making substantial progress in curing the patients, not only in the context of PH, but also pulmonary embolism and other vascular diseases of the lung."

"As soon as enough data come through, I do think that the medical community will embrace FRI and incorporate it into their routine procedures," concludes Zamanian. "A typical PH workup already includes a CT scan so it's not unreasonable to think that along with that CT scan one would request an FRI analysis of the vasculature."

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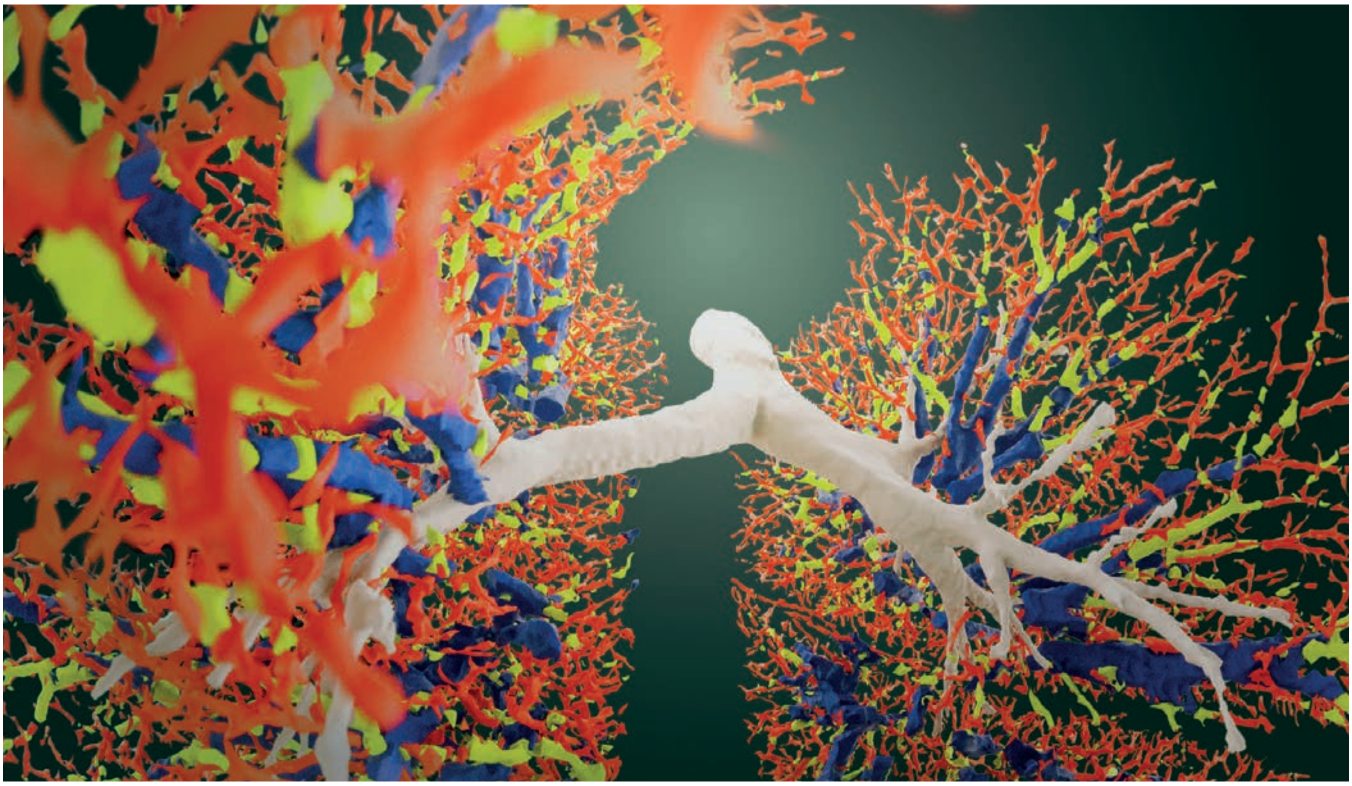
1. BV5% is the percentage of blood volume in vessels with a cross-sectional area between 1.25 and 5 mm^2 relative to the total pulmonary blood volume



FLUIDDA
Respiratory solutions for better patient care

From COPD to COVID-19: The potential of FRI in general pulmonology

Technological advances have unleashed the potential to better treat prevalent lung diseases. Approaches like quantitative computerized tomography (CT) are increasingly used in routine care to guide the diagnosis, treatment, and follow-up of diseases like chronic obstructive pulmonary disease (COPD) in developed countries. Dr. Victor Kim, Professor of Thoracic Medicine and Surgery, explains how imaging technologies will soon play a bigger role in pulmonary care.

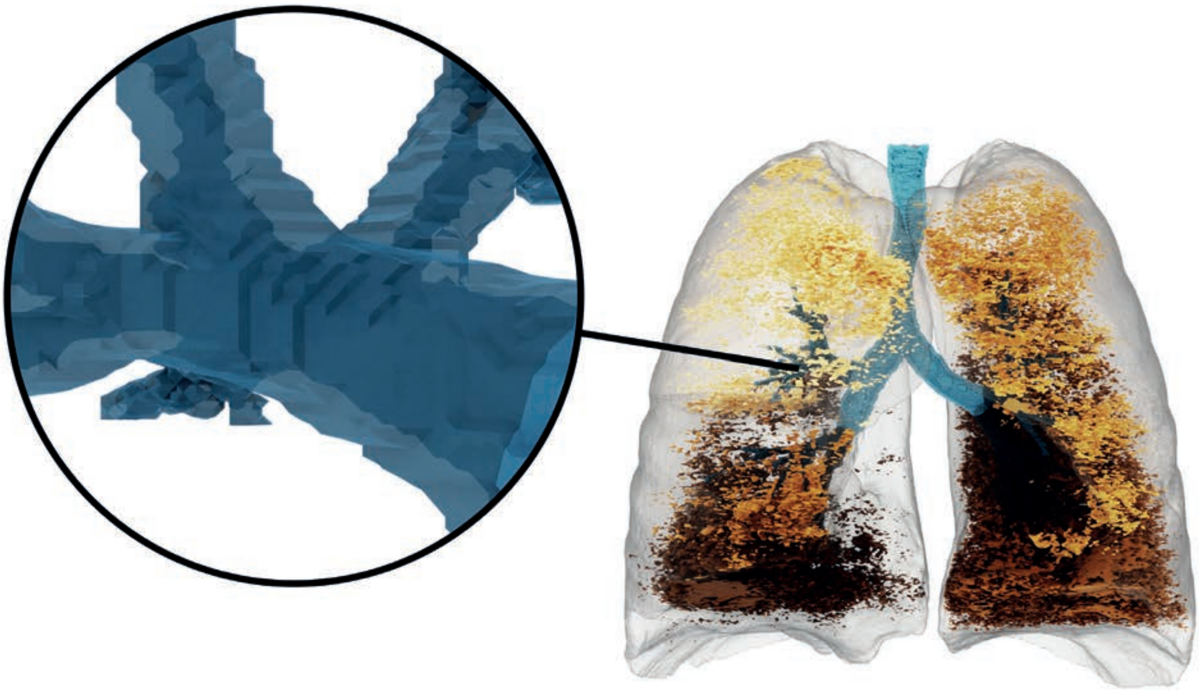
VICTOR KIM

Victor Kim, MD, is a professor of thoracic medicine and surgery at the Lewis Katz School of Medicine at Temple University. He is a pulmonary, critical care, and sleep physician who is heavily involved in clinical and translational research in COPD, particularly chronic bronchitis.

"A decade ago, we predominantly diagnosed lung diseases by surgical lung biopsy,' says Kim. "This involves exposing an already ill patient to the increased risks of an invasive procedure. Thanks to advances in technology, now we can use patient-friendly approaches like CT imaging, radiographic patterns, and genetic phenotyping to diagnose and categorize these individuals. These technological advances definitely provide better options of care for pulmonary patients."

QUANTITATIVE CT TECHNOLOGY IN COPD

In countries like the United States, CT scans have become commonly used to diagnose lung diseases and direct the course of treatment. With better resolution of CT scans, it is now possible to extract more information from these images. Quantitative CT (qCT), an umbrella term that describes technologies extracting numerical data from CT scans, such as FRI, can take this practice to the next level and create more data around pulmonary conditions.



The COPD community has a long history of employing qCT to guide patient diagnosis. Over the past 3 decades, techniques such as CT densitometry have been increasingly used to gather information about air trapping and airway abnormalities. "qCT provides more information than spirometry and chest X-rays. It allows us to make better-informed decisions in diseases like COPD," explains Kim. "We are currently using qCT to establish the extent and pattern of emphysema, which allows us to determine the patients' eligibility for procedures like lung reduction. There are emerging interventions for chronic bronchitis, and the ideal candidates for those are with less emphysema. qCT also plays a role in this setting. These quantitative technologies allow us to obtain otherwise unavailable information and significantly improve patients' lives," he adds.

THE POTENTIAL ROLE OF FRI

FRI does not have a place in the clinical practice of COPD yet, but it may in the future. "There is currently a lot of interest from the research community about using new CT technology to establish phenotypes for different lung diseases," clarifies Kim. "The ability of FRI to assess parameters like blood volume, dynamic airway volume, and total airway count will be paramount in this process." Most of the current reference studies to establish phenotypes in lung diseases were performed using pathology specimens; however, with the advent of non-invasive technologies providing more detailed data, as in the case of FRI, it might be possible to advance the field to a point where risky procedures can be completely avoided.

As new data on COPD imaging is generated, the utility of FRI in management of this disease improves. Kim states, "We have performed several multi-institutional research projects, looking at many COPD patients over 10–15 years using repeated imaging. The results of these studies are developing right now, which opens the door for technologies like FRI to provide relevant information on COPD progression."

"FRI could replace outdated technologies that we still use in routine clinical care," says Kim. "We currently use ventilation perfusion scans – a nuclear medicine study – to measure how much air is being ventilated into certain regions of the lung. This technique is cumbersome, but we still use it for surgical planning and transplantation. FRI could provide regional gas exchange data with greater detail. Thus, giving us a tool to treat patients with greater accuracy."

CHALLENGES IN GLOBAL IMPLEMENTATION

As more data emerges, the possible applications of FRI in lung diseases like COPD seem endless. Nevertheless, challenges still exist when it comes to worldwide implementation. The global guidelines for lung diseases are still based on the current standard of care, spirometry. Global guidelines consider healthcare settings that may not have access to such technologies, despite these technologies providing richer, more personalized information. Kim explains, "In developed countries, it is quite easy to do CT scans of lung patients. In our practice, we do it as a routine procedure, and you could apply FRI to those images to get a better idea of the patient's lung function. However, you also must consider the kind of care that patients get in low- and middle-income countries. It might be

> **The ability of FRI to assess parameters like blood volume, dynamic airway volume, and total airway count will be paramount in determining new phenotypes of lung disease.**

difficult to have access to CT scans in these countries, as some even struggle to have access to spirometry. So, global guidelines are currently cautious to advocate for widespread use of imaging tools, despite their clear potential." Countries that can afford to use imaging techniques will continue using them to improve patient care, and this will decrease the cost of CT scans over time, in turn making the technology more readily available to everyone.

USING FRI TO ADVANCED COVID-19 RESEARCH

The COVID-19 pandemic changed research priorities in pulmonology, and clinical centers worldwide had to rapidly adapt to deal with this new disease in the best way possible. Now with the number of long COVID patients increasing, new data are becoming available on potential treatments, diagnostic tools, risk factors, predictors for severe disease, and long-term phenotypes. Promptly generating reliable data to provide better care to these patients is of paramount importance. In the post-COVID era, researchers and clinicians will establish new collaborations with industry to test new technologies, enabling FRI to gain more visibility, perhaps even in clinical practice.

Kim was aware of FRI already before the pandemic, but he became more interested in the technology when he saw its potential to assess the pathophysiology of COVID-19 in a non-invasive way. So far, he has done two collaborations with Fluidda. The first focused on the relationship between blood volumes and post-COVID lung function [1]. The study found that patients with COVID-19 who had pulmonary vascular abnormalities at the time of hospitalization, especially in the medium and large vessels, were at higher risk of having low diffusion capacity of carbon monoxide (DLCO, a measure of lung function) even three months after discharge.

The second study included more patients and focused on patients who complained of breathlessness after COVID-19 [2]. Kim explains, "We found a relationship between alterations in the blood flow patterns of the lung and the perception of breathlessness after infection. These types of relationships are difficult to quantify based on traditional lung function parameters like exercise or physiology. So, having access to FRI was determinant in this case." The results of this study were presented at the 2021 annual meeting of the American College of Chest Physicians.

THE FUTURE OF FRI IN GENERAL PULMONOLOGY

The COVID-19 pandemic changed how the world looked at lung diseases, leading to a drastic change in research priorities and a worldwide interest in the consequences of neglecting holistic pulmonary care. This has opened the door for novel imaging technologies to become more readily available and play a more prominent role worldwide. Kim postulates, "I think that advanced radiology techniques like FRI will have a greater role in acute and outpatient care of pulmonary patients in the future. This technology could help us identify several phenotypes in lung disease, inform which patients are the best candidates for certain procedures, and determine how to treat patients with greater accuracy."

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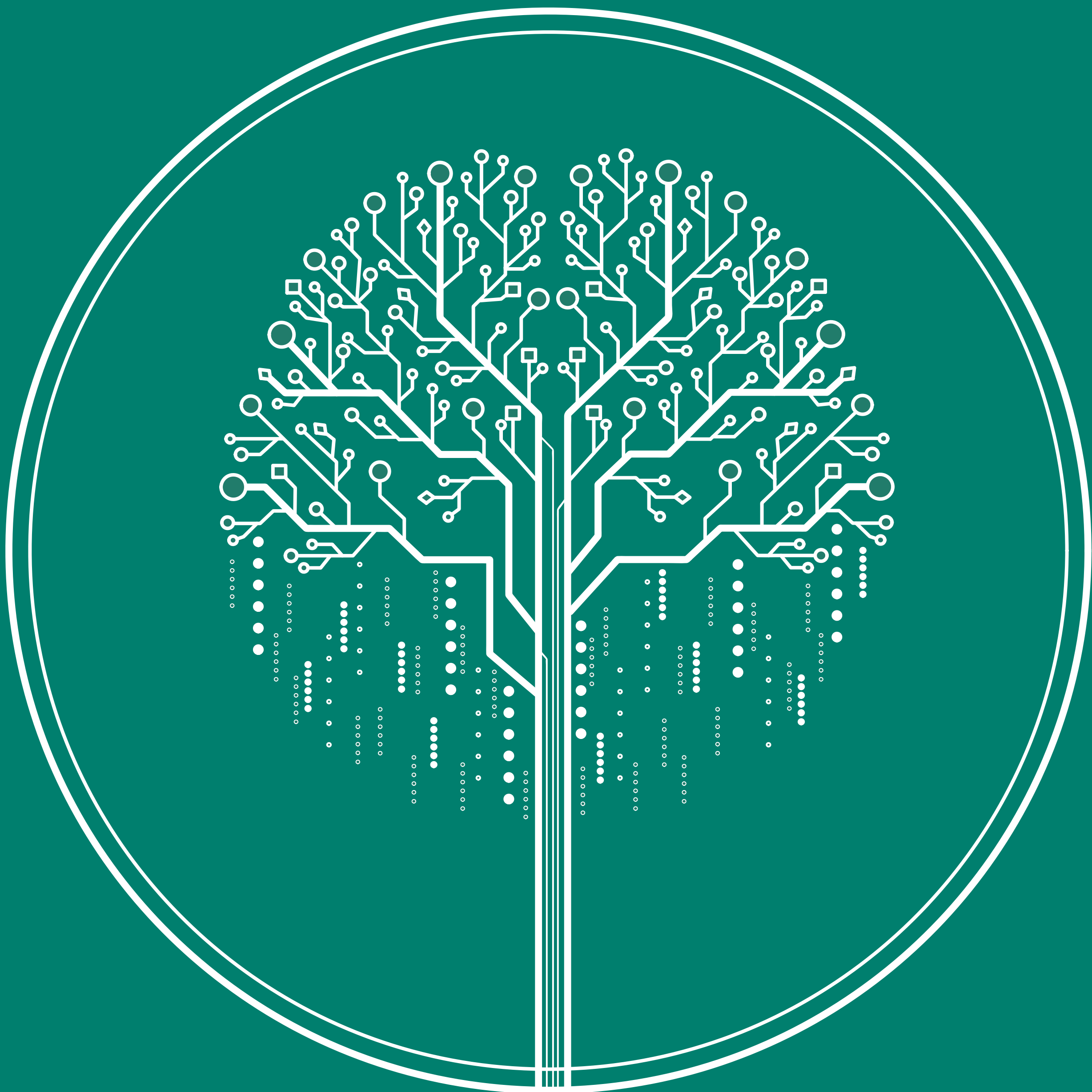

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