Biomedical digital twins of the heart and lungs: from bench to bedside

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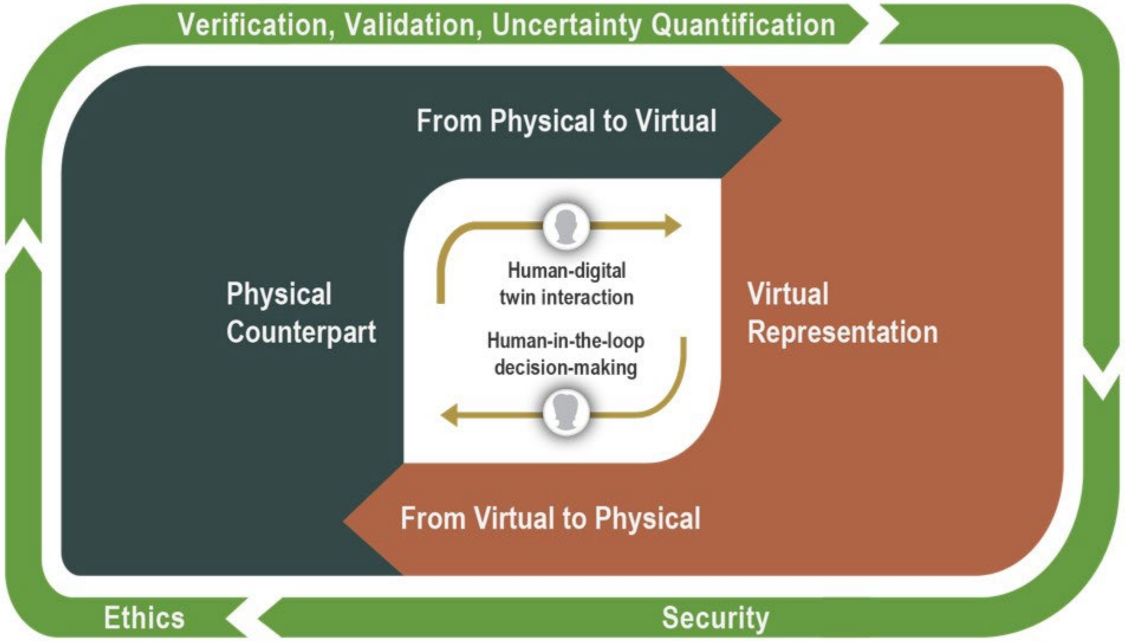
Professor, Department of Internal Medicine and the Oden Institute for Computational Engineering and Sciences

Director of the Center for Computational Medicine

Biomedical Digital Twins (my synopsis)

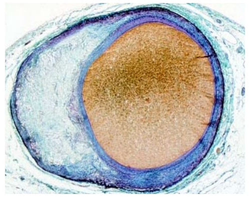
Virtual model of biological system that …

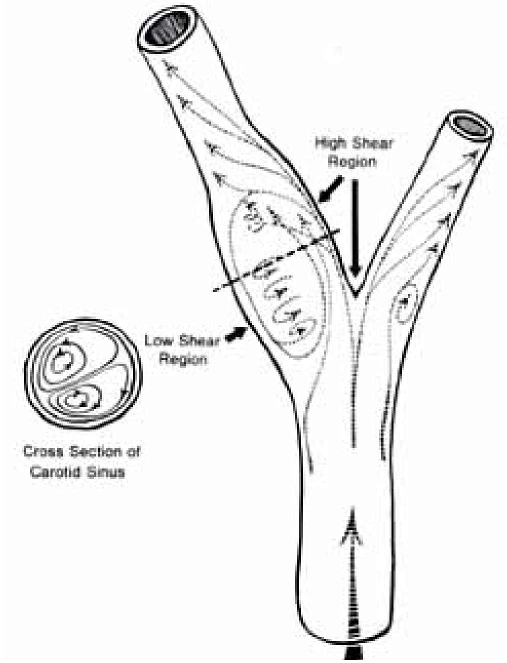
1. mimics the biological system
2. is fit for purpose
3. is created & updated with data from its biological twin
4. has a predictive capability to inform decisions for the biological twin



Methods for Quantifying Blood Flow circa 1980's and 1990's

<u>In Vitro models of flow in Carotid Arteries (1983)</u>
(Zarins, Giddens, Glagov - Univ. Chicago, GA Tech.)

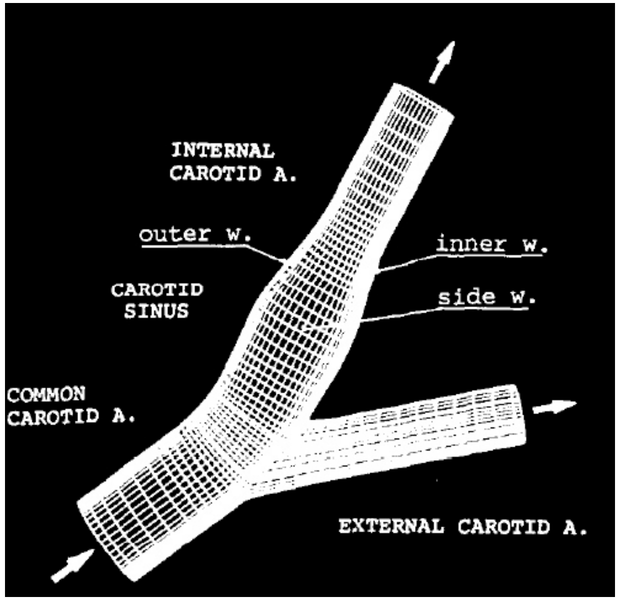


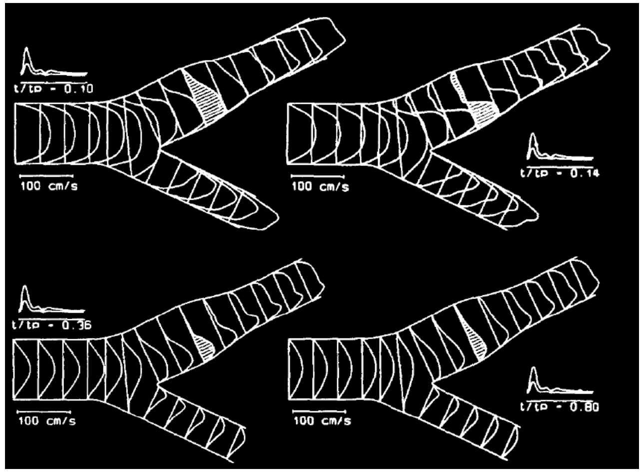


Localization of atherosclerosis in low shear region of carotid sinus

Zarins et. al. Circ Res 53:502-514, 1983

<u>Computer Models of Blood Flow (1980's-1990's)</u>
(K. Perktold – Graz, Austria)



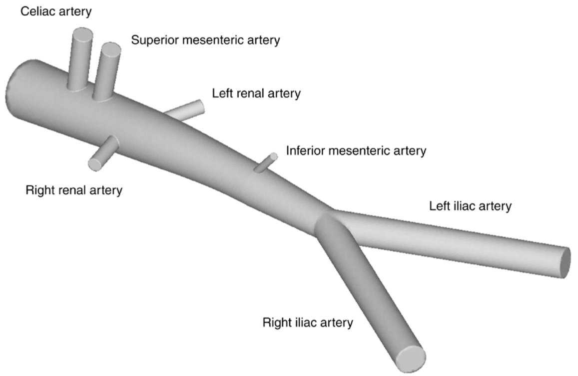


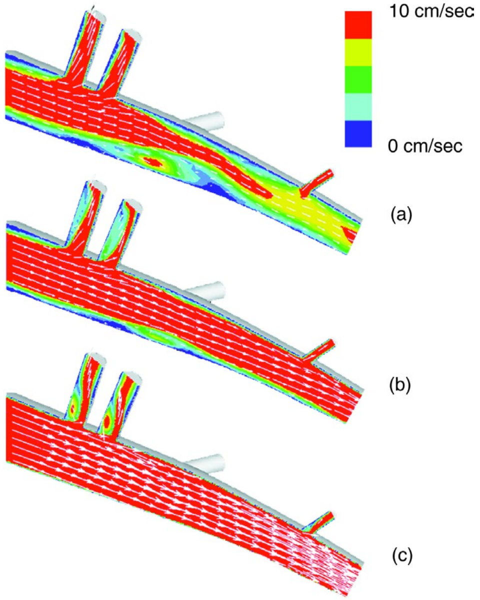
3D CFD Solution of pulsatile flow and wall shear stress in the carotid artery bifurcation

Perktold et. al. J. Biomech. 24: 409-20, 1991.

Modeling Blood Flow in Arteries - mid 1990's

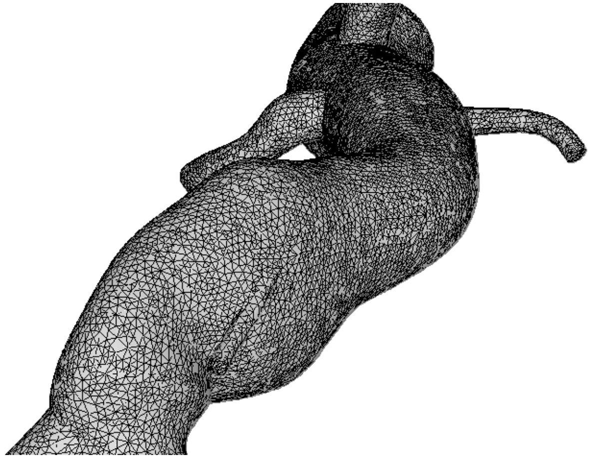
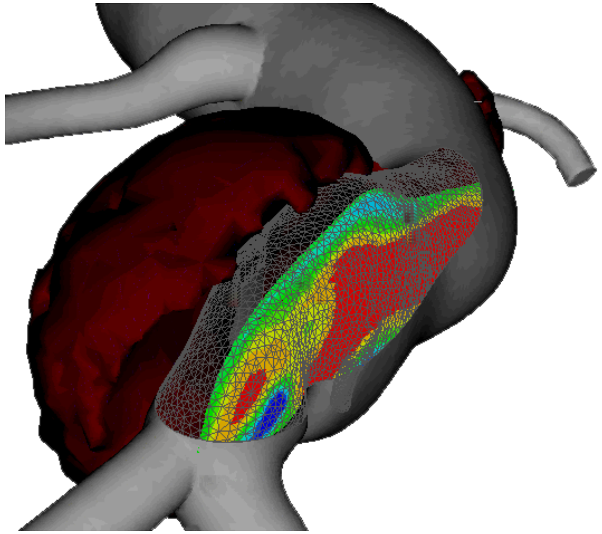
- Taylor *et al*. solved 3D pulsatile flow in abdominal aorta to examine role of hemodynamics in localization of atherosclerosis[1,2]
- Vessel walls were assumed rigid, geometries very simple, boundary conditions highly idealized
- No ability to predict flow distribution or model pressure at physiologic levels





1. C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1998) Finite Element Modeling of 3-dimensional Pulsatile Flow in the Abdominal Aorta: Relevance to Atherosclerosis. Annals of Biomedical Engineering. Vol. 26, No. 6, pp. 1-13.
2. C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1999) Effect of Exercise on Hemodynamic Conditions in the Abdominal Aorta. Journal of Vascular Surgery. Vol. 29, No. 6, pp. 1077-89

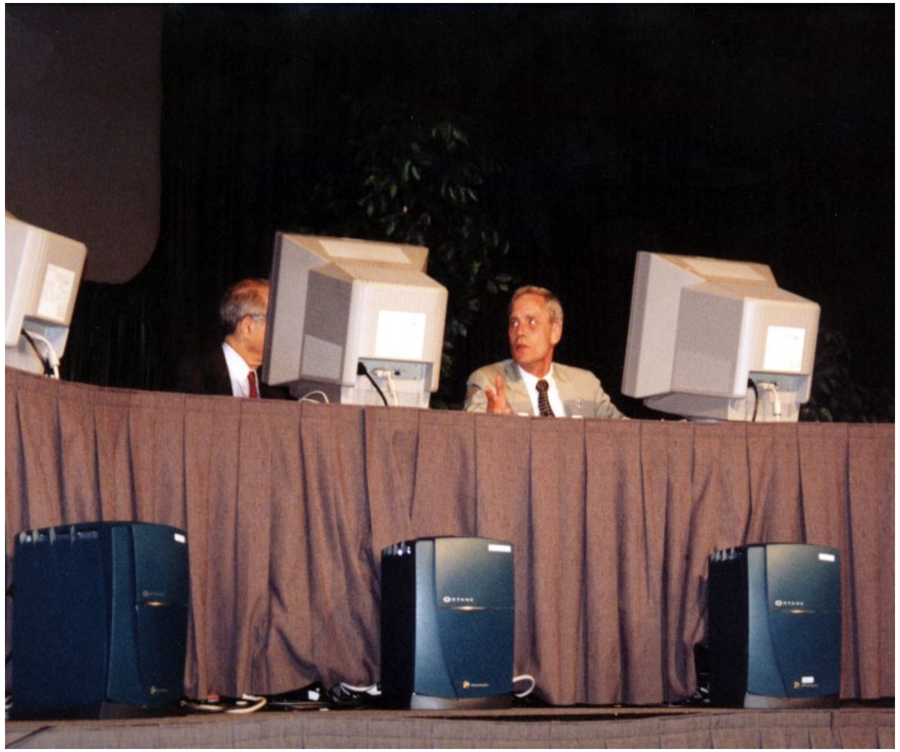
Patient-specific Modeling of Blood Flow started at Stanford University in 1995

1. C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1996) Computers in Physics, Vol. 10, No. 3, pp. 224-232.
2. C.A. Taylor, T.J.R. Hughes, and C.K. Zarins, (1998) Finite Element Modeling of Blood Flow in Arteries. Computer Methods in Applied Mechanics and Engineering. Vol. 158, Nos. 1-2, pp. 155-196.

Predictive Medicine circa 1998

ASPIRE System



Live Demo at 1998 Society for Vascular Surgeons

Taylor et al., Predictive Medicine: Computational Techniques in Therapeutic Decision-Making, *Computer Aided Surgery*, Vol. 4, No. 5, pp. 231-247, 1999.

Predictive Medicine paper published >25 years ago …

Computer Aided Surgery 4:231–247 (1999)

Biomedical Paper

Predictive Medicine: Computational Techniques in Therapeutic Decision-Making

Charles A. Taylor, Ph.D., Mary T. Draney, M.S., Joy P. Ku, M.S., David Parker, B.S., Brooke N. Steele, M.S., Ken Wang, M.S., and Christopher K. Zarins, M.D.
Division of Vascular Surgery, Department of Surgery (C.A.T., C.K.Z.), Department of Mechanical Engineering (C.A.T., M.T.D., D.P., B.N.S.), and Department of Electrical Engineering (J.P.K., K.W.), Stanford University, Stanford, California, USA

ABSTRACT The current paradigm for surgery planning for the treatment of cardiovascular disease relies exclusively on diagnostic imaging data to define the present state of the patient, empirical data to evaluate the efficacy of prior treatments for similar patients, and the judgement of the surgeon to decide on a preferred treatment. The individual variability and inherent complexity of human biological systems is such that diagnostic imaging and empirical data alone are insufficient to predict the outcome of a given treatment for an individual patient. We propose a new paradigm of *predictive medicine* in which the physician utilizes computational tools to construct and evaluate a combined anatomic/physiologic model to predict the outcome of alternative treatment plans for an individual patient. The predictive medicine paradigm is implemented in a software system developed for Simulation-Based Medical Planning. This system provides an integrated set of tools to test hypotheses regarding the effect of alternate treatment plans on blood flow in the cardiovascular system of an individual patient. It combines an internet-based user interface developed using Java and VRML, image segmentation, geometric solid modeling, automatic finite element mesh generation, computational fluid dynamics, and scientific visualization techniques. This system is applied to the evaluation of alternate, patient-specific treatments for a case of lower extremity occlusive cardiovascular disease. Comp Aid Surg 4:231–247 (1999). ©1999 Wiley-Liss, Inc.

INTRODUCTION

Significant advances have been made in the diagnosis and treatment of cardiovascular disease since the introduction of modern medical imaging technology and surgical and pharmacologic therapeutic options. In recent years, three-dimensional (3D) cardiovascular imaging techniques and medical visualization software have enabled physicians to interactively view the cardiovascular anatomy externally and even to "fly through" blood vessels in order to examine sites of disease.[27,30,37–40] In addition to obtaining anatomic data, physicians can obtain physiologic data from a variety of sources, including Doppler ultrasound and magnetic resonance imaging. It is now possible to obtain time-resolved 3D flow fields in the cardiovascular system using magnetic resonance imaging (MRI) techniques in a matter of minutes.[14] In parallel with these developments in diagnostic methods, therapeutic options including conventional surgical repair, minimally invasive endoluminal approaches, and drug and gene therapy have emerged. Within these different classes of therapeutic options lie many more subclasses. The physician must choose

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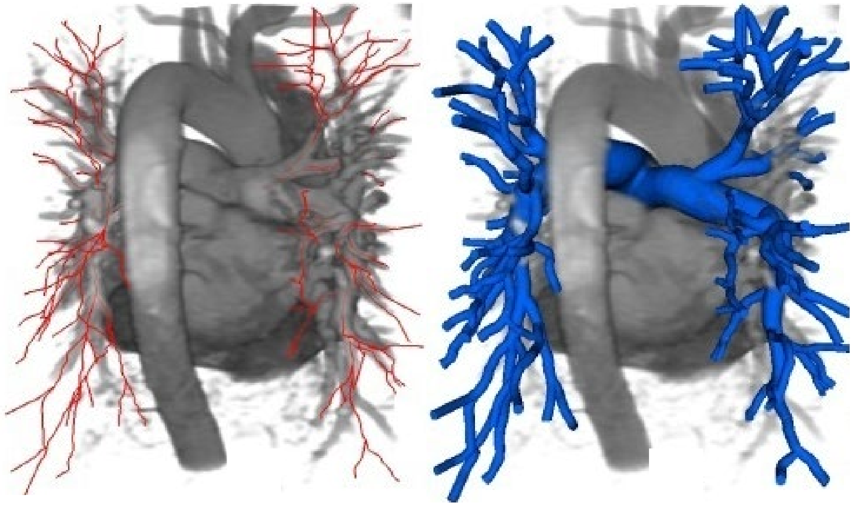
The predictive medicine paradigm, whereby a physician would use diagnostic data to reconstruct a model of an individual's anatomy and physiology, and then use simulation techniques, implemented in a simulation-based medical planning software system, will have important applications in medicine of the future. This approach could allow physicians to "design" improved, patient-specific treatment plans.

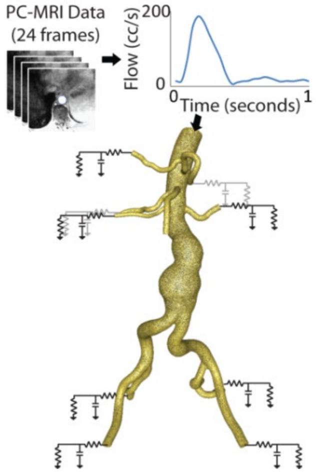
Taylor et al., Predictive Medicine: Computational Techniques in Therapeutic Decision-Making, *Computer Aided Surgery*, Vol. 4, No. 5, pp. 231-247, 1999.

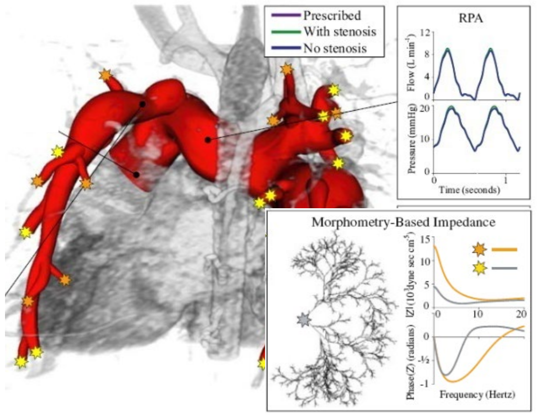
Patient-specific Modeling Core Technology – 2000-2010

Image-based geometric modeling



Physiologically Realistic Boundary Conditions





Fluid-structure interaction methods

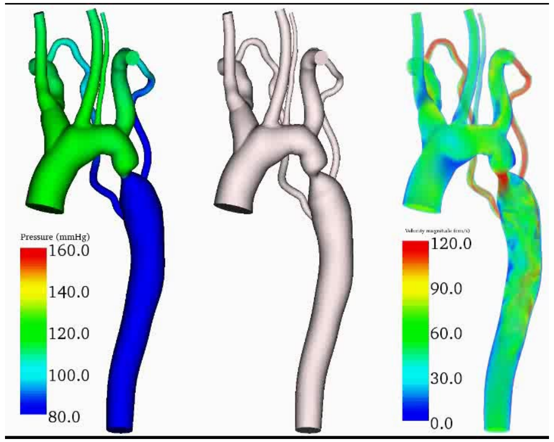
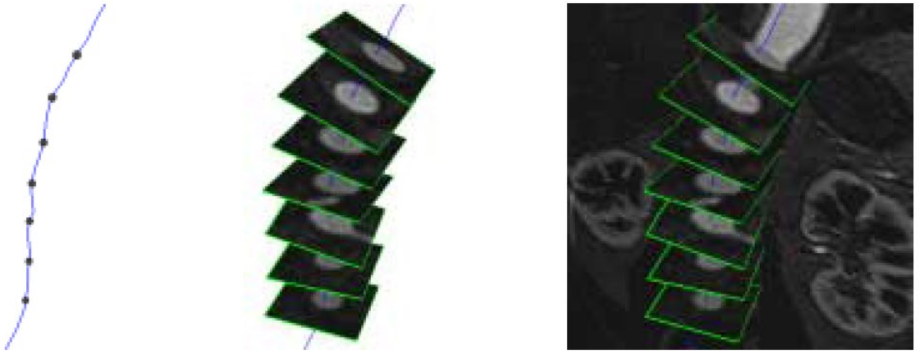
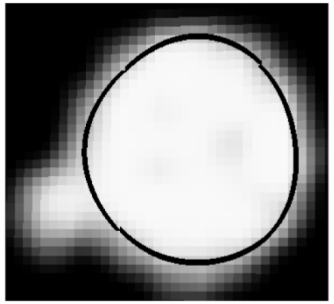


Image-based Geometric Modeling (2D segmentation)

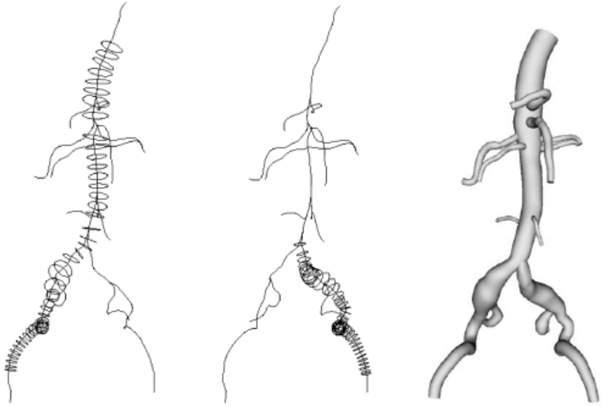
Re-sample image along centerline



Segment vessel on 2D cross-section

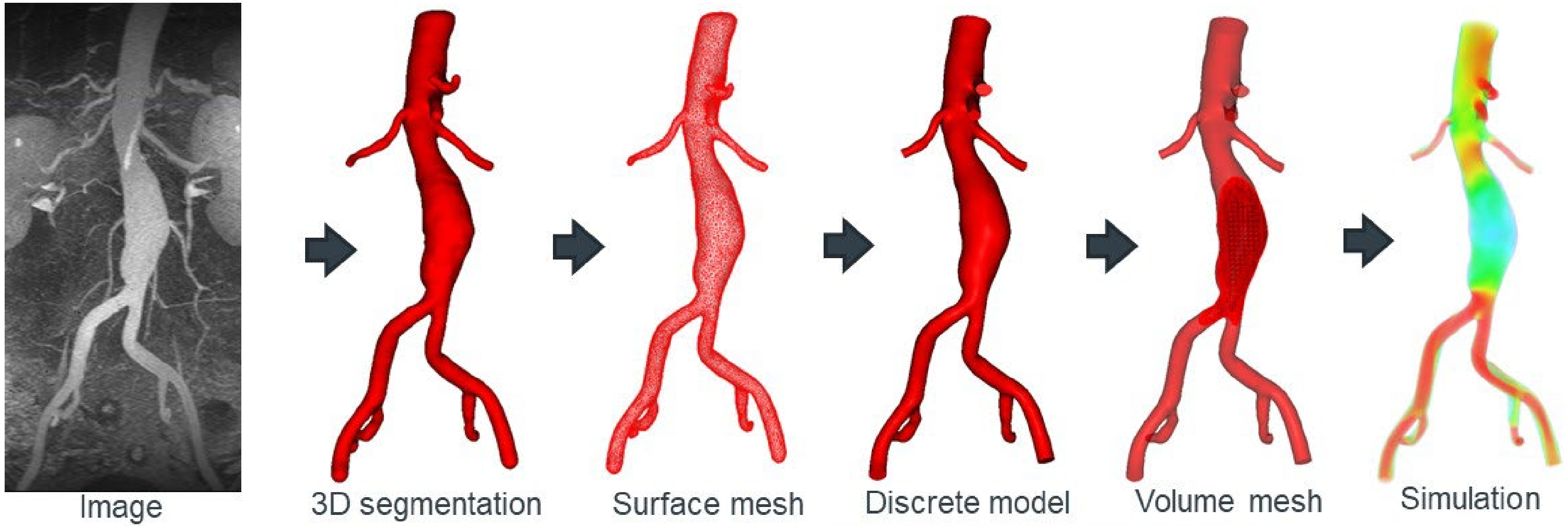


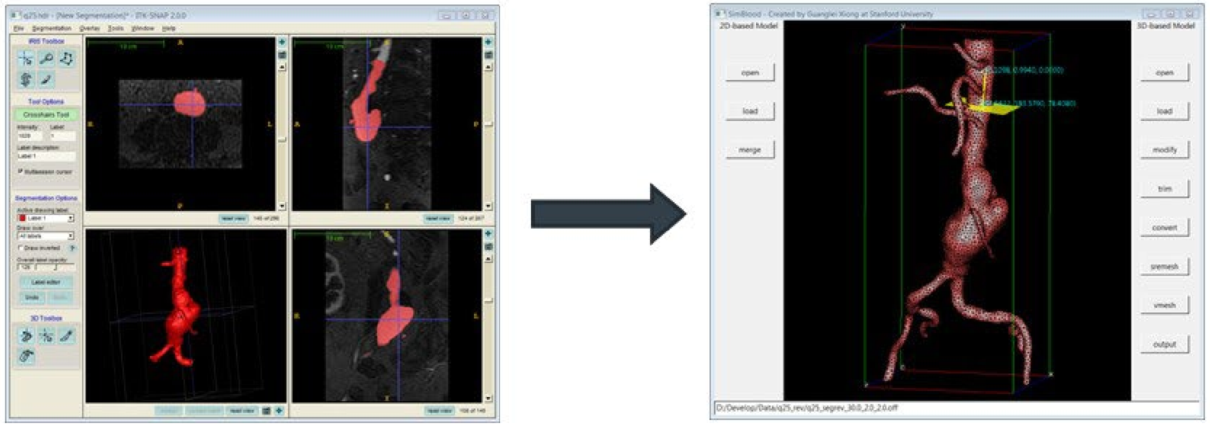
Orient lumen contours along centerlines, loft NURBS surfaces and use geometric union operation to create final 3D model



K.C. Wang, R.W. Dutton, C.A. Taylor, (1999) Improving geometric model construction for blood flow modeling - Geometric Image Segmentation and Image-based Model Construction for Computational Hemodynamics. IEEE Engineering in Medicine and Biology. Vol. 18, No. 6, pp. 33-39.

Image-based Geometric Modeling (Direct 3D segmentation)





G. Xiong, C.A. Figueroa, N. Xiao, C.A. Taylor (2010) Simulation of Blood Flow in Deformable Vessels using Subject-specific Geometry and Spatially-varying Wall Properties. International Journal for Numerical Methods in Biomedical Engineering. Vol. 27, No. 7, pp. 1000–1016.

Coupled Multidomain Method for modeling blood flow[1]…

1. Navier-Stokes equations:

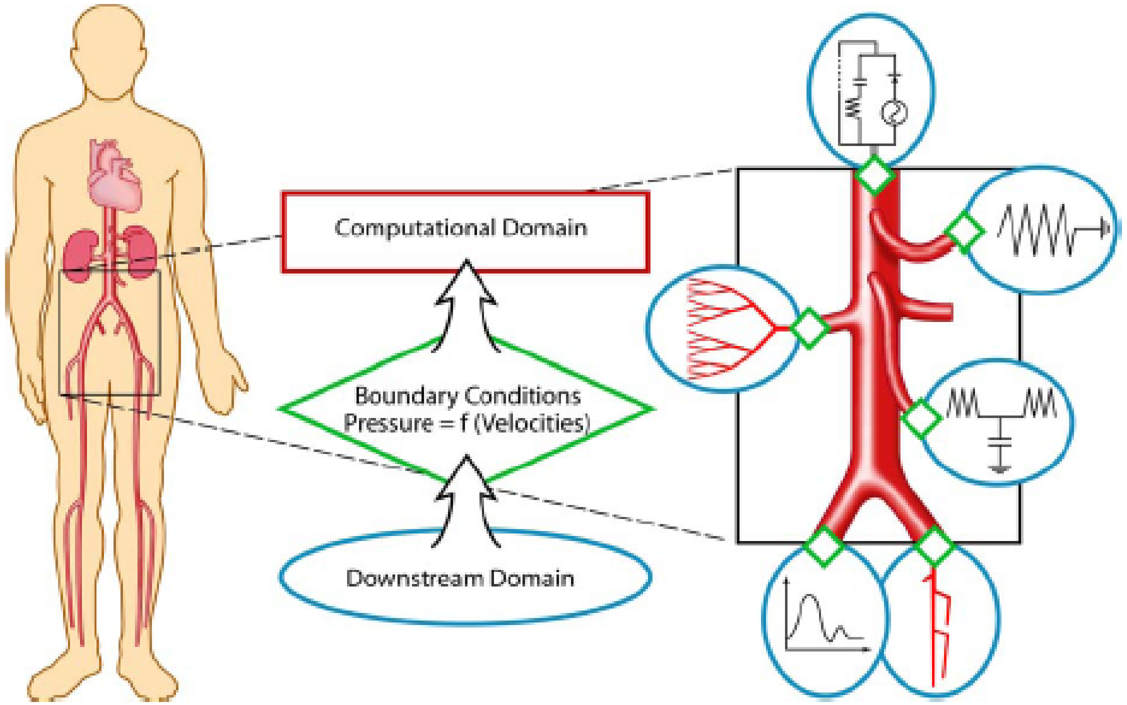
$$\rho\vec{v}_{,t} + \rho\vec{v}\cdot\nabla\vec{v} = -\nabla p + \mu\Delta\vec{v}$$
$$\nabla\cdot\vec{v} = 0$$

2. Weak form:

$$\int_{\Omega}\left\{\vec{w}\cdot\left(\rho\vec{v}_{,t} + \rho\vec{v}\cdot\nabla\vec{v} - \vec{f}\right) + \nabla\vec{w}:\left(-p\underset{\sim}{I} + \mu\Delta\vec{v}\right) - \nabla q\cdot\vec{v}\right\}d\vec{x}$$
$$-\int_{\Gamma_h}\vec{w}\cdot\vec{h}ds + \int_{\Gamma} q\vec{v}\cdot\vec{n}ds = 0$$

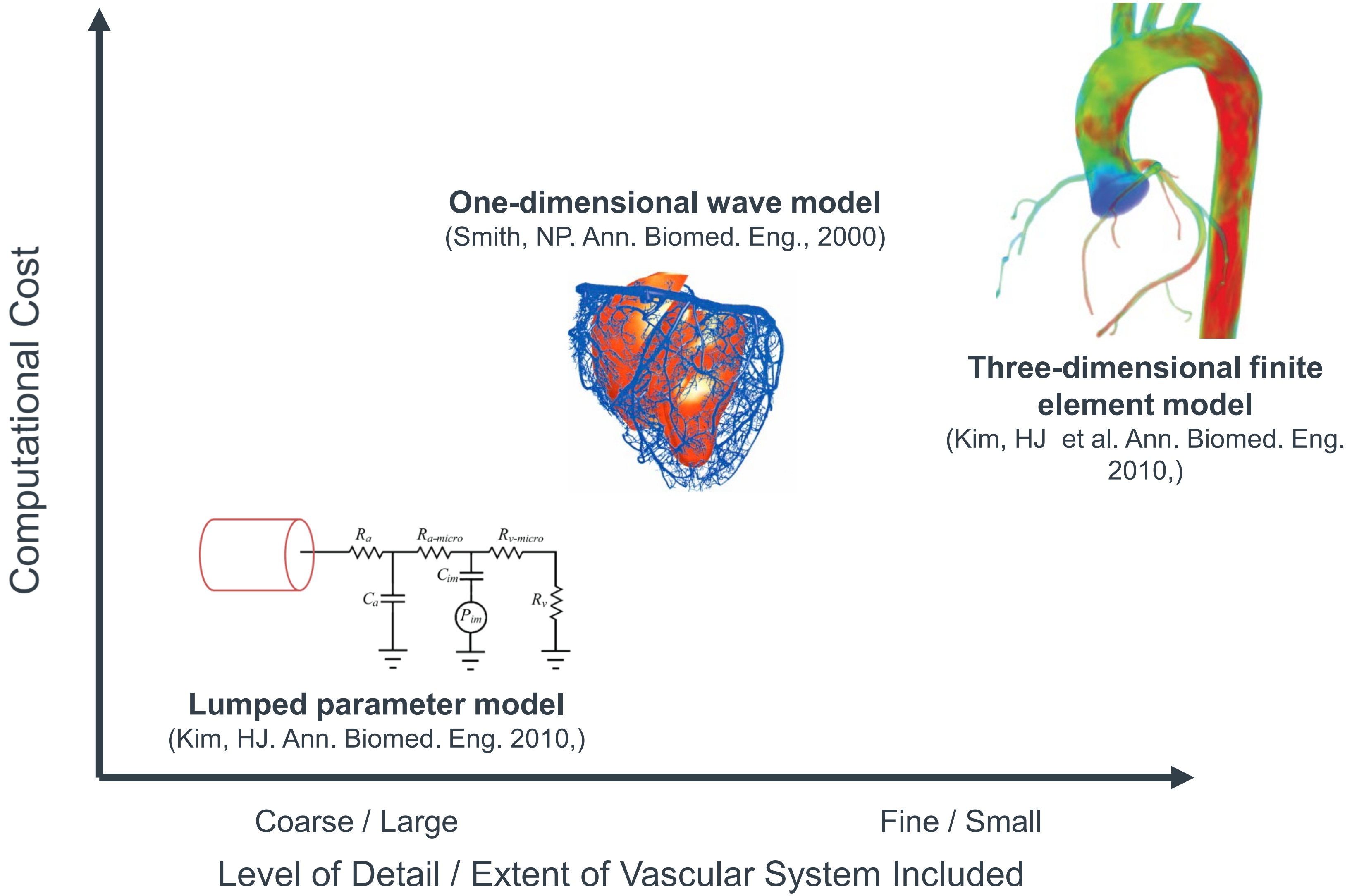
3. Multidomain weak form:

$$\int_{\hat{\Omega}}\hat{\vec{w}}\cdot\left(\rho\hat{\vec{v}}_{,t} + \rho\hat{\vec{v}}\cdot\nabla\hat{\vec{v}} - \vec{f}\right) + \nabla\hat{\vec{w}}:\left(-\hat{p}\underset{\sim}{I} + \underset{\sim}{\hat{\tau}}\right)d\vec{x} - \int_{\hat{\Gamma}_h}\hat{\vec{w}}\cdot\left(-\hat{p}\underset{\sim}{I} + \underset{\sim}{\hat{\tau}}\right)\cdot\hat{\vec{n}}ds$$
$$-\boxed{\int_{\Gamma_B}\hat{\vec{w}}\cdot\left(\underset{\sim}{M}_m(\hat{\vec{v}},\hat{p}) + \underset{\sim}{H}_m\right)\cdot\hat{\vec{n}}ds} - \int_{\hat{\Omega}}\nabla\hat{q}\cdot\hat{\vec{v}}d\vec{x} + \int_{\hat{\Gamma}}\hat{q}\hat{\vec{v}}\cdot\hat{\vec{n}}ds + \boxed{\int_{\Gamma_B}\hat{q}\left(\vec{M}_c(\hat{\vec{v}},\hat{p}) + \vec{H}_c\right)\cdot\hat{\vec{n}}ds} = 0$$

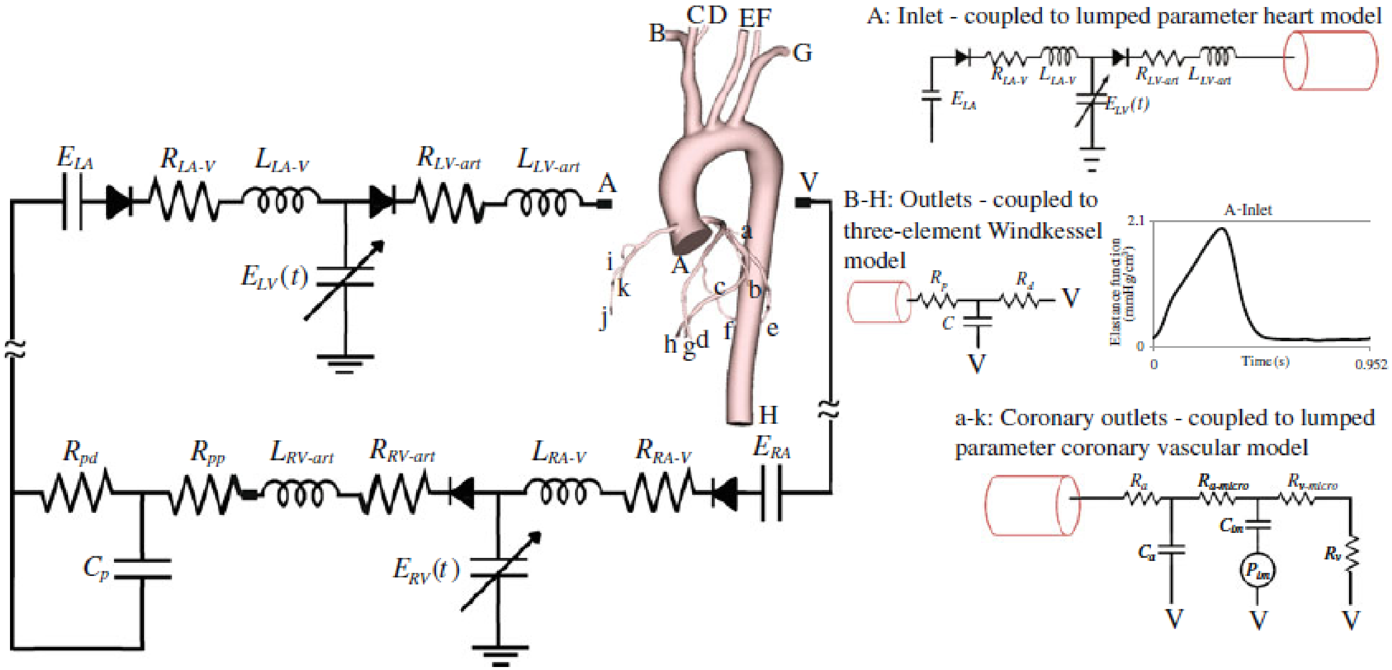


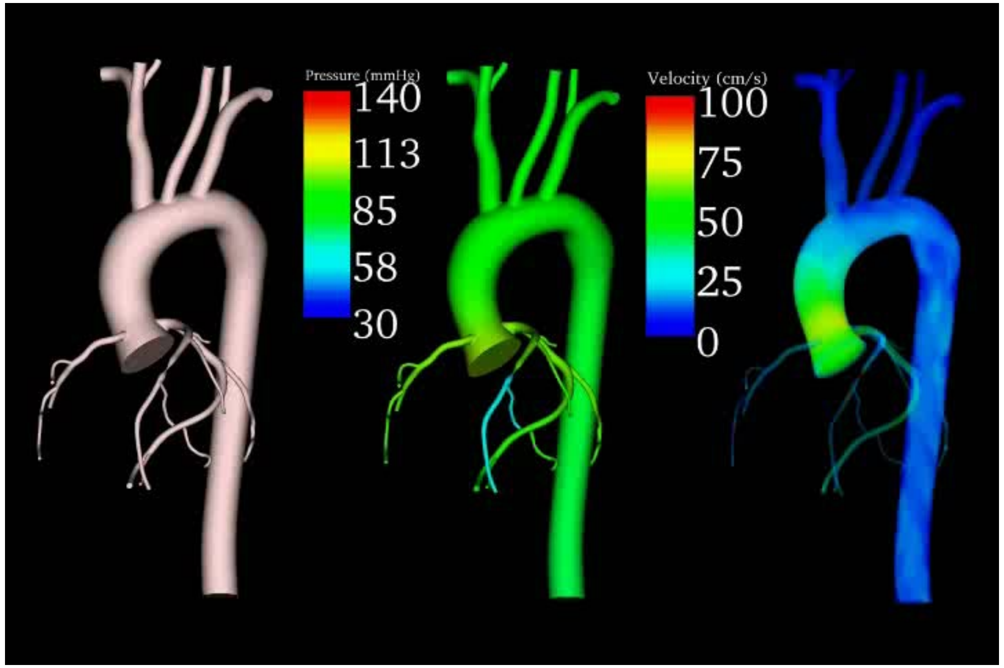
1. I. Vignon-Clementel, C.A. Figueroa, K.C. Jansen, C.A. Taylor (2006) Outflow Boundary Conditions for Three-Dimensional Finite Element Modeling of Blood Flow and Pressure in Arteries. Computer Methods in Applied Mechanics and Engineering, Vol. 195, pp. 3776-3796.

The Coupled Multidomain Method enables efficient and robust coupling between 3D, 1D and 0D models of blood flow



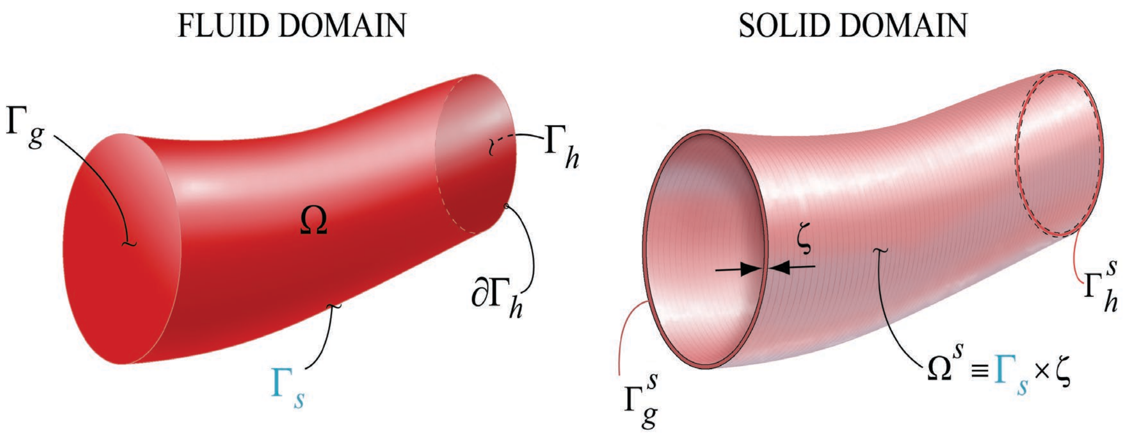
Patient-specific Modeling of Coronary Blood Flow[1]





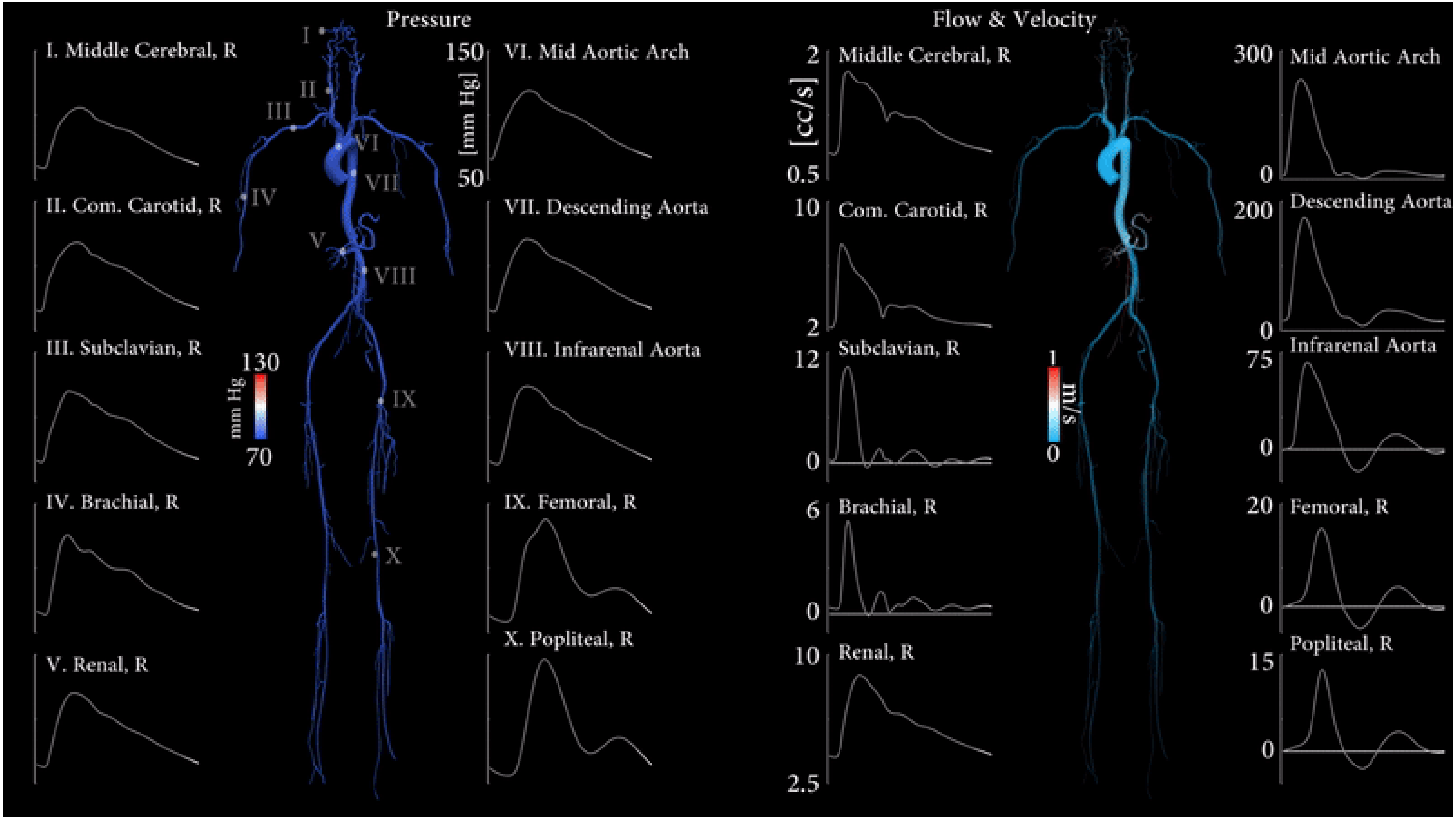
1. H.J. Kim, I.E. Vignon-Clementel, J. Shih, C.A. Figueroa, K.E. Jansen, C.A. Taylor (2010) Patient-specific Modeling of Blood Flow and Pressure in Human Coronary Arteries. Annals of Biomedical Engineering. Vol. 38, No. 10, pp. 3195-3209.

Coupled Momentum Method for modeling vessel wall dynamics[1]



$\nabla \cdot \vec{v} = 0$ $\rho\vec{v}_{,t} + \rho\vec{v}\cdot\nabla\vec{v} = -\nabla p + \nabla\cdot\underset{\sim}{\tau} + \vec{f}$ $\quad (\vec{x},t) \in \Omega \times (0,T)$	$\rho^s \vec{u}_{,tt} = \nabla \cdot \underset{\sim}{\sigma}^s + \vec{b}^s \quad (\vec{x},t) \in \Omega^s \times (0,T)$
$\vec{v} = \vec{g} \quad (\vec{x},t) \in \Gamma_g \times (0,T)$ $\vec{t}_{\vec{n}} = \underset{\sim}{\sigma}\vec{n} = [-p\underset{\sim}{I} + \underset{\sim}{\tau}]\vec{n} = \vec{h} \quad (\vec{x},t) \in \Gamma_h \times (0,T)$ $\vec{t}_{\vec{n}} = \underset{\sim}{\sigma}\vec{n} = \vec{t}^f \quad (\vec{x},t) \in \Gamma_s \times (0,T)$	$\vec{u} = \vec{g}^s \quad (\vec{x},t) \in \Gamma_g^s \times (0,T)$ $\vec{t}_{\vec{n}} = \underset{\sim}{\sigma}^s\vec{n} = \vec{h}^s \quad (\vec{x},t) \in \Gamma_h^s \times (0,T)$
$\vec{v}(\vec{x},0) = \vec{v}^0(\vec{x});\quad p(\vec{x},0) = p^0(\vec{x}) \quad \vec{x} \in \Omega$	$\vec{u}(\vec{x},0) = \vec{u}^0(\vec{x})$ $\vec{u}_{,t}(\vec{x},0) = \vec{u}_{,t}^0(\vec{x}) \quad \vec{x} \in \Omega^s$

C.A. Figueroa, I.E. Vignon-Clementel, K.C. Jansen, T.J.R. Hughes, C.A. Taylor (2006) A Coupled Momentum Method For Modeling Blood Flow In Three-Dimensional Deformable Arteries. Computer Methods in Applied Mechanics and Engineering, Vol. 195, Issues 41-43, pp. 5685-5706.



Xiao et. al. Journal of computational physics. 2013;244:22-40.

TEXAS
The University of Texas at Austin

WHAT STARTS HERE CHANGES THE WORLD

Patient-specific / Image-based Modeling 2009-10

Comput. Methods Appl. Mech. Engrg. 198 (2009) 3514–3523

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ELSEVIER

Open problems in computational vascular biomechanics: Hemodynamics and arterial wall mechanics

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ABSTRACT

The vasculature consists of a complex network of vessels ranging from large arteries to arterioles, capillaries, venules, and veins. This network is vital for the supply of oxygen and nutrients to tissues and the removal of carbon dioxide and waste products from tissues. Because of its primary role as a pressure-driven chemomechanical transport system, it should not be surprising that mechanics plays a vital role in the development and maintenance of the normal vasculature as well as in the progression and treatment of vascular disease. This review highlights some past successes of vascular biomechanics, but emphasizes the need for research that synthesizes complementary advances in molecular biology, biomechanics, medical imaging, computational methods, and computing power for purposes of increasing our understanding of vascular physiology and pathophysiology as well as improving the design of medical devices and clinical interventions, including surgical procedures. That is, computational mechanics has great promise to contribute to the continued improvement of vascular health.

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1. Introduction

Despite significant progress in clinical care and public education, cardiovascular diseases remain the leading cause of death and disability in industrialized nations. Continued advances in molecular and cell biology, biomechanics, medical imaging, computational methods, and computational power promise, however, to revolutionize our understanding and thus treatment of these devastating diseases. There is a pressing need, therefore, to synthesize these many advances into a consistent clinically useful tool.

The goal of this paper is to review biomechanical aspects of some of the primary diseases that affect the vasculature, to note briefly the state of the art in vascular biofluid and biosolid mechanics, and to identify important open problems in both basic research and clinical care. That mechanics plays a fundamental role in cardiovascular health and disease has been known for centuries (e.g., see Young [1], who considered the hemodynamics, or Roy [2], who considered wall mechanics), yet it has only been since the mid-1970s that we have understood why mechanics is truly important. Experiments on vascular cells isolated in culture – both the endothelial cells that line every blood vessel and the smooth muscle cells that endow these vessels with an ability to dilate and contract and thereby control local blood flow – reveal that altered mechanical loading can induce changes in gene expression. It is, of course, the associated changes in cellular activity (e.g., proliferation, migration, differentiation, synthesis and degradation of proteins, programmed cell death) that result in both appropriate adaptations during development, maturity, and exercise and maladaptive consequences during disease progression. Let us begin, therefore, with a brief discussion of the normal vasculature.

2. Brief on vascular organization and structure

The vasculature serves as a conduit for blood flow. It thereby facilitates the exchange of oxygen/carbon dioxide, hormones, nutrients, and waste products between the blood and tissues throughout the body; it facilitates immune and reparative processes; and it aids in the regulation of body temperature. Consisting of a complex network of billions of nearly cylindrical branching tubes, the vasculature can be divided into five types of vessels: arteries, arterioles, capillaries, venules, and veins. Each vessel serves a unique function and, consequently, possesses unique structure and properties. We focus on arteries in this paper, but emphasize the importance of understanding the biomechanics of each part of the vasculature (e.g., see [3]), particularly the veins which are often used as arterial substitutes in coronary bypass surgeries. Moreover, biomechanical conditions in arteries are strongly affected by the microcirculation downstream and, via coupling through the heart, the venous return upstream.

There are two arterial systems: systemic (blood flow to the body) and pulmonary (blood flow to the lungs). In the absence of

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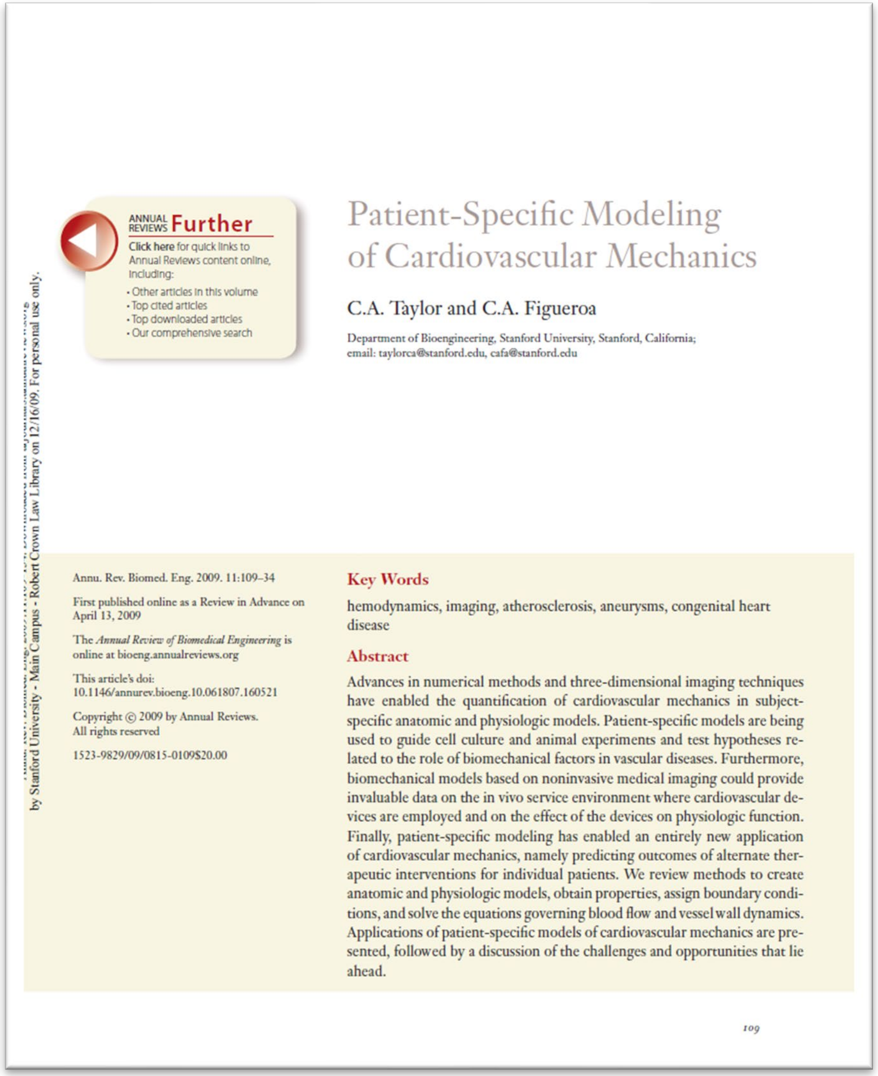

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Patient-Specific Modeling of Cardiovascular Mechanics

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Key Words

hemodynamics, imaging, atherosclerosis, aneurysms, congenital heart disease

Abstract

Advances in numerical methods and three-dimensional imaging techniques have enabled the quantification of cardiovascular mechanics in subject-specific anatomic and physiologic models. Patient-specific models are being used to guide cell culture and animal experiments and test hypotheses related to the role of biomechanical factors in vascular diseases. Furthermore, biomechanical models based on noninvasive medical imaging could provide invaluable data on the in vivo service environment where cardiovascular devices are employed and on the effect of the devices on physiologic function. Finally, patient-specific modeling has enabled an entirely new application of cardiovascular mechanics, namely predicting outcomes of alternate therapeutic interventions for individual patients. We review methods to create anatomic and physiologic models, obtain properties, assign boundary conditions, and solve the equations governing blood flow and vessel wall dynamics. Applications of patient-specific models of cardiovascular mechanics are presented, followed by a discussion of the challenges and opportunities that lie ahead.

Annals of Biomedical Engineering, Vol. 38, No. 3, March 2010 (© 2010) pp. 1188–1203
DOI: 10.1007/s10439-010-9901-0

Position Paper

Image-Based Modeling of Blood Flow and Vessel Wall Dynamics: Applications, Methods and Future Directions

Sixth International Bio-Fluid Mechanics Symposium and Workshop, March 28–30, 2008
Pasadena, California

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[1] Departments of Bioengineering and Surgery, Stanford University, Stanford, CA, USA; and [2] Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, ON, Canada

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Associate Editor Larry V. McIntire oversaw the review of this article.

Abstract—The objective of our session at the 2008 International Bio-Fluid Symposium and Workshop was to review the state-of-the-art in image-based modeling of blood flow, and identify future directions. Here we summarize progress in the field of image-based modeling of blood flow and vessel wall dynamics from mid-2005 to early 2009. We first describe the tremendous progress made in the application of image-based modeling techniques to elucidate the role of hemodynamics in vascular pathophysiology, plan treatments for congenital and acquired diseases in individual patients, and design and evaluate endovascular devices. We then review the advances that have been made in improving the methodology for modeling blood flow and vessel wall dynamics in image-based models, and consider issues related to extracting hemodynamic parameters and verification and validation. Finally, the strengths and weaknesses of current work in image-based modeling and the opportunities and threats to the field are described. We believe that with a doubling of our efforts toward the clinical application of image-based modeling tools, the next few years could surpass the tremendous gains made in the last few.

Keywords—Image-based modeling, Patient-specific, Hemodynamics, Atherosclerosis, Aneurysms, Surgical planning.

ABBREVIATIONS

AAA	Abdominal aortic aneurysms
ALE	Arbitrary Lagrangian–Eulerian
CFD	Computational fluid dynamics
CT	Computed tomography
IMT	Intima-media thickness
IUVS	Invasive intravascular ultrasound
MRA	Magnetic resonance angiograms
MRI	Magnetic resonance imaging
PC-MRI	Phase contrast magnetic resonance imaging
US	Ultrasound
WSS	Wall shear stress

INTRODUCTION

As noted in our prior review of the first decade of research in image-based modeling of blood flow,[136] while much progress had been made, significant challenges needed to be addressed in the second decade of this nascent field. These included the need for algorithmic improvements related to geometric modeling, boundary conditions, fluid–structure interactions between the blood stream and vessel wall, multiscale modeling, and simulation of vascular adaptation and disease to name a few. In that previous review of the field, we noted that the relative ease of simulating blood flow in image-based models was simultaneously a blessing and a curse. Used appropriately, these methods could provide investigators with powerful new tools, rivaling and even surpassing experimental fluid mechanics methods to investigate mechanisms of disease, and design and evaluation of medical devices and therapeutic interventions. However, we expressed concern that these tools had the potential to fuel a hemodynamic data explosion without concomitant gains in understanding. Finally, we noted the dearth of

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0090-6964/10/0300-1188/0 © 2010 Biomedical Engineering Society

Taylor & Humphrey, CMAME 2009   **Taylor & Figueroa, CMAME 2009**   **Taylor & Steinman, ABME 2010**

Doctoral students (25) and Postdocs (5) from Taylor lab at Stanford

Erik Bekkers, M.D., Ph.D.
Chris Cheng, Ph.D.
Gilwoo Choi, Ph.D.
Mary Draney, Ph.D.
Alberto Figueroa, Ph.D.
Craig Goergen, Ph.D.
Hyun Jin Kim, Ph.D.
Joy Ku, Ph.D.
Ethan Kung, Ph.D.
John LaDisa, Ph.D.
Andrea Les , Ph.D.
Alison Marsden, Ph.D.
Phillipe Moireau, Ph.D.
Tina Morrison, Ph.D.
Mary O'Connell, Ph.D.
Rashmi Raghu, Ph.D.
Hedi Razavi, Ph.D.
Sanaz Saatchi, Ph.D.
Shawn Shadden, Ph.D.
Jessica Shih, Ph.D.
Ryan Spilker, Ph.D.
Brooke Steele, Ph.D.
Ga Young Suh, Ph.D.
Beverly Tang, Ph.D.
Aaron Wang, Ph.D.
Kenneth Wang, M.D., Ph.D.
Nathan Wilson, Ph.D.
Irene Vignon-Clementel, Ph.D.
Nan Xiao, Ph.D.
Guanglei Xiong, Ph.D.

SimVascular Software originated in my lab at Stanford, was first released in 2008 and is now widely used for patient-specific cardiovascular modeling

SimVascular: Cardiovascular Modeling and Simulation

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SimVascular: An Open Source Pipeline for Cardiovascular Simulation (2016)
Abstract View

Provides a platform for patient-specific cardiovascular modeling and simulation.

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SimVascular is an open source software suite for cardiovascular simulation, providing a complete pipeline from medical image data to 3D model construction, meshing, and blood flow simulation. SimVacular represents the state of the art in cardiovascular simulation, including advanced tools for physiologic boundary conditions, fluid structure interaction, and an accurate and efficient finite element Navier-Stokes solver. SimVascular integrates custom code with best-in-class open source packages to support clinical and basic science research.

DOCUMENTATION and CLINICAL EXAMPLES are available on the main project website at:
http://www.simvascular.org

Demo projects and examples for SimVascular can be downloaded at:
https://simtk.org/projects/sv_tests

Interested users should join the mailing list for the SimVascular project on simtk.org to be notified about upcoming releases and workshop announcements.

If you use SimVascular for your work, please cite the following publication:


Alison Marsden


Shawn Shadden

Research supported by the National Science Foundation and the National Institutes of Health

NSF

NIH
National Institutes of Health

National Science Foundation

(NSF 0205741)

ITR/AP: Simulation-Based Medical Planning for Cardiovascular Disease

Funding Period: 8/01/02-7/31/07

National Institutes of Health/NIGMS

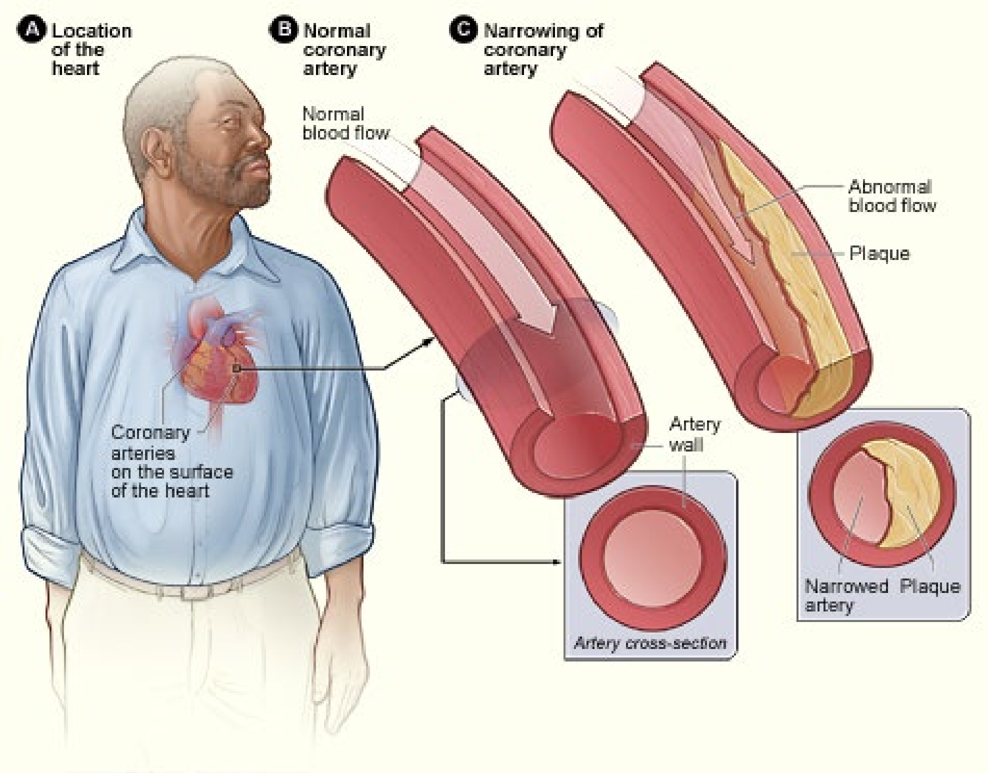
(U54 RR020336-01)

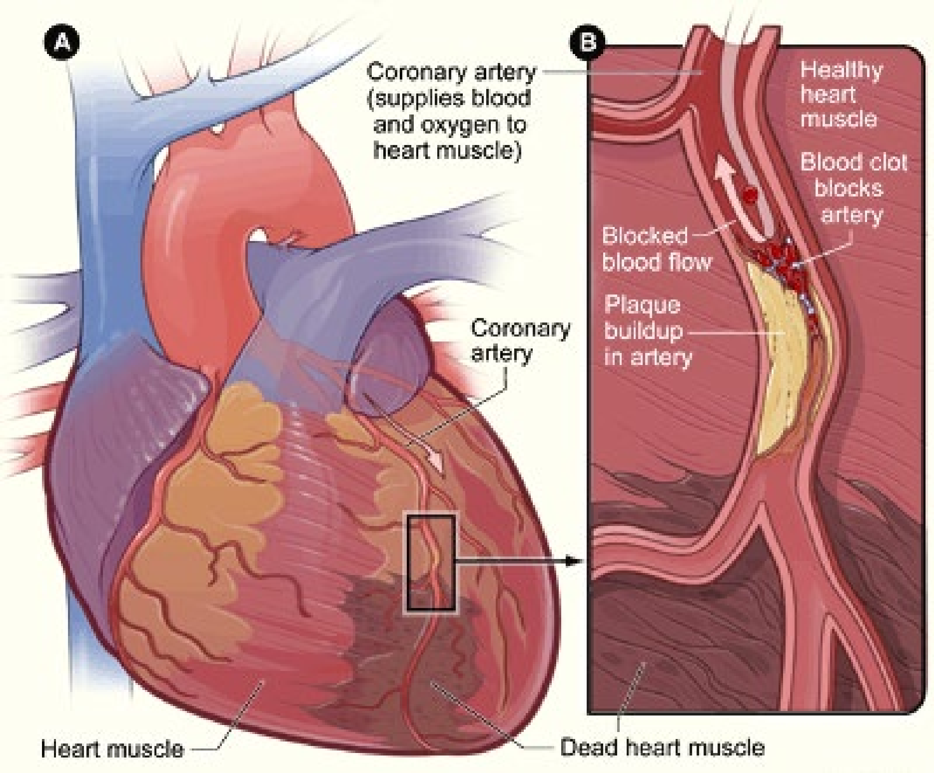
Physics-Based Simulation of Biological Structures

Funding Period: 9/15/04 – 7/31/09

HeartFlow Founded in 2010 by Taylor and Zarins to improve diagnosis of Heart Disease

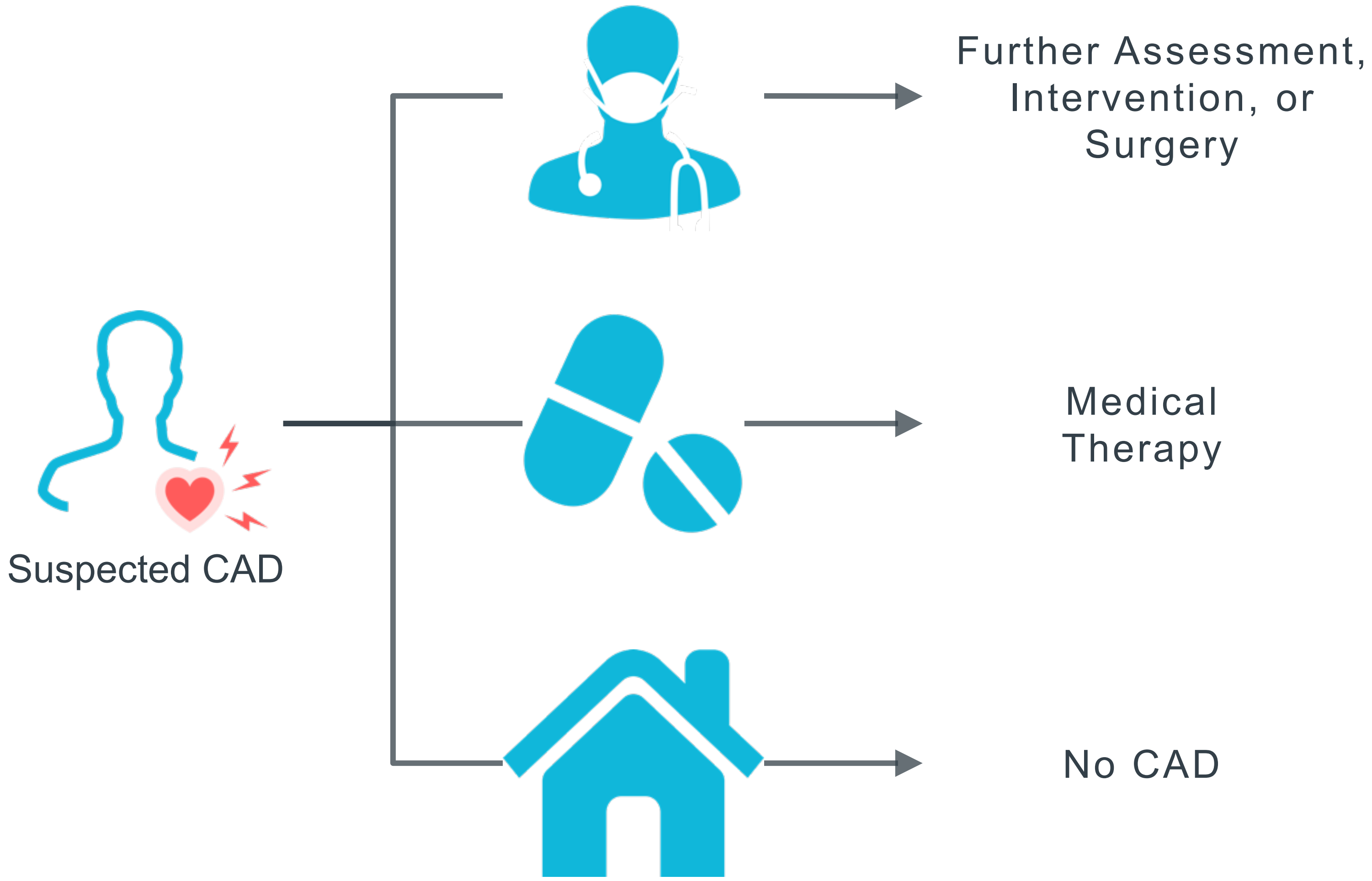
Coronary Artery Disease (CAD) one of primary heart diseases



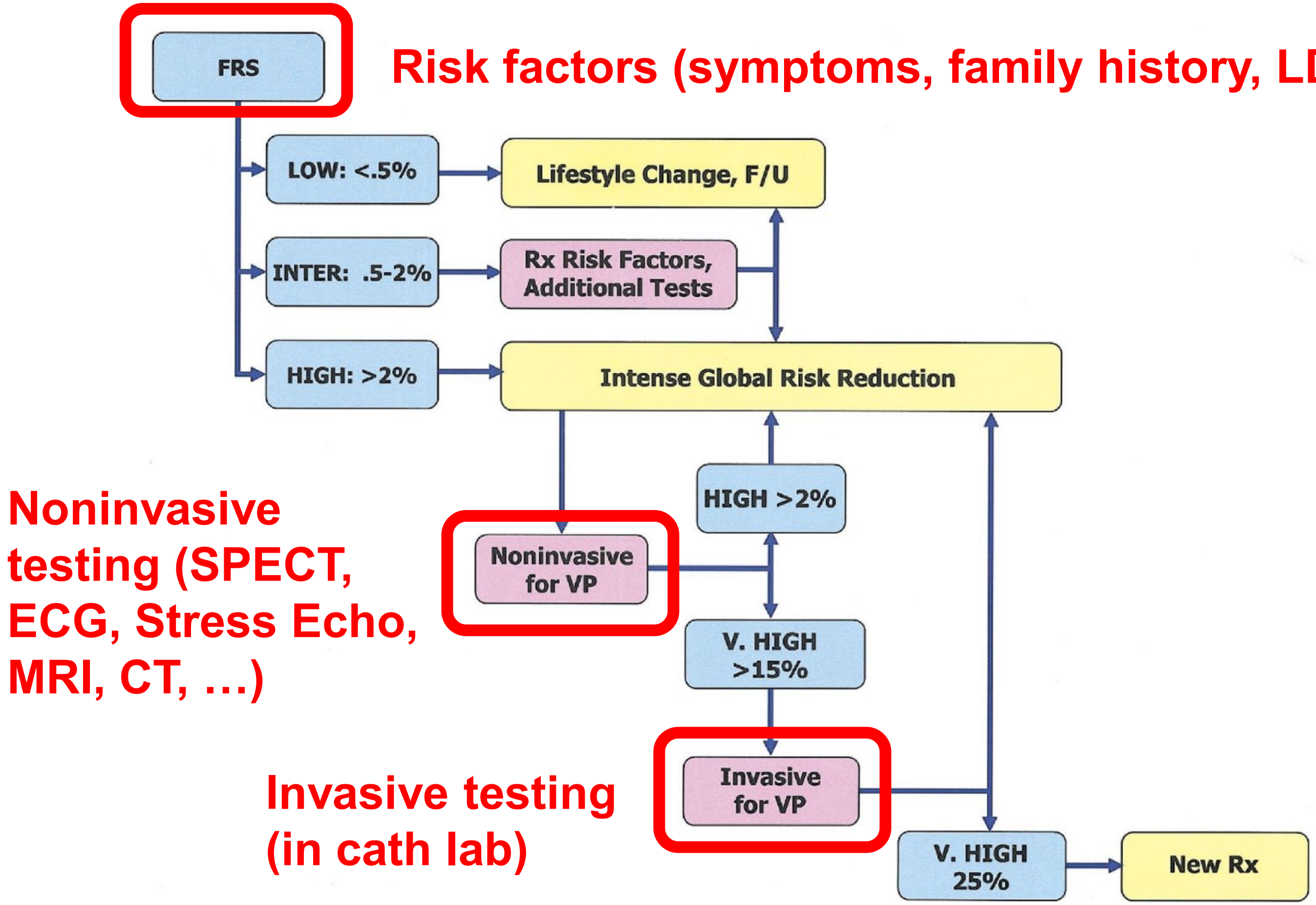


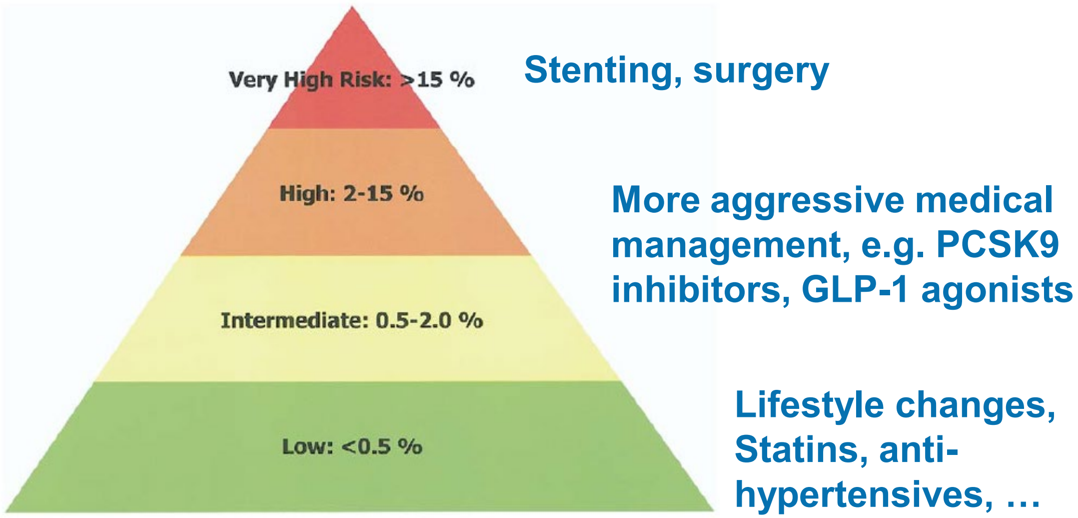
Source: NIH NHLBI

Cardiac Testing Should Help Physicians Determine the Right Treatment Pathway for Each Patient with Suspected Coronary Artery Disease (CAD)



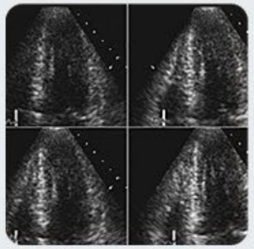
Sequential testing strategy used to risk stratify patients with suspected CAD and determine appropriate therapy, i.e. lifestyle changes, medical management or revascularization (e.g. stenting, surgery)



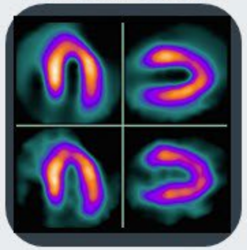


Braunwald, "What Do Clinicians Expect From Imagers?", JACC 2006

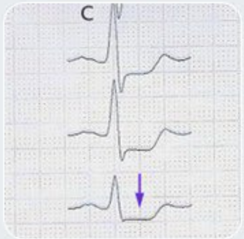
Patients with suspected Heart Disease are often Referred to Non-invasive Functional Testing, but these tests are limited in detecting Coronary Artery Disease (CAD)



Stress Echo

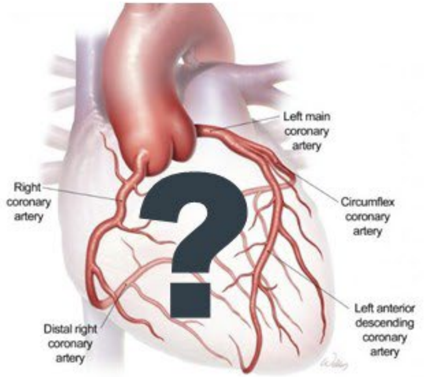


SPECT



Treadmill

No direct information on disease in the coronary arteries



High rate of **unnecessary downstream testing**

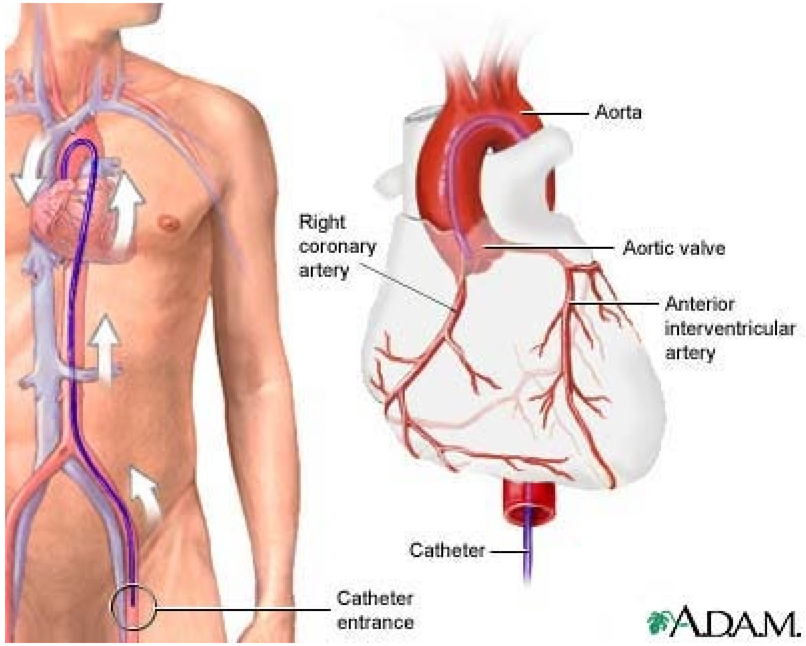
More than 50% of patients sent for an invasive angiogram have **no obstructive CAD**[1]

High rate of **missing CAD**

20-30% of patients are sent home with their coronary disease **undetected**[2]

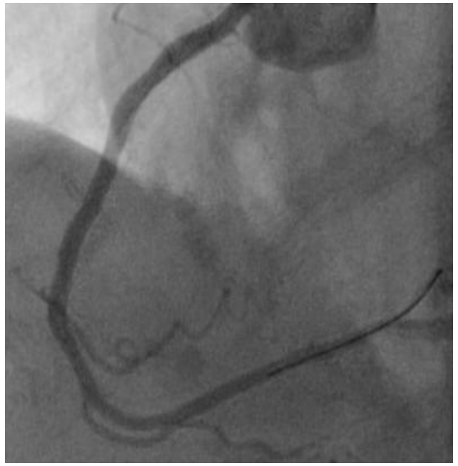
1. Patel, et al. N Engl J Med 2010. Patel, et al. AHJ 2014. Danad, et al. JAMA Cardiology 2017.
2. Arbab-Zadeh, Heart Int 2012. Yokota, et al. Neth Heart J 2018. Nakanishi, et al. J Nucl Cardiol 2018.

Due to Limitations in Noninvasive Cardiac Stress Testing, many patients are referred for Invasive Diagnostic Tests

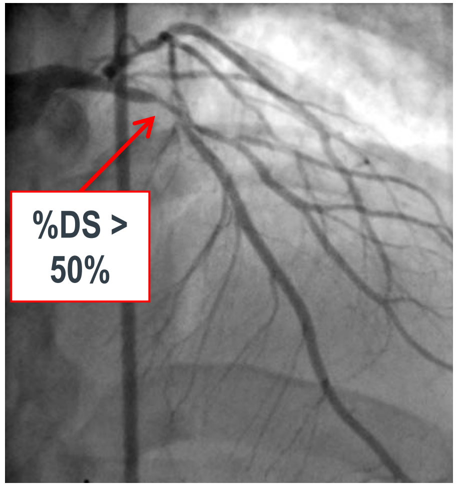


Courtesy of Paul Yock, M.D.

Normal right coronary artery

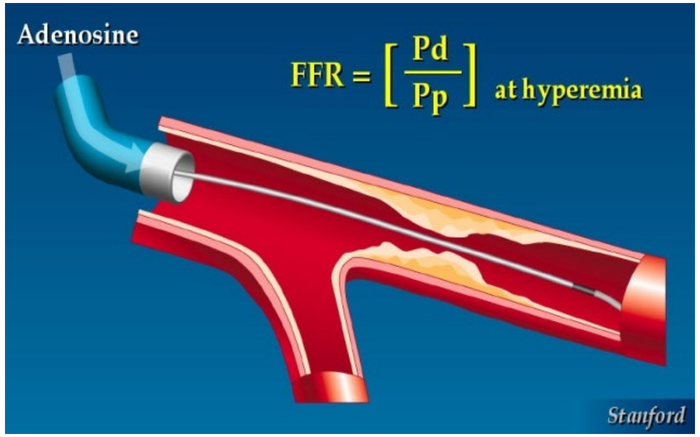


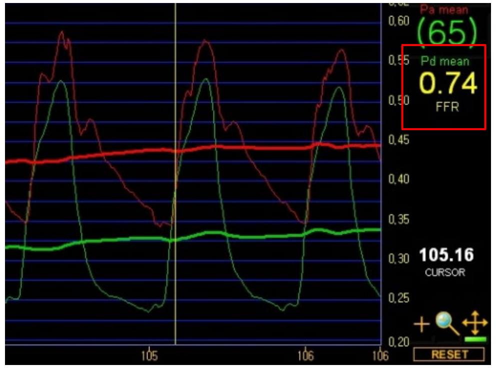
Diseased left coronary artery

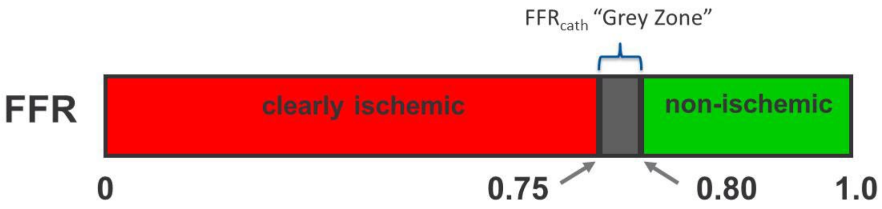


Invasive coronary physiology measurements have emerged as the gold-standard test to identify whether disease is limiting blood supply to the heart and consequently whether a patient may benefit from PCI

- Fractional Flow Reserve (FFR)
  - Defines the functional significance of coronary lesions*
  - Measured with pressure wire during coronary angiography

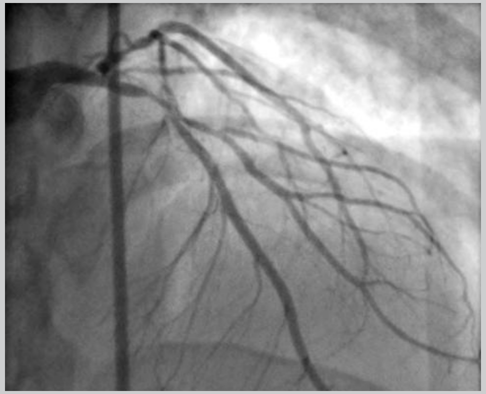
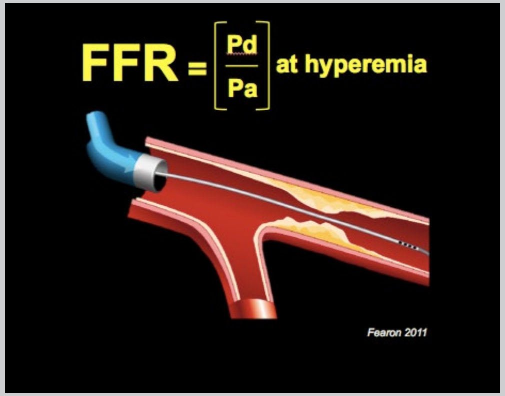






*Pijls NH et al. J Am Coll Cardiol. 2007
Pijls NH et al. J. Am. Coll. Cardiol. 2010

Diagnosing Anatomic and Functionally-Significant CAD Invasively

	ANATOMY ***Identify obstructive CAD***	***FUNCTION*** ***Identify lesion-specific ischemia that may benefit from PCI***
Invasive		

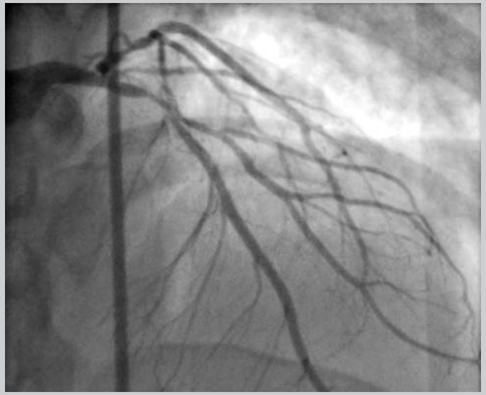
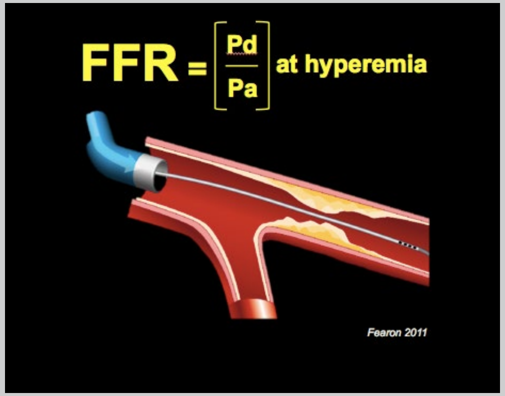
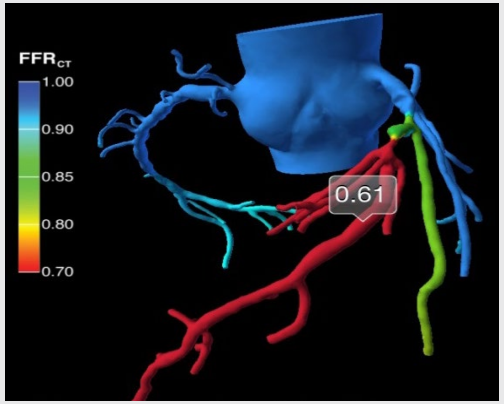
- Angiography and FFR require invasive cardiac catheterization
- ≈40% of patients that enter the cath lab have obstructive CAD[1]
- ≈40% of patients with obstructive CAD on angiography have +'ve FFR[2]

→ Only 16% of patients in cath lab have both obstructive CAD and +'ve FFR

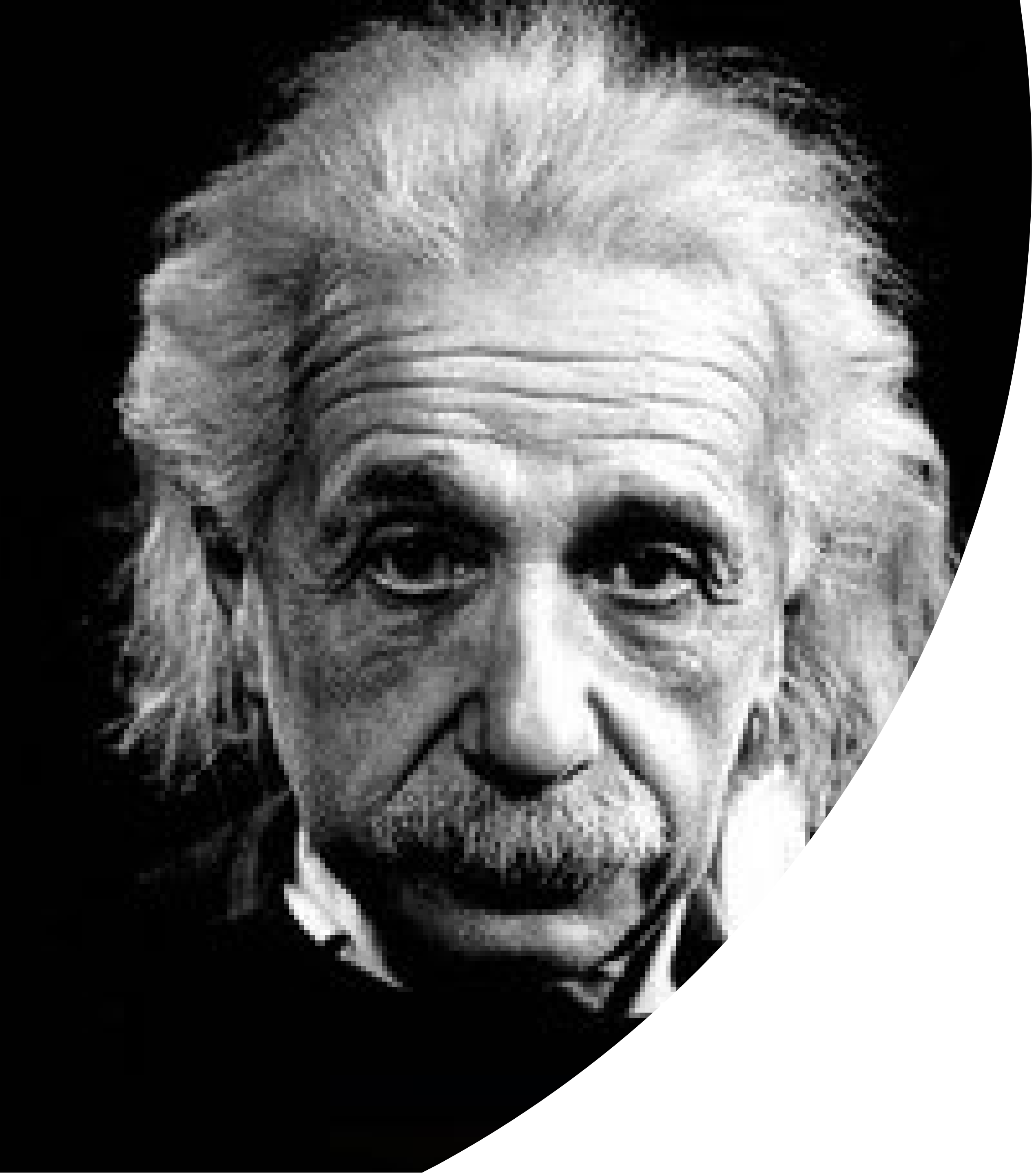
Can we identify obstructive CAD and quantify FFR ***before*** *cardiac cath?*

1. Patel et al, NEJM 2010, 2. Tonino et. al., NEJM 2009.

Diagnosing Anatomic and Functionally-Significant CAD Noninvasively

	ANATOMY Identify obstructive CAD	***FUNCTION*** Identify lesion-specific ischemia that may benefit from PCI
Invasive		
Noninvasive		

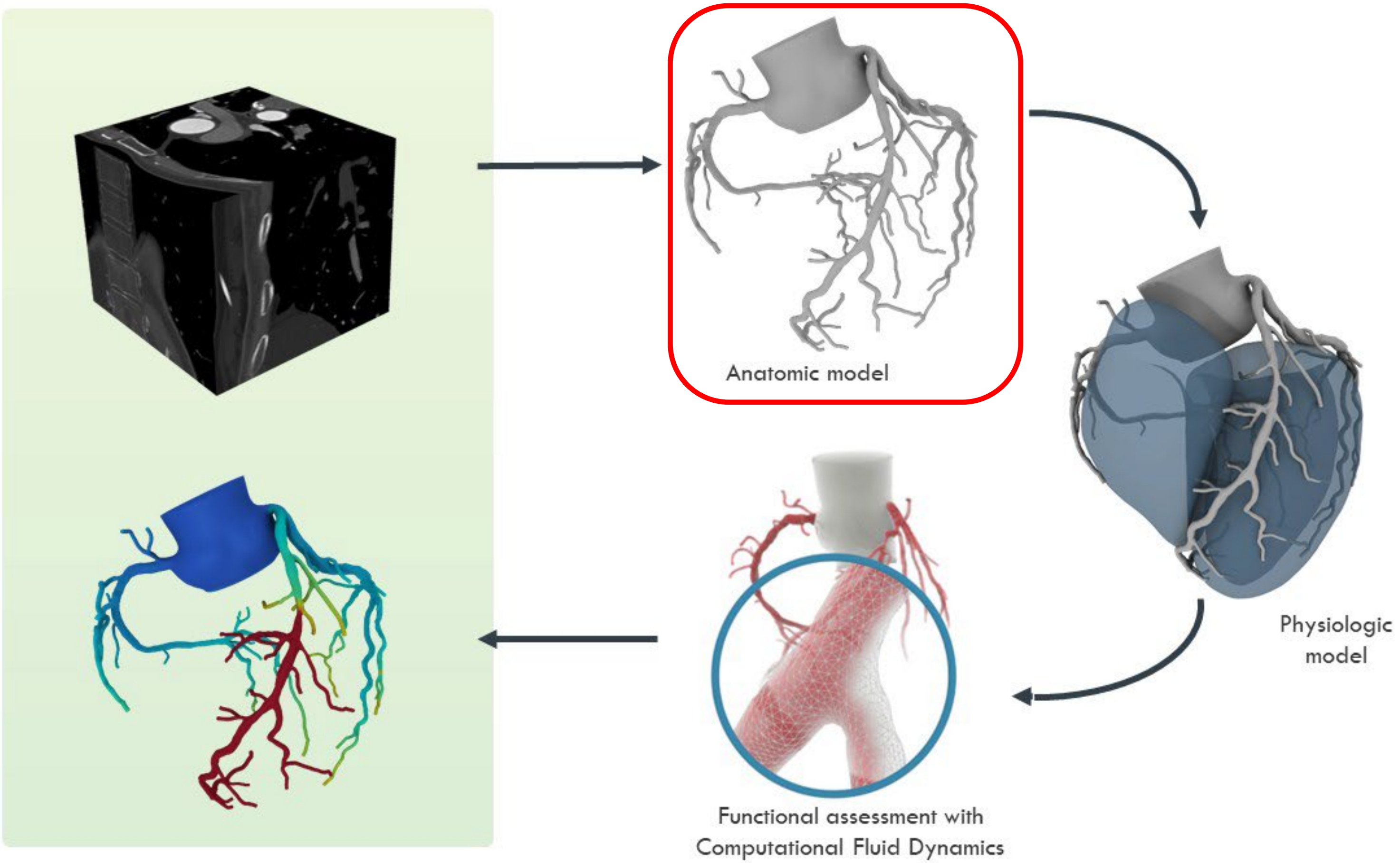
FFR_{CT}



"You make experiments and I make theories. Do you know the difference? A theory is something nobody believes, except the person who made it. An experiment is something everybody believes, except the person who made it.

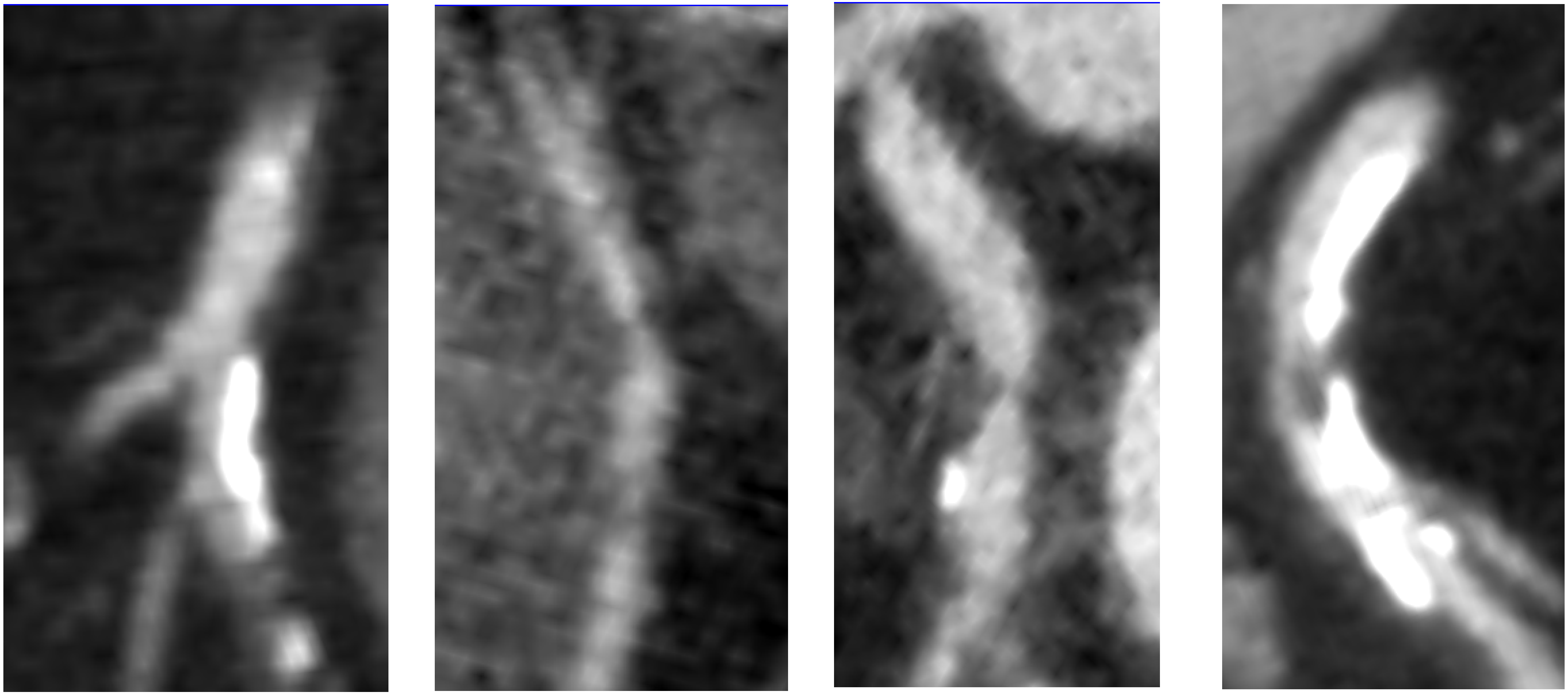
Albert Einstein

Deriving FFR from CT

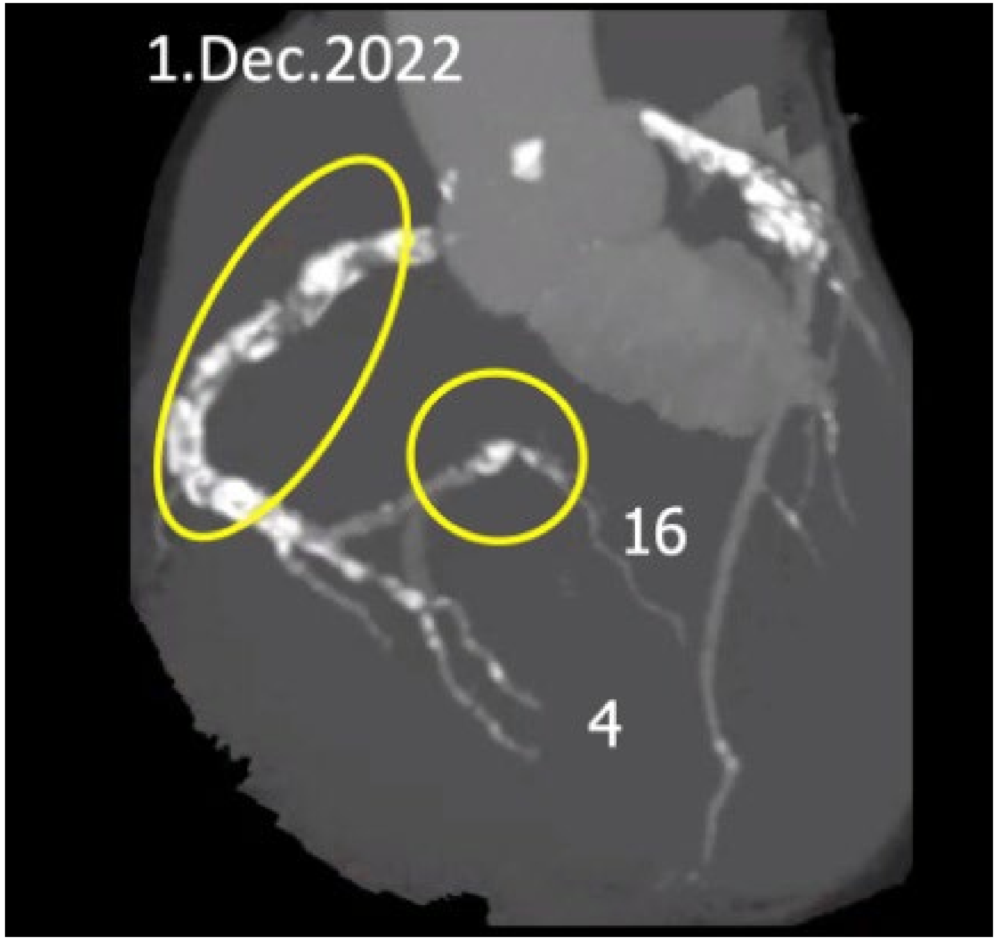


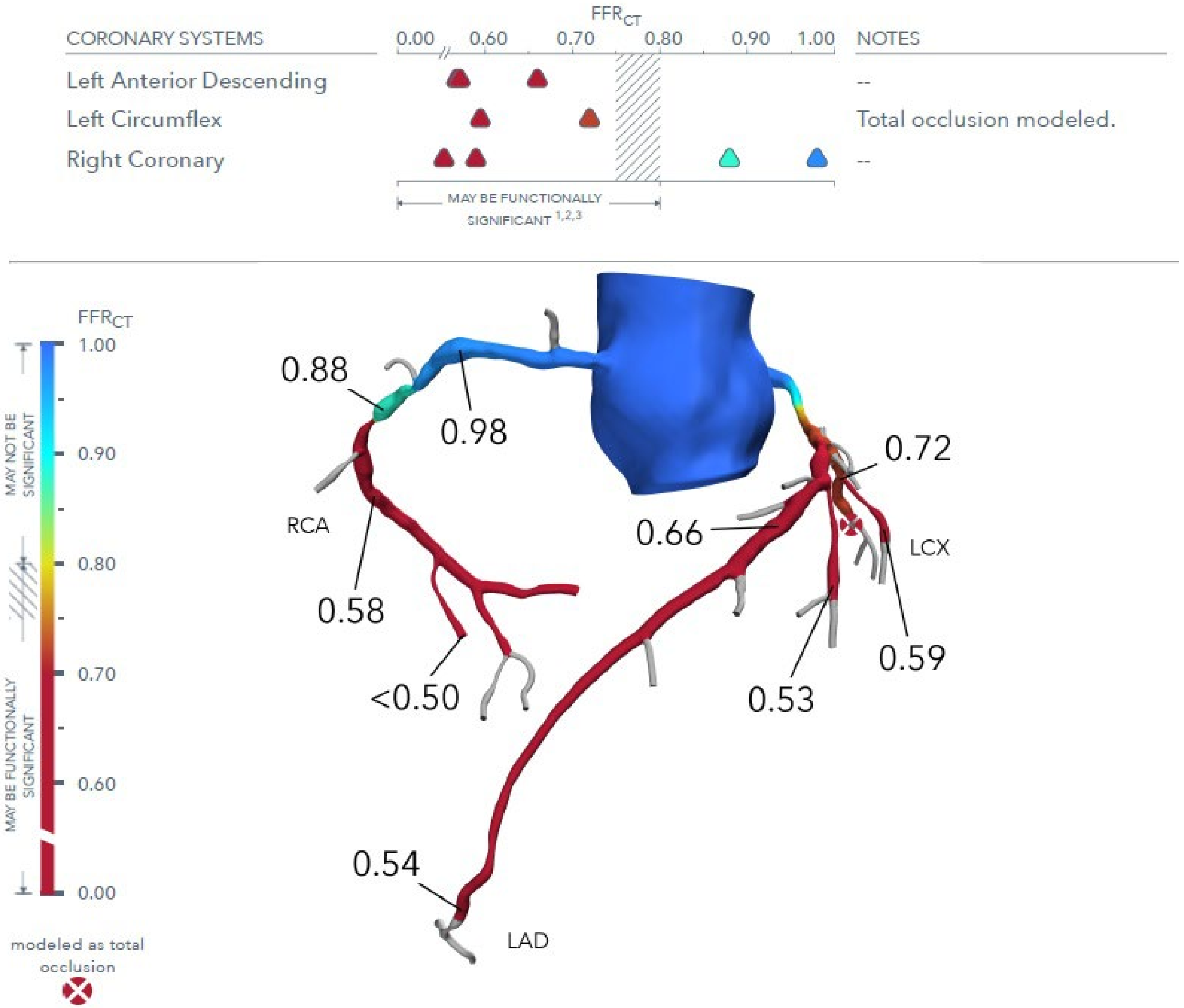
Taylor et. al. (2013) Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve: Scientific Basis. Journal of the American College of Cardiology. Vol. 61, Issue 22, pp. 2233-2241.

Extracting anatomic data from CT imaging is challenging …



Extracting anatomic data from CT imaging is challenging …





AI to the Rescue?

The New York Times

A.I. Here, There, Everywhere

Many of us already live with artificial intelligence now, but researchers say interactions with the technology will become increasingly personalized.

Meet Waymo One™

The world's first autonomous ride-hailing service

Be one of the first

FDA has now cleared more than 1,000 AI models, including many in cardiology

Dave Fornell | January 10, 2025 | Cardiovascular Business | Artificial Intelligence

NEJM AI

Evaluating clinical AI: Be empowered with the evidence you need.

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Radiology: Artificial Intelligence

SCIENCE | GLOBAL ISSUES

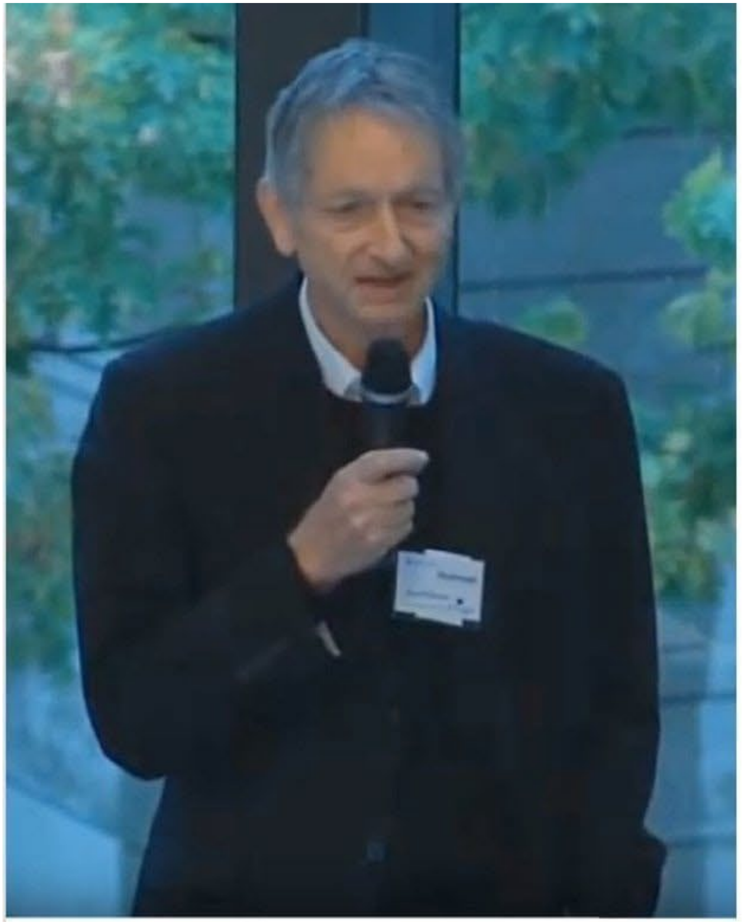
Can you trust AI medical advice from ChatGPT?

Fred Schwaller
02/21/2025

Deep Fusion analyzes every pixel from multiple exposures.

For mid- to low-light shots, Deep Fusion kicks in — using the Neural Engine to perform a pixel-by-pixel analysis of various exposures and

State of AI in Medicine



Geoffrey Hinton

"I think that if you work as a radiologist, you are like Wile E. Coyote in the cartoon. You're already over the edge of the cliff, but you haven't yet looked down. There's no ground underneath. People should stop training radiologists now. It's just completely obvious that in five years deep learning is going to do better than radiologists."

Nov 24, 2016

State of AI in Medicine

BUSINESS

Bill Gates says AI will replace doctors, teachers within 10 years — and claims humans won't be needed 'for most things'

What do the REAL experts think?

Will AI replace doctors in 10 years?

ChatGPT 4o

No, AI will not replace doctors in 10 years — but it *will dramatically change how doctors work.*

Here's a breakdown:

✅ What AI *can* do in 10 years:

- **Radiology & Pathology Support**: Analyze medical images and lab slides quickly and with high accuracy.
- **Clinical Decision Support**: Suggest diagnoses or flag issues based on symptoms, lab results, and EHRs.
- **Administrative Automation**: Handle documentation, prior authorizations, and note-taking.
- **Remote Monitoring & Triage**: Track chronic conditions and assist with telemedicine and symptom triage.

❌ What AI *cannot* do by 2035:

- **Perform surgery independently** (outside of highly constrained environments).
- **Manage uncertainty in complex cases** where intuition and holistic judgment are critical.
- **Build trust and rapport** — crucial for patient compliance and mental health care.
- **Take full legal/ethical responsibility** for life-and-death decisions.

Bottom line: AI will be a powerful assistant — not a substitute — for doctors in the next decade. The best outcomes will come from *human-AI collaboration*, not competition.

9 years after Geoffery Hinton's comments …

DIAGNOSTIC IMAGING

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Where Things Stand with the Radiologist Shortage

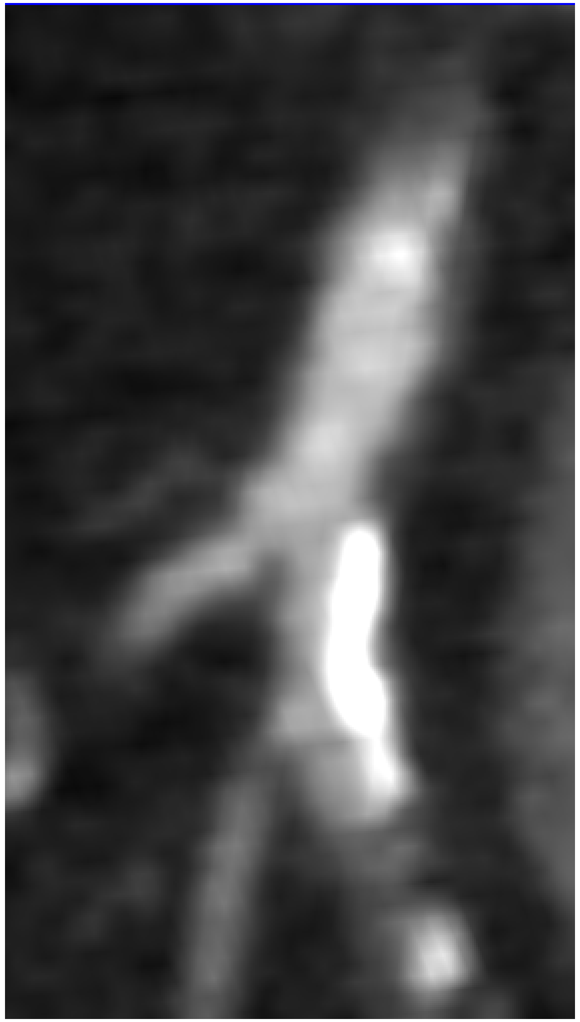
June 18, 2025
By Jeff Hall

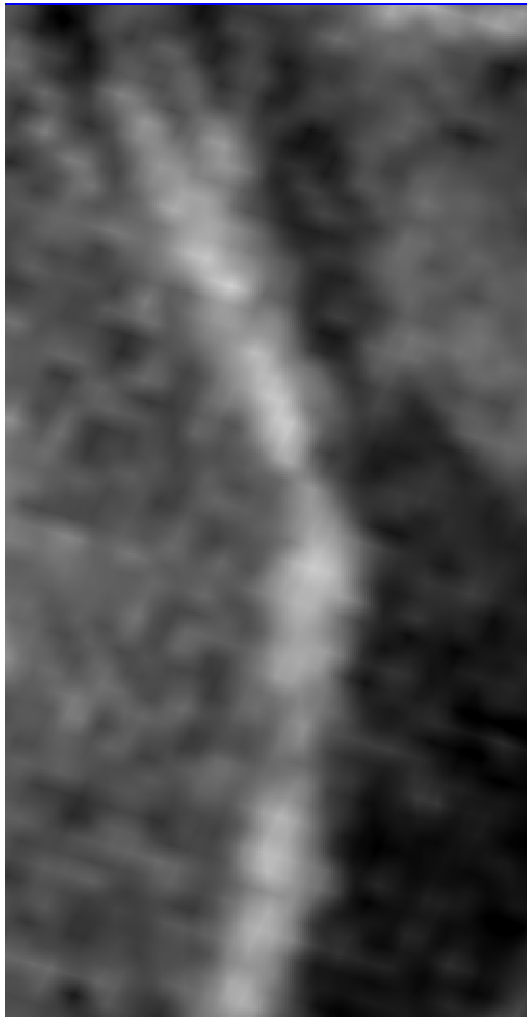
News Article

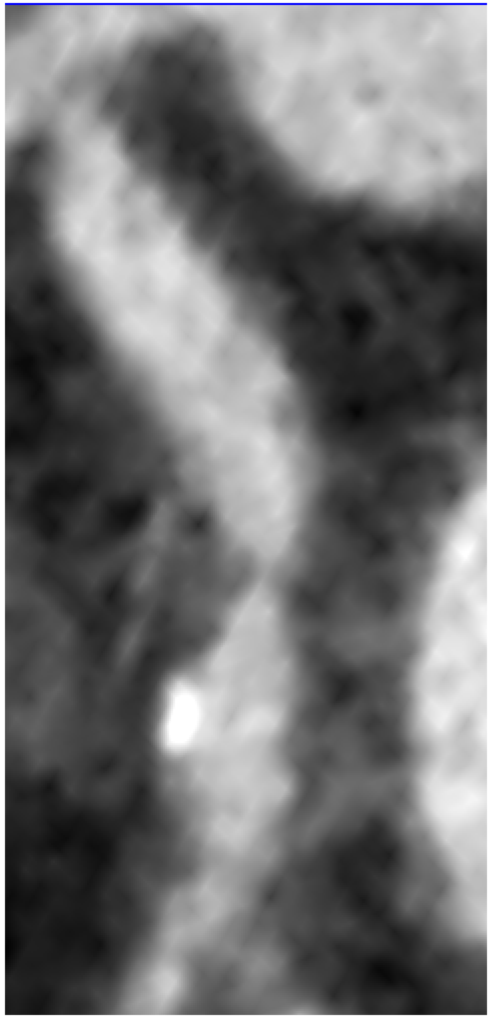
A new report conveys the cumulative impact of ongoing challenges with radiologist residency positions, reimbursement, post-COVID-19 attrition rates and the aging of the population upon the persistent shortage of radiologists in the United States.

New research continues to suggest a widening chasm between the increased imaging demand for an aging population and a prevailing shortage of radiologists.

How do we leverage Artificial and Human Intelligence to extract lumen anatomy for these cases?







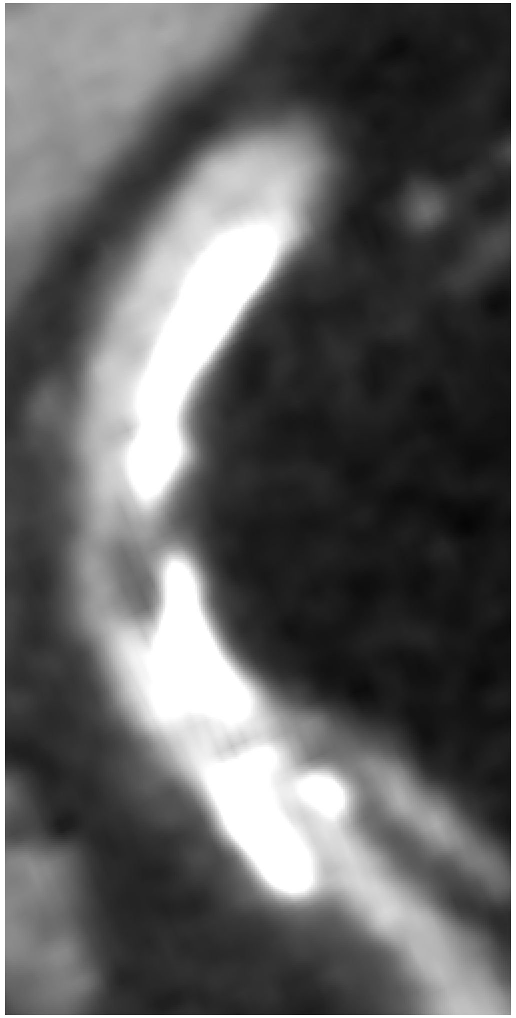


Image segmentation methods developed and validated using invasive imaging data

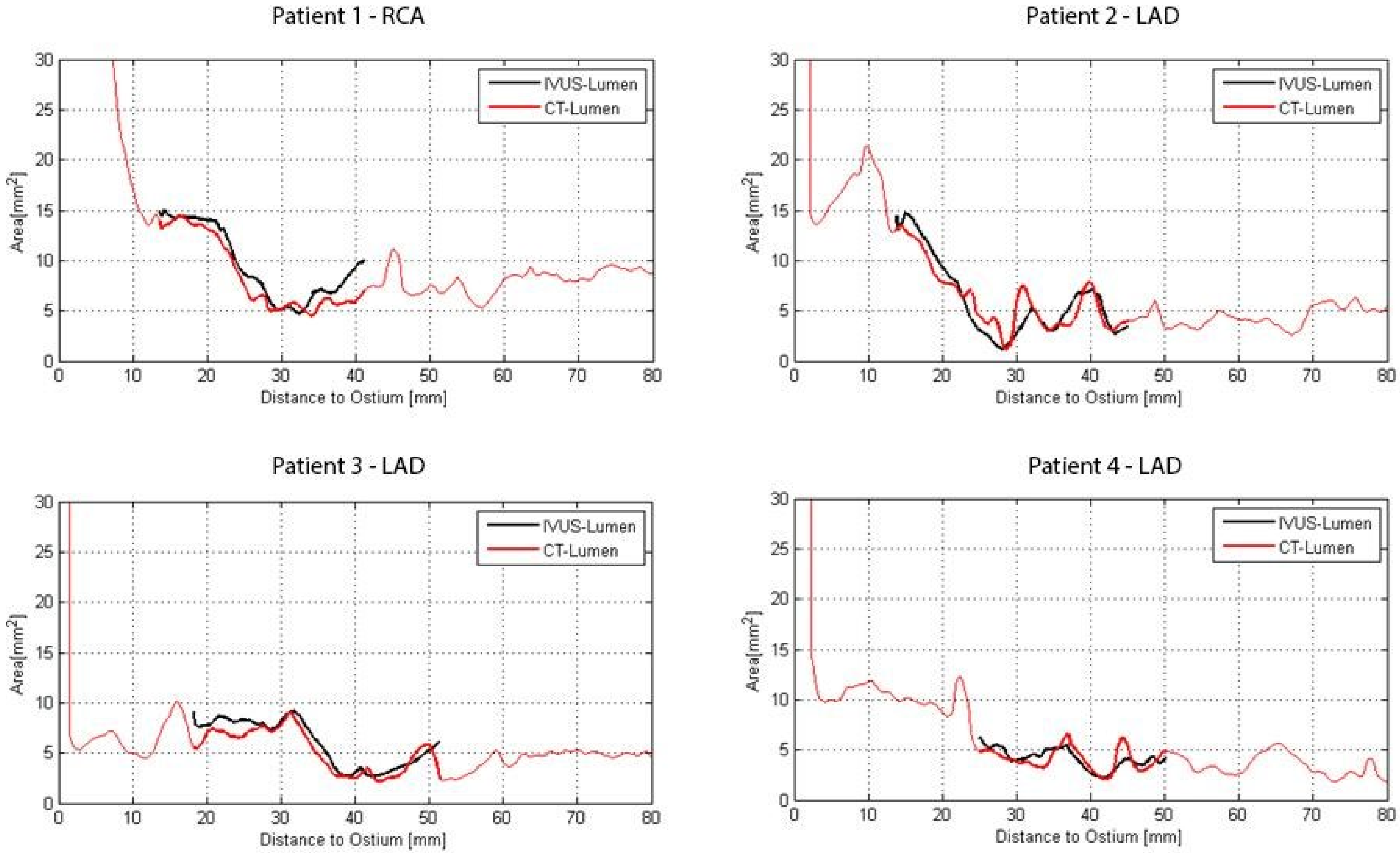
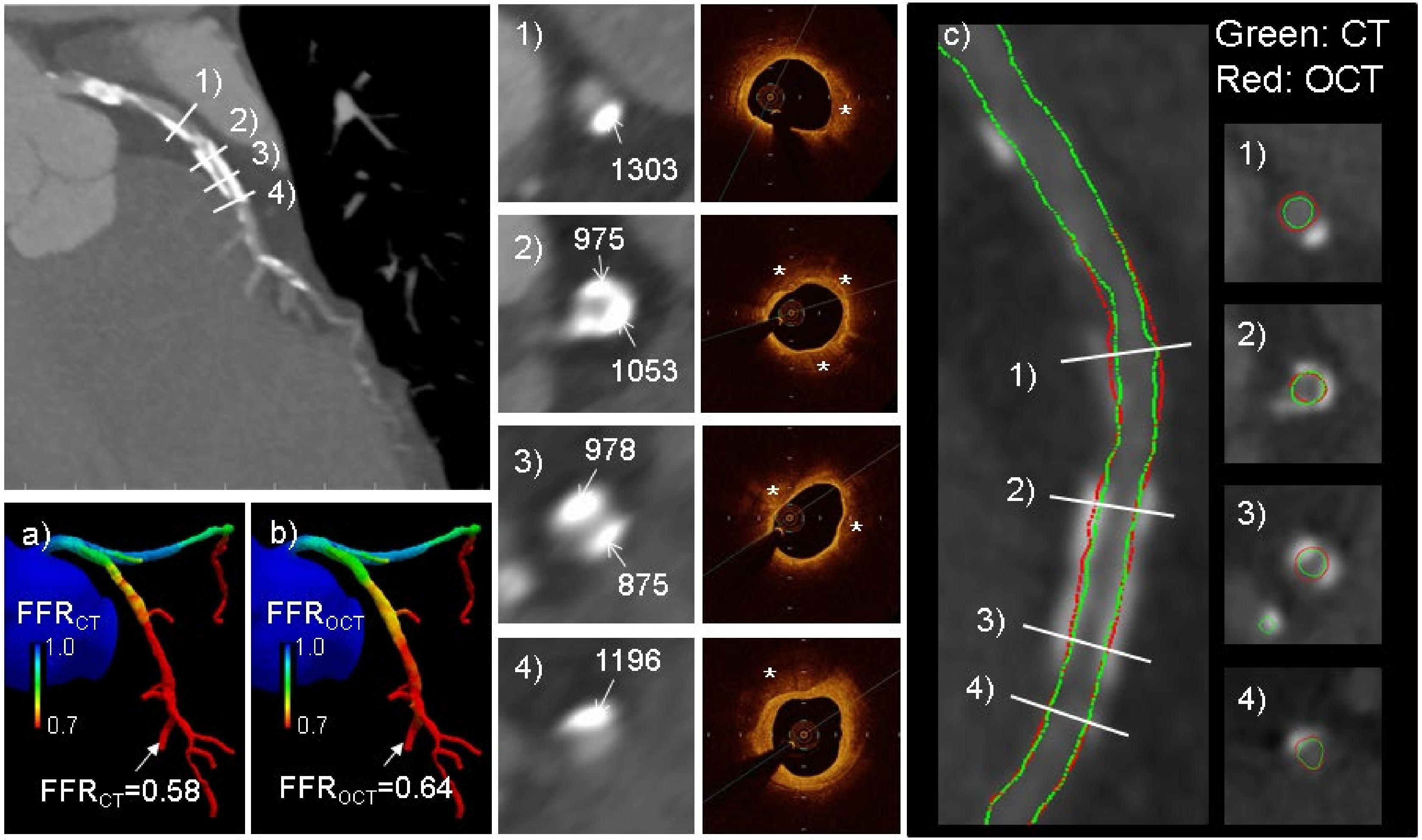
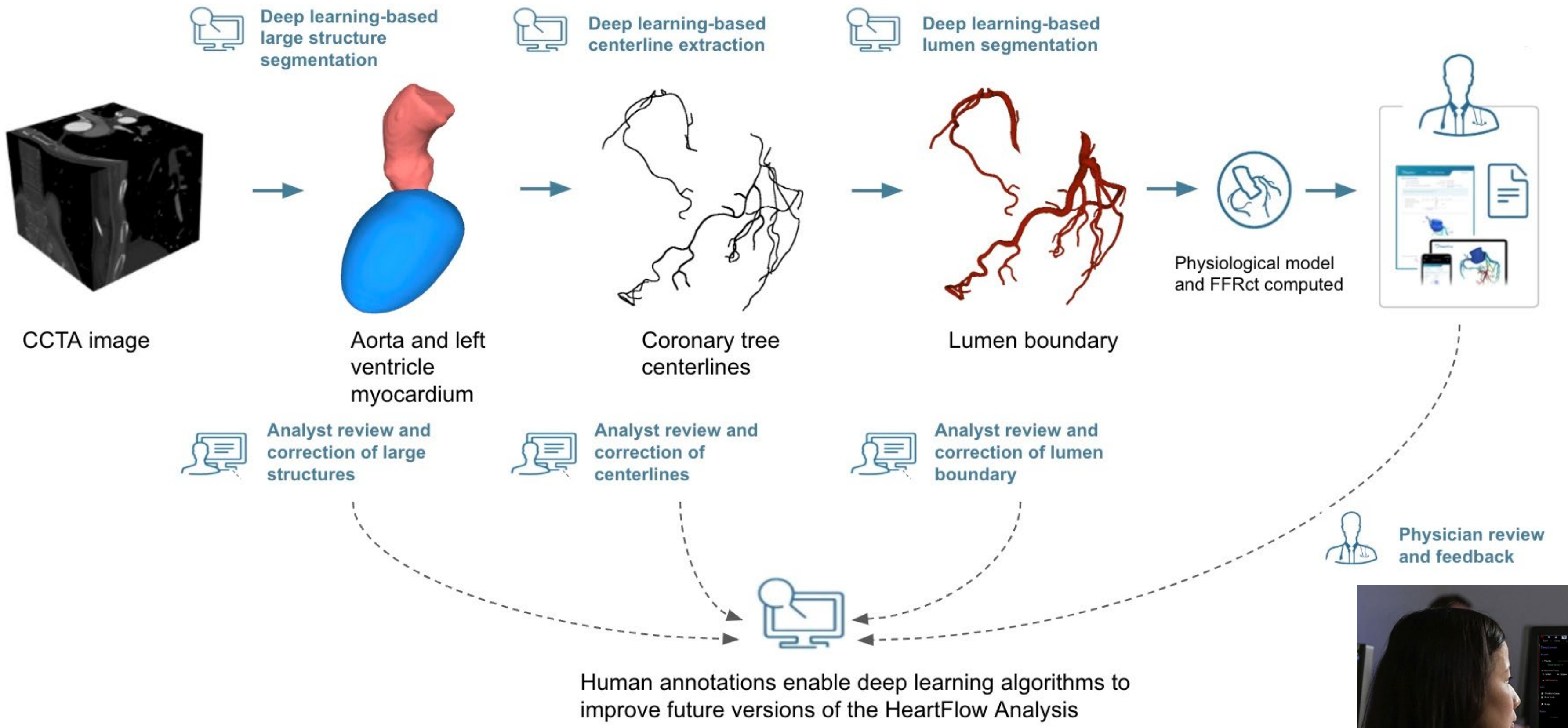


Image segmentation methods developed and validated using invasive imaging data

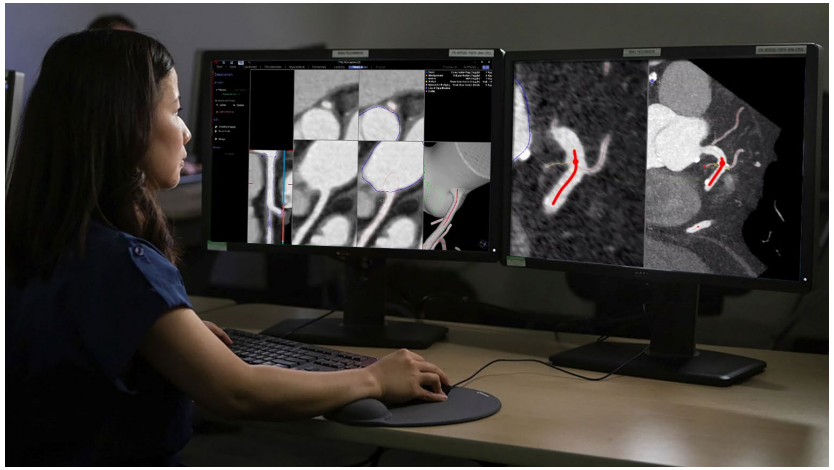


Uzu et.al. EuroIntervention. 2019;14:e1609-e1618.

Human-in-the-loop AI Foundation

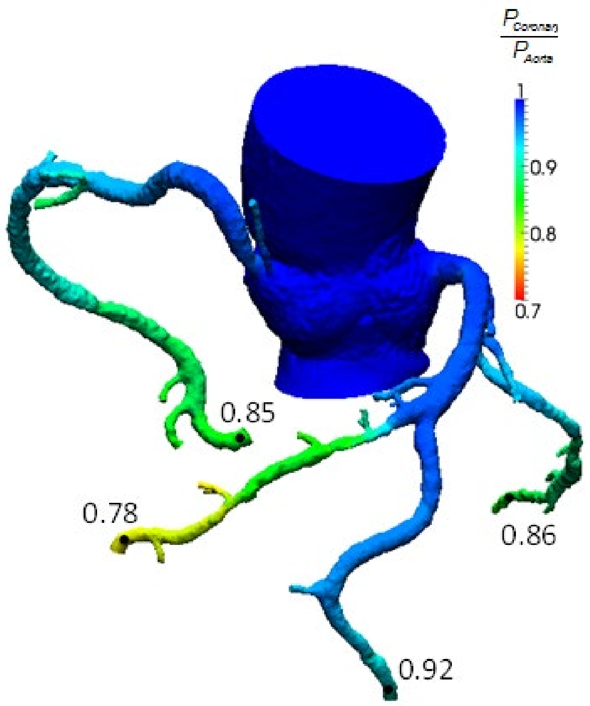


Taylor et. al. Computer Methods in Applied Mechanics and Engineering, 2023

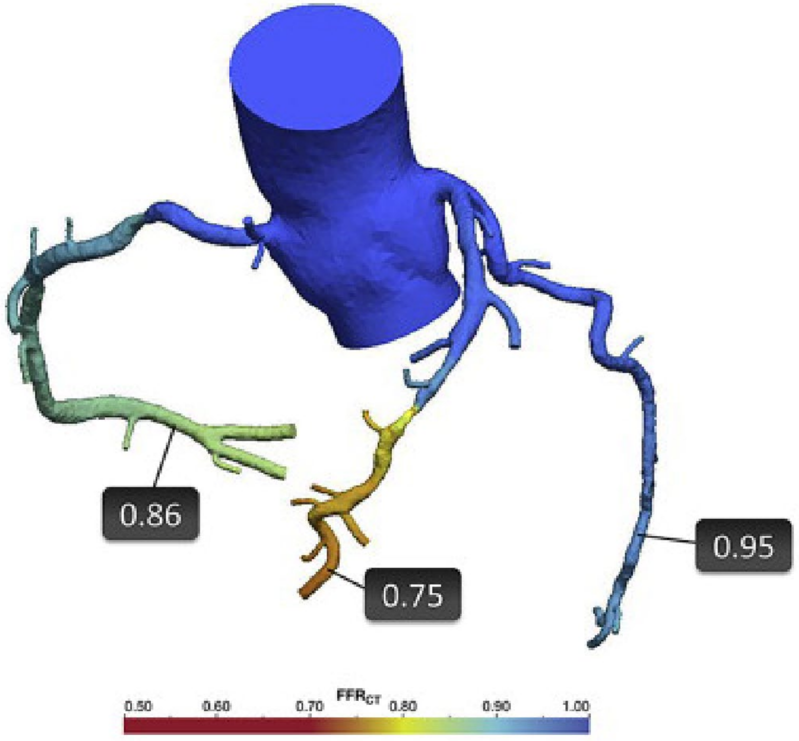


The fidelity of the FFR_{CT} anatomic models have improved significantly over the years

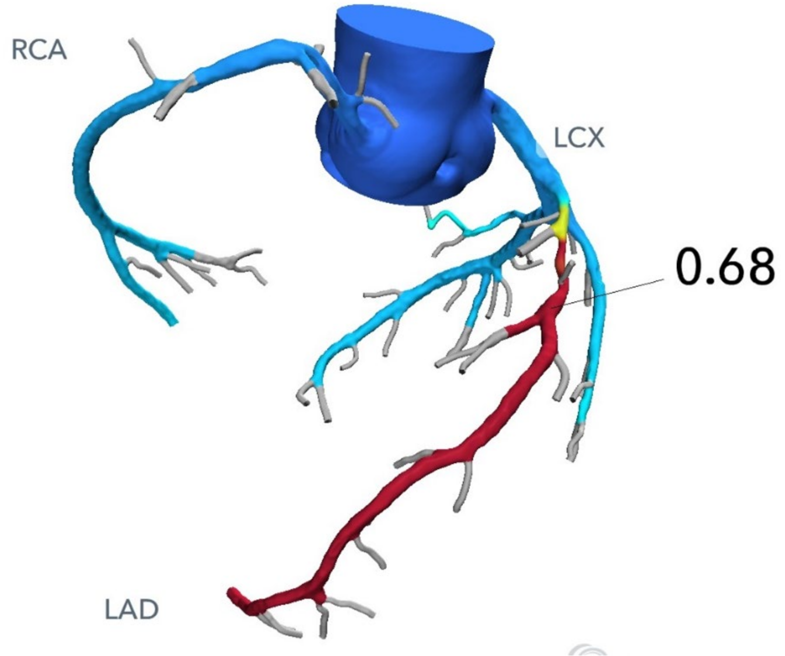
Patient #1 - El Camino Hospital October 2009



FFRct v1.4 – Circa 2014

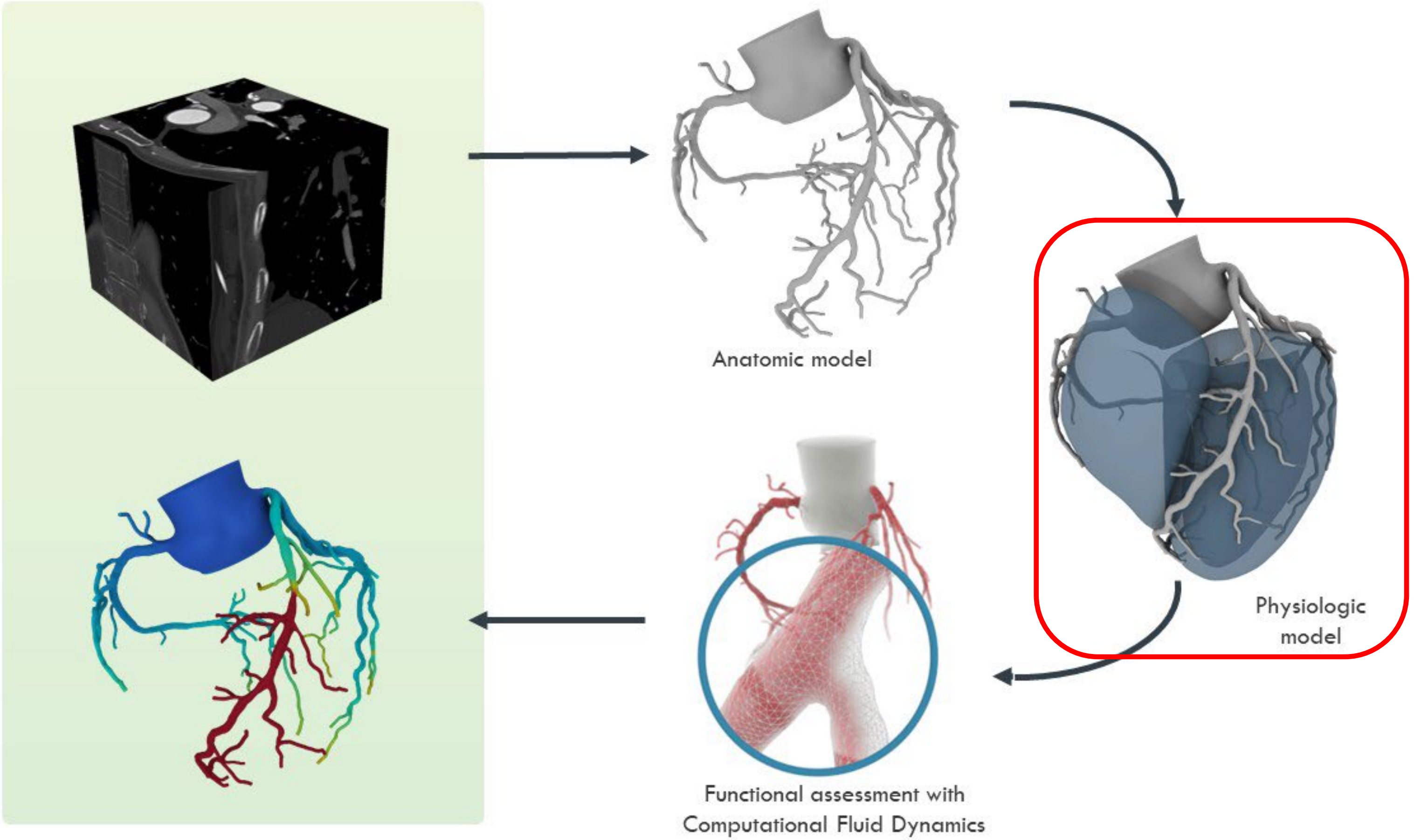


FFRct v2.19 – 2018



***Deep Learning** methods first introduced in FFR_{CT} v2.2 in January, 2017.*
More than 100 Software Releases since then.

Deriving FFR from CT



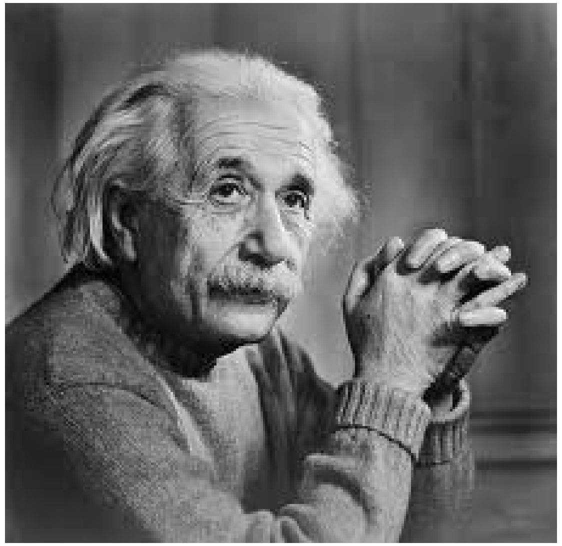
Taylor et. al. (2013) Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve: Scientific Basis. Journal of the American College of Cardiology. Vol. 61, Issue 22, pp. 2233-2241.

Scientific Approach to Developing Physiology Model

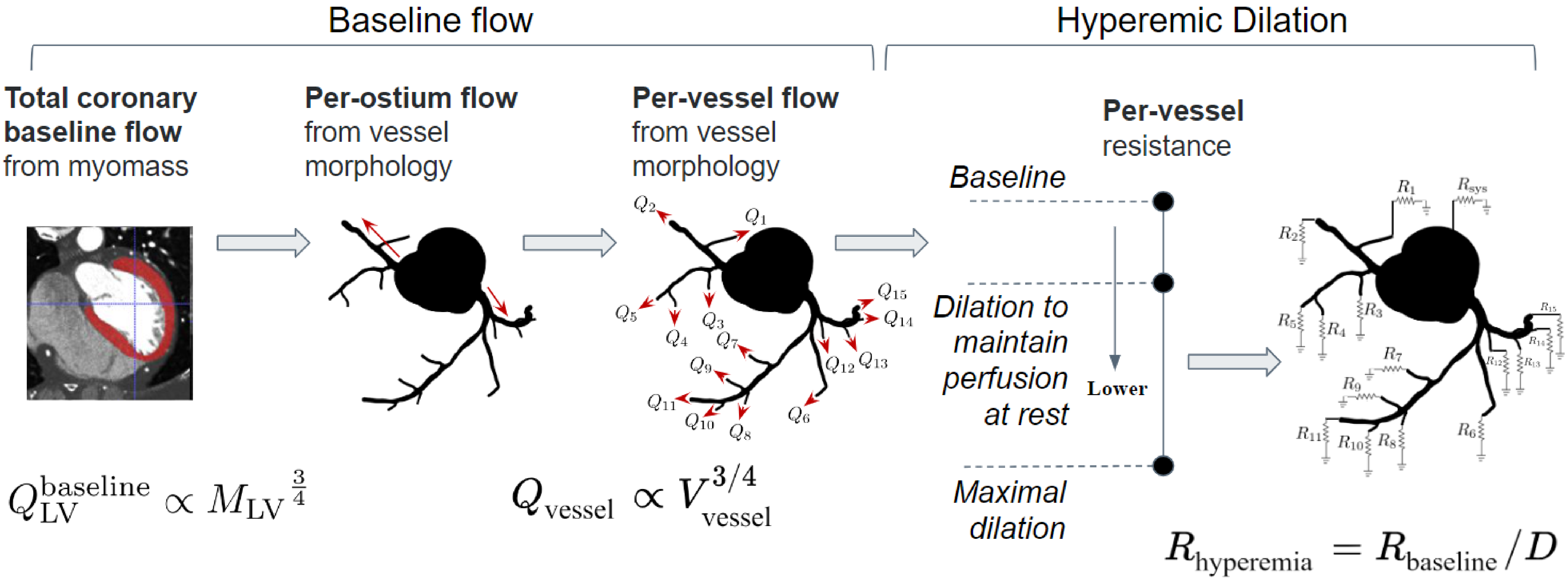
"It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience."

Albert Einstein

From "On the Method of Theoretical Physics," the Herbert Spencer Lecture, Oxford, June 10, 1933



Physiologic Model of FFR_{CT} – 3rd Generation (Released 2021)

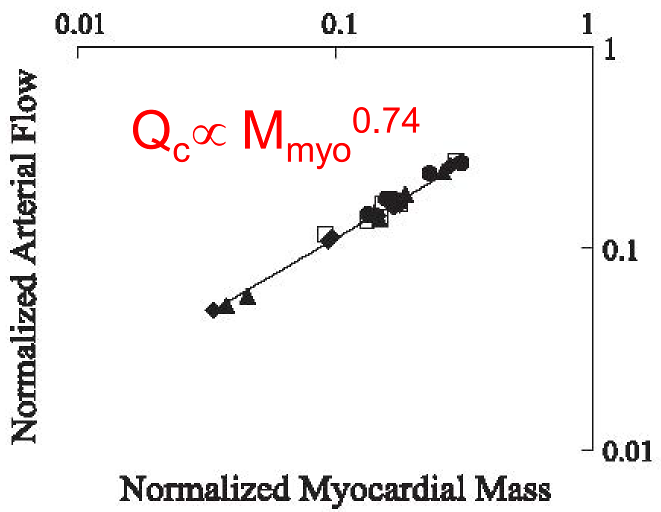


Taylor et. al. Computer Methods in Applied Mechanics and Engineering, 2023

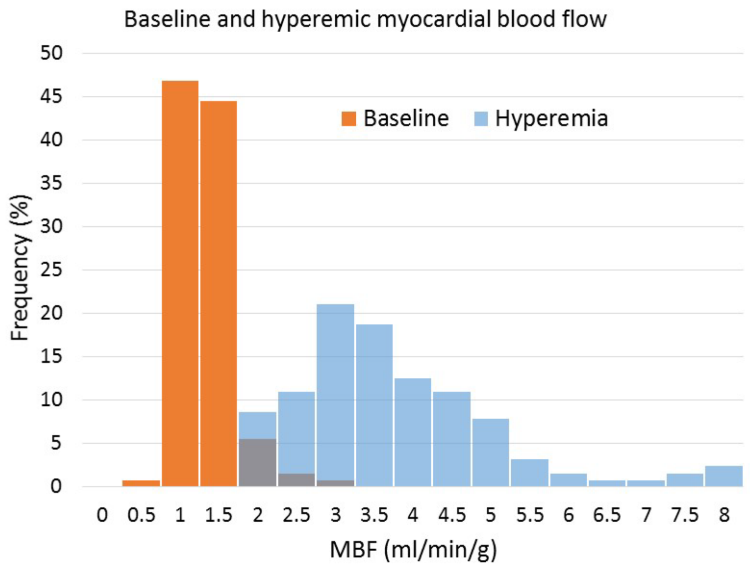
Scientific Principle #1

Baseline coronary blood flow is proportional to myocardial mass and is minimally affected by CAD

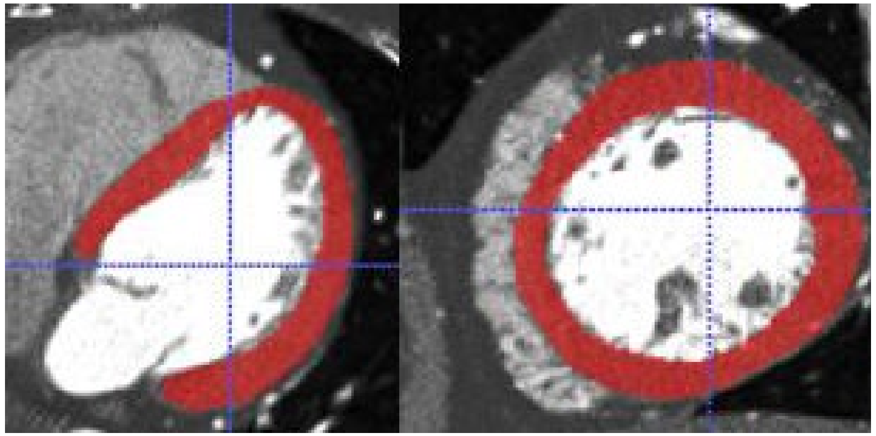
Data from animal studies and perfusion imaging demonstrates that baseline coronary blood flow is indeed proportional to myocardial mass



Choy et. al., J Appl Physiol, 2008.



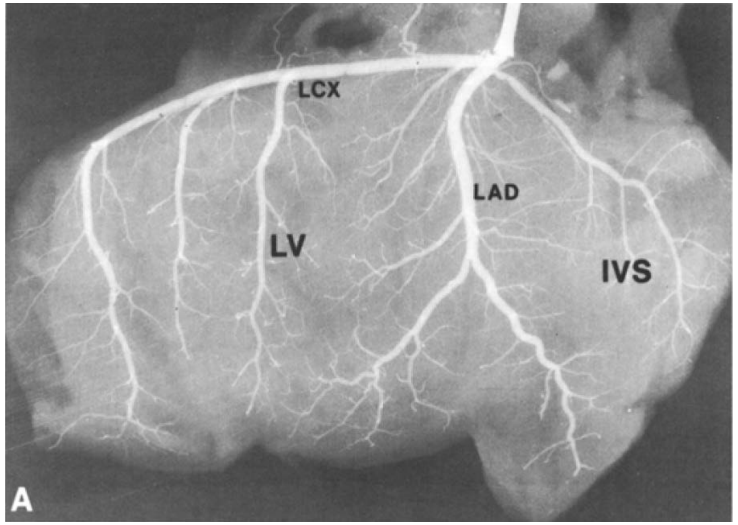
Adapted from Danad et. al., Eur J Nucl Med Mol Imaging. 2012

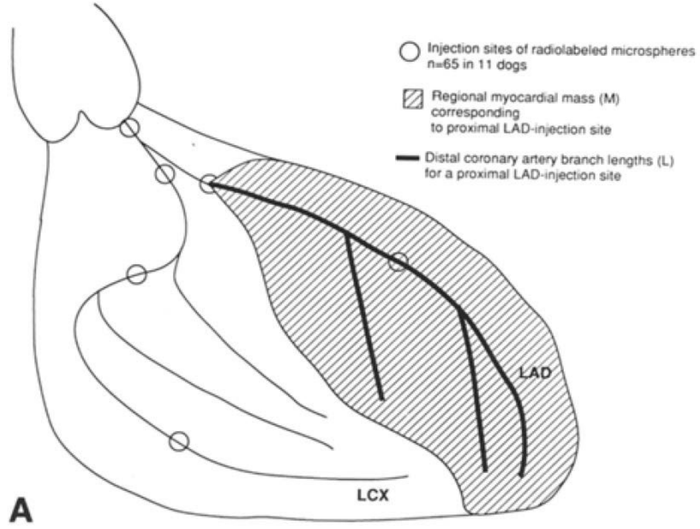


Left Ventricle Myocardial Volume can be extracted from CT data and used to compute average total coronary blood flow at rest

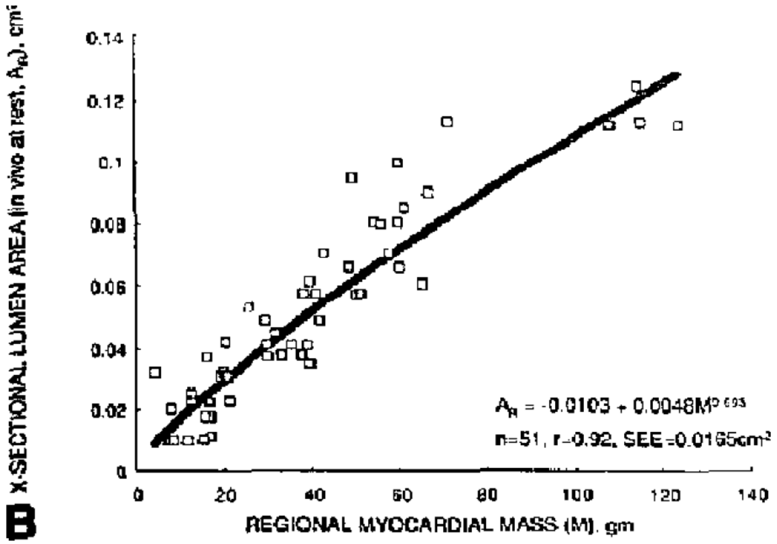
Scientific Principle #2

Resistance of microcirculatory vascular bed at rest is inversely proportional to size of feeding vessel





Regional Myo Mass ∝ Cross-sectional Area



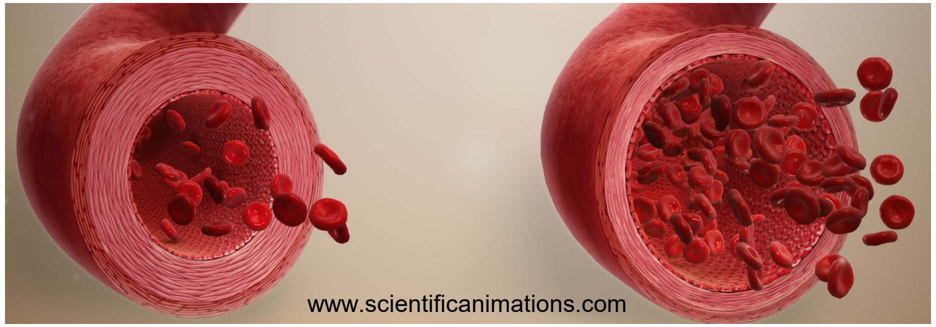
Myocardial Perfusion territory ⇒ Coronary Artery Flow ⇒ Coronary Artery Size

Therefore, epicardial coronary artery size is related to coronary artery flow

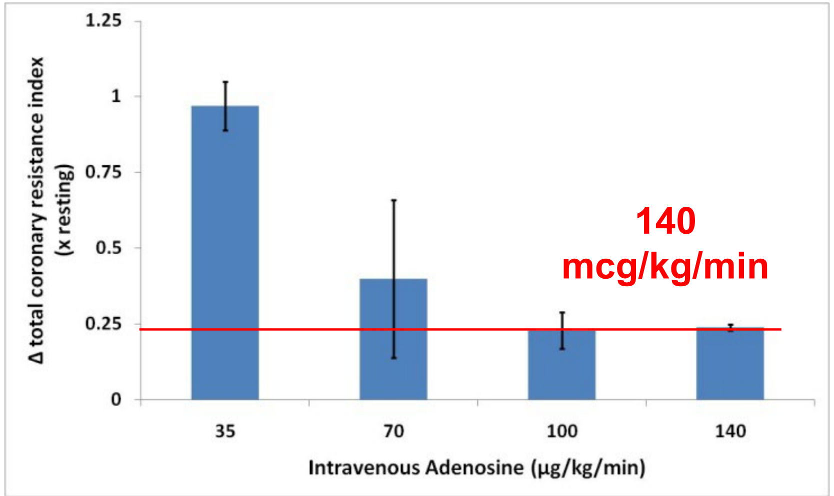
Scientific Principle #3

Predictable microcirculatory response to adenosine

1. When the heart lacks O_2, breakdown of ATP results in release of Adenosine → vasodilation
2. Exogenous administration of Adenosine elicits the maximum hyperemic response by forcing complete smooth muscle cell relaxation
3. Standard of care for induction of hyperemia in non-invasive tests and the cath lab

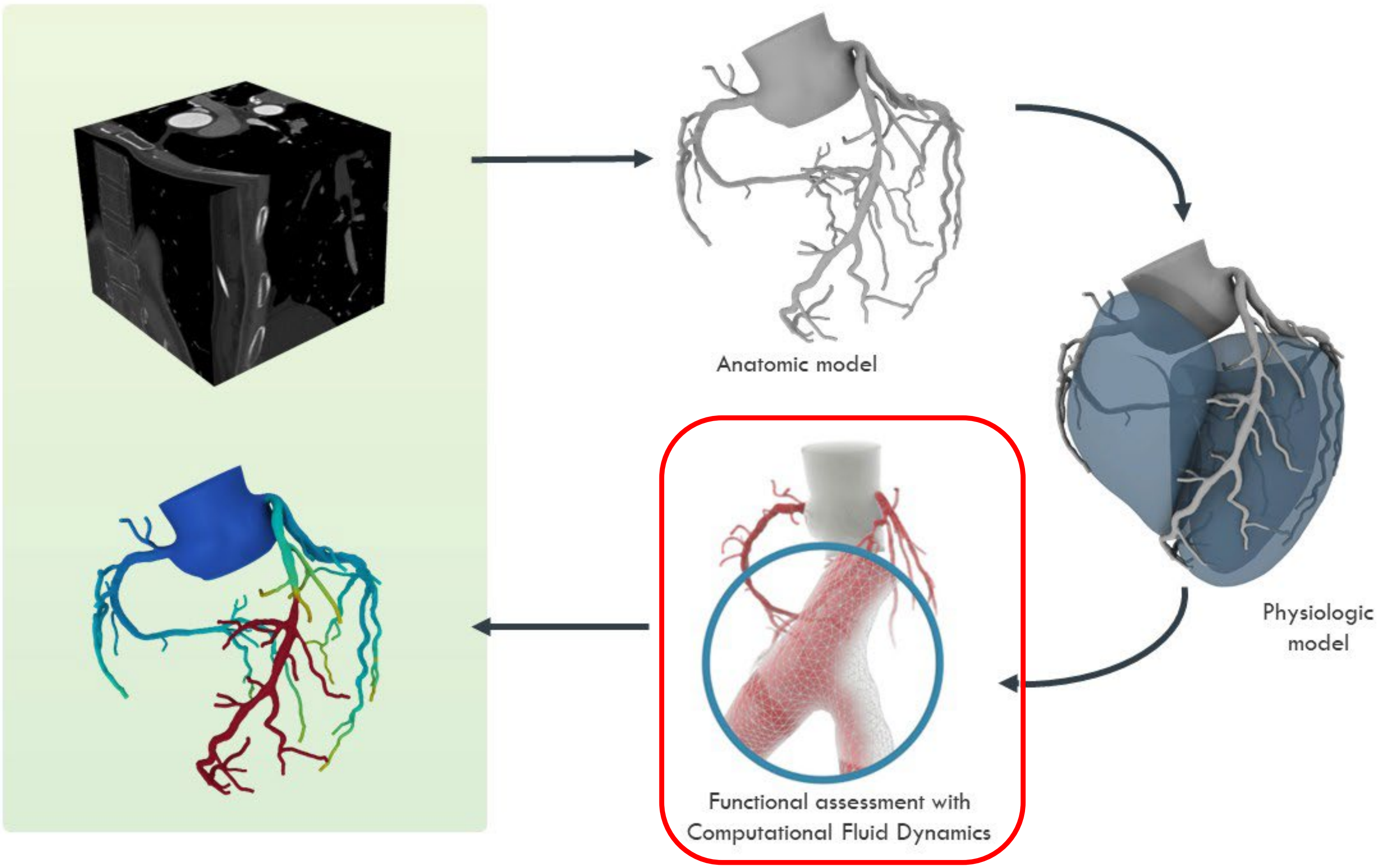


Adenosine relaxes smooth muscle cells lining arterioles resulting in **vasodilation**



Intravenous administration of adenosine elicits remarkably **consistent vasodilatory response** in normal subjects at sufficient doses (*Adapted from Wilson, et. al., Circulation 1990*)

Deriving FFR from CT



Taylor et. al. (2013) Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve: Scientific Basis. Journal of the American College of Cardiology. Vol. 61, Issue 22, pp. 2233-2241.

Computational Fluid Dynamics used to quantify blood flow and pressure

1. Navier-Stokes equations:

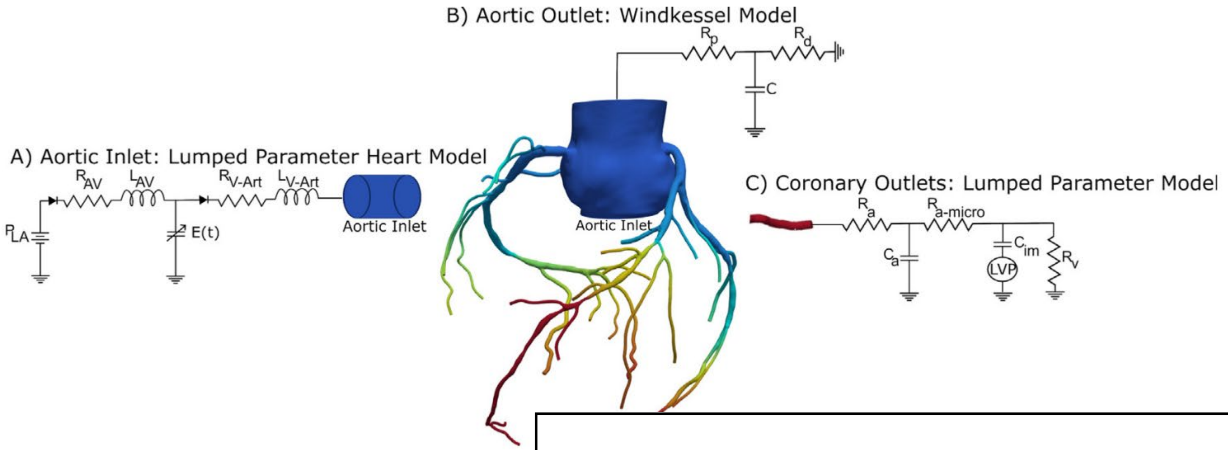
$$\rho\vec{v}_{,t}+\rho\vec{v}\cdot\nabla\vec{v}=-\nabla p+\mu\Delta\vec{v}$$
$$\nabla\cdot\vec{v}=0$$

2. Weak form:

$$\int_{\Omega}\left\{\vec{w}\cdot\left(\rho\vec{v}_{,t}+\rho\vec{v}\cdot\nabla\vec{v}-\vec{f}\right)+\nabla\vec{w}:\left(-p\underset{\sim}{I}+\mu\Delta\vec{v}\right)-\nabla q\cdot\vec{v}\right\}d\vec{x}$$
$$-\int_{\Gamma_h}\vec{w}\cdot\vec{h}ds+\int_{\Gamma}q\vec{v}\cdot\vec{n}ds=0$$

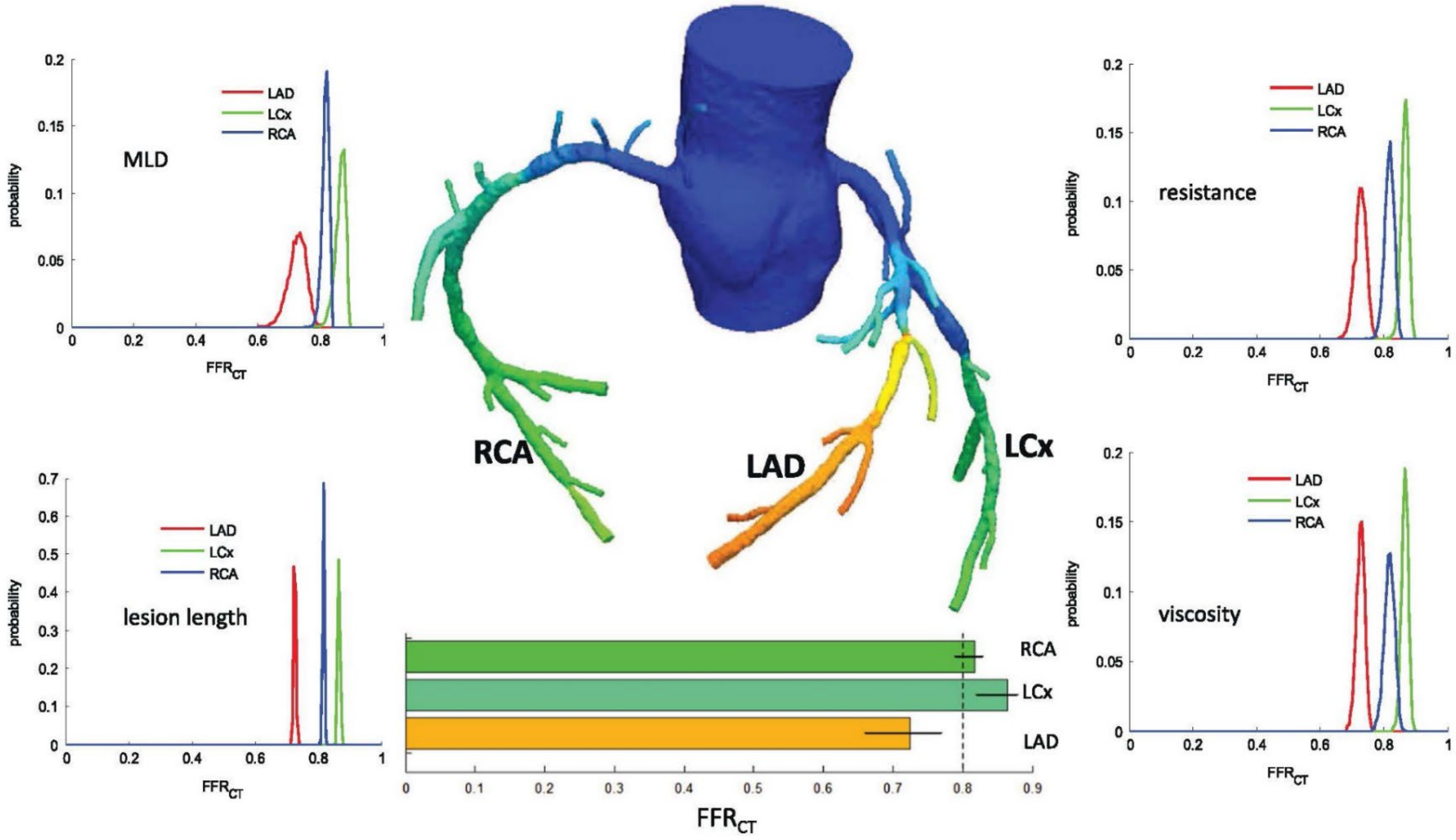
3. Multidomain weak form:

$$\int_{\hat{\Omega}}\hat{\vec{w}}\cdot\left(\rho\hat{\vec{v}}_{,t}+\rho\hat{\vec{v}}\cdot\nabla\hat{\vec{v}}-\vec{f}\right)+\nabla\hat{\vec{w}}:\left(-\hat{p}\underset{\sim}{I}+\underset{\sim}{\tau}\right)d\vec{x}-\int_{\hat{\Gamma}_h}\hat{\vec{w}}\cdot\left(-\hat{p}\underset{\sim}{I}+\underset{\sim}{\tau}\right)\cdot\hat{\vec{n}}ds$$
$$-\boxed{\int_{\Gamma_B}\hat{\vec{w}}\cdot\left(\underset{\sim}{M}_m(\hat{\vec{v}},\hat{p})+\underset{\sim}{H}_m\right)\cdot\hat{\vec{n}}ds}-\int_{\hat{\Omega}}\nabla\hat{q}\cdot\hat{\vec{v}}d\vec{x}+\int_{\hat{\Gamma}}\hat{q}\hat{\vec{v}}\cdot\hat{\vec{n}}ds+\boxed{\int_{\Gamma_B}\hat{q}\left(\vec{M}_c(\hat{\vec{v}},\hat{p})+\vec{H}_c\right)\cdot\hat{\vec{n}}ds}=0$$



1. I. Vignon-Clementel, C.A. Figueroa, K.C. Jansen, C.A. Taylor (2006) Outflow Boundary Conditions for Three-Dimensional Finite Element Modeling of Blood Flow and Pressure in Arteries. Computer Methods in Applied Mechanics and Engineering, Vol. 195, pp. 3776-3796.

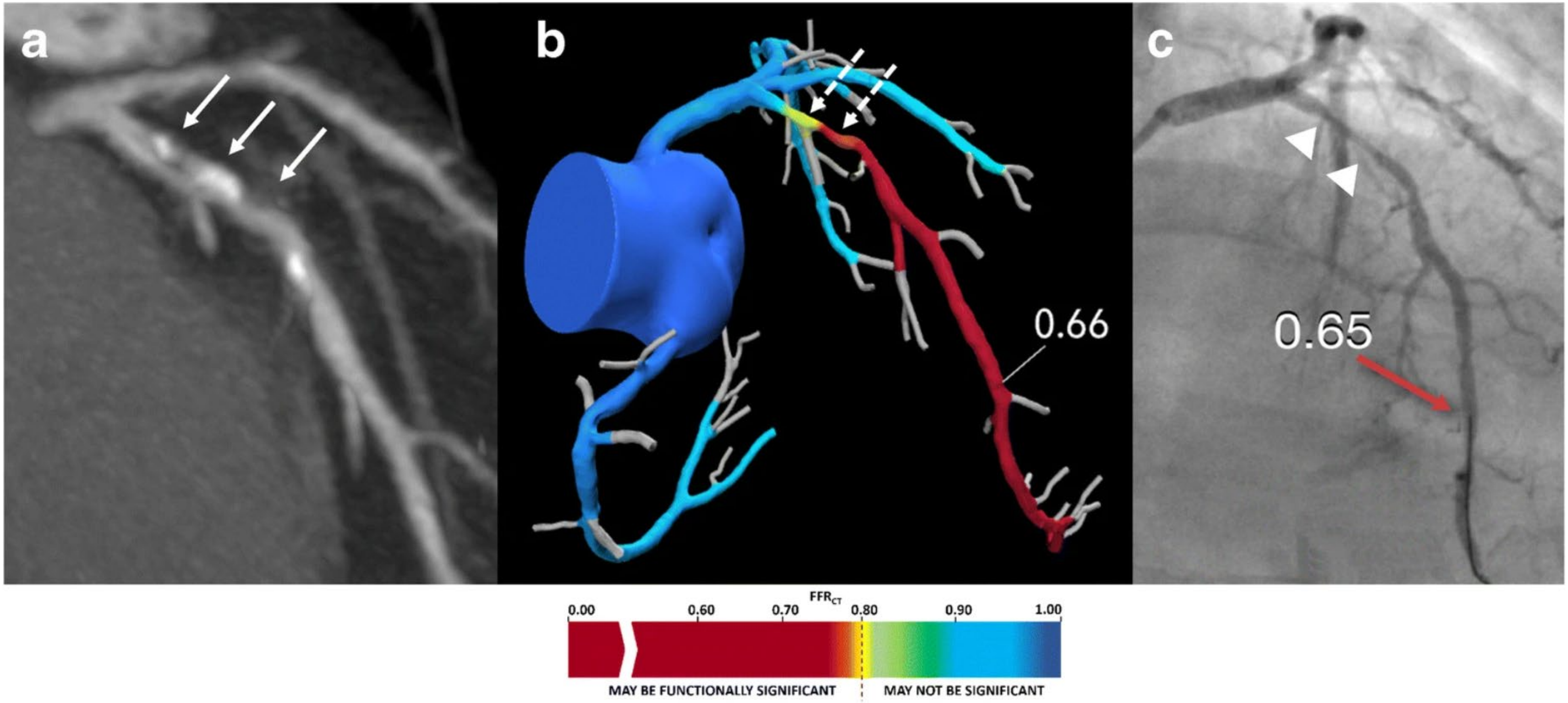
Patient-specific Sensitivity analysis and Uncertainty Quantification demonstrated relative importance of model variables



S. Sankaran, L. Grady, C.A. Taylor (2015) Fast Geometric Sensitivity Analysis in Hemodynamic Simulations Using Machine Learning. Computer Methods in Applied Mechanics and Engineering. Vol. 297, pp. 167–190.

S. Sankaran, H.J. Kim, G. Choi, C.A. Taylor (2015). Uncertainty quantification in coronary blood flow simulations: impact of geometry, boundary conditions and blood viscosity. Journal of Biomechanics, 2016.

FFR_{CT} data available along length of vessels



Sreedharan, S., Zekry, S.B., Leipsic, J.A. et al. Updates on Fractional Flow Reserve Derived by CT (FFRCT). Curr Treat Options Cardio Med 22, 17 (2020).

Clinical evidence supporting accuracy, utility and economic impact

600+

Publications

100+

Studies

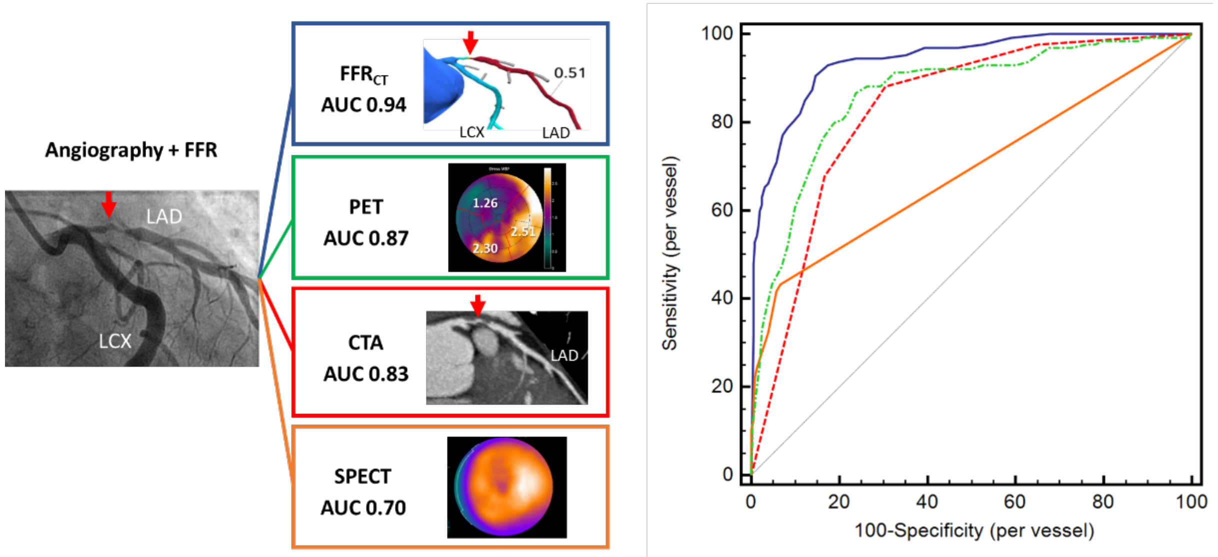
✓ **Accuracy evaluated against invasive standards**	NXT PACIFIC REVEALPLAQUE
✓ **Clinical utility evaluated with outcomes data**	PRECISE (RCT) ADVANCE FISH&CHIPS DECODE
✓ **Economic benefit compared to standard care**	PRECISE (RCT) PLATFORM

The NEW ENGLAND JOURNAL of MEDICINE · JAMA The Journal of the American Medical Association · JACC Journal of the American College of Cardiology · European Heart Journal · nature medicine

1. Nørgaard et al., "Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial," JACC, 2014.
2. Driessen et al., "Comparison of Coronary Computed Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis," JACC, 2019.
3. Narula et al. Quantitative Assessment of Deep Learning-based Coronary Plaque by CT Angiography Prospectively Compared with Intravascular Ultrasound. SCCT Scientific Sessions, 2023; Narula et al. Prospective deep learning–based quantitative assessment of coronary plaque by computed tomography angiography compared with intravascular ultrasound: the REVEALPLAQUE study. EHJ CVI 2024 https://doi.org/10.1093/ehjci/jeae115
4. Douglas et al., "Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease," JAMA Cardiol, 2023.Fairbairn et al.

FFR_{CT} diagnostic accuracy

Discriminative ability for the detection of per-vessel FFR-defined ischemia



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 2, 2019
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PUBLISHED BY ELSEVIER

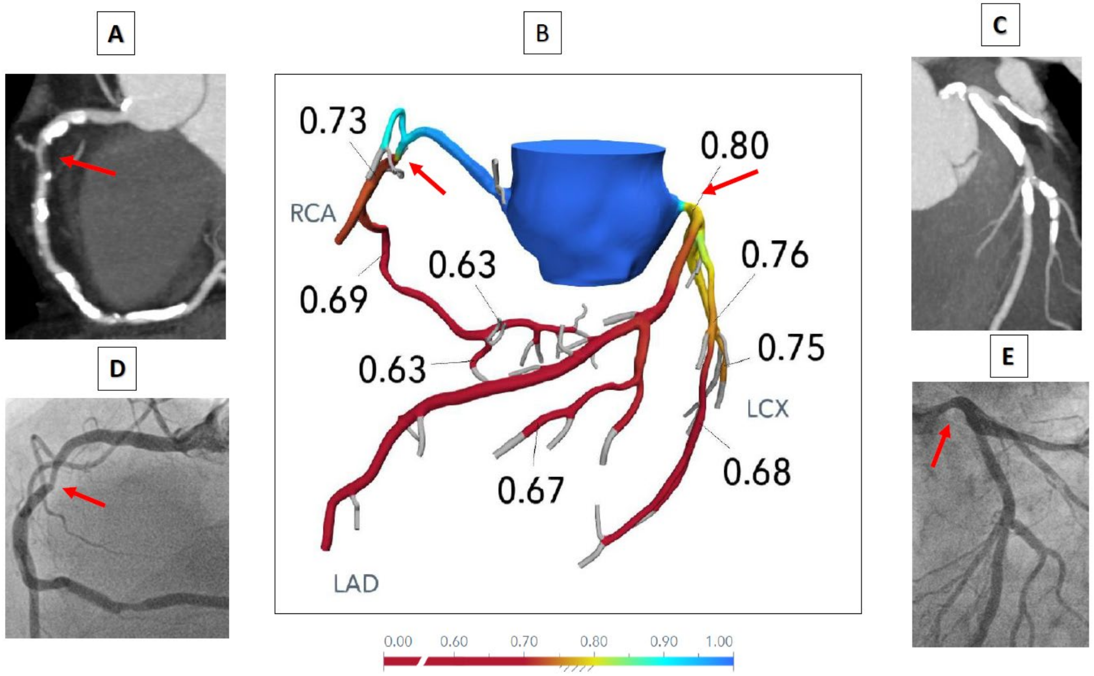
Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis

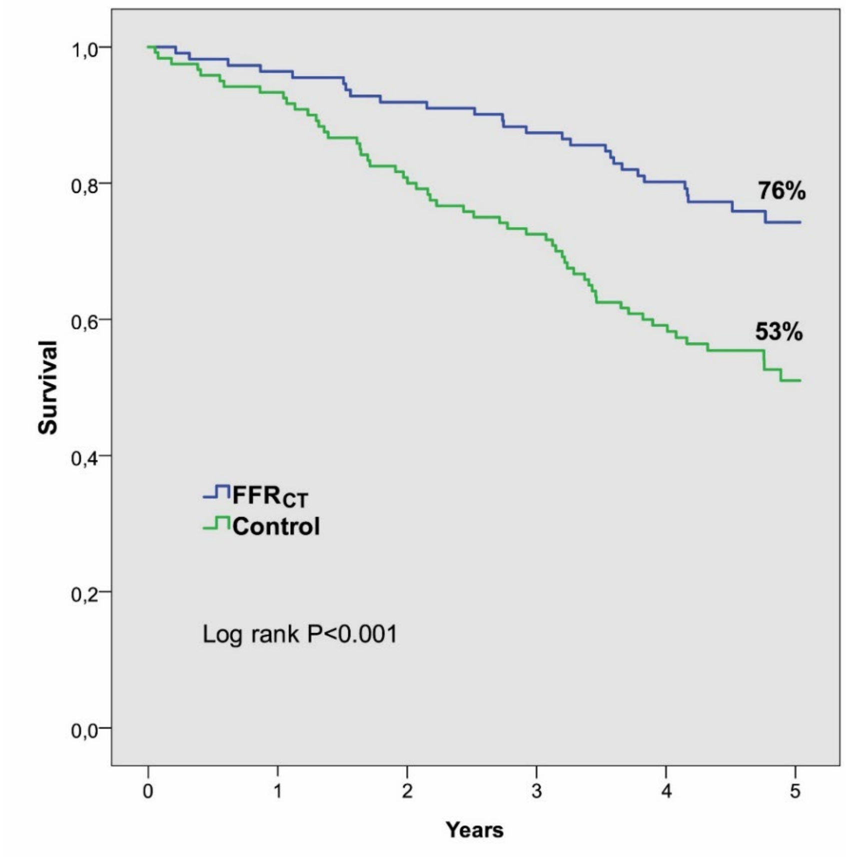
Roel S. Driessen, MD,[a] Ibrahim Danad, MD,[a] Wijnand J. Stuijfzand, MD,[a] Pieter G. Raijmakers, MD, PhD,[b] Stefan P. Schumacher, MD,[a] Pepijn A. van Diemen, MD,[a] Jonathon A. Leipsic, MD,[c] Juhani Knuuti, MD, PhD,[d] S. Richard Underwood, MD, PhD,[e] Peter M. van de Ven, PhD,[f] Albert C. van Rossum, MD, PhD,[a] Charles A. Taylor, PhD,[g,h] Paul Knaapen, MD, PhD[a]

"FFRct has highest accuracy among noninvasive tests to predict FFR"

Driessen et. al. JACC 2019

CT + FFRct identifies Coronary Artery Disease in patients with PAD (CLTI)





FFR_{CT} - guided

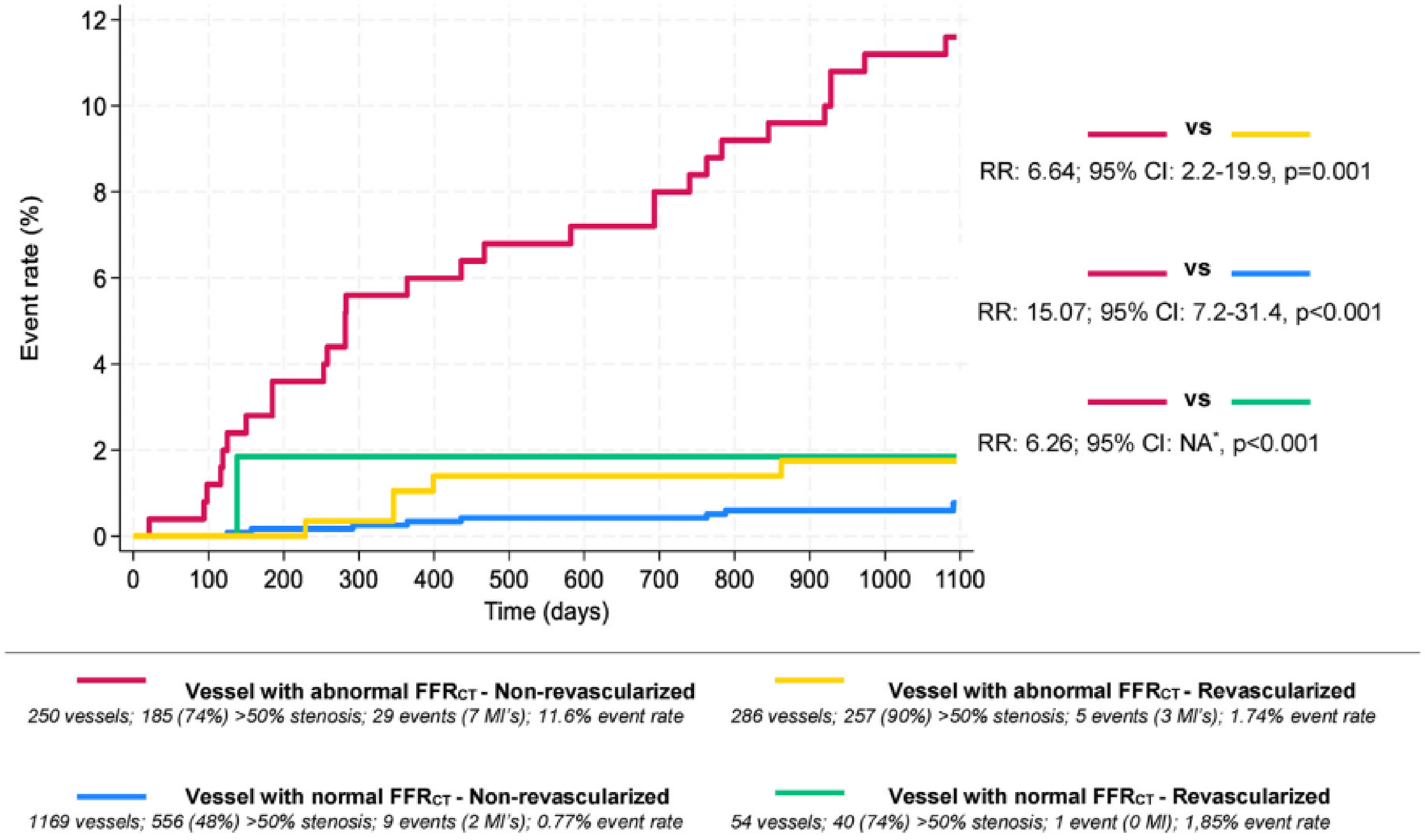
Control

67 year old man with no cardiac history or symptoms admitted to the hospital for treatment of ischemic rest pain of the left foot with an ankle-brachial index of 0.44.

Use of FFR_{CT} Analysis to inform cardiac treatment improved survival in patients with no CAD history or symptoms that were treated for chronic limb threatening ischemia

Krievens et. al. Journal of Vascular Surgery, 2021., Zellens et. al. J. Critical Limb Ischemia, 2021, Latkovskis et. al. EJVES, 2024.

Vessels with Abnormal FFR_{CT} have lower event rate when Revascularized compared to Non-revascularized

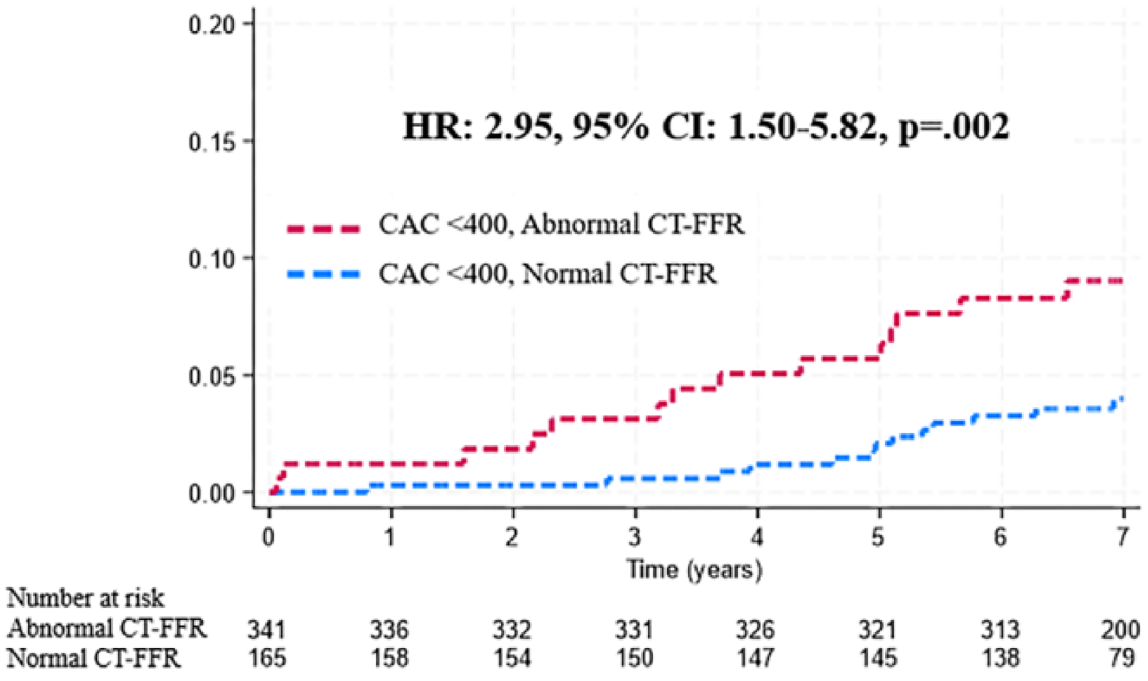


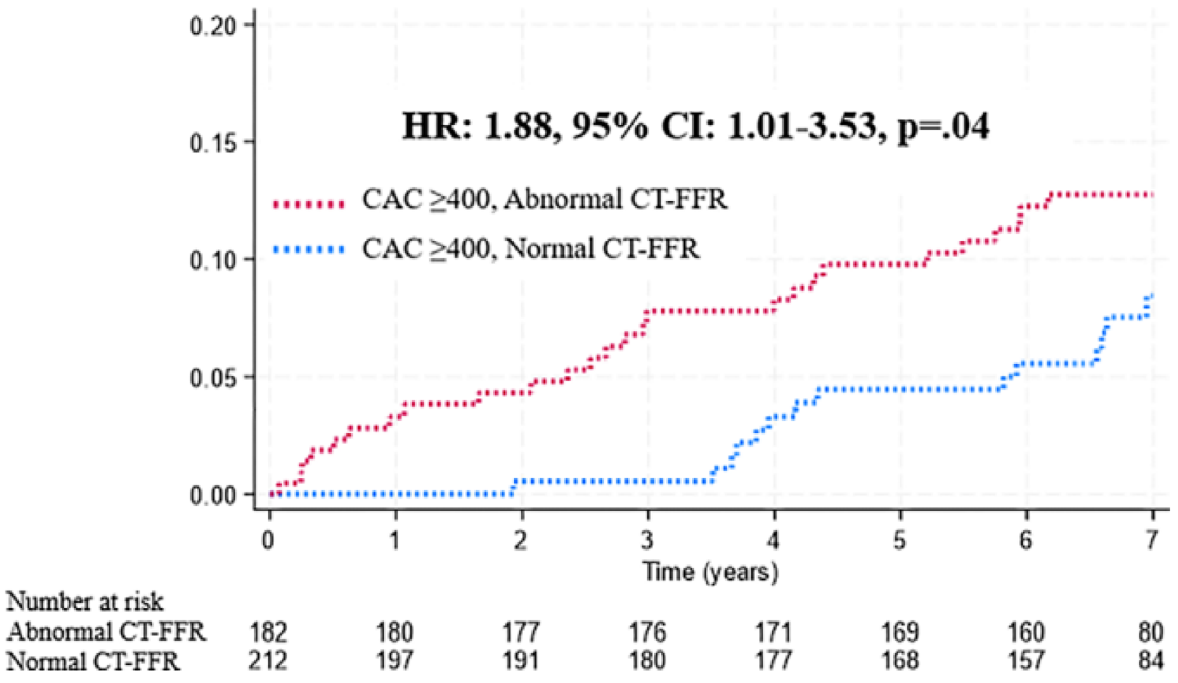
Event rate: late (>90 day) revascularization or non-fatal MI

Madsen et. al. Journal of Cardiovascular Computed Tomography 18 (2024) 494–502

FFR_{CT} identifies increased risk of cardiovascular death or spontaneous M.I. for patients with low or high Calcium scores

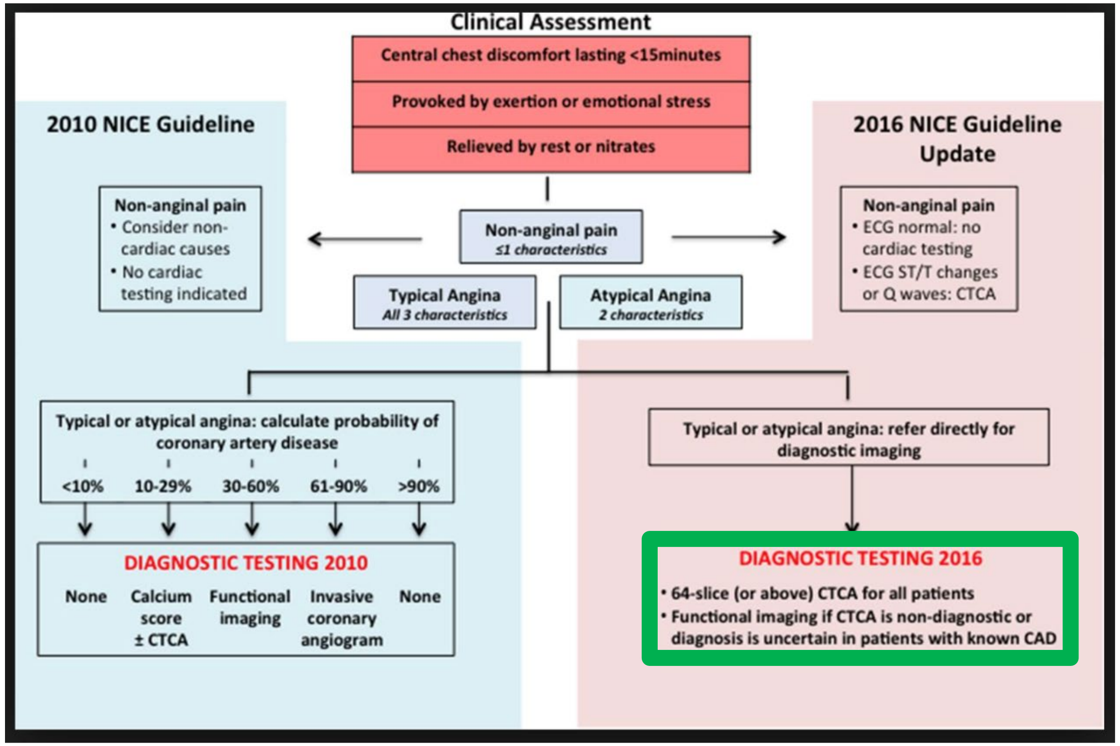
N=900 participants were included, 377 (42%) with abnormal CT-FFR and 394 (44%) with high CAC (≥ 400).

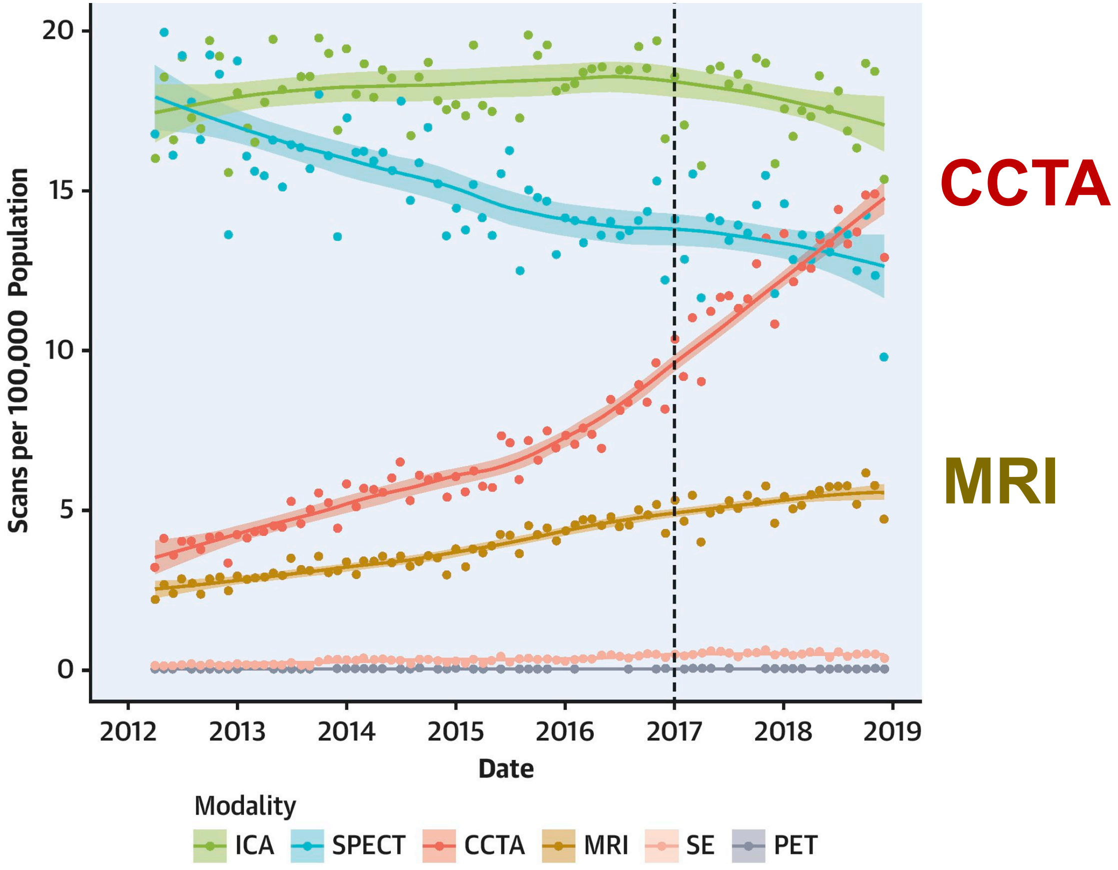




Madsen KT., Radiology, Published Online: October 14, 2025
https://doi.org/10.1148/radiol.251788

Chest-pain guidelines in the U.K. were updated in 2016 to recommend CCTA anatomic imaging followed by functional testing if diagnosis is uncertain. Rate of CCTA and Cardiac MRI have increased dramatically since 2016.





Timmis, A et al., *Heart*, May 2017 "NICE updates the stable chest pain guideline"

Weir-McCall et al. *J Am Coll Cardiol Img* 2023 "National Trends in Coronary Artery Disease Imaging"

FFR_{CT} received positive review from NICE (National Institute for Health and Care Excellence) in 2017 and, in 2021, was one of first products to be mandated by NHS England

NHS mandates AI-powered analysis to treat coronary heart disease

1 FEBRUARY 2021 08:49

HeartFlow has announced that the National Health Service England (NHSE) and NHS Improvement have mandated that English hospitals adopt the AI-powered HeartFlow FFRct Analysis to fight coronary heart disease (CHD).


THE TIMES

Tuesday May 4 2021 | thetimes.co.uk | No 73462

Our 16-year age gap
Can the relationship really last?

INSIDE TIMES2
Forget the 5:2 diet. Think 3:2

Reopening of holiday hotspots weeks away

Britons told to be patient for 'big bang' in June

New scan finds heart disease in 20 minutes

FISH&Chips study in NHS hospitals reveals FFRct is safe while reducing invasive angiograms and downstream noninvasive cardiac testing

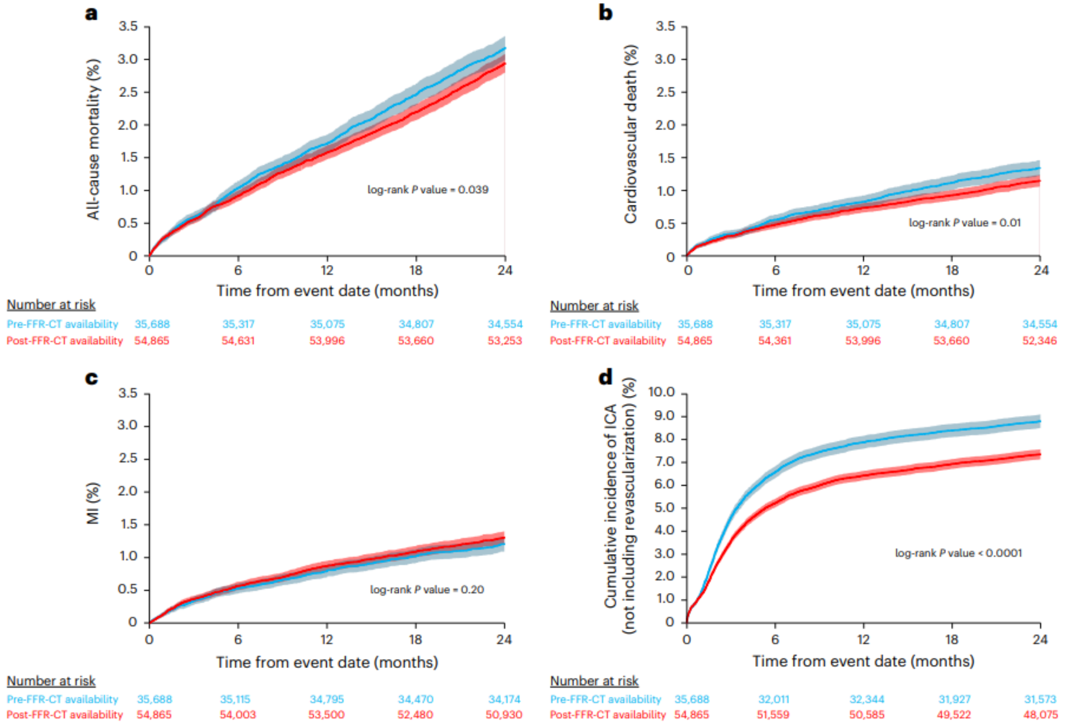
Real world, multi-center, retrospective study including **more than 90,000 patients assessing at a national level** the **incremental impact of adding FFR_{CT}** to a CCTA-first diagnostic paradigm for evaluating CAD.

nature medicine

Article https://doi.org/10.1038/s41591-025-03620-y

Implementation of a national AI technology program on cardiovascular outcomes and the health system

"**FFR-CT was safe**, with **no difference in all-cause** (n = 1,134 (3.2%) versus 1,612 (2.9%), **adjusted-hazard ratio** (aHR) 1.00 (0.93–1.08), P = 0.97) **or cardiovascular mortality** (n = 465 (1.3%) versus 617 (1.1%), aHR 0.96 (0.85–1.08), P = 0.48), **while reducing invasive coronary angiograms** (n = 5,720 (16%) versus 8,183 (14.9%), aHR 0.93 (0.90–0.97), P < 0.001) **and noninvasive cardiac tests** (189/1,000 patients versus 167/1,000), P < 0.001)."



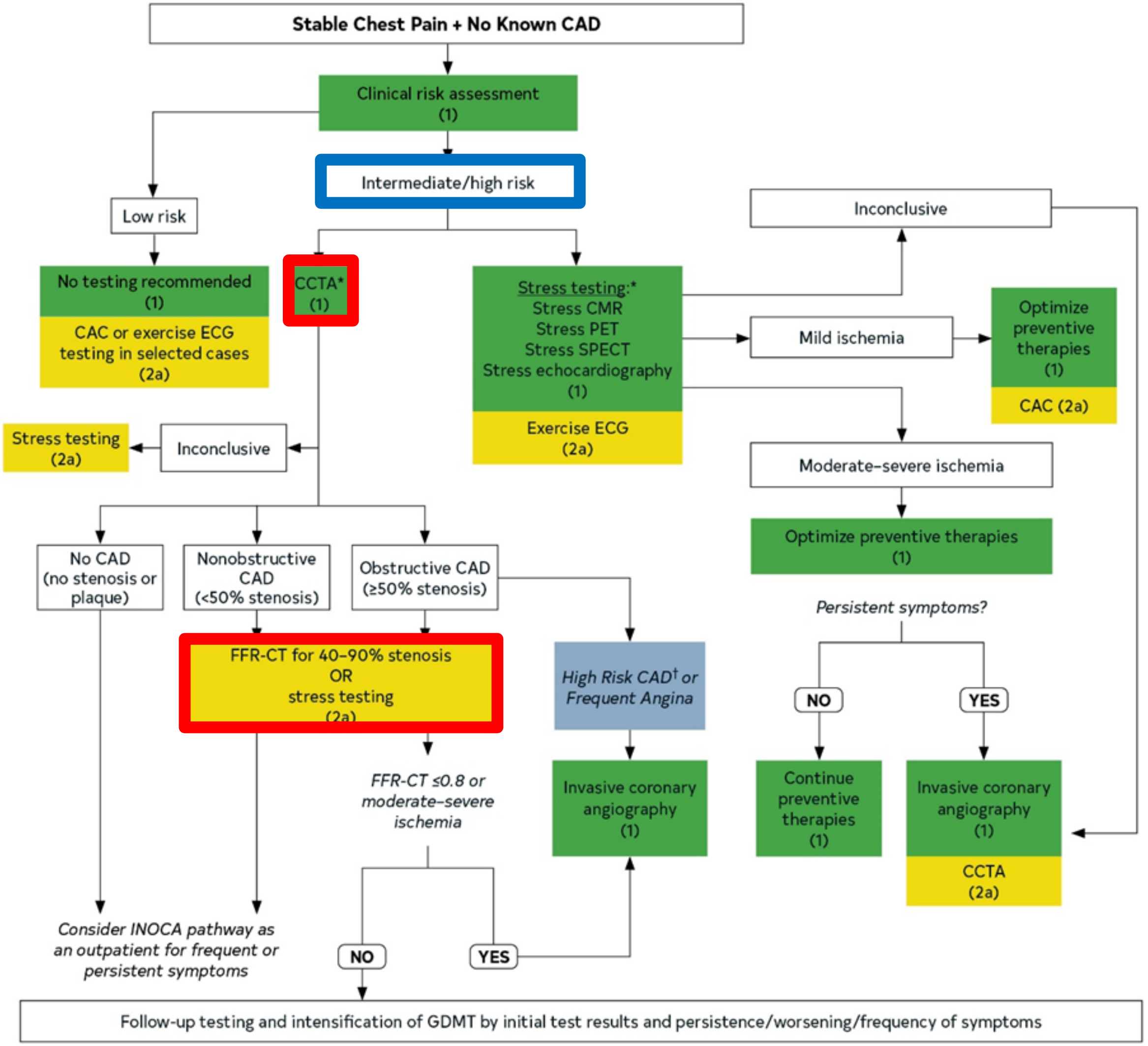
In 2021, American College of Cardiology / American Heart Association Clinical Guidelines were updated to elevate CT-first pathway (Level 1A) followed by functional assessment

American Heart Association.

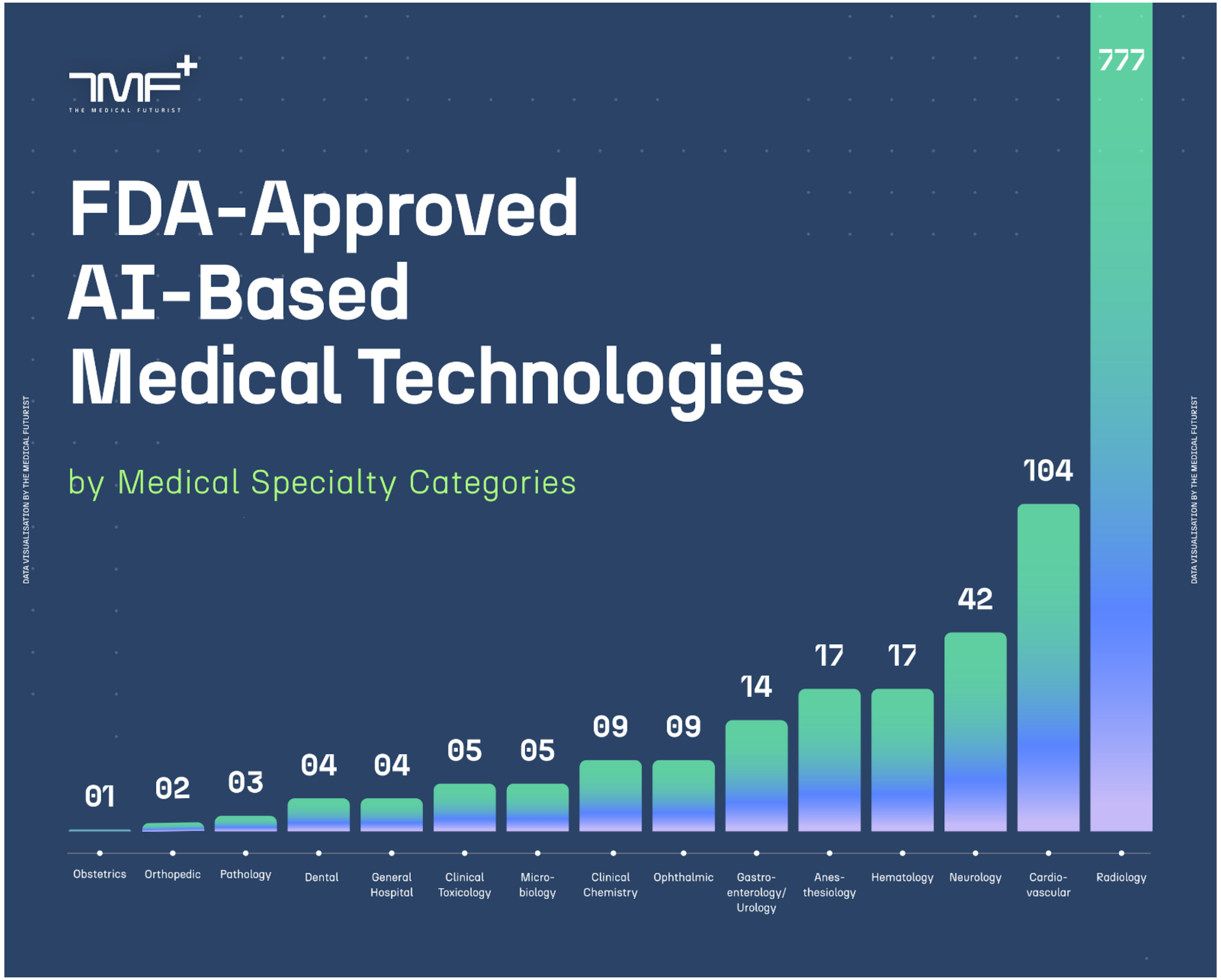
AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

Endorsed by the American Society of Echocardiography, American College of Chest Physicians, Society for Academic Emergency Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance



There are >1000 FDA-cleared AI products



However, few of these AI products are being PAID for. HeartFlow FFR_{CT} recognized as most widely reimbursed AI product in U.S. Healthcare system.

NEJM AI
DOI: 10.1056/AIoa2300030
ORIGINAL ARTICLE

Characterizing the Clinical Adoption of Medical AI Devices through U.S. Insurance Claims

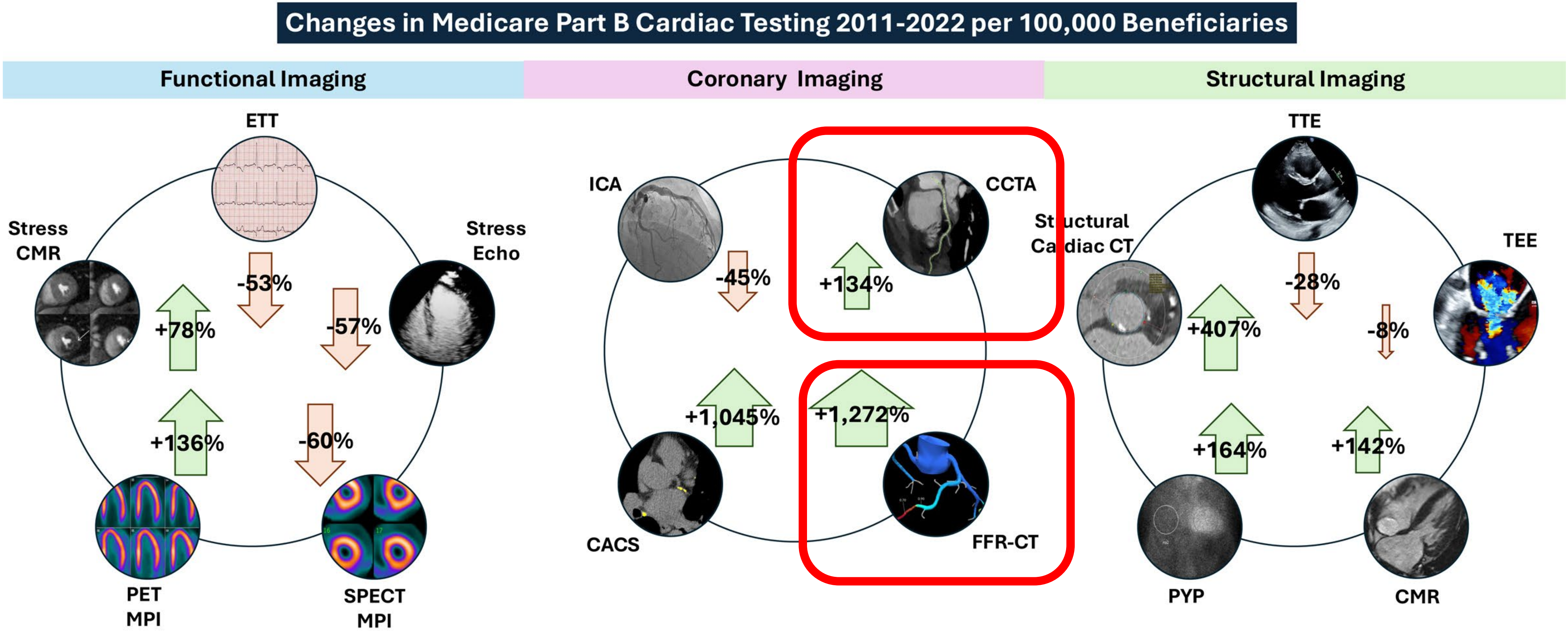
Kevin Wu, M.S.,[1] Eric Wu, M.S.,[2] Brandon Theodorou,[3] Weixin Liang, M.S.,[4] Christina Mack, Ph.D.,[5] Lucas Glass, Ph.D.,[5] Jimeng Sun, Ph.D.,[3,6] and James Zou, Ph.D.[1,2,4]

Received: July 9, 2023; Revised: September 15, 2023; Accepted: Se

Table 1. Summary of AI CPT Codes.*

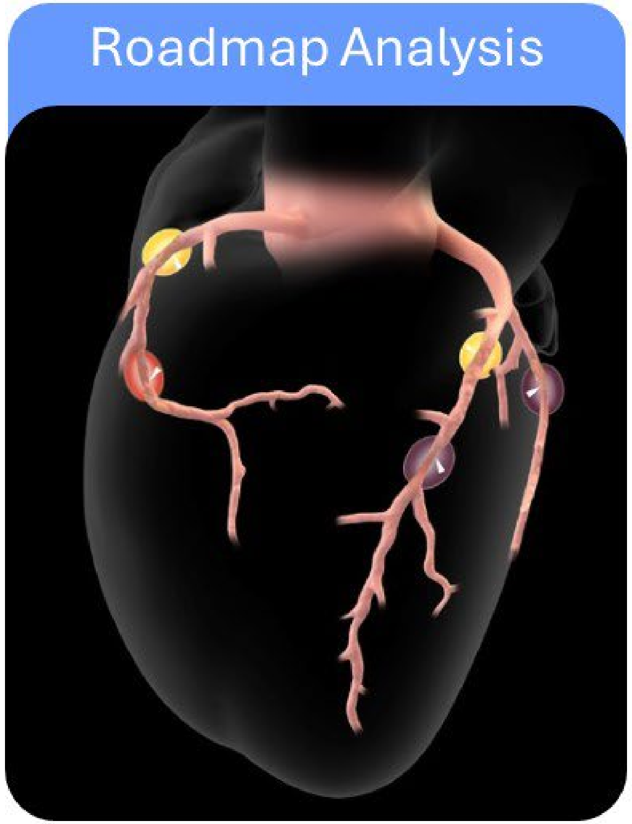
Total Claims	Condition or Medical AI Procedure	CPT Code(s)	Example Product Name	Effective Date
67,306	Coronary artery disease	0501T–0504T	HeartFlow Analysis[48]	June 1, 2018
15,097	Diabetic retinopathy	92229	LumineticsCore[49]	January 1, 2021
4,459	Coronary atherosclerosis	0623T–0626T	Cleerly[50]	January 1, 2021
2,428	Liver MR	0648T–0649T	Perspectum LiverMultiScan[51]	January 1, 2021
591	Multiorgan MRI	0697T–0698T	Perspectum CoverScan[52]	January 1, 2022
552	Breast ultrasound	0689T–0690T	Koios DS[53]	January 1, 2022
435	ECG cardiac dysfunction	0764T–0765T	Anumana[50]	January 1, 2023
331	Cardiac acoustic waveform recording	0716T	CADScor[50]	July 1, 2022
237	Quantitative MR cholangiopancreatography	0723T–0724T	Perspectum MRCP+[54]	July 1, 2022
67	Epidural infusion	0777T	CompuFlo[55]	January 1, 2023
4	Quantitative CT tissue characterization	0721T–0722T	Optellum Virtual Nodule Clinic[56]	July 1, 2022
1	Autonomous insulin dosage	0740T–0741T	d-Nav[57]	January 1, 2023
1	CT vertebral fracture assessment	0691T	HealthVCF[50]	January 1, 2022
1	Noninvasive arterial plaque analysis	0710T–0713T	ElucidVivo[50]	January 1, 2022
0	Facial phenotype analysis	0731T	Face2Gene[50]	July 1, 2022
0	X-ray bone density	0749T	OsteoApp[50]	January 1, 2023

Cardiac CT and FFR-CT utilization are growing rapidly for Coronary Imaging

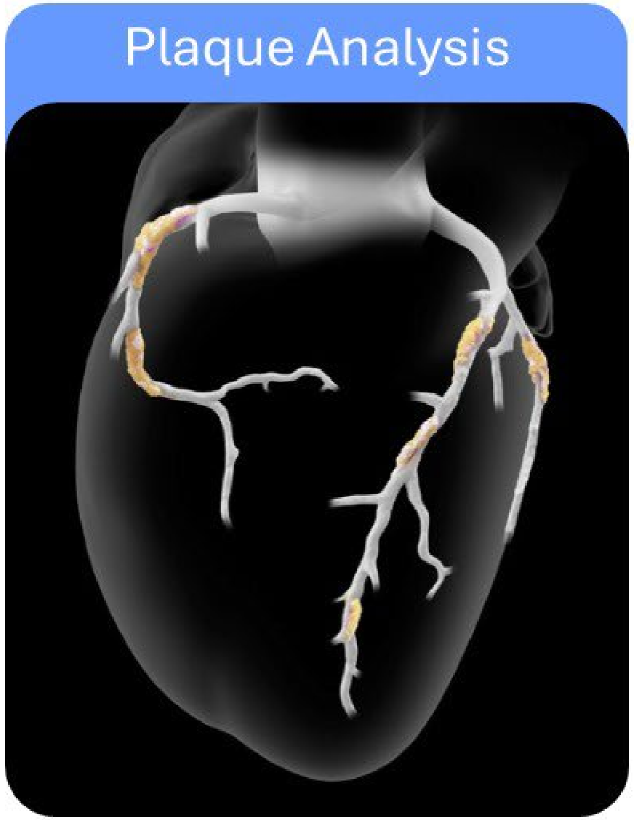


Yosef A. Cohen. Circulation: Cardiovascular Imaging. Temporal Trends in Noninvasive and Invasive Cardiac Testing From 2010 to 2022 in the US Medicare Population, Volume: 18, Issue: 4, Pages: e017567, DOI: (10.1161/CIRCIMAGING.124.017567)

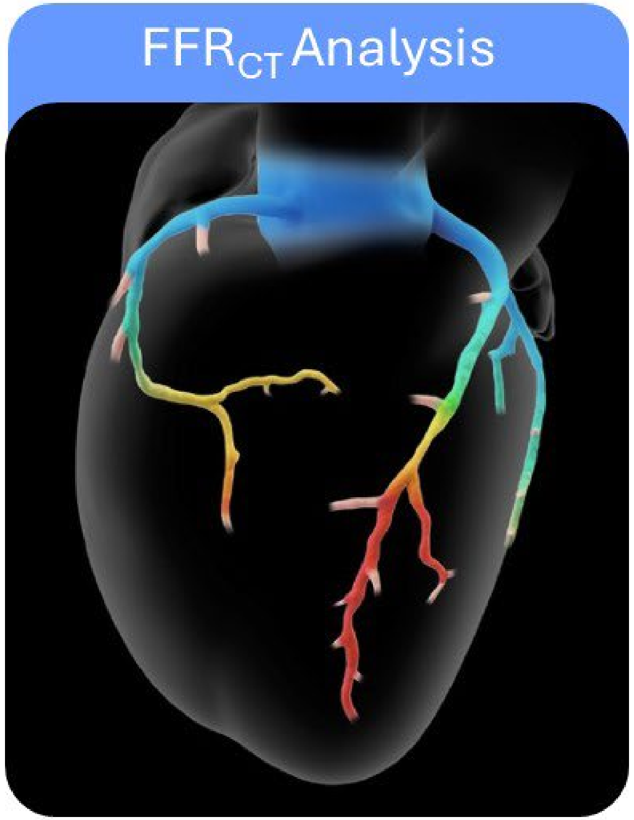
Anatomy, Plaque & Physiology Data all available from CCTA



Guide CT Reading



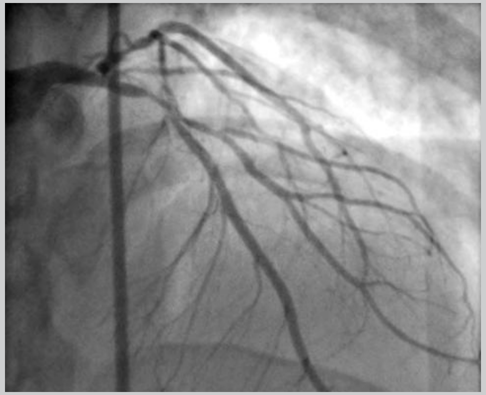
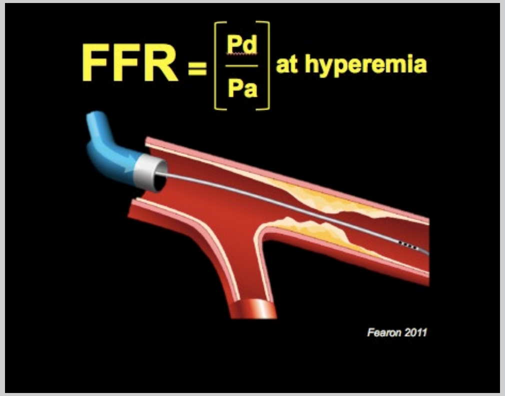
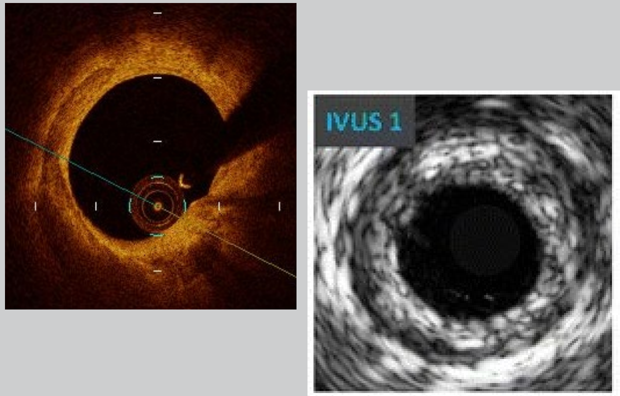
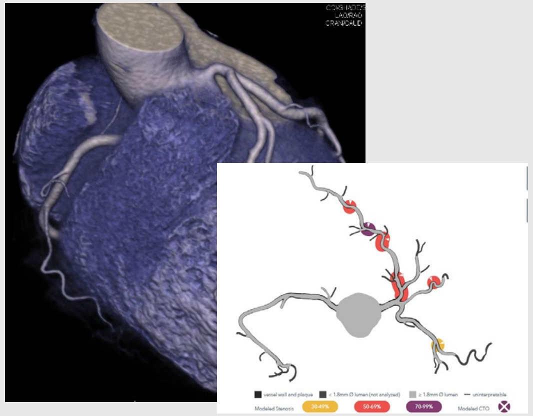
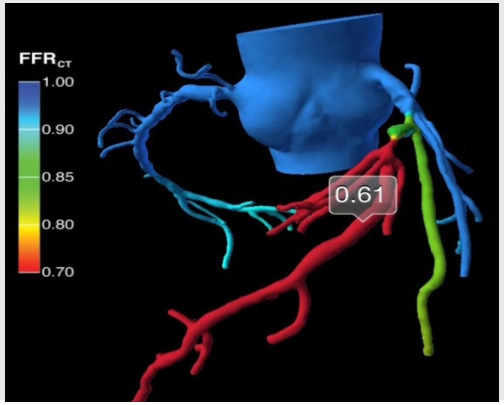
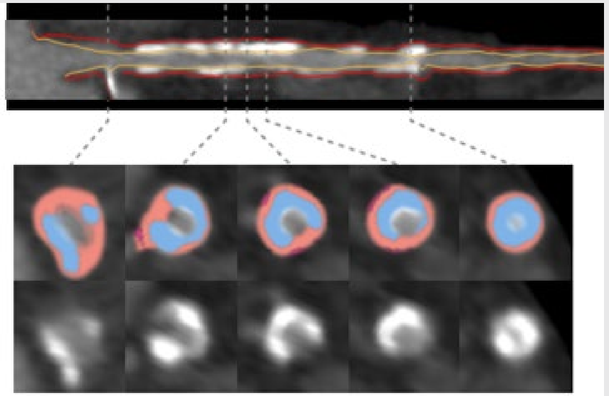
Risk Stratification / Medication Management



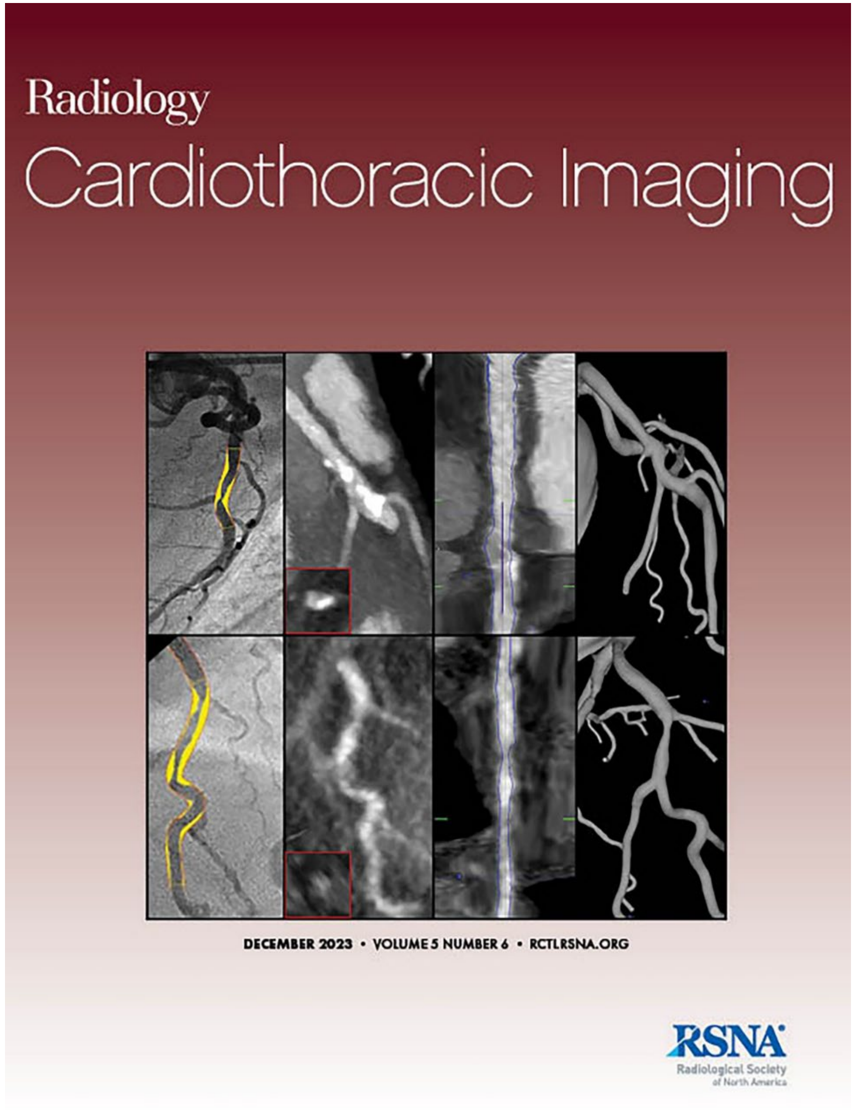
Intervention Decision

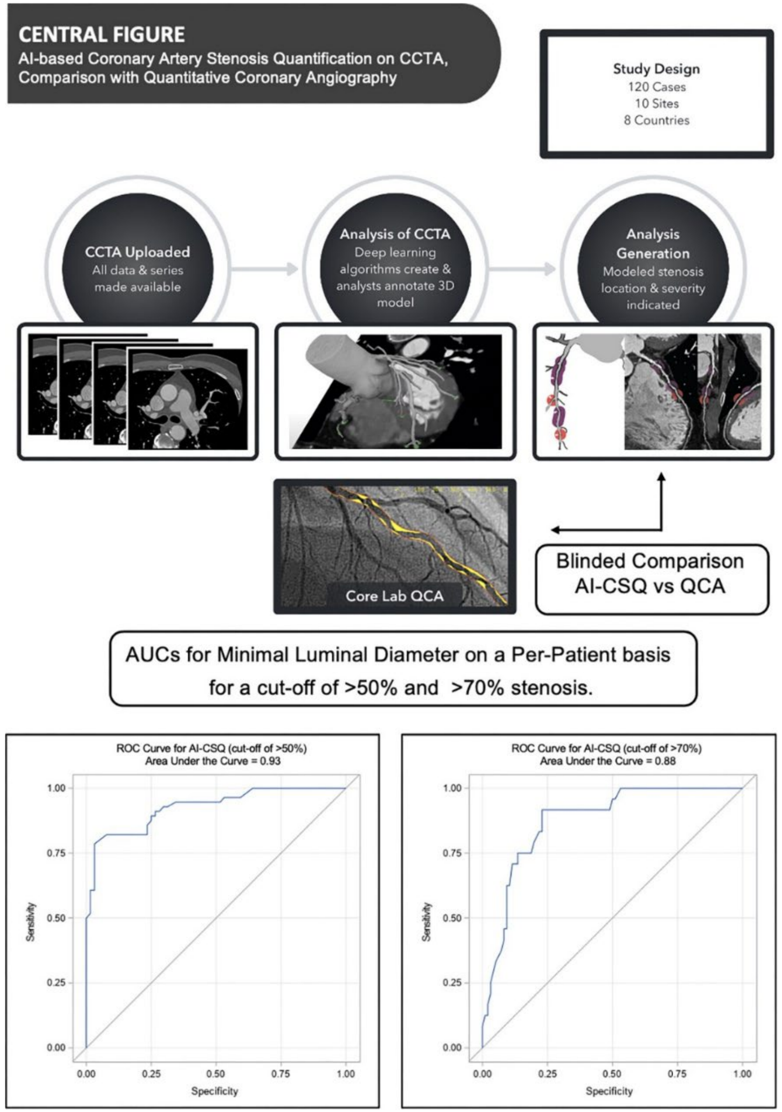
FDA Cleared AI Quantitative Coronary Plaque Analysis (AI-QCPA) Products - HeartFlow

Methods to assess coronary anatomy, physiology and plaque

	ANATOMY Identify obstructive CAD	**PHYSIOLOGY** Identify lesion-specific ischemia that may benefit from PCI	**PLAQUE** Characterize and Quantify atherosclerosis
Invasive			
Noninvasive			

FDA Cleared AI Quantitative Anatomy Product - HeartFlow





Performance of AI Quantitative Coronary Plaque Analysis

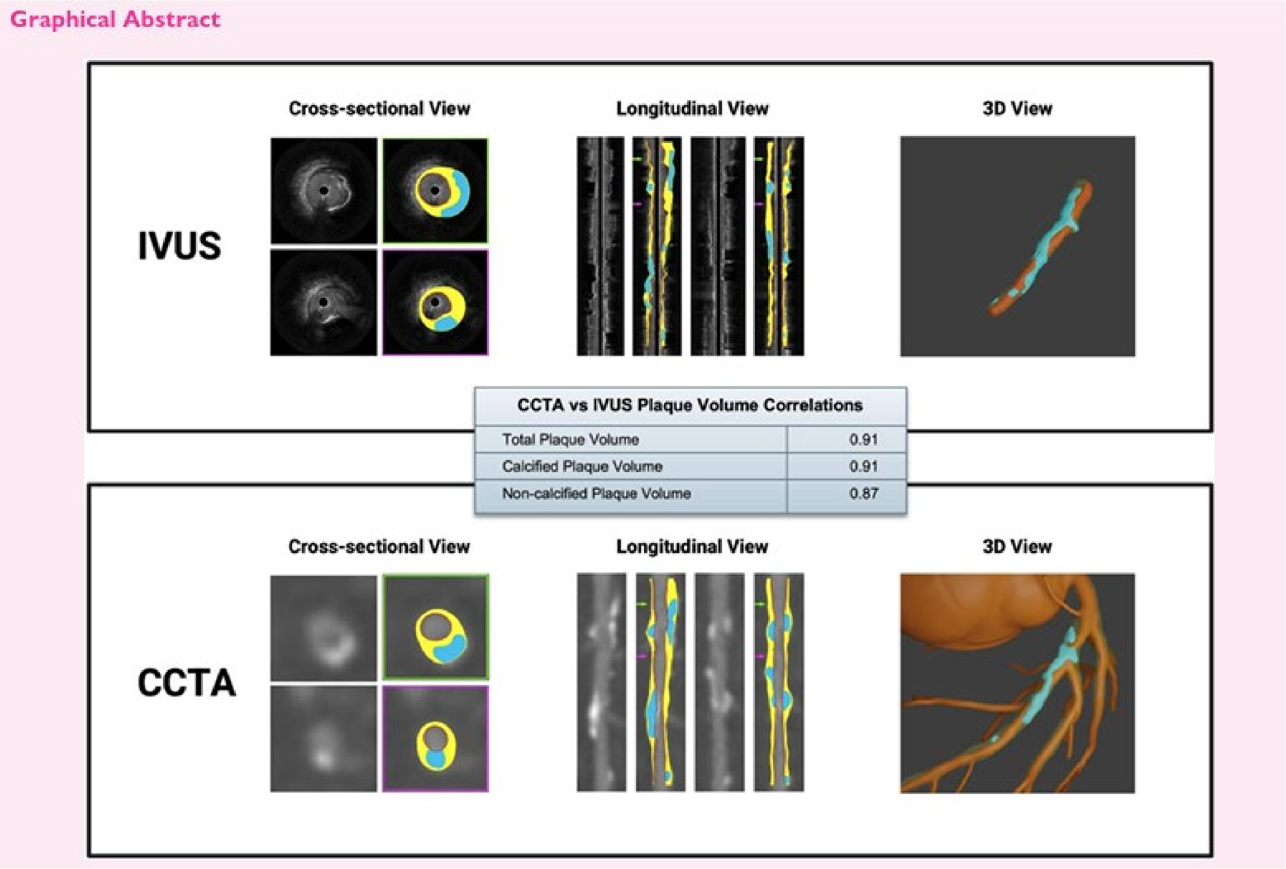
ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2024) **25**, 1287–1295
https://doi.org/10.1093/ehjci/jeae115
ORIGINAL PAPER

Prospective deep learning–based quantitative assessment of coronary plaque by computed tomography angiography compared with intravascular ultrasound: the REVEALPLAQUE study

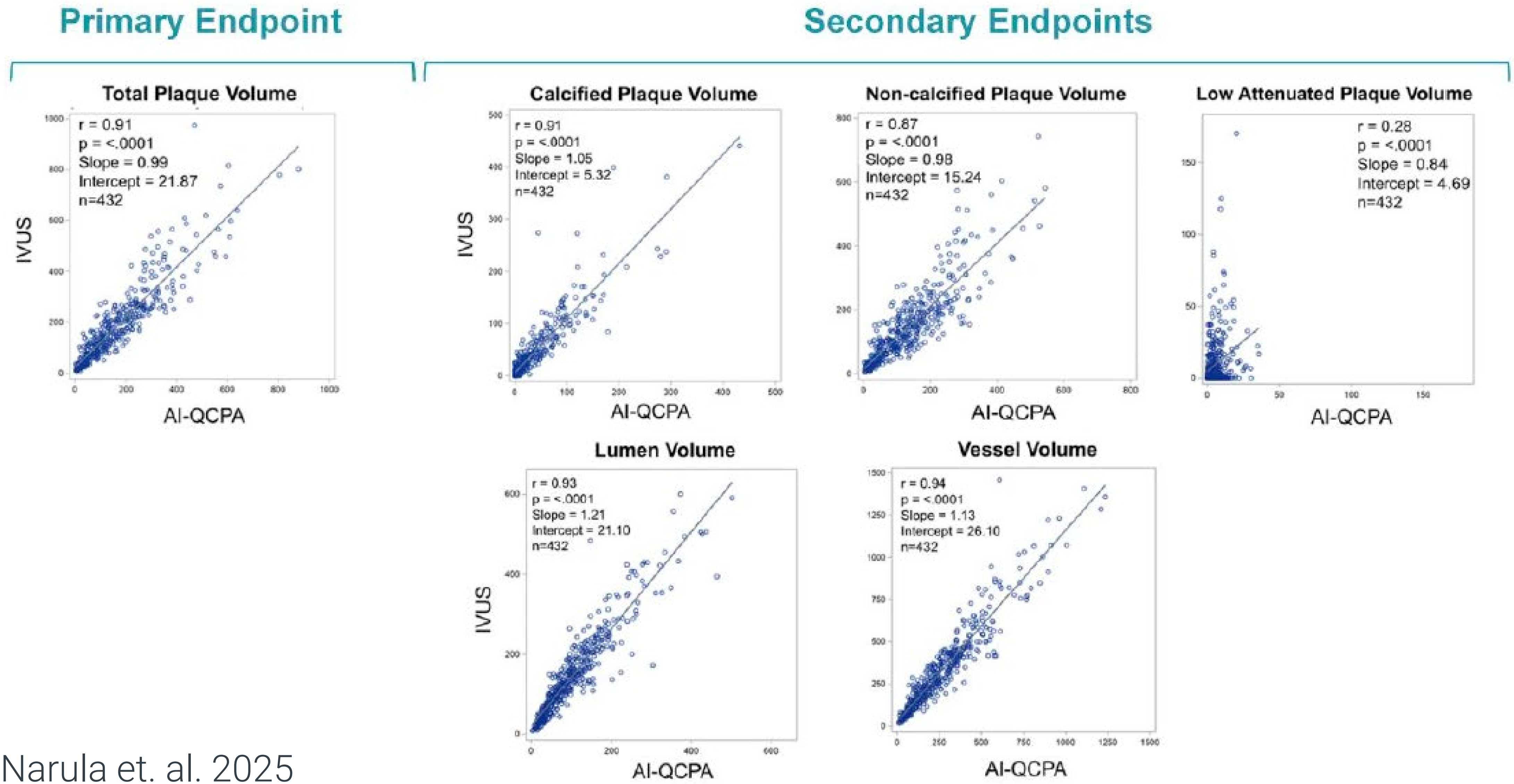
Jagat Narula[1]*, Thomas D. Stuckey[2], Gaku Nakazawa[3], Amir Ahmadi[4], Mitsuaki Matsumura[5], Kersten Petersen[6], Saba Mirza[6], Nicholas Ng[6], Sarah Mullen[6], Michiel Schaap[6], Jonathan Leipsic[7], Campbell Rogers[6], Charles A. Taylor[6], Harout Yacoub[8], Himanshu Gupta[9], Hitoshi Matsuo[10], Sarah Rinehart[11], and Akiko Maehara[12]

<u>Objective</u>:

Determine accuracy of AI-Plaque Analysis vs IVUS via a global prospective study with independent, blinded, core lab adjudication



Performance of AI Quantitative Coronary Plaque Analysis

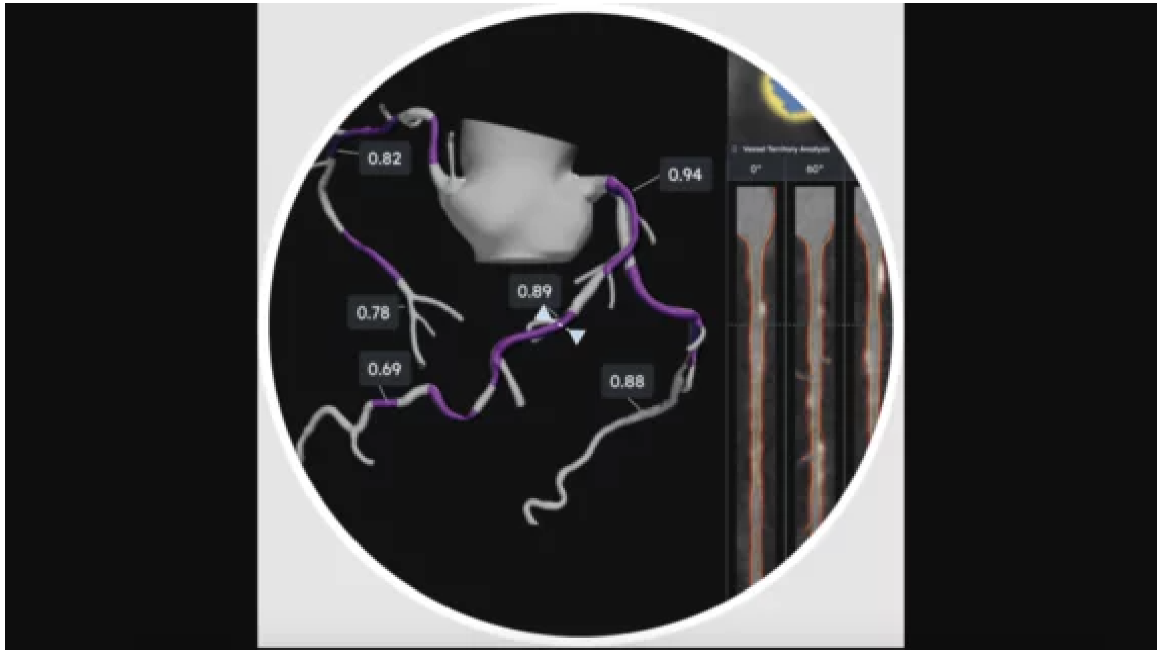


Narula et. al. 2025

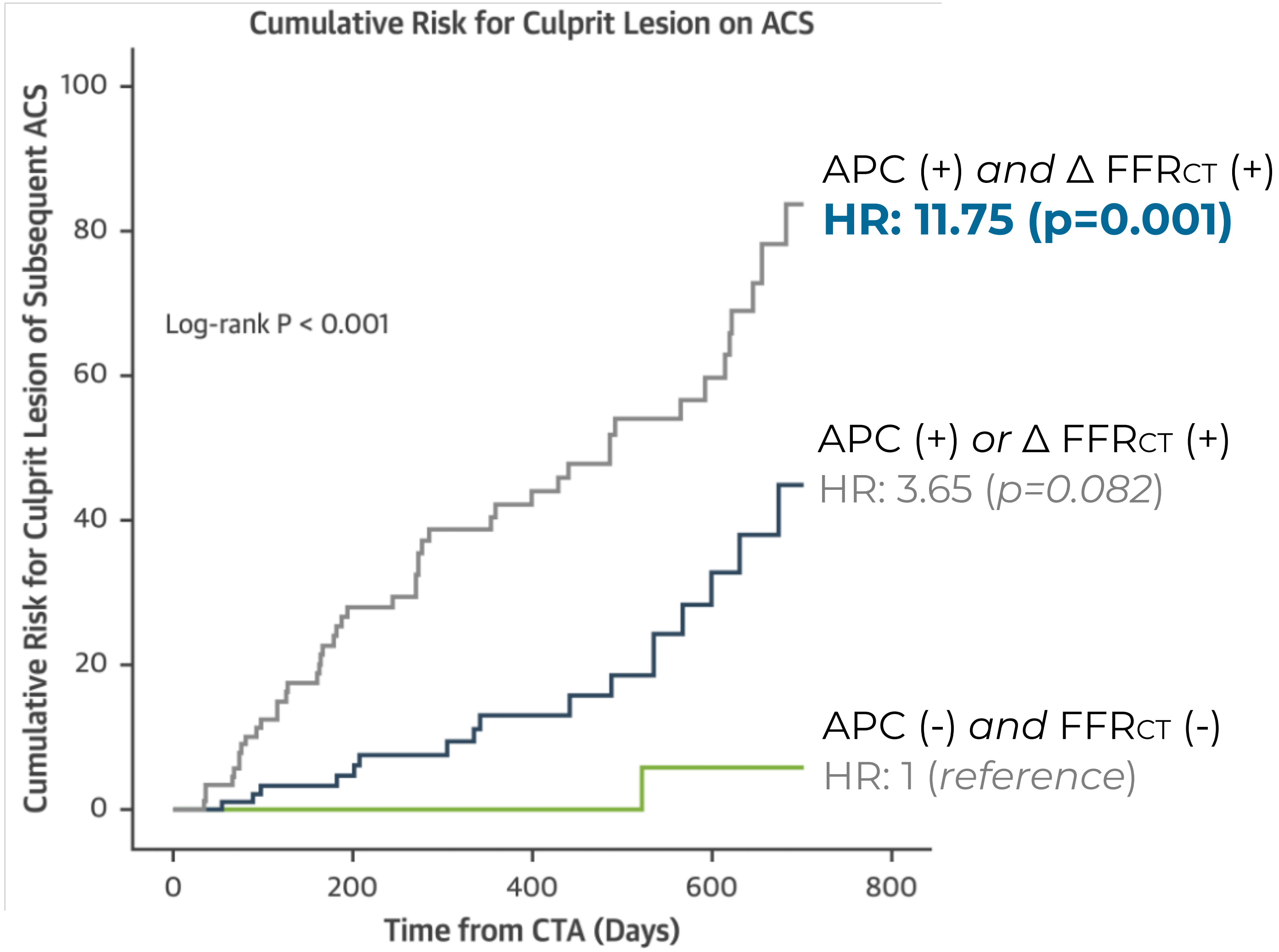
Innovate Healthcare
Cardiovascular Business
FOR LEADERS IMPROVING ECONOMICS, OPERATIONS & OUTCOMES

New Category I CPT code issued for AI-enabled coronary plaque analysis software

Michael Walter | October 18, 2024 | Cardiovascular Business | Computed Tomography



EMERALD I - Combining Plaque + Physiology to predict Risk of ACS



P.I. Bon Kwon Koo, M.D., Ph.D.

Professor, Director of Cardiovascular Center and Chair in Cardiology Division at Seoul National University Hospital, Seoul, KR.

Observations:

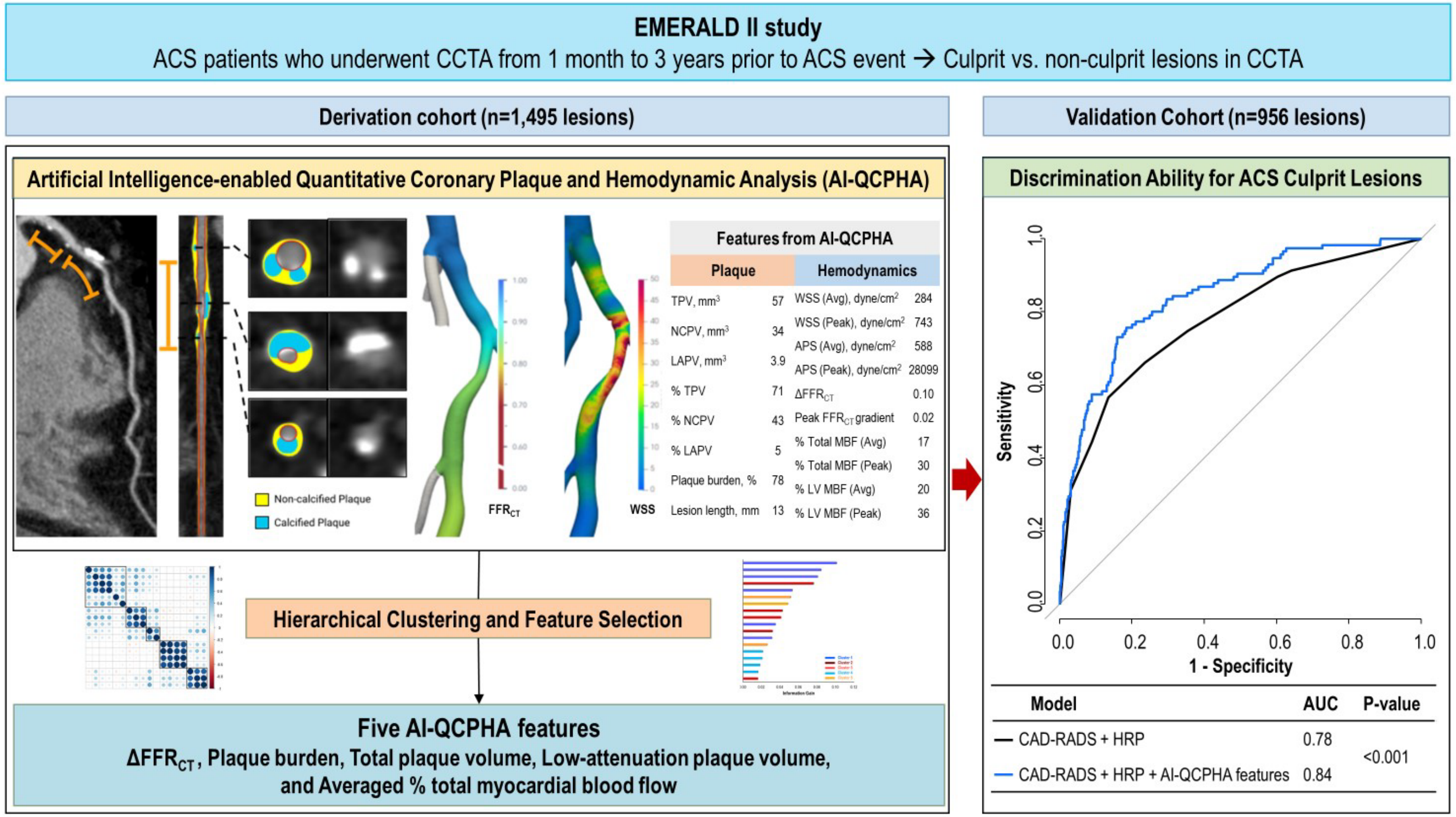
Plaque-specific risk is significantly heightened in the presence of both adverse plaque characteristics (APC) and abnormal physiology (ΔFFRCT).

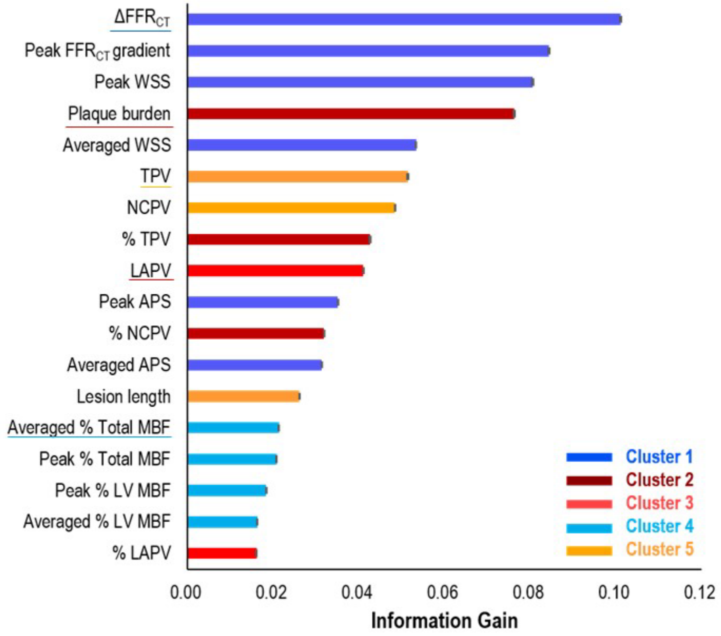
Identification of these factors may inform treatment to mitigate risk.

Emerald I - Lee, et al, JACC Imaging 2019. doi.org/10.1016/j.jcmg.2018.01.023

EMERALD II (351 Patients, 2,451 lesions) showed that coronary lesions experiencing large hemodynamic forces are more likely to cause ACS in the future

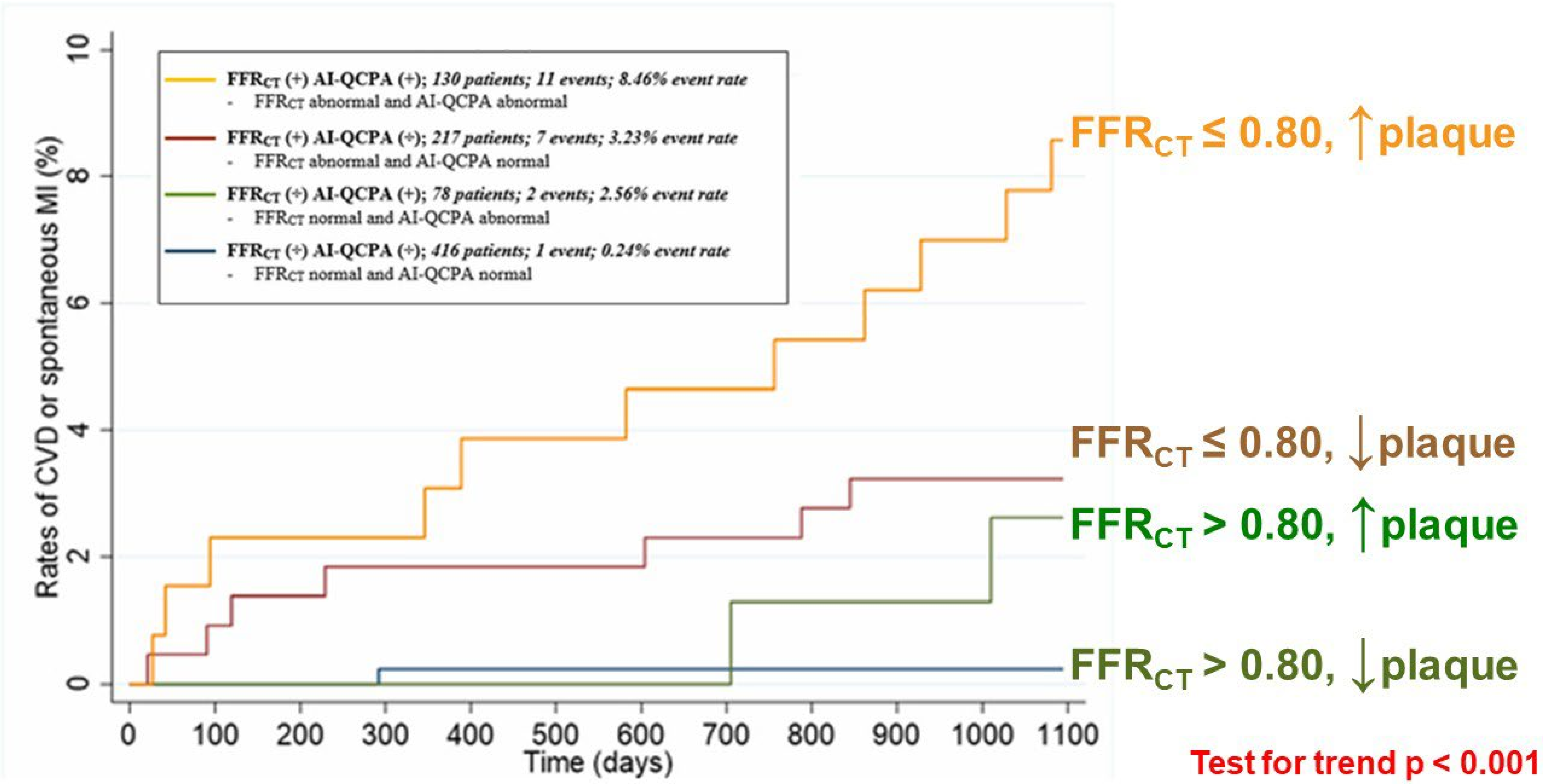
Central Illustration.





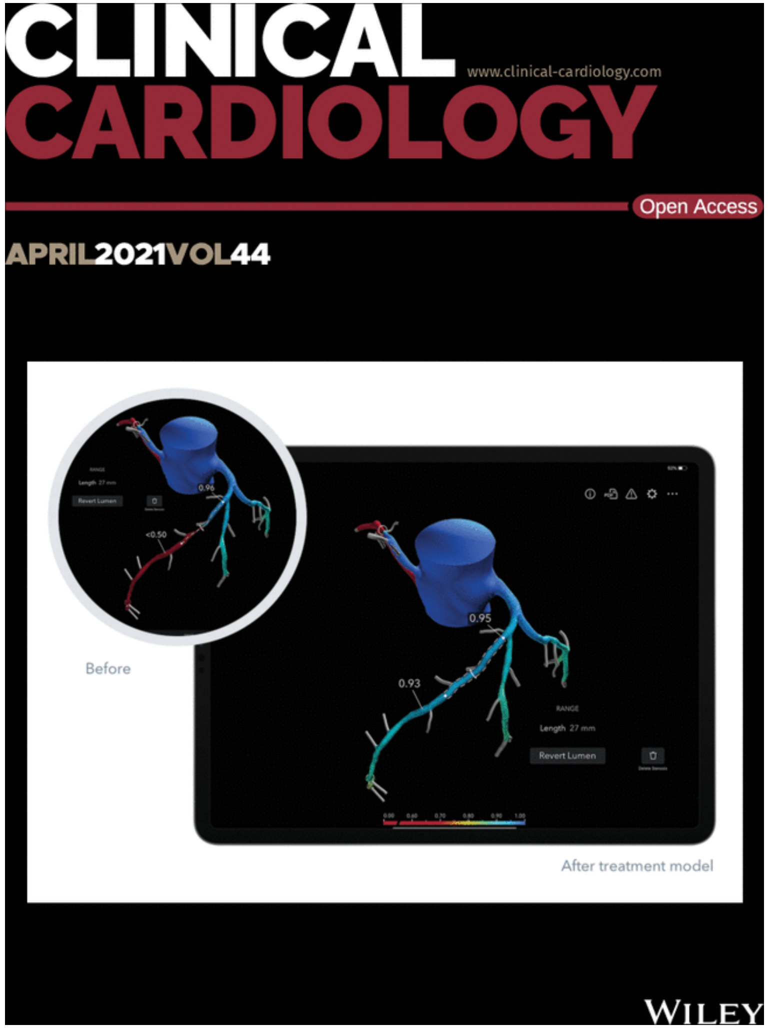
Koo et. al. JACC Imaging, 2024

Combining Physiology and Plaque data may predict MACE (CV Death & Spontaneous MI)



Madsen et al. JACC 2023; 82:B173-B173.

Planner for CT-guided PCI



Post-PCI FFR can be predicted. Validated in P3 trial.

JACC: CARDIOVASCULAR IMAGING
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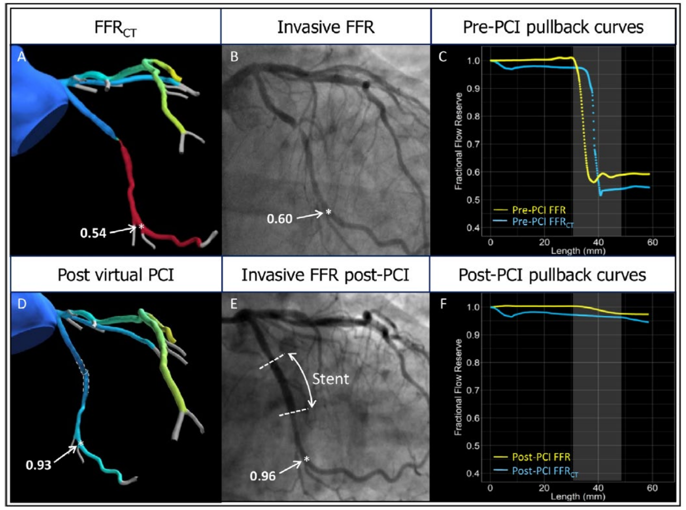
NEW RESEARCH PAPER

Clinical Validation of a Virtual Planner for Coronary Interventions Based on Coronary CT Angiography

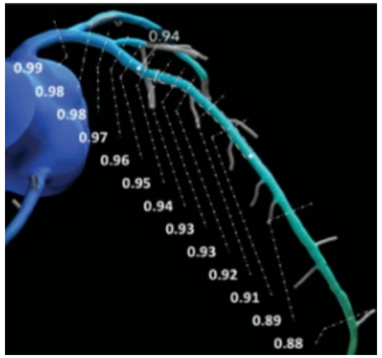
Jeroen Sonck, MD,[a,b] Sakura Nagumo, MD, PhD,[a,c] Bjarne L. Norgaard, MD, PhD,[d] Hiromasa Otake, MD, PhD,[e] Brian Ko, MD, PhD,[f] Jinlong Zhang, MD,[g] Takuya Mizukami, MD, PhD,[a,h] Michael Maeng, MD, PhD,[d] Daniele Andreini, MD, PhD,[i,j] Yu Takahashi, MD, PhD,[e] Jesper Møller Jensen, MD, PhD,[d] Abdul Ihdayhid, MD, PhD,[f] Ward Heggermont, MD, PhD,[a] Emanuele Barbato, MD, PhD,[a,b] Niya Mileva, MD,[a] Daniel Munhoz, MD,[a,b,k] Jozef Bartunek, MD, PhD,[a] Adam Updegrove, PhD,[l] Amy Collinsworth, MS,[l] Martin Penicka, MD, PhD,[a] Lieven Van Hoe, MD,[m] Jonathon Leipsic, MD, PhD,[n] Bwon-Kon Koo, MD, PhD,[g] Bernard De Bruyne, MD, PhD,[a,o] Carlos Collet, MD, PhD[a]

"HeartFlow technology is accurate and precise for predicting FFR after PCI"

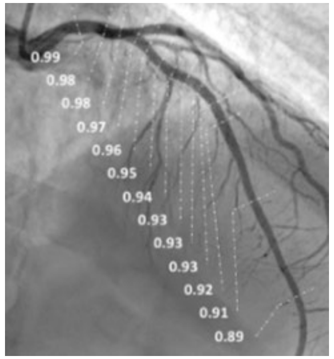
(A) Focal functional coronary artery disease



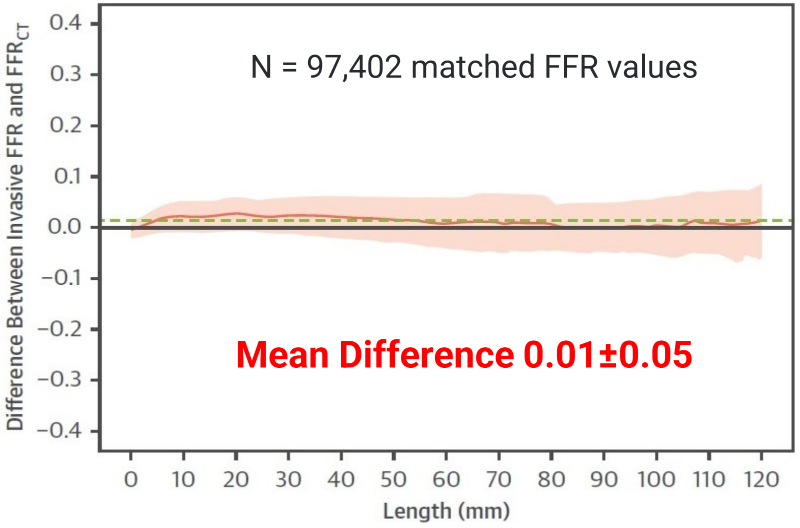
HeartFlow Predicted Post-PCI FFR



Post-PCI Invasive FFR



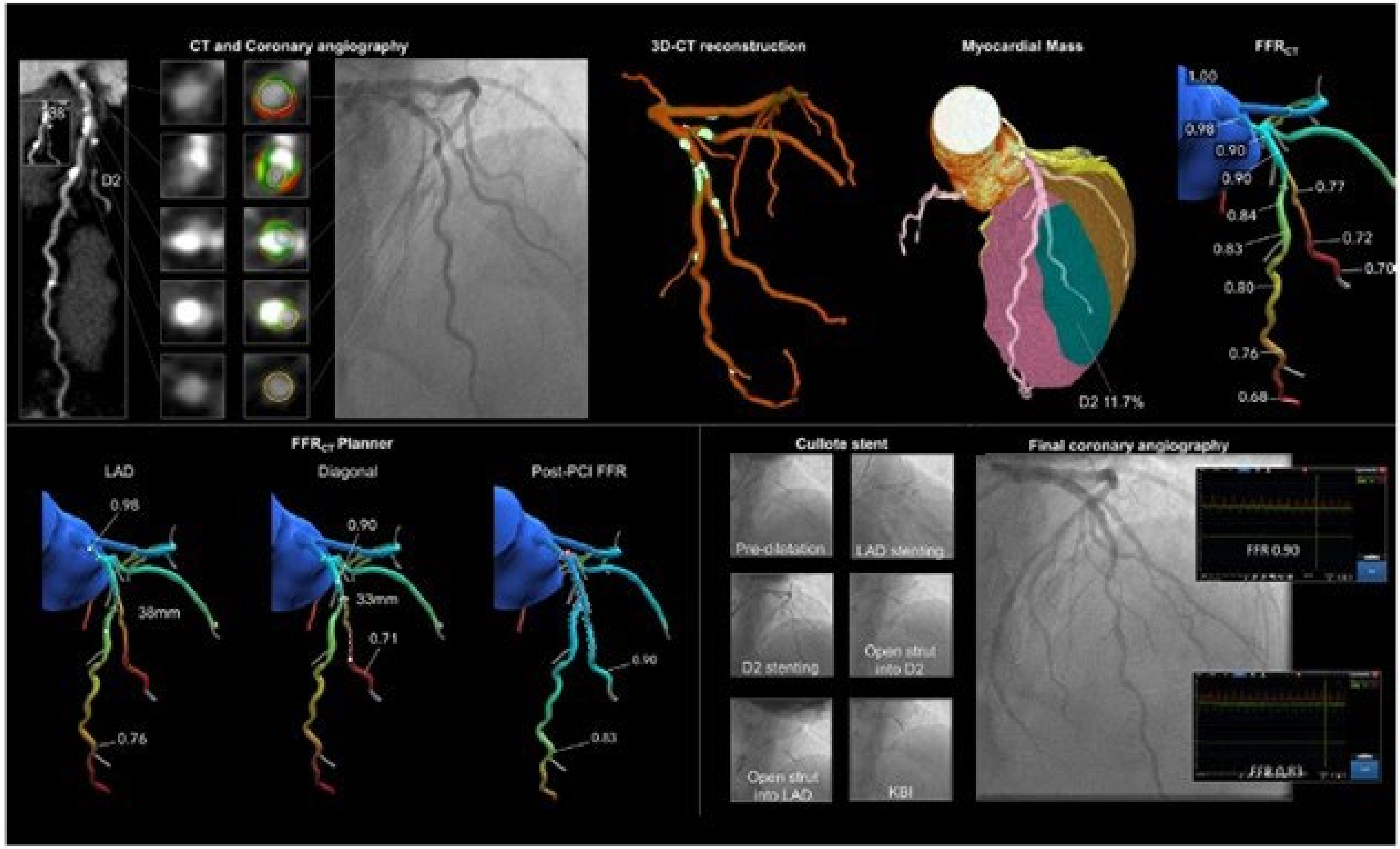
Mean Difference between FFRCT Planner and Invasive Post-PCI FFR Pullback Curves



Nagumo et. al., Clinical Cardiology, 2021.

Sonck et. al., JACC Imaging, 2023.

Precise Procedural and PCI Planning Using Coronary CT Angiography (P4) clinical trial testing hypothesis that a CT-guided PCI strategy is non-inferior to IVUS guided PCI with respect to MACE



Study Design:

- Randomized Controlled Trial
- 20 sites, 1090 patients (Stable CAD patients with stenosis >70% and FFR_{CT} ≤0.80)
- Endpoint: Death, MI, Ischemia-driven TVR at 1 Year

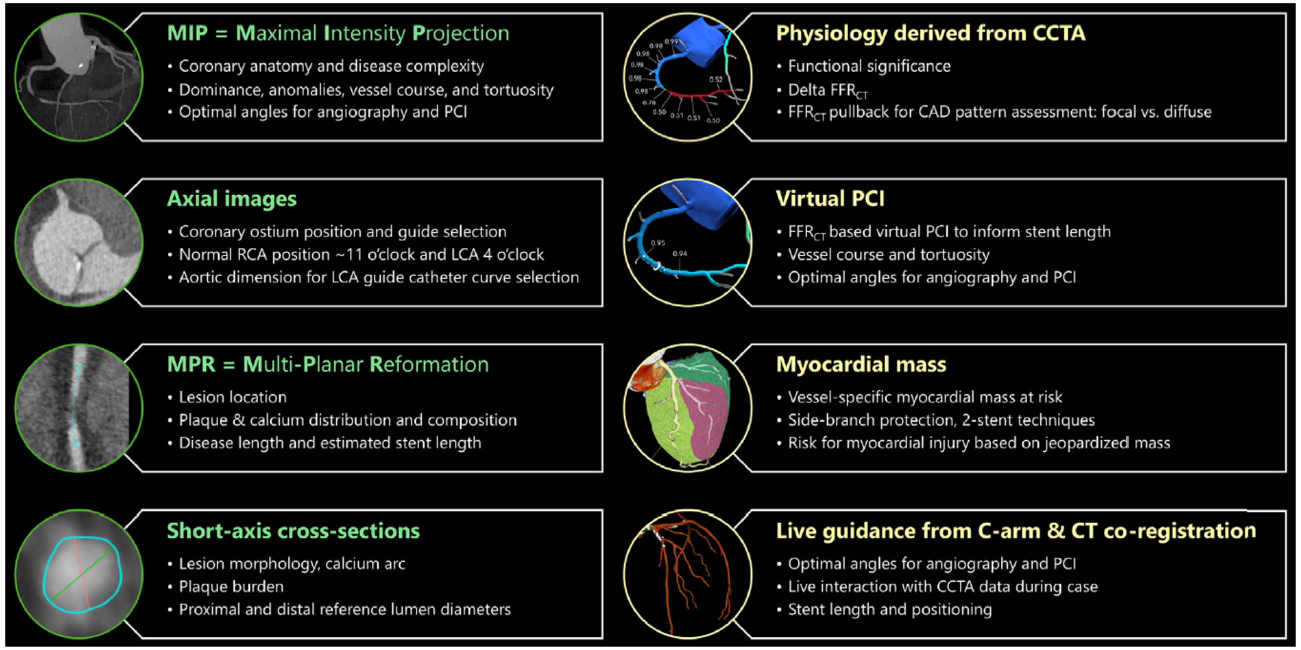
Ohashi et al. JACC 2023.

JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Standards and Guidelines

Coronary Computed Tomography Angiography to Guide Percutaneous Coronary Intervention: Expert Opinion from a SCAI/SCCT Roundtable

Yader Sandoval, MD (Chair)[a,b,*], Jonathon A. Leipsic, MD (Co-Chair)[c,d], Carlos Collet, MD, PhD[e], Ziad A. Ali, MD, DPhil[f,g], Lorenzo Azzalini, MD, PhD, MSc[h], Emanuele Barbato, MD, PhD[i,j], João L. Cavalcante, MD[a,k], Ricardo A. Costa, MD, PhD[l], Hector M. Garcia-Garcia, MD, PhD[m], Daniel A. Jones, MD, PhD[n], John K. Khoo, MBBS[c], Anbukarasi Maran, MD[o], Koen Nieman, MD[p], Natalia Pinilla-Echeverri, MD, PhD[q], Arnold H. Seto, MD[r], Evan Shlofmitz, DO[f], Emmanouil S. Brilakis, MD, PhD[a,b]



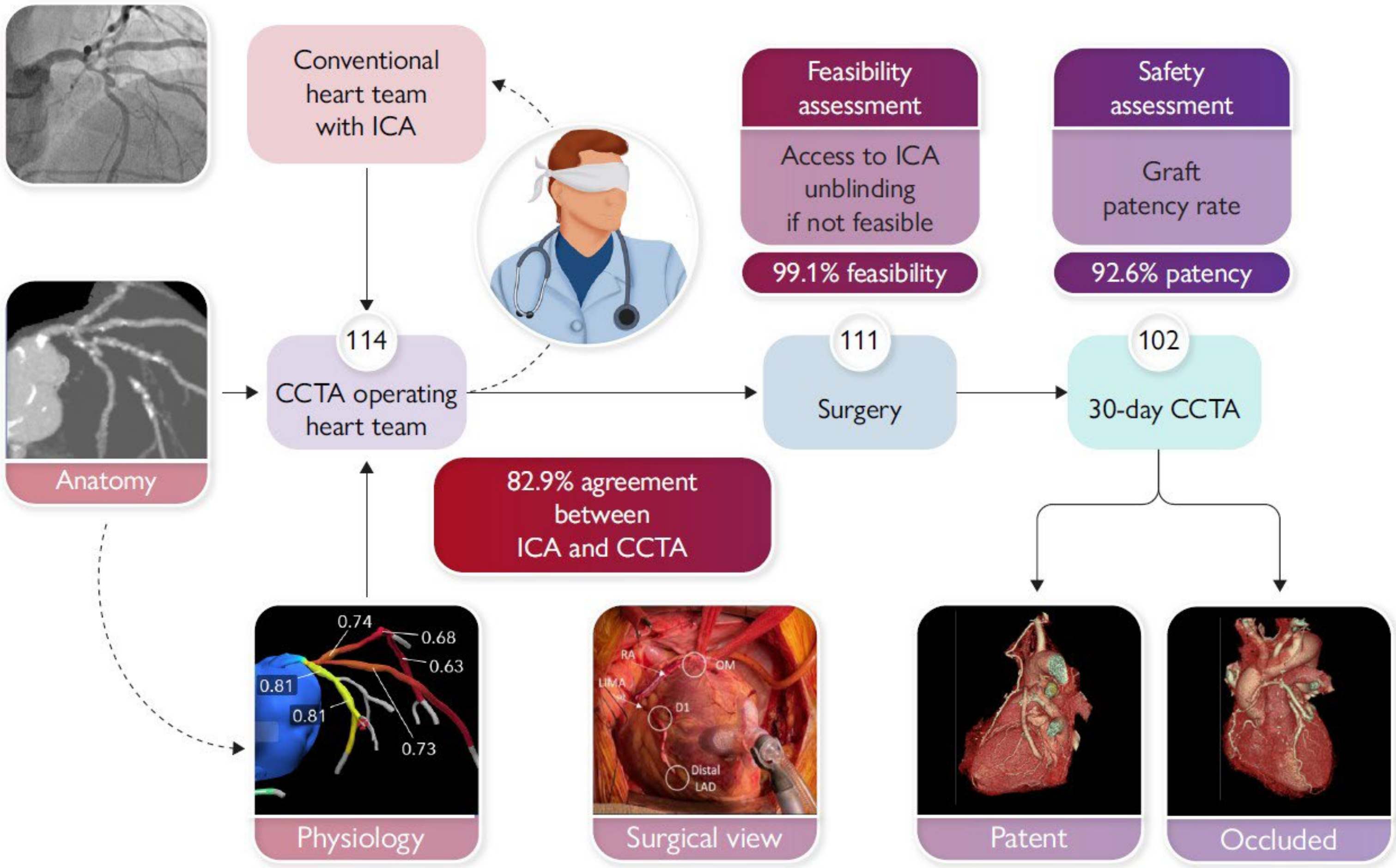
CCTA and FFR_{CT} can be used to plan CABG Procedures

ESC European Society of Cardiology
European Heart Journal (2024) 00, 1–12
https://doi.org/10.1093/eurheartj/ehae199
FASTTRACK – CLINICAL RESEARCH
Cardiac and vascular surgery

Coronary bypass surgery guided by computed tomography in a low-risk population

Patrick W. Serruys[1*], Shigetaka Kageyama[1], Giulio Pompilio[2,3], Daniele Andreini[4,5], Gianluca Pontone[2], Saima Mushtaq[2], Mark La Meir[6], Johan De Mey[7], Kaoru Tanaka[8], Torsten Doenst[9], Ulf Teichgräber[10], Ulrich Schneider[9], John D. Puskas[11], Jagat Narula[12], Himanshu Gupta[13], Vikram Agarwal[11], Jonathon Leipsic[14], Shinichiro Masuda[1], Nozomi Kotoku[1], Tsung-Ying Tsai[1], Scot Garg[15], Marie-Angele Morel[1], and Yoshinobu Onuma[1]

"CABG guided by CCTA is feasible and has an acceptable safety profile in a selected population of complex coronary artery disease."



Serruys et. al., Coronary bypass surgery guided by computed tomography in a low-risk population. European Heart Journal 2024.

Conclusions

- Patient-specific mathematical models of blood flow are now used in routine care
- ACC/AHA Guidelines recommend FFR_{CT} for patients with at least one stenosis in the 40-90% range
- FFR_{CT} can be used to explain chest pain, defer cardiac catheterization when negative and when positive can identify patients most likely to benefit from stenting
- AI-enabled quantification of coronary artery plaque is now widely available and will enable screening and management for CAD
- Anatomic, physiology and plaque data derived from CT can be used to discriminate between culprit and non-culprit lesions causal of heart attacks

15 Years Solving the Technical, Business and Regulatory Challenges Necessary to Unlock All Barriers to Adoption

2010
HeartFlow founded

2011
FFR_{CT} CE Mark obtained

2014
FFR_{CT} US FDA De Novo Clearance

2016
FFR_{CT} Japan PMDA Approval

2017
FFR_{CT} commercial coverage began

2018
FFR_{CT} CPT codes established

CMS initiated coverage for FFR_{CT}

2019
FFR_{CT} ESC Guidelines

Majority of commercial payers allow CT as first line test

2021
ACC/AHA chest pain guidelines

2022
FDA Plaque Analysis and Roadmap Analysis Clearance

2024
CMS initiates coverage for Plaque Analysis

2025
FDA Next Gen Plaque Analysis Clearance

Plaque Analysis commercial coverage began

Ongoing Development of Clinical Evidence

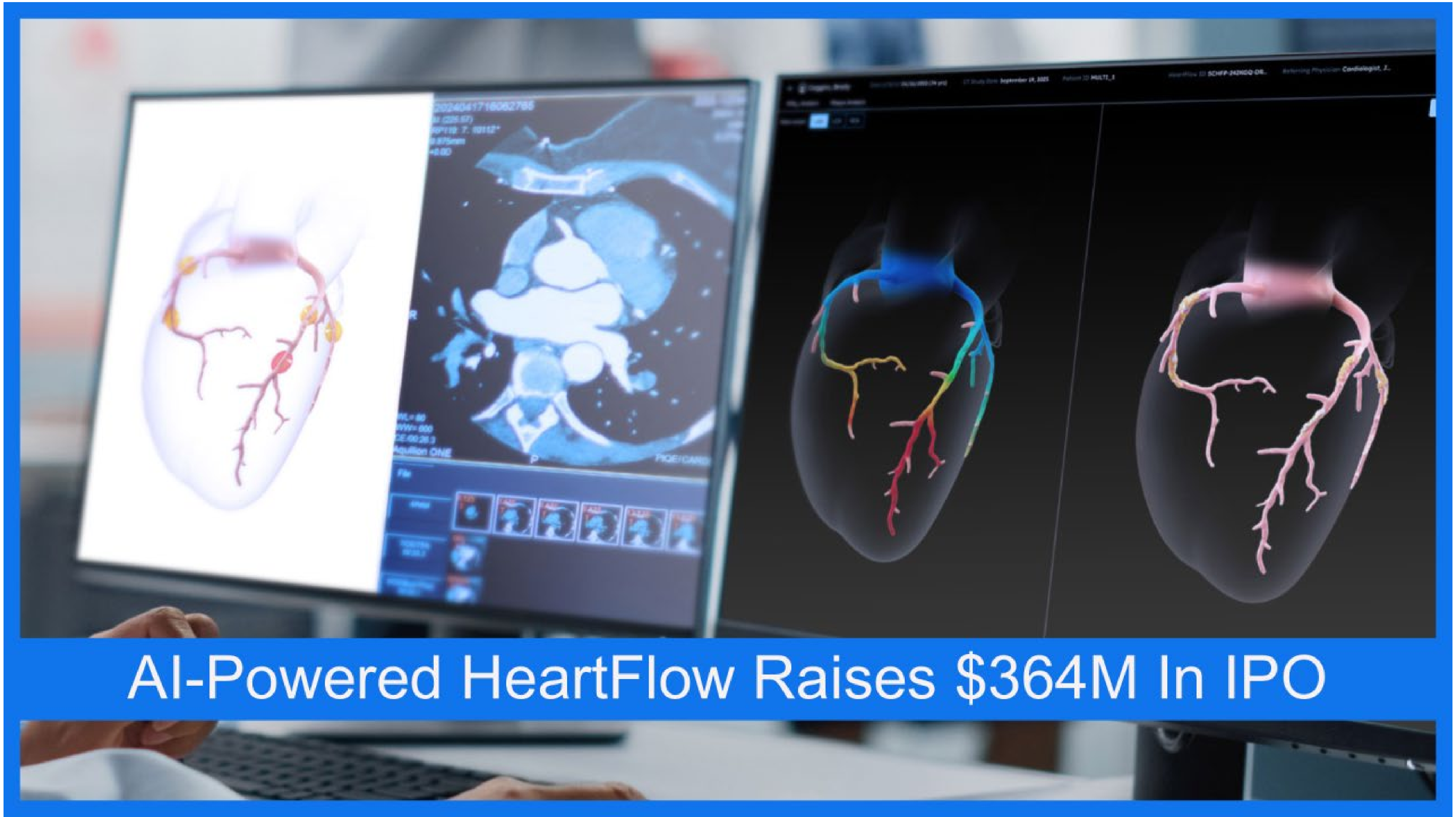
- ✓ **Clinical Evidence:** 600+ peer-review publications
- ✓ **Regulatory Clearance:** CE Mark, FDA Clearance, Japan PMDA
- ✓ **Society Endorsements:** ACC / AHA chest pain guidelines
- ✓ **Payer Engagement:** Established coding, coverage, and payment

Clinical Evidence

2015: PLATFORM 90 day data
2018: ADVANCE 90 day data
2019: PACIFIC
2023: PRECISE RCT
2024: REVEALPLAQUE
2025: DECIDE Registry

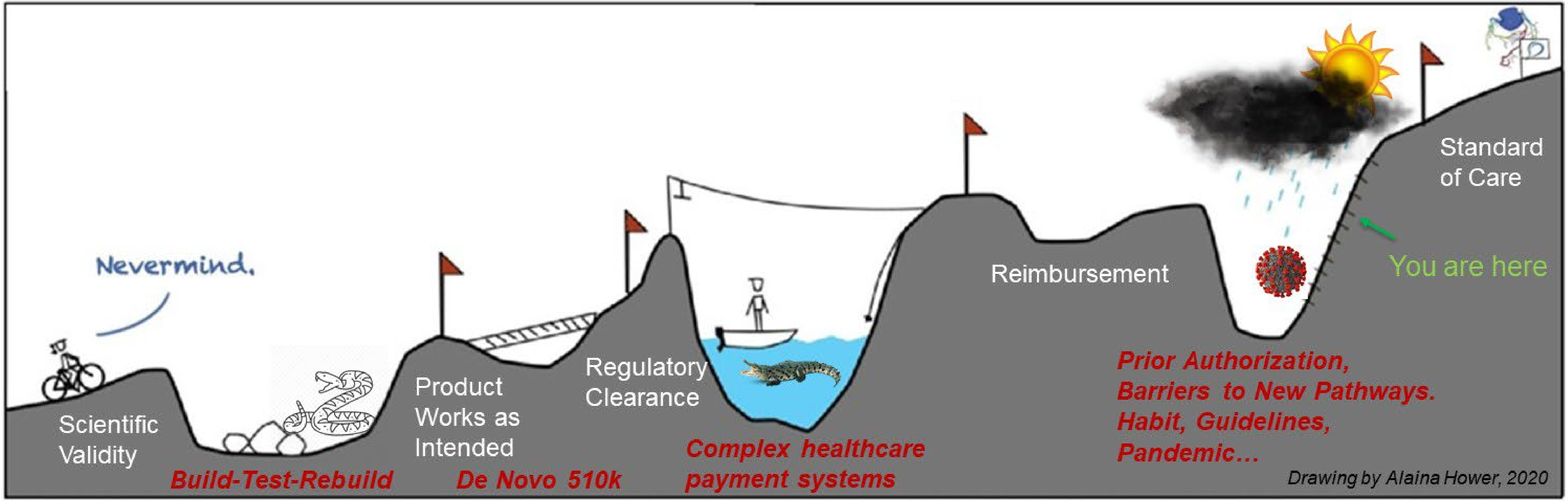
- Regulatory body progress
- Reimbursement progress
- Endorsement progress

On August 8, 2025, HeartFlow went public on the Nasdaq (HTFL)

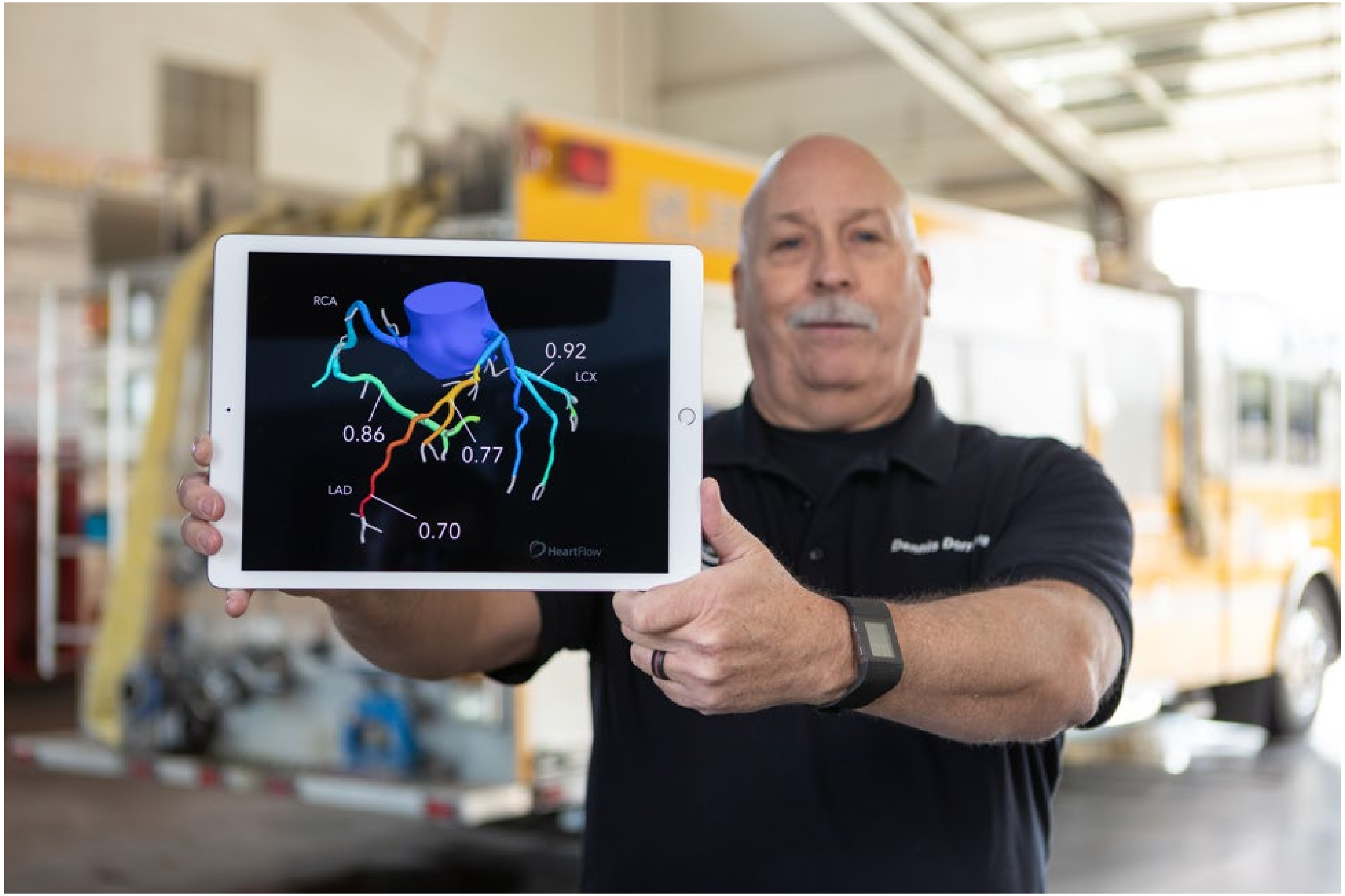


The journey from the bench to bedside was not smooth. We had to navigate multiple "valleys of death".

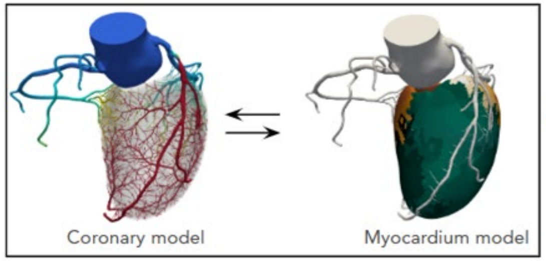
HTFL

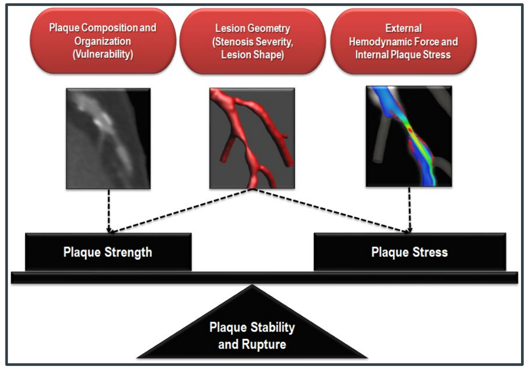


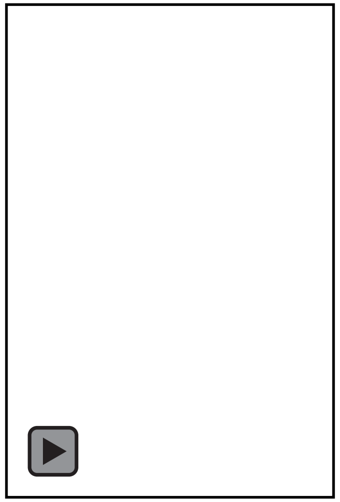
It was worth it – to date, these products have been used for >500,000 patients



UT Projects







RESEARCH

Current projects in Cardiology are

- Building patient-specific models **coupling blood flow from the large arteries to the microcirculation to the myocardium**
- **Predicting risk of heart attacks** based on noninvasive data to support screening of CAD and **eradication of premature death due to heart disease** (w/ Prof. Tom Hughes, Prof. Vagheesh Narasimhan, UT Integrative Biology)

Planned projects in Pulmonology

- Creating **lung digital twin models** to improve diagnosis and treatment of chronic lung diseases including COPD, lung cancer, Interstitial Lungs Diseases (ILDs)

TRANSLATION

- Establishing **Medical Digital Twin Venture Studio** w/ UT Discovery to Impact Program to support and mentor UT entrepreneurs

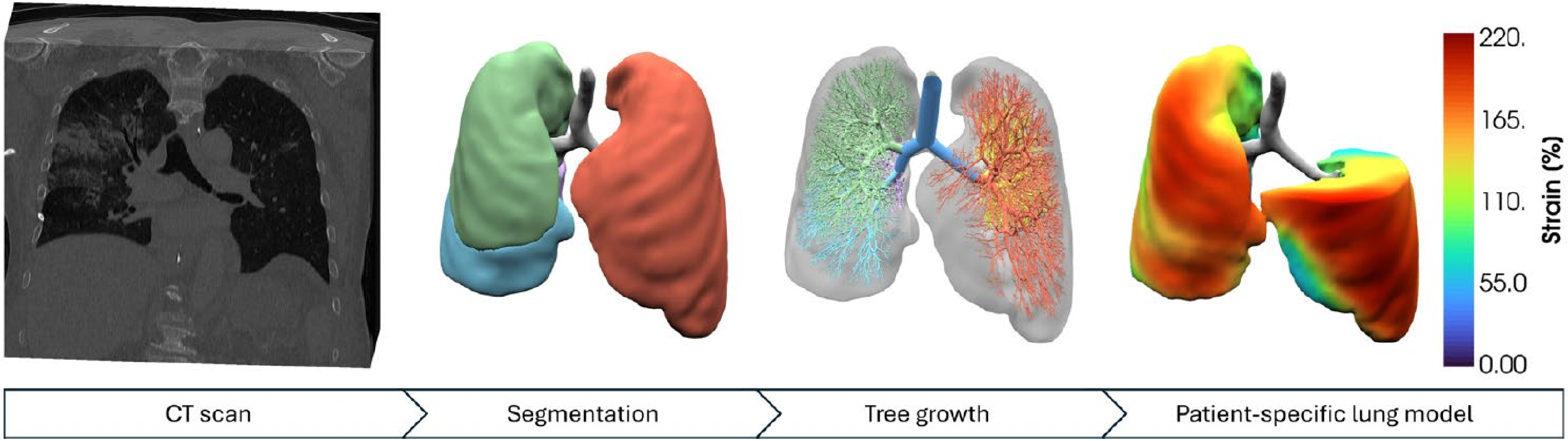
Lung Digital Twins created from CT data for personalized, precision mechanical ventilation

american physiological society
JOURNAL OF APPLIED PHYSIOLOGY
J Appl Physiol 139: 1029–1049, 2025.
First published August 28, 2025; doi:10.1152/japplphysiol.00313.2025

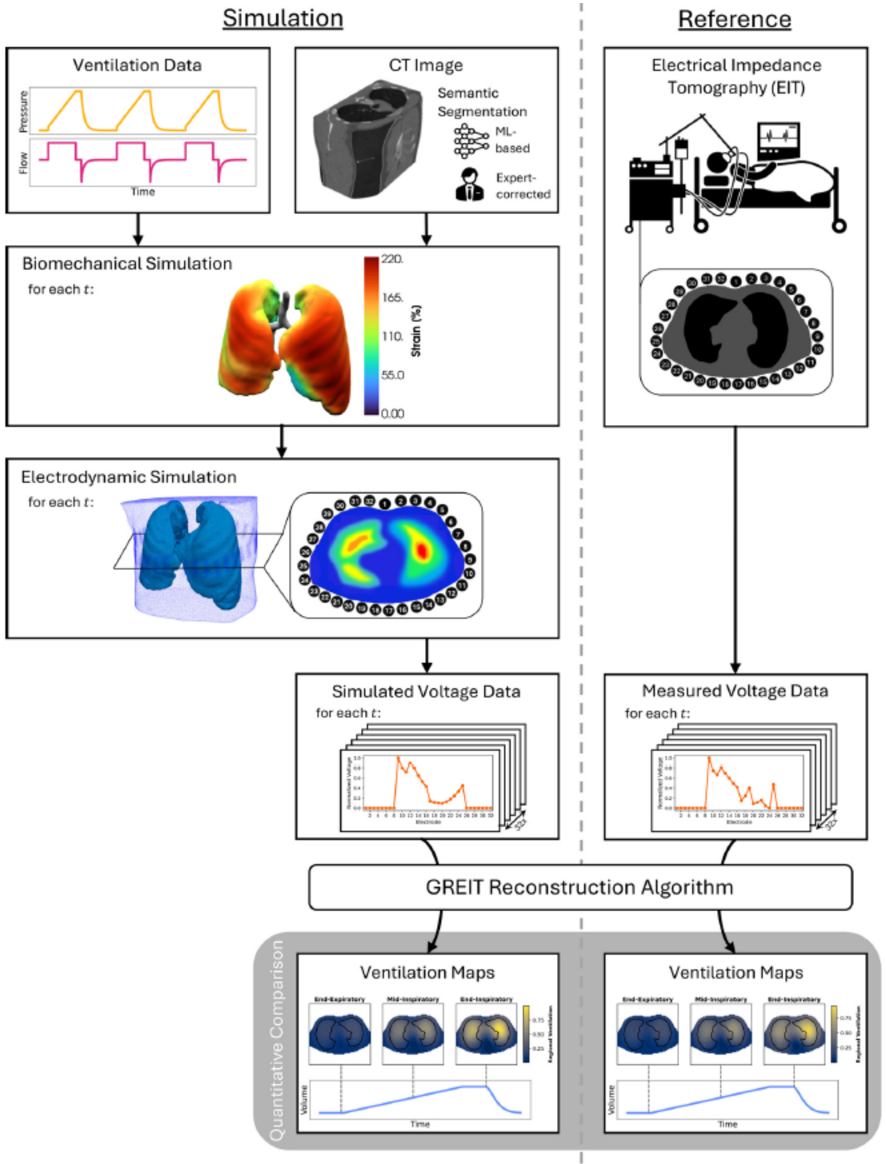
RESEARCH ARTICLE

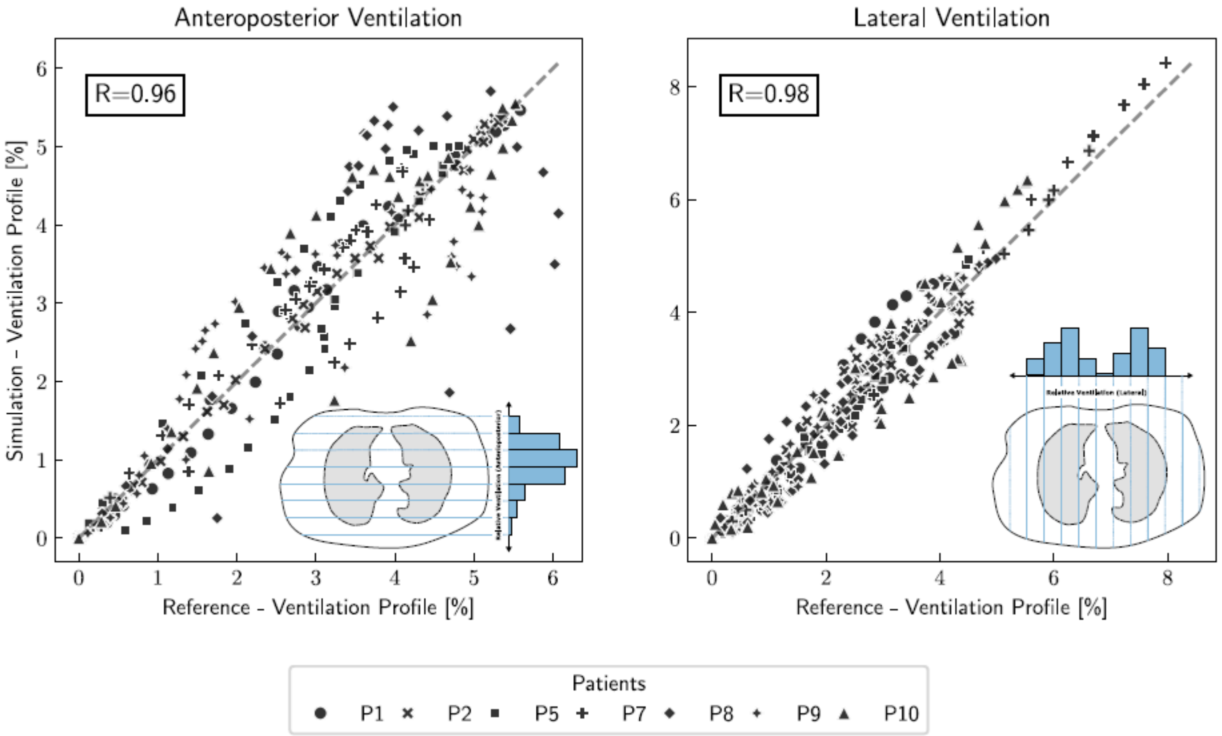
Patient-specific prediction of regional lung mechanics in patients with ARDS with physics-based models: a validation study

Maximilian Rixner,[1] Maximilian Ludwig,[2] Matthias Lindner,[3] Inéz Frerichs,[3] Armin Sablewski,[3] Karl-Robert Wichmann,[1] Max-Carl Wachter,[1] Kei W. Müller,[1] Dirk Schädler,[3] Wolfgang A. Wall,[1,2] Jonas Biehler,[1]* and Tobias Becher[3]*
[1]*Ebenbuild Gr*
Computation,
Anesthesiolog



Lung Digital Twins validated with Electrical Impedance Tomography





Rixner et. al. J Appl Physiol doi:10.1152/japplphysiol.00313.2025

Lung Digital Twin Models can be used to simulate inhaled therapeutics

In silico high-resolution whole lung model to predict the locally delivered dose of inhaled drugs

Maximilian J. Grill[1*], Jonas Biehler[1], Karl-Robert Wichmann[1], David Rudlstorfer[1], Maximilian Rixner[1], Marie Brei[1], Jakob Richter[1], Joshua Bügel[1], Nina Pischke[1], Wolfgang A. Wall[1,2], Kei W. Müller[1]

[1]Ebenbuild GmbH, Munich, Germany.
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*Corresponding author(s). E-mail(s): grill@ebenbuild.com;

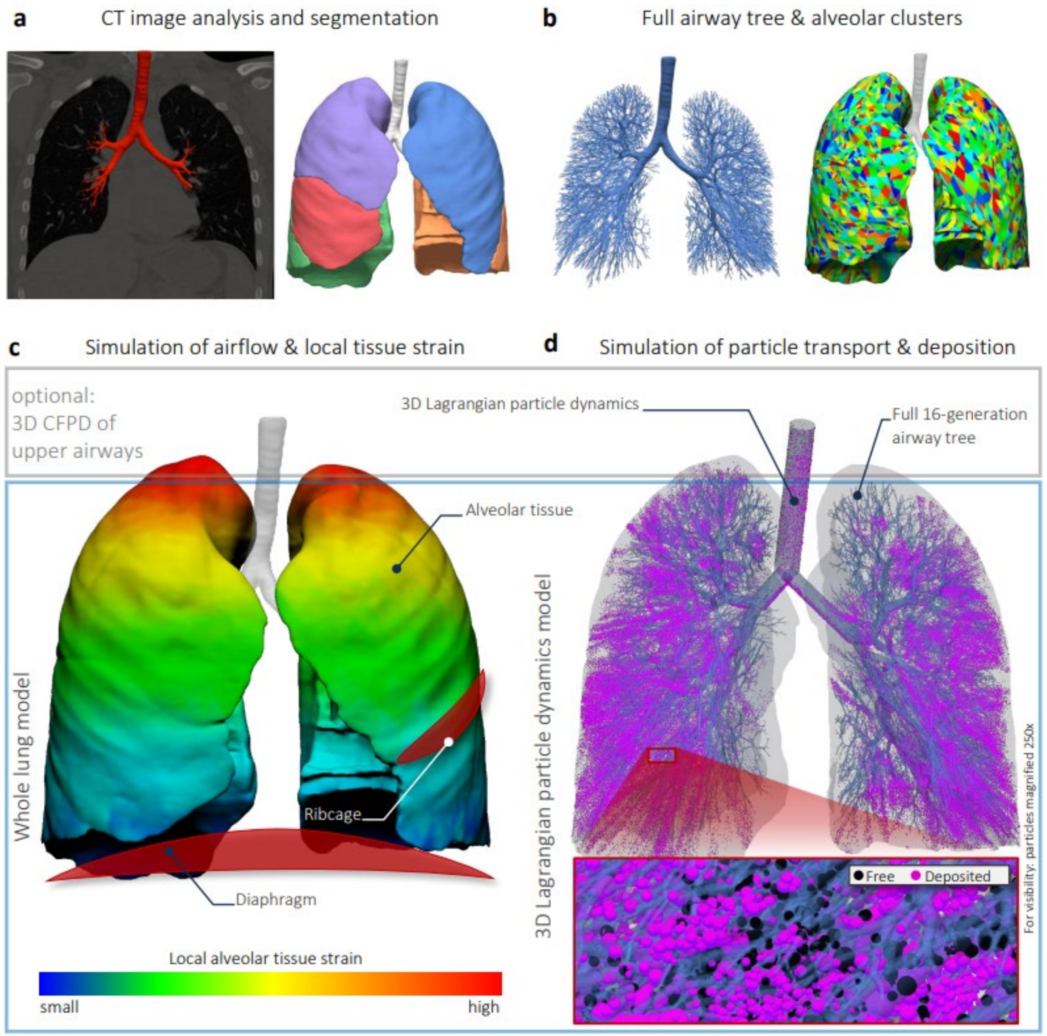

Fig. 1 Illustration of the model design and its subject-specific generation process (here: subject H04). **a** Extraction of detailed volumetric information about lung, lobes, airways, and local gas volumes from the CT image. **b** Creation of the full 16 generation airway tree and alveolar clusters based on segmented volumetric information and a physiology-based space-filling growth algorithm. **c** Illustration of the reduced-dimensional whole lung model for the simulation of airflow and local tissue strain [43–45]. **d** Particle transport and deposition model describing particle dynamics in a Lagrangian formulation in 3D throughout the entire whole lung model. Note that a 3D computational fluid and particle dynamics (CFPD) model of the upper airways can be coupled optionally.

Modeling inhaled therapeutic for Idiopathic Pulmonary Fibrosis

nature communications

Article https://doi.org/10.1038/s41467-025-58568-x

Preclinical concept studies showing advantage of an inhaled anti-CTGF/CCN2 protein for pulmonary fibrosis treatment

Received: 25 January 2024

Accepted: 20 March 2025

Published online: 05 April 2025

Check for updates

Vanessa Neiens[1], Eva-Maria Hansbauer[1], Thomas J. Jaquin[1], Janet K. Peper-Gabriel[1], Poornima Mahavadi[2,3], Mark E. Snyder[4,5,6], Maximilian J. Grill[7], Cornelia Wurzenberger[1], Antonio Konitsiotis[1], Adriana Estrada-Bernal[8], Kristina Heinig[1], Athanasios Fysikopoulos[1], Nicolas Schwenck[1], Stefan Grüner[1], Denis Bartoschek[1], Theresia Mosebach[1], Sandra Kerstan[1], Joe Wrennall[9], Marleen Richter[1], Kentaro Noda[10], Konrad Hoetzenecker[11], Janette K. Burgess[12,13], Robert Tarran[9], Claudia Wurzenberger[1], Karl-Robert Wichmann[7], Jonas Biehler[7], Kei W. Müller[7], Andreas Guenther[2,3,14,15,16], Oliver Eickelberg[8], Mary F. Fitzgerald[1], Shane A. Olwill[1,17], Gabriele Matschiner[1,17] & Marina Pavlidou[1,17]

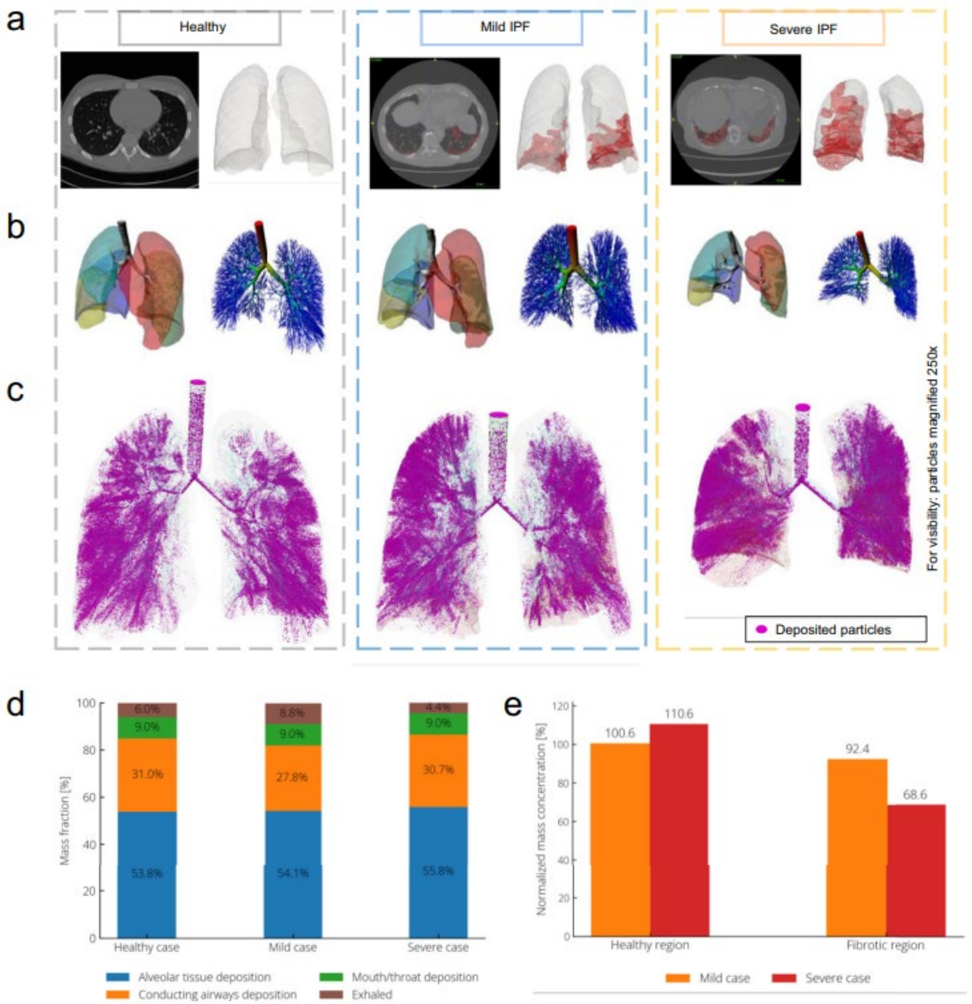

Fig. 6 | In silico inhalation study of PRS-220 in 3 human subjects shows a broad deposition pattern of PRS-220 containing aerosol in healthy and IPF lungs. **a** CT image analysis and segmentation of fibrotic tissue (red) and **b** airways, lungs, and lobes (left) as first step of the subject-specific model generation process. Generation of the full 16-generation tree of conducting airways (right) and viscoelastic alveolar clusters (Supplementary Fig. 4) based on segmented volumetric information and a physiology-based, space-filling growth algorithm. **c** Final pattern of deposited PRS-220 aerosol particles after simulation of airflow, particle transport and deposition for one complete breathing cycle. **d** Mass fraction of deposited aerosol per category: Mouth/throat (green), conducting airways (orange), alveolar tissue (blue), and exhaled (brown). **e** Normalized concentration of deposited aerosol mass per volume for healthy vs. fibrotic regions of the lungs (mild case = orange; severe case = red). Values smaller/>100% indicate under/over-proportional deposition in the respective sub-volume.

“Hospital of the Future” being built at The University of Texas at Austin will incorporate medical digital twins