Using imaging AI to optimize clinical trials

MIT – April 2023

Alex Goehler, MD, PhD
Global Head, Clinical and Precision Medicine, Novartis Institutes for Biomedical Research

Objectives

During this presentation we will review opportunities and challenges of using imaging biomarkers in clinical drug development

By end, you will have a better understanding of

- Role of imaging within the broader venue of clinical biomarkers
- Reproducibility and scalability of imaging biomarkers in drug development
- Intersection of imaging biomarker and AI methods

A. Candle flame

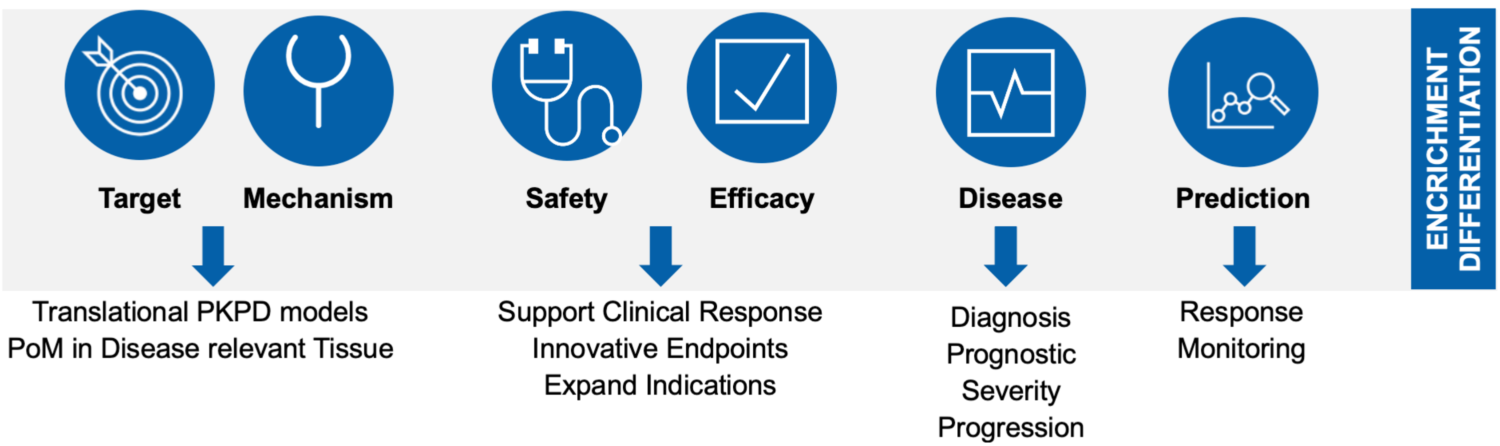
B. Kneecap

C. Artichoke

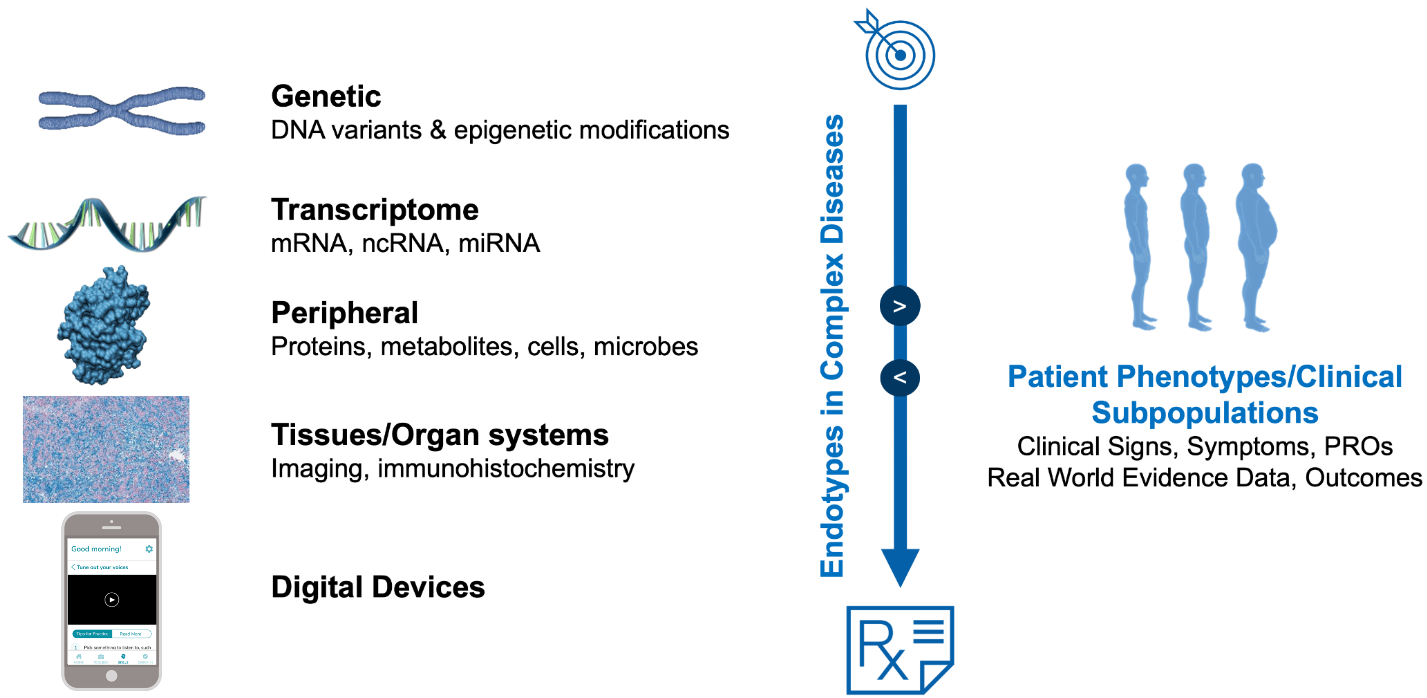
D. Flowing lava

Clinical Trial Phases
PHASE I
Safety
20-80 Participants
PHASE II
Safety and Dosing
100-300 Participants
PHASE III
Safety and Efficacy
300-3000 Participants
FDA Review
PHASE IV
Post approval surveillance
1000+ Participants
Drug approved for testing in humans
Drug submitted for FDA approval
Drug approved

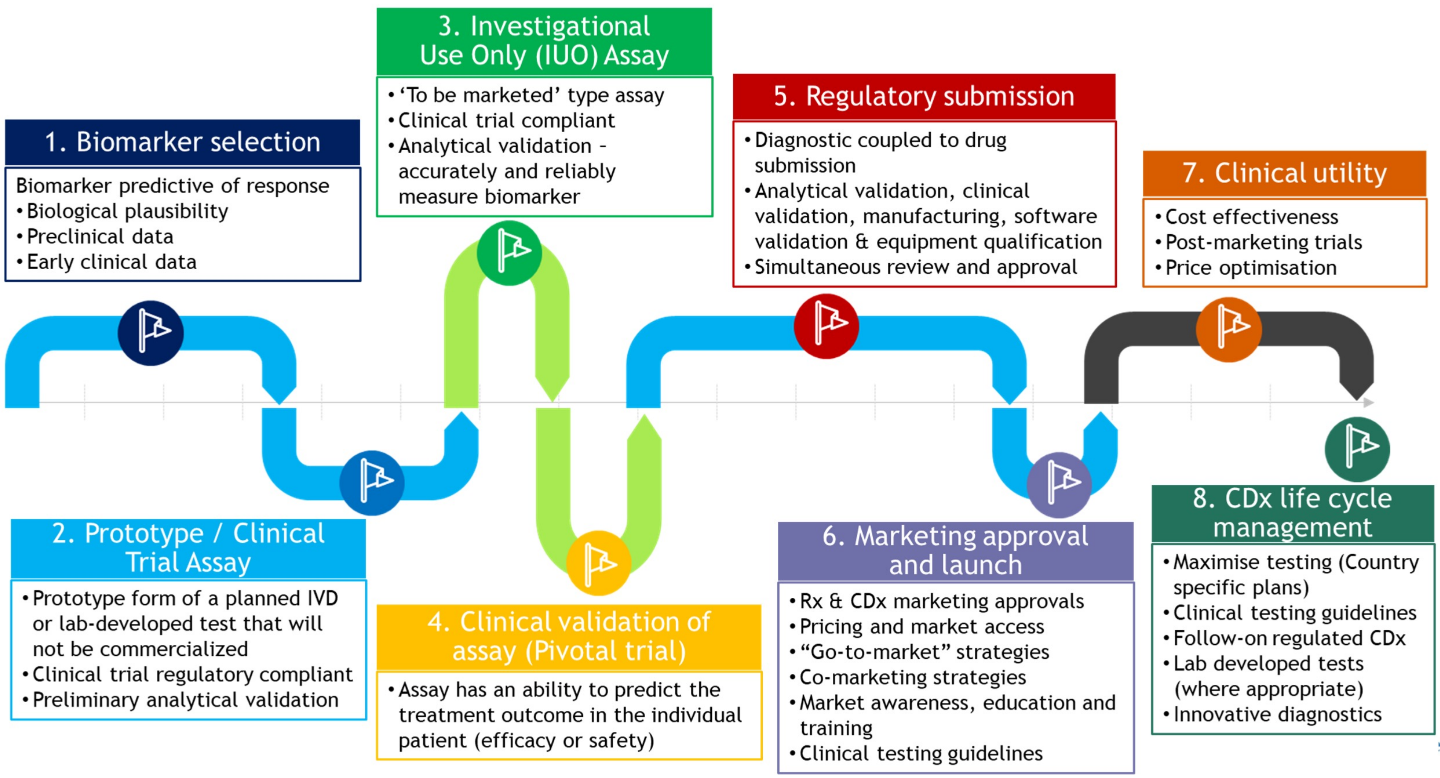
Clinical biomarker depends on the context of use



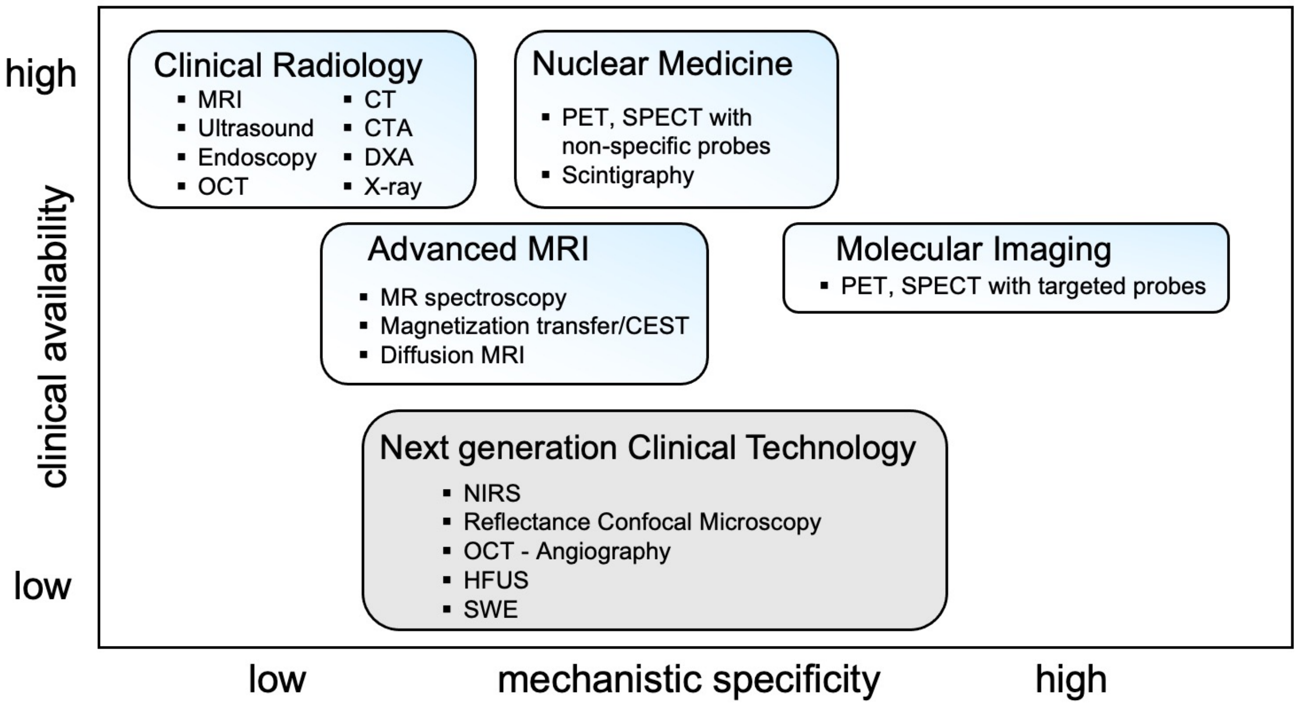
Precision Medicine| Understanding complex diseases and therapeutic response biology to deliver high value medicines

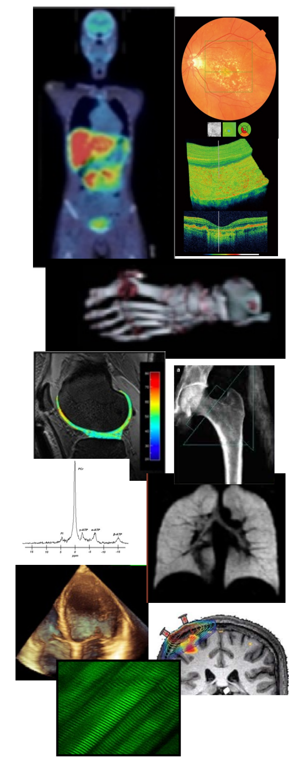


Roadmap | exploratory biomarker to regulated diagnostic

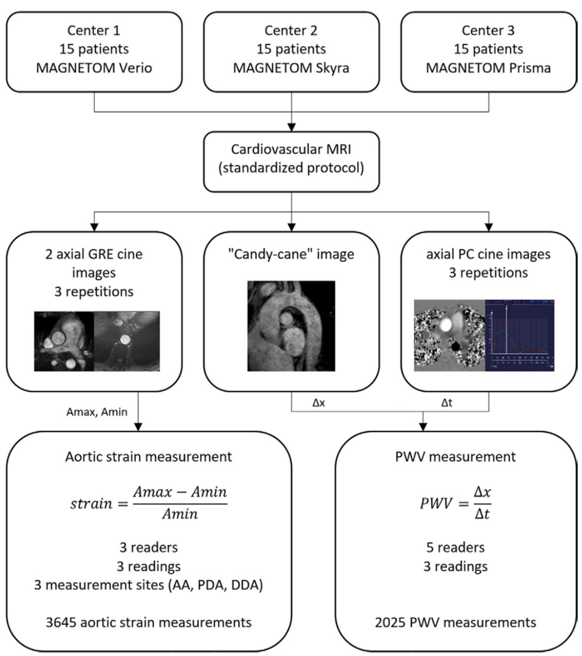


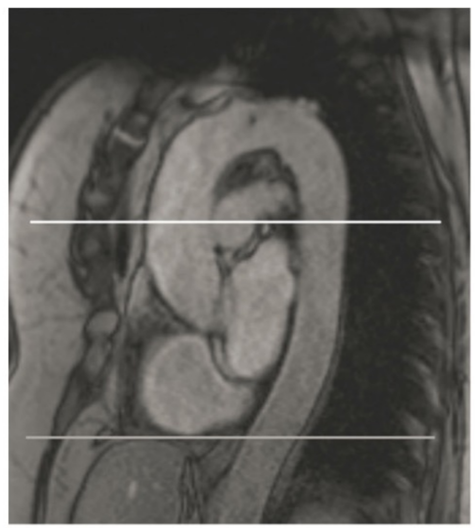
Modalities | balancing availability & complexity vs mechanistic specificity

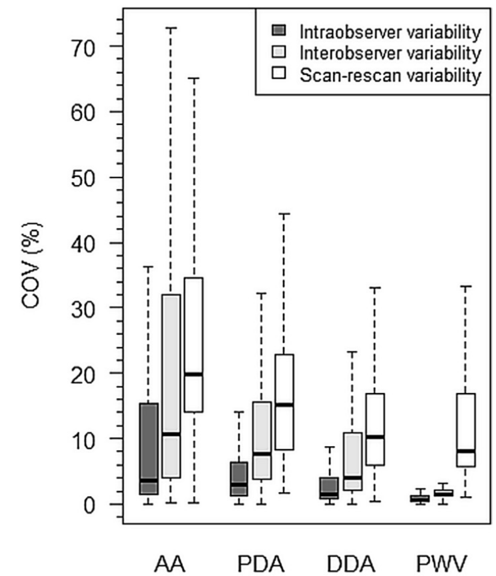




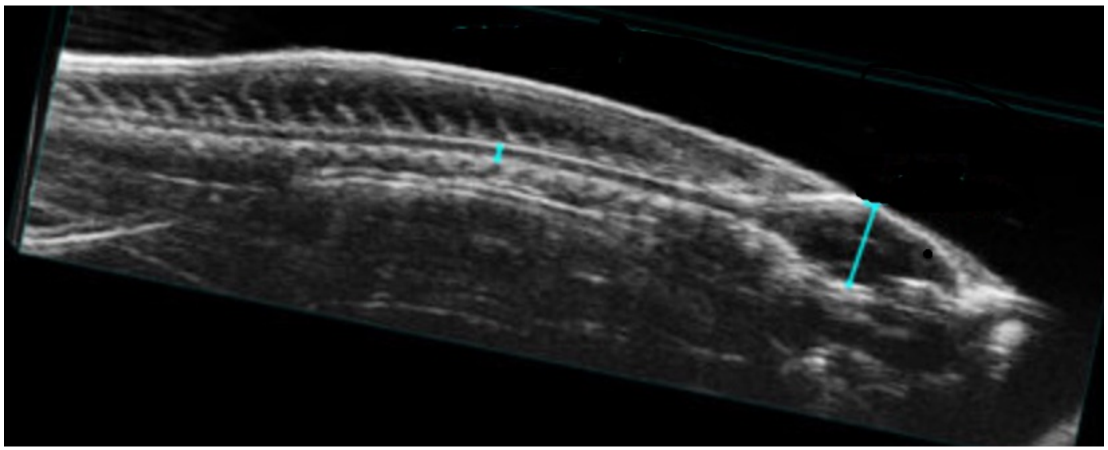
Variability assessment | standardized protocols matter







Source: Hrabak-Paar. Card Img. 2020



A. Zebrafish

B. Human Spine

C. Balloon catheter

Enriching the target population | using imaging as inclusion criteria

Open Access Full Text Article

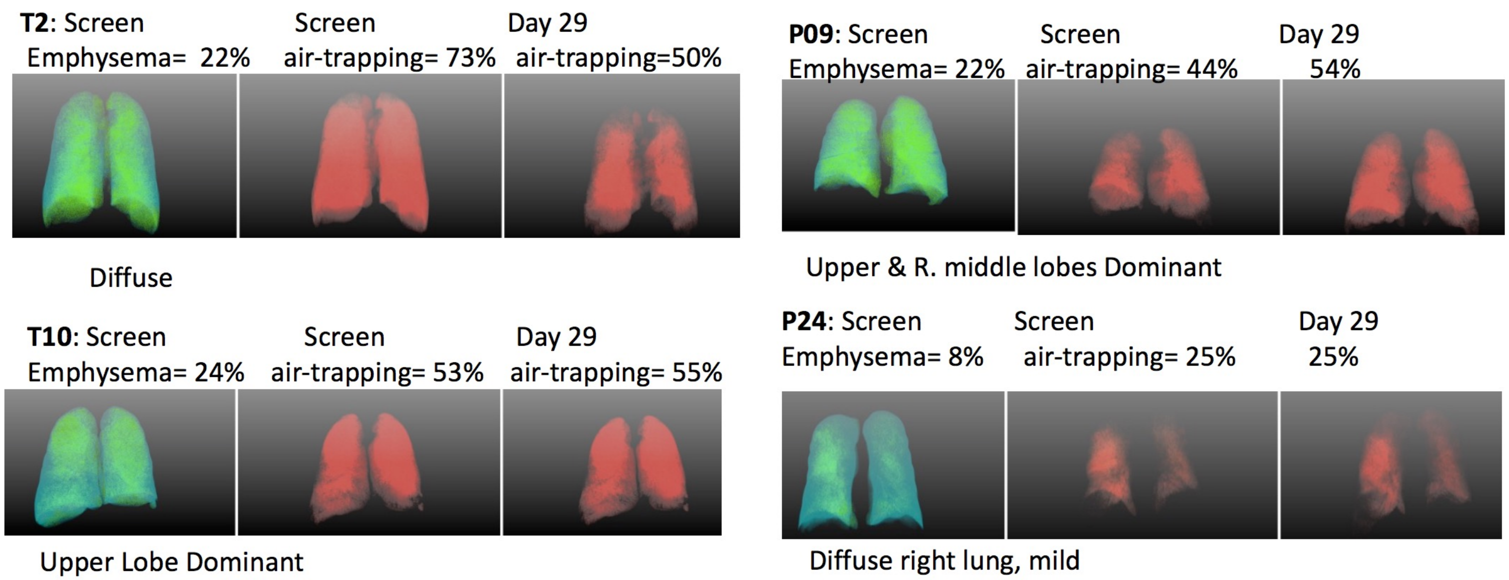
CLINICAL TRIAL REPORT

Efficacy and Safety of the CFTR Potentiator Icenticaftor (QBW251) in COPD: Results from a Phase 2 Randomized Trial

International Journal of Chronic Obstructive Pulmonary Disease 2020:15 2399–2409 **2399**

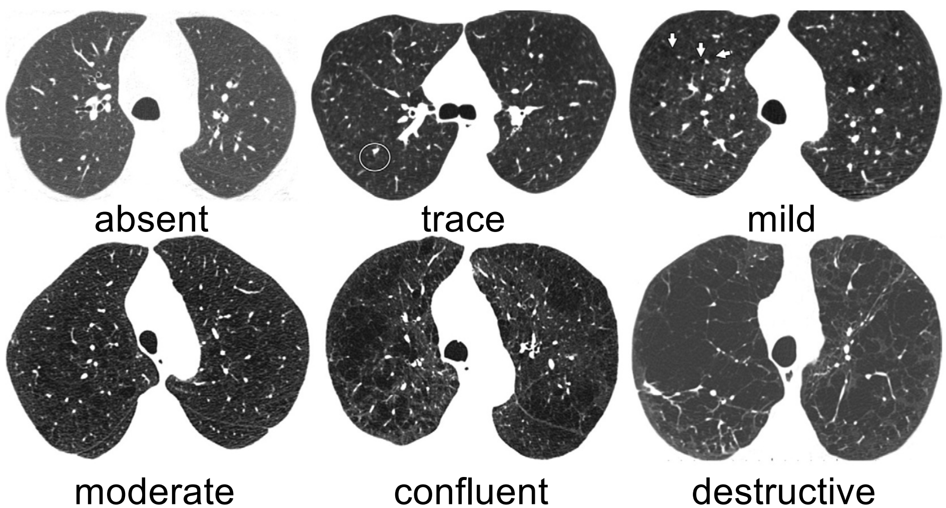
Patients aged ≥35 and ≤75 years with a diagnosis of COPD and symptoms of CB and with lung clearance index (LCI) ≥8 at screening were included. Patients diagnosed with severe bronchiectasis or significant radiographic emphysema were excluded. Whole lung emphysema extent <25% (TLC % < −950 HU) and quantitative air trapping >15% (RV >15% −856 HU) were assessed by high resolution computed tomography (HRCT) for inclusion. Additional criteria are provided in the supplementary material (Table E1).

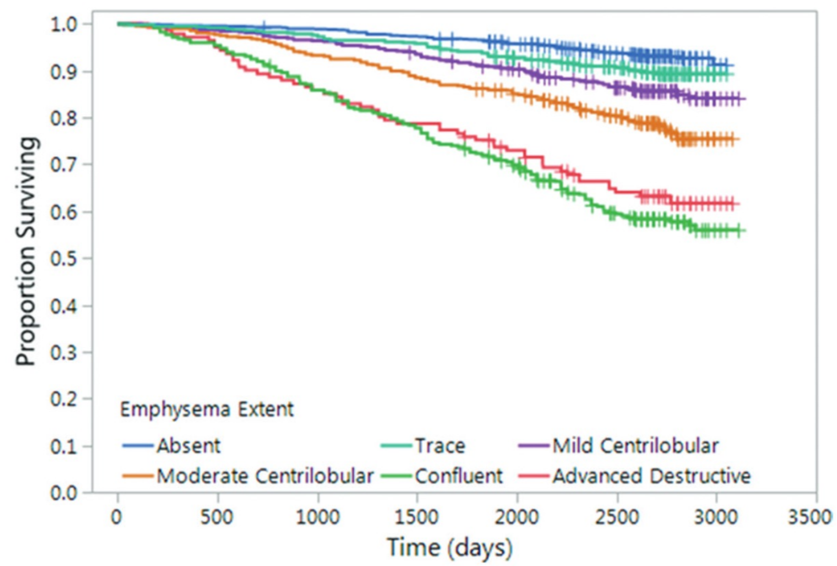
Representative cases of 3D rendering of CT images



International Journal of Chronic Obstructive Pulmonary Disease 2020:15 2399–2409 **2399**

Extent of emphysema is associated with mortality risk | evidence from 7,341 patients in the COPD gene registry





Source: Lynch, Radiology: 2018: 28-3

Deep learning enables classification of emphysema pattern on CT | leveraging the COPD gene registry

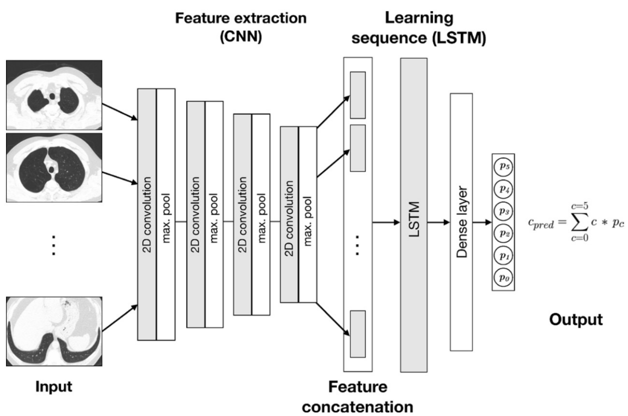


Table 1: Comparison of Visual and Deep Learning Emphysema Scores in the COPDGene Test Cohort (*n* = 7143)

	Deep Learning Algorithm					
Visual Score	Absent	Trace	Mild	Moderate	Confluent	Advanced Destructive
Absent	637*†	1495†	324	41	2	0
Trace	126	751*	377	66	2	0
Mild	35	380	678*	296	20	0
Moderate	2	23	166	643*	211	4
Confluent	0	1	4	154	428*	69
Advanced destructive	0	0	0	8	108	92*

- AI classified 34% ‘one level higher’ compared to visual score
- AI classified 13% ’one level lower’

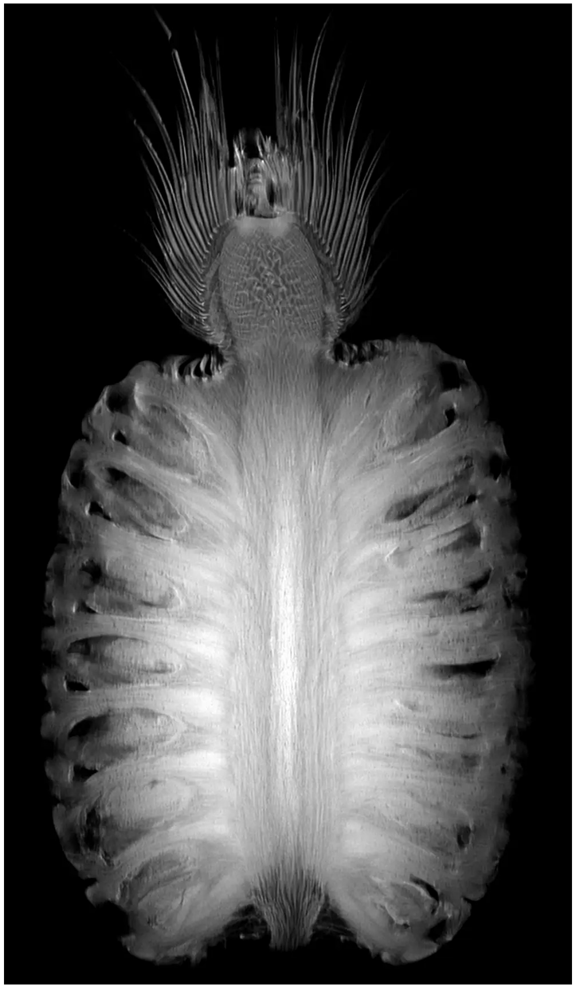
Source: Hasenstab. Radiology 2021

A. GOT Dragon

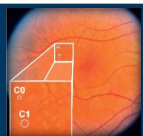
B. Turtle

C. Goliath Beetle

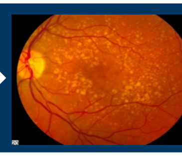
D. Pineapple



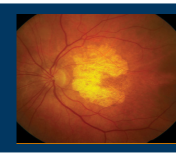
Imaging to enrich iAMD trials | opportunity for AI



early AMD



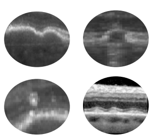
intermediate AMD



late AMD

HAWK

Based on fellow-eye analysis in historical trial, ~20% of patients with iAMD progressed to late AMD within 2 years



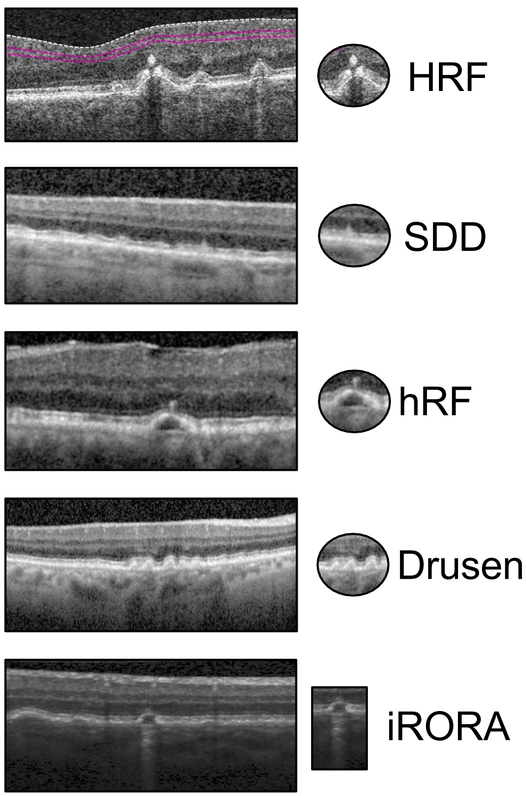
Presence of ≥ 2 high risk features on OCT increases risk of conversion within 2 years to more than 40%

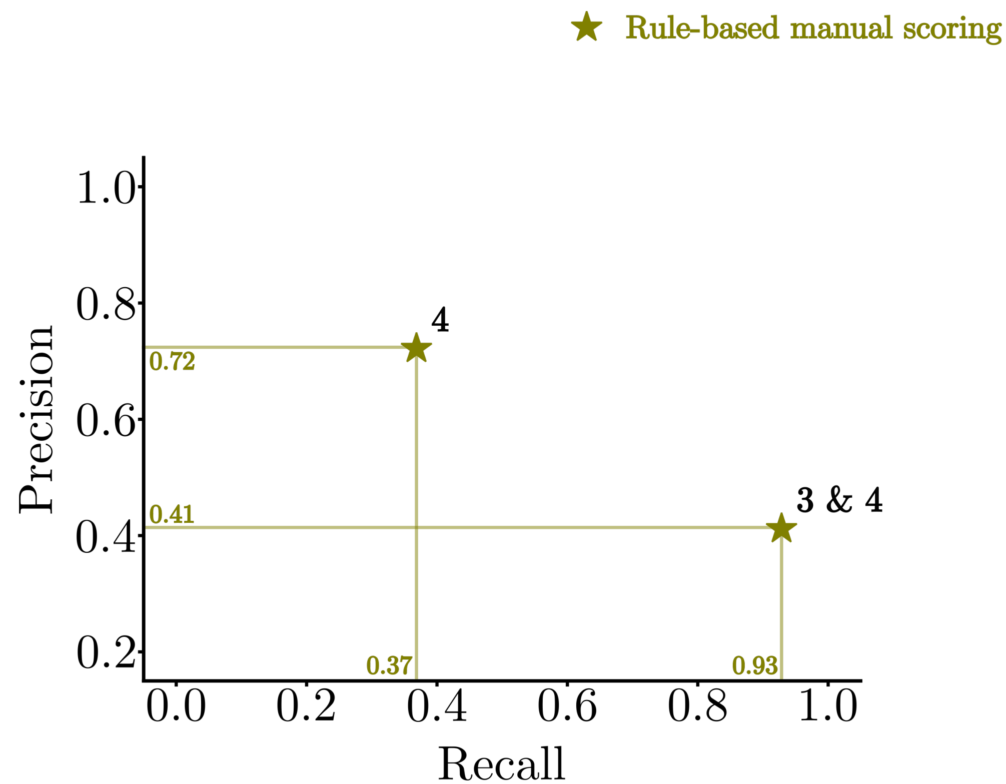
OCT screening is part of current iAMD trial

OCT: optical coherence tomography

Predicting fast progressors | manual scoring

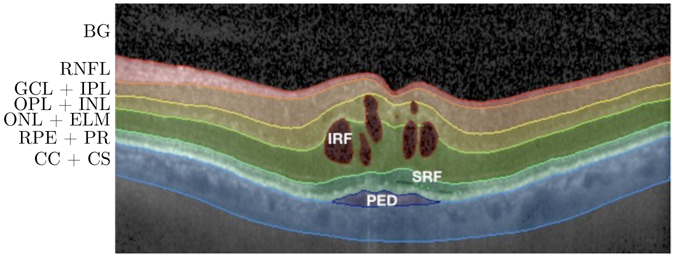
Known High Risk Features
for conversion to Late AMD



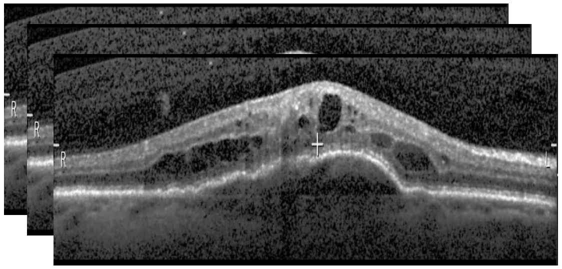


Predicting iAMD progression | initial modeling approaches

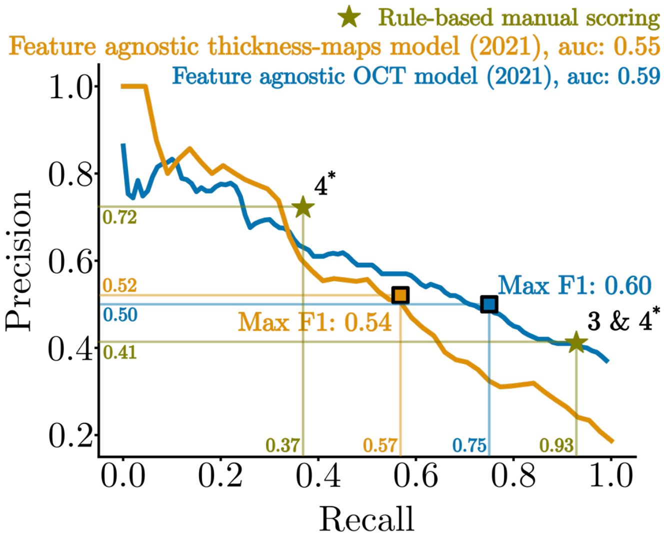
Deep Learning – imaging models



Retinal layers



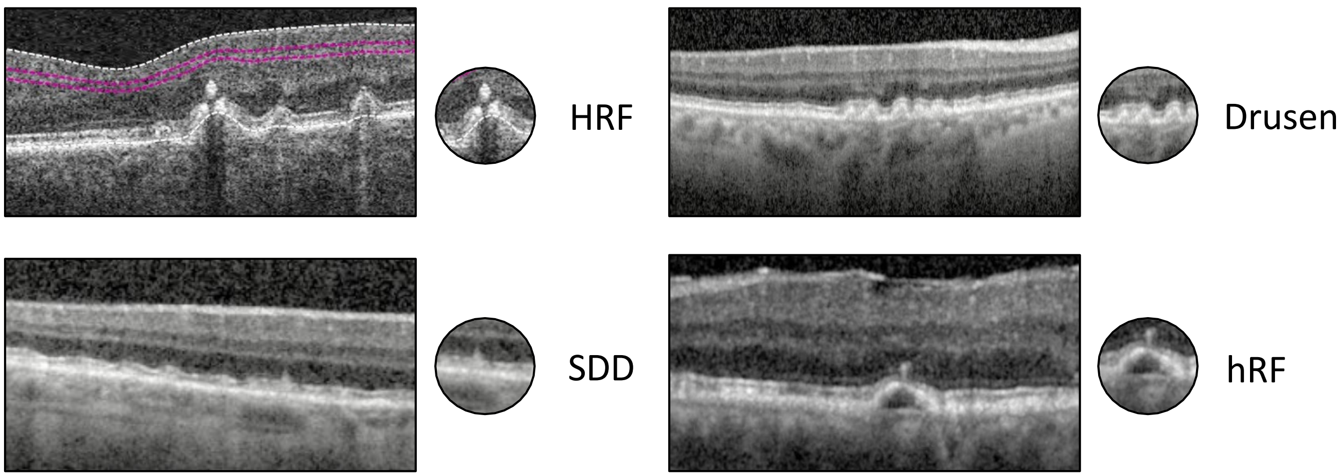
OCT images

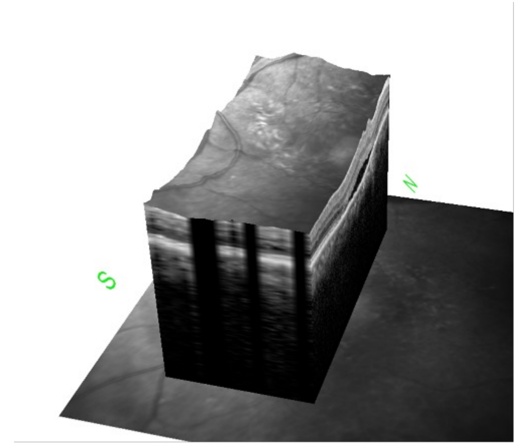


*Nassisi et al., OCT Risk Factors for Development of Late Age-Related Macular Degeneration in the Fellow Eyes of Patients Enrolled in the HARBOR Study, *Ophthalmology* (2019)

How is the manual scoring performed?

Counting high-risk features



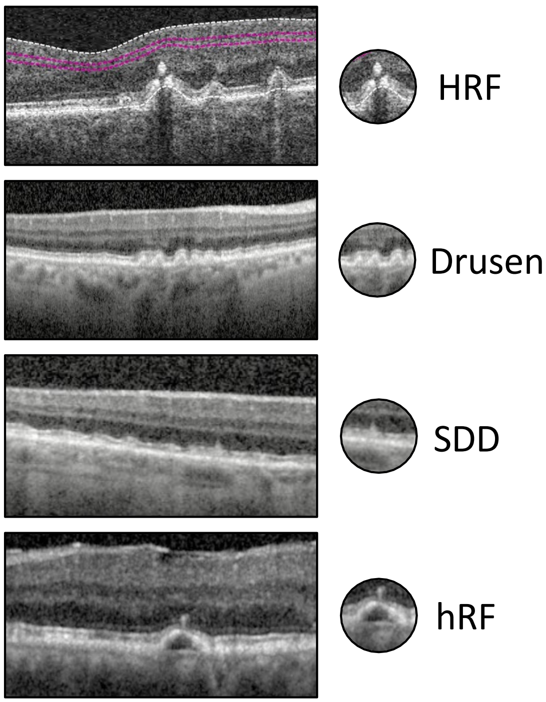


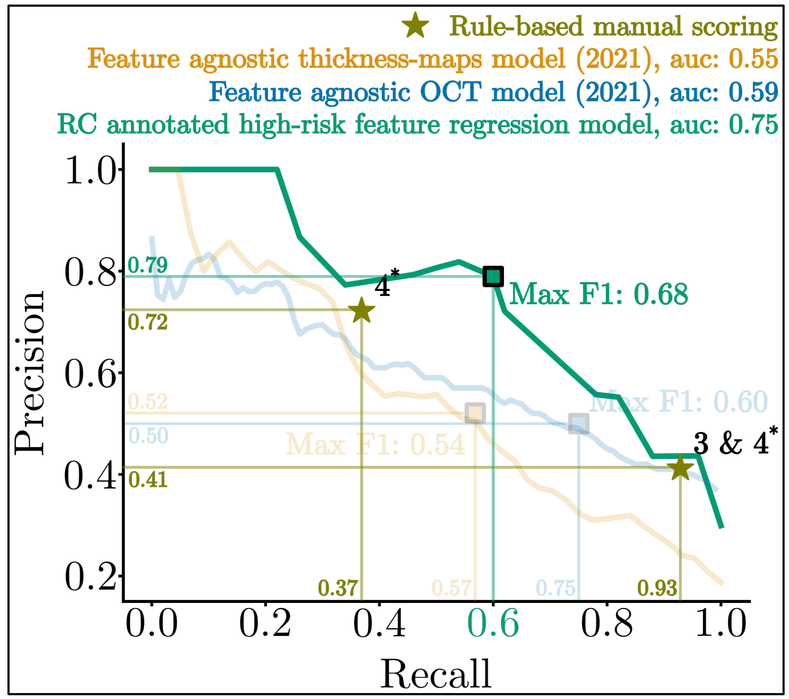
Rule-based manual scoring simply counts the number of high-risk features in the fellow eye without weighting one feature over the other for identifying fast progressors

*Nassisi et al., OCT Risk Factors for Development of Late Age-Related Macular Degeneration in the Fellow Eyes of Patients Enrolled in the HARBOR Study, *Ophthalmology* (2019)

Adding a stonger baseline

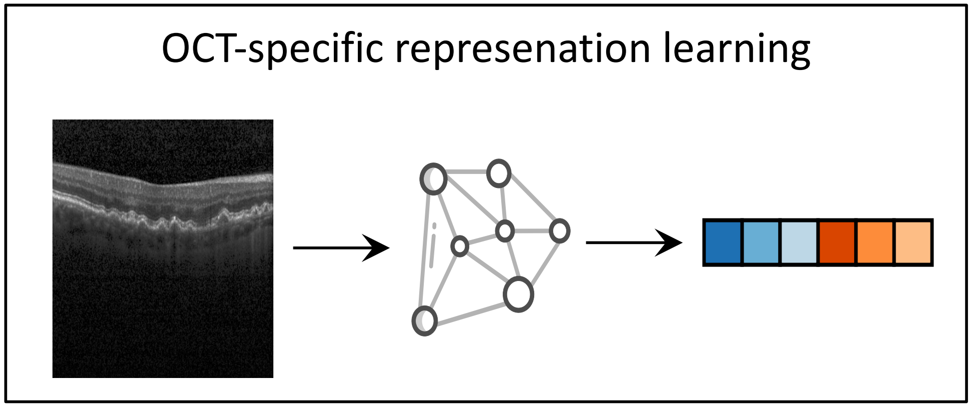
Weighting the high-risk features using a logistic regression model

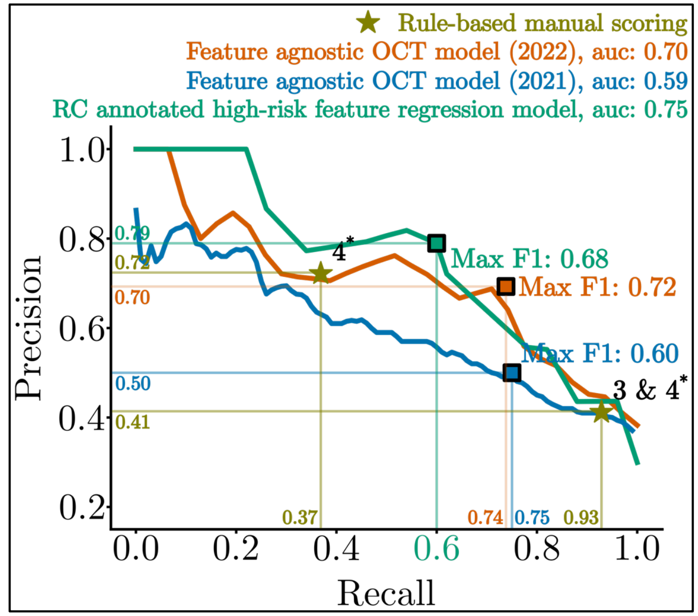




*Nassisi et al., OCT Risk Factors for Development of Late Age-Related Macular Degeneration in the Fellow Eyes of Patients Enrolled in the HARBOR Study, *Ophthalmology* (2019)

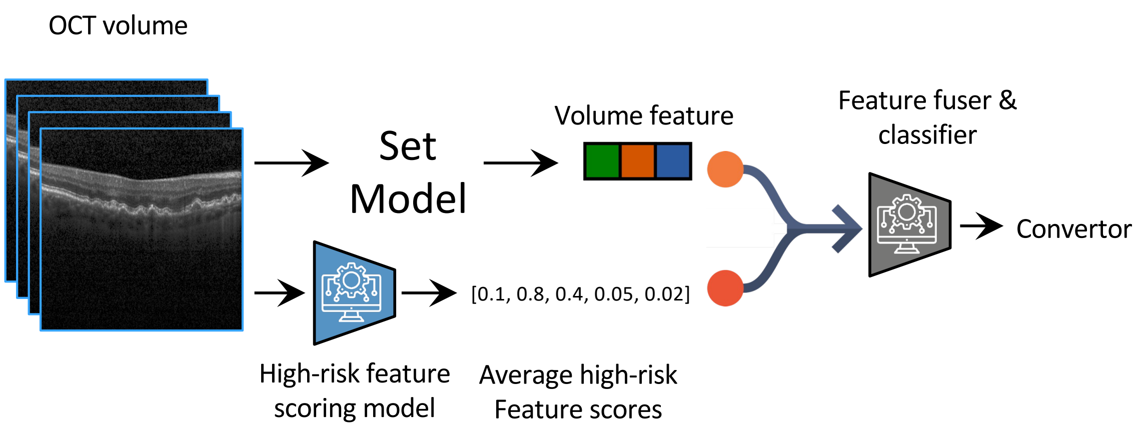
Predicting fast progressors | feature agnostic models (using OCT specific model)

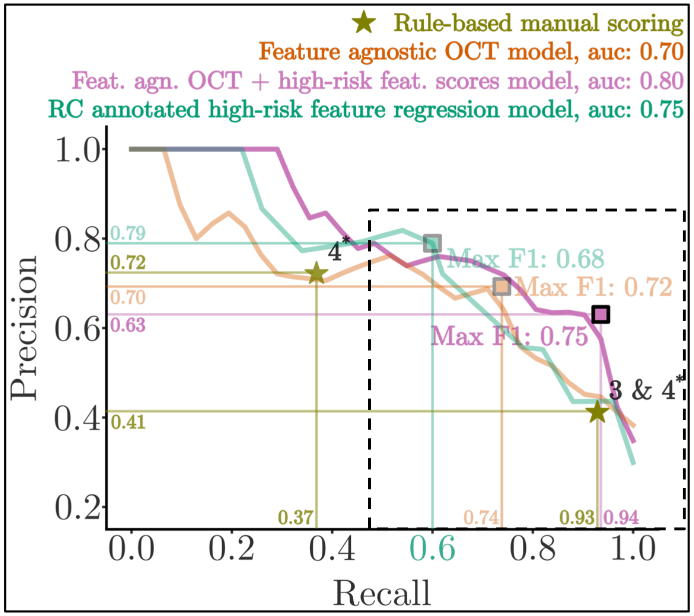




Identifying progressors from intermediate to late AMD

OCT features + high-risk feature scores model





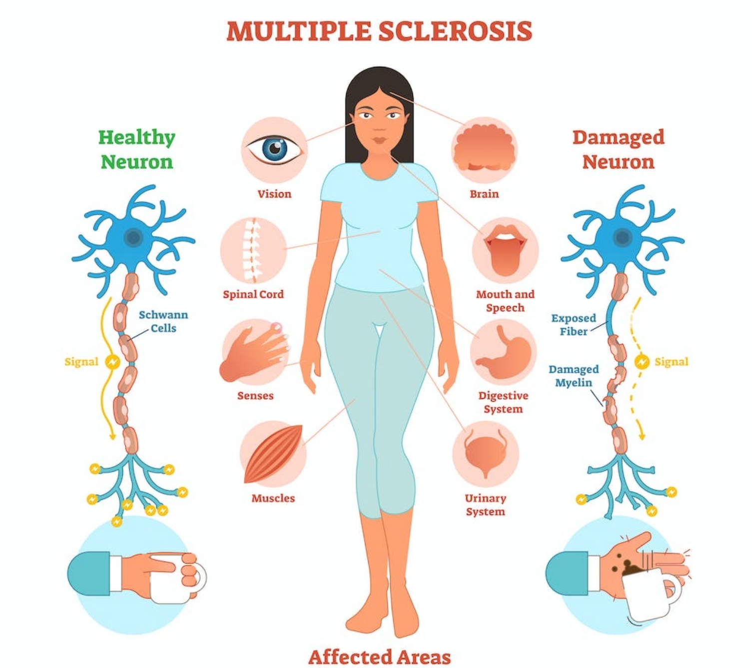
A. Older patient

B. Cat

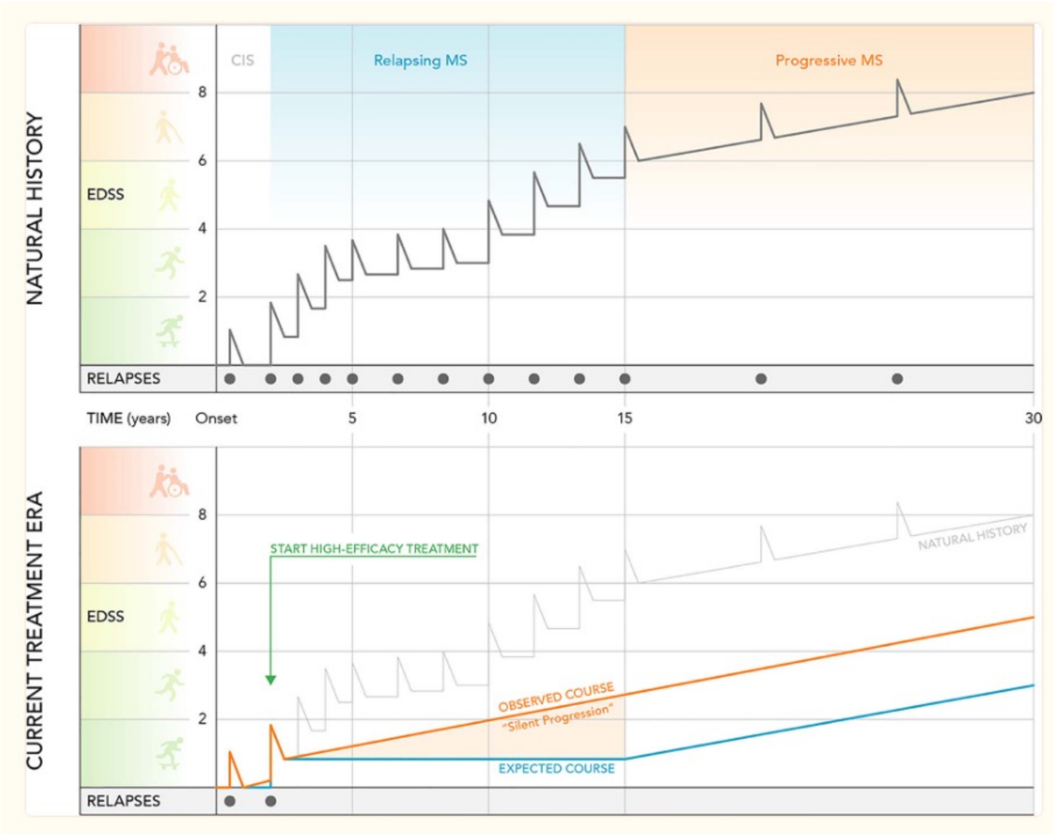
C. Child

D. Dog

Multiple sclerosis | neurodegenerative disease affecting the entire body

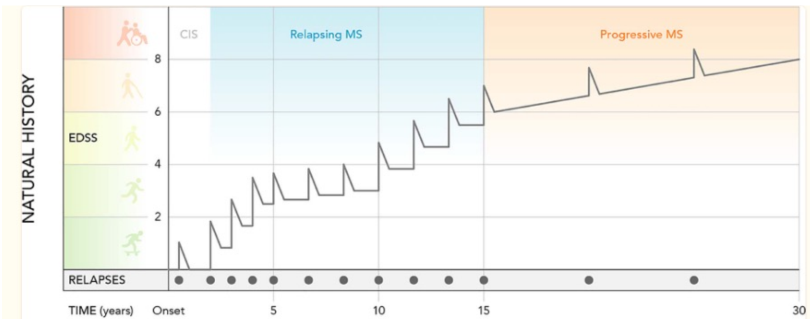


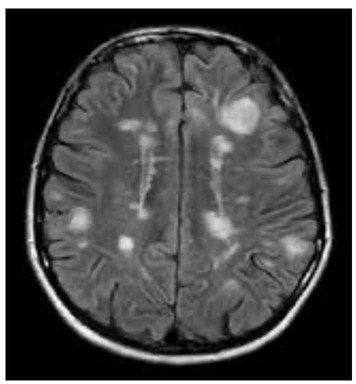
MS therapy | unmet medical need



Source: Hauser and Cree. Am J Med 2020

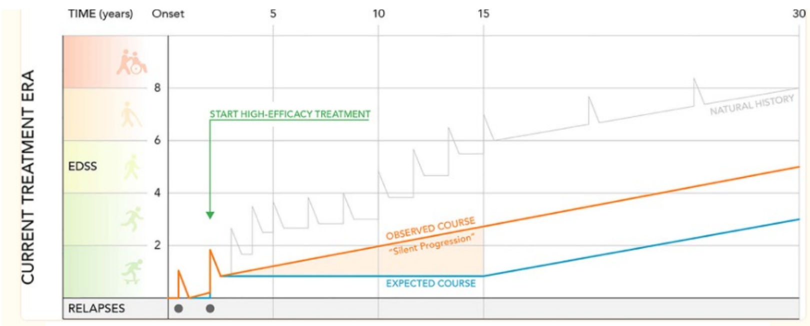
Predicting disability progression | relapses

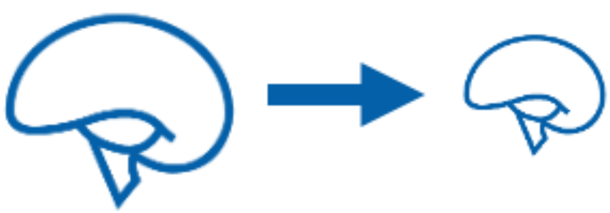




- New and enhancing brain lesion on MRI are sign of relapses
- Number / frequency of brain lesions is highly correlated with disability progression

Predicting disability progression | no relapses

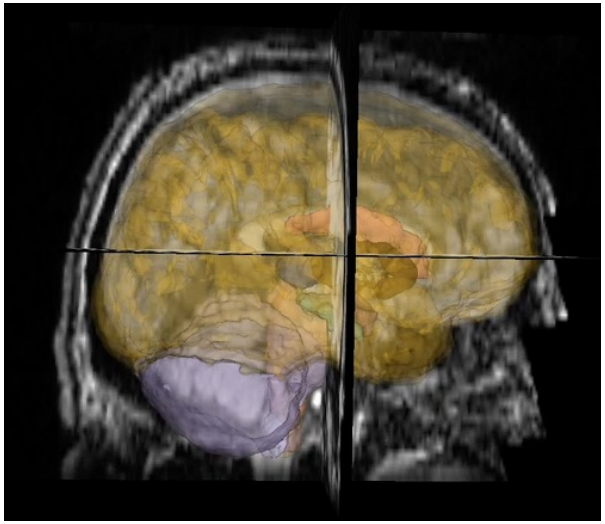




- Total brain volume change is correlated with MS progression independent of relapses
- Annualized change in brain volume in MS is small (0.5 -1 %) and only slightly above that of healthy controls (0.3% per year)
- Known measurement variability due to physiological parameters (hydration status) and difference in quantification methodology

Can we do better ? | Potential alternatives to total brain volume changes

- DGM (total)
- Thalamus
- Caudate
- Cortical grey matter
- White matter
- Brainstem
- Cerebellum
- Ventricles



NO.MS | leveraging information from up to 34 trials

Multiple Sclerosis Journal
Volume 27, Issue 13, November 2021, Pages 2062-2076

https://doi.org/10.1177/1352458520988637

Original Research Papers

Characterisation of MS phenotypes across the age span using a novel data set integrating 34 clinical trials (NO.MS cohort): Age is a key contributor to presentation

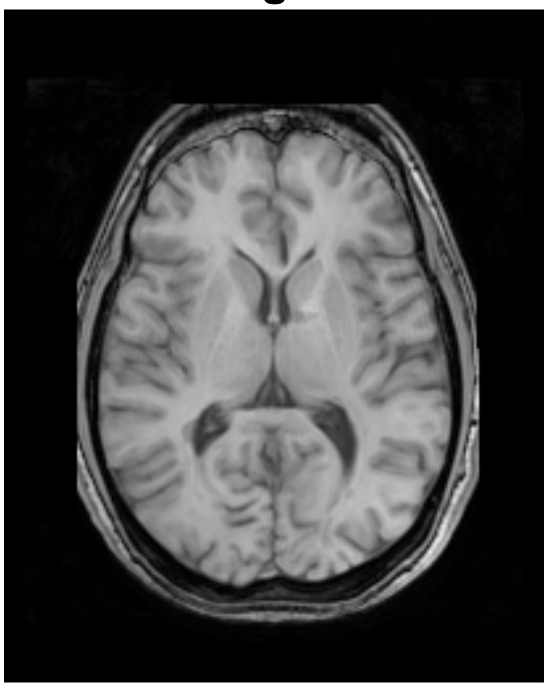
Frank Dahlke[1], Douglas L Arnold[2], Piet Aarden[3], Habib Ganjgahi[4], Dieter A Häring[5], Jelena Čuklina[6], Thomas E Nichols[7], Stephen Gardiner[8], Robert Bermel[9], and Heinz Wiendl[10]

Methods

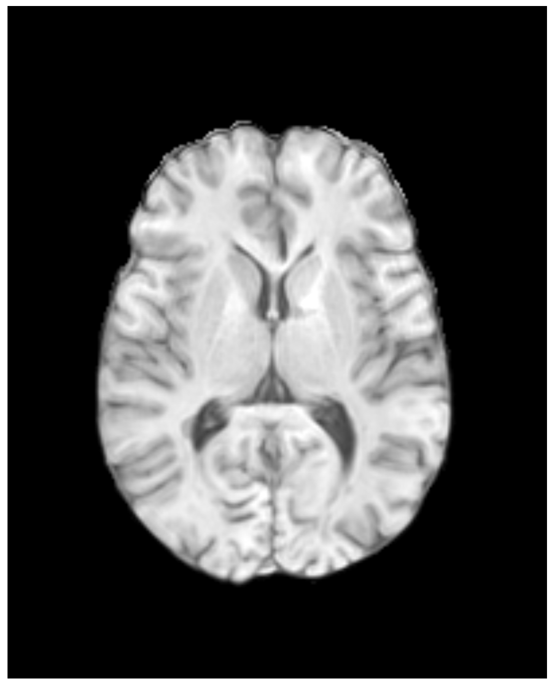
- EXPAND trial | SPMS, siponimod, placebo-controlled trial, 1,645 patients, conducted ~ 2013 - 2015
- Atlas based segmentation of 19 anatomic substructures of the baseline data
- Subsequent timepoints were diffeomorphically registered and volumetric changes were estimated via mean Jacobian determinant in the region of interests
- PIRA events were defined per Lublin et al (Brain 2022)
- Neural network developed (based on atlas segmentation) for batch processes/speed

EXPAND | substructural segmentation example

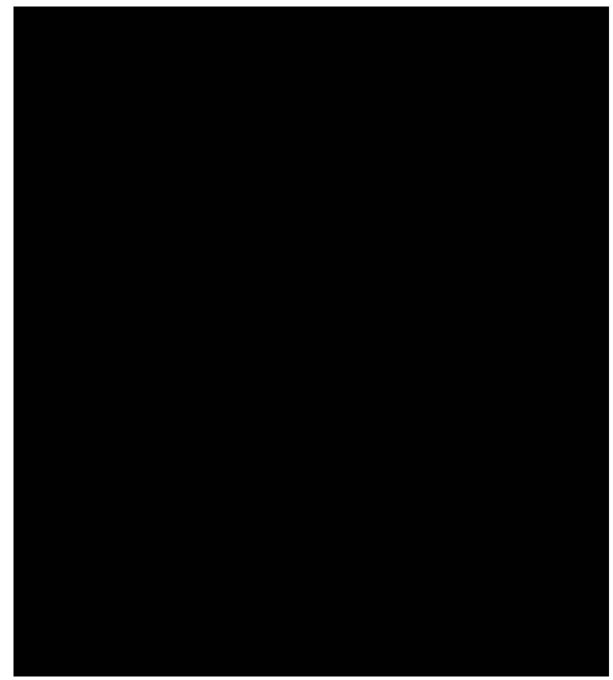
Original



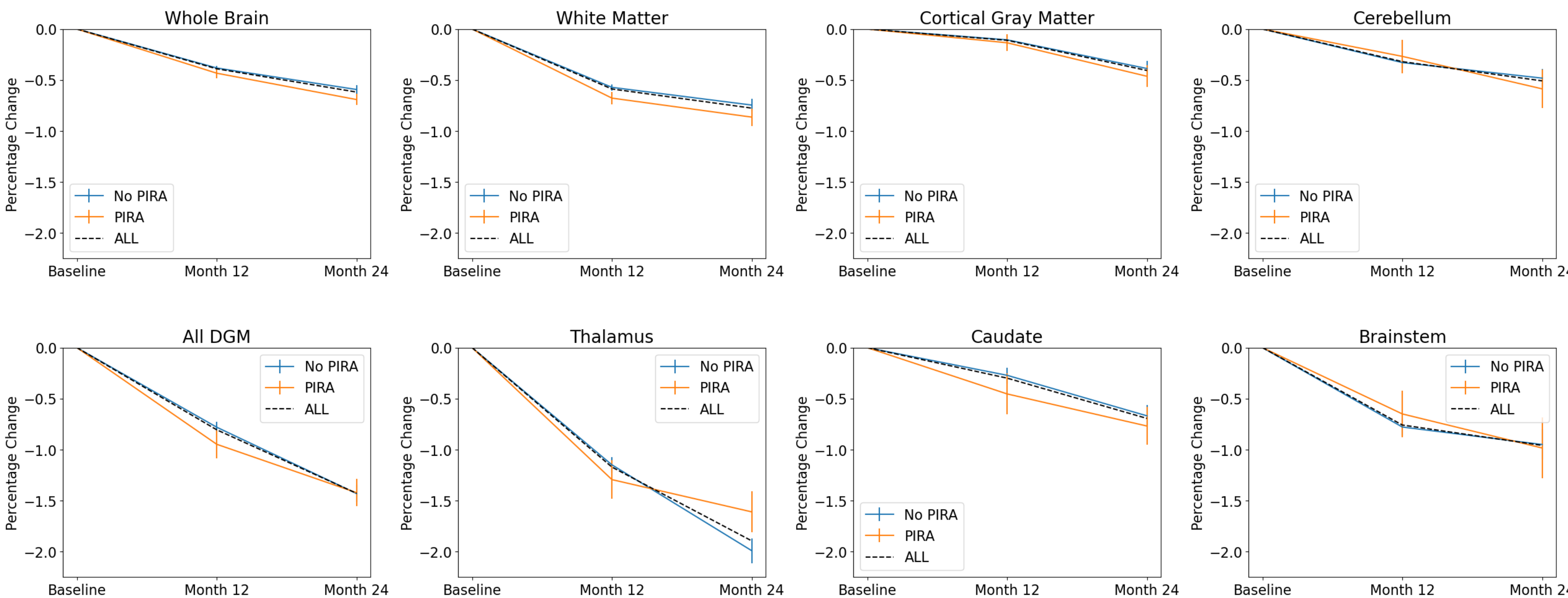
Processed



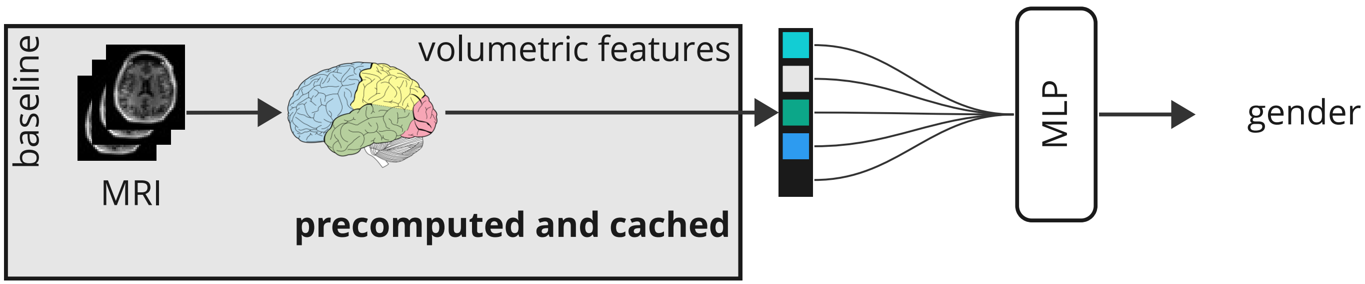
Segmented



Potential alternatives | exploratory insights on EXPAND



DNN Baseline Experiment

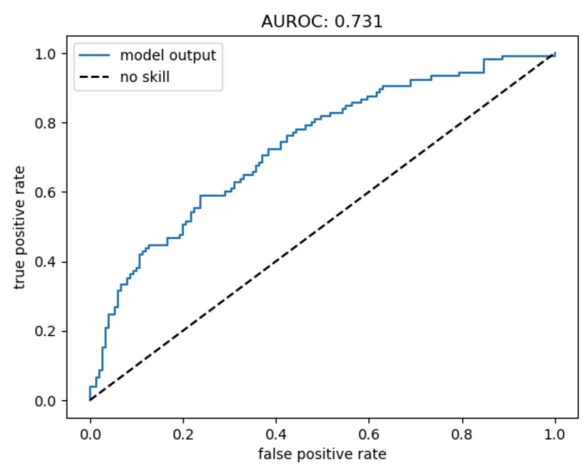


Jonathan Ziegler

gender classification on
8 brain volume features

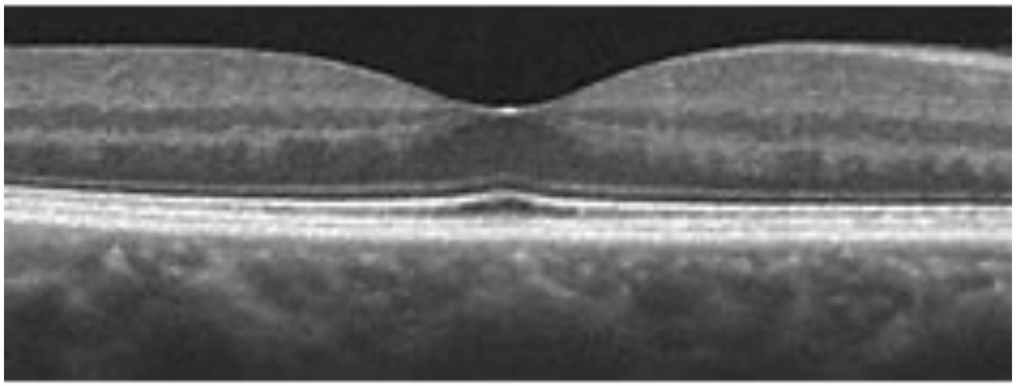
764 train samples

321 validation samples



Confusion Matrix

TN 63	FP 88
FN 15	TP 90



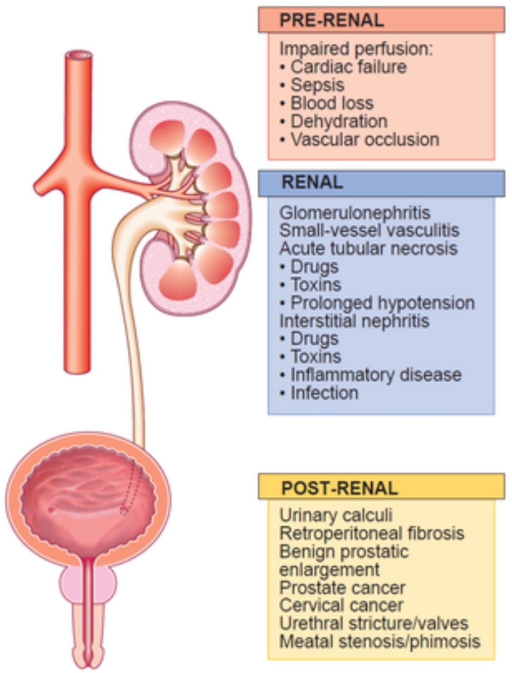
A. Mountain

B. Mustached upper lip

C. Retina

D. Turkey Sandwich

Assessing renal perfusion | measures to prevent acute kidney injury



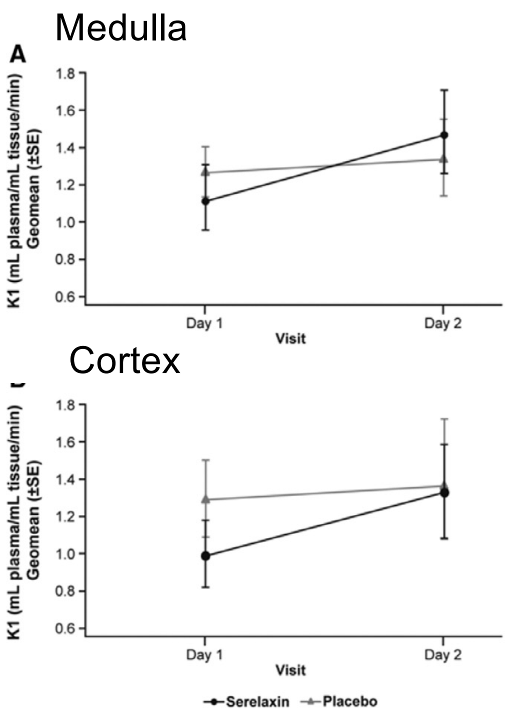
Causes of acute kidney injury.
Source : Davidsons Essentials of Medicine, 2e

Decreased blood flow

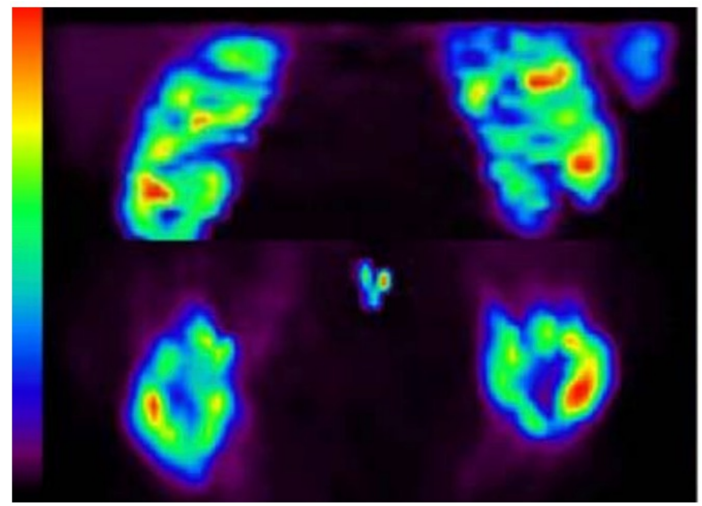
Direct damage to the kidneys

Blockage of the urinary tract

$H_2^{15}0$ PET | Assessing renal flow in CHF patients



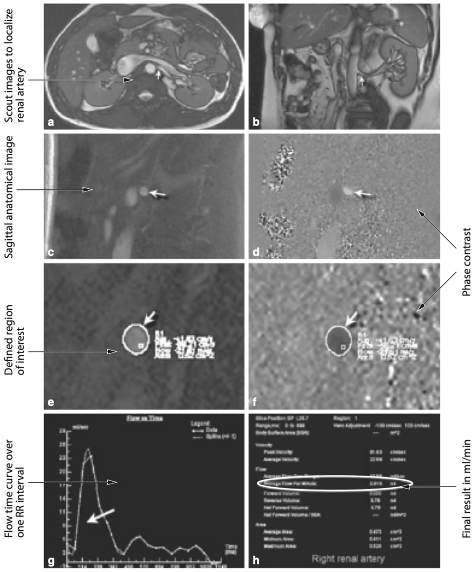
Source: Voors. Circ Heart Fail. 2014



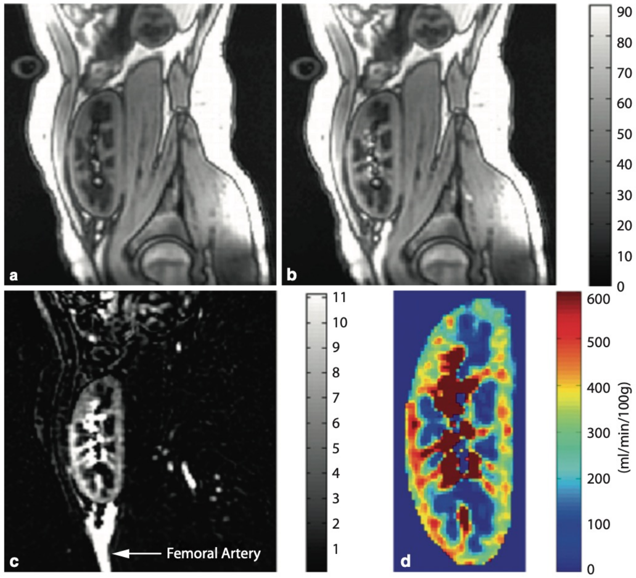
- Serelaxin, a recombinant vasodilator hormone, was assessed in 65 acute heart failure patients
- $H_2^{15}0$ PET in subset of 22 patients demonstrated 20% more perfusion in the renal medulla than in the cortex of txt group, but no change in the placebo group

Advanced MRI methods to assess renal perfusion | challenge to scale for phase II & III trials

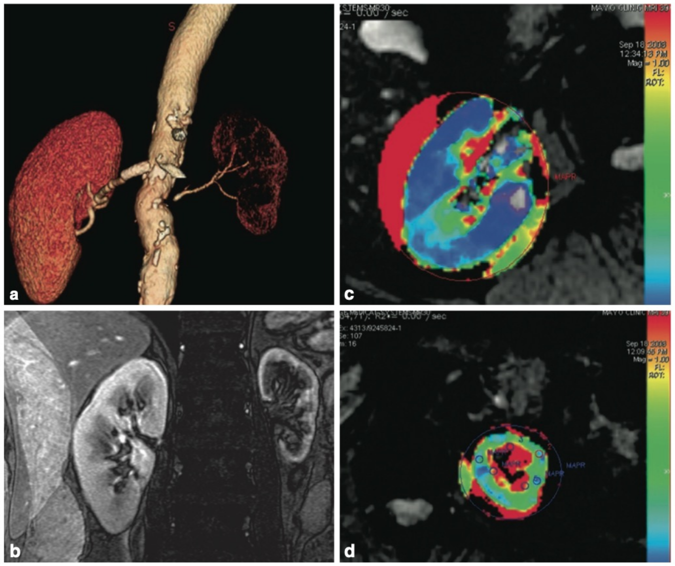
Cine phase-contrast MRI



Arterial spin labeling (ASL) MRI

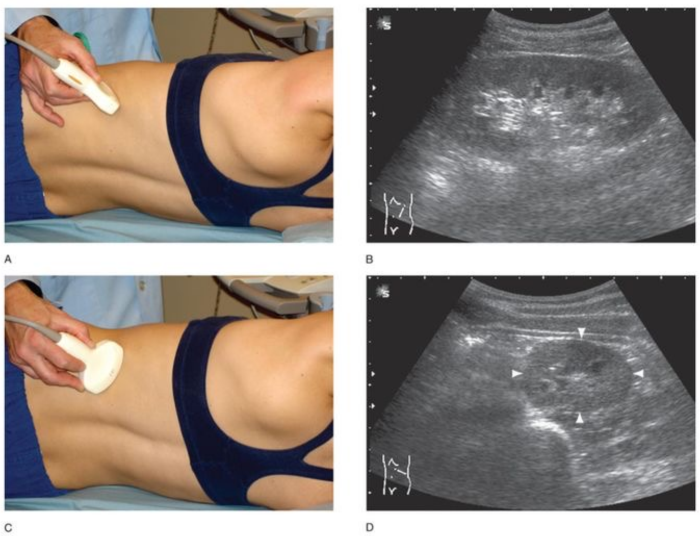


Blood oxygen level-dependent (BOLD) MRI



Source: Schneider. Critical Care 2013.

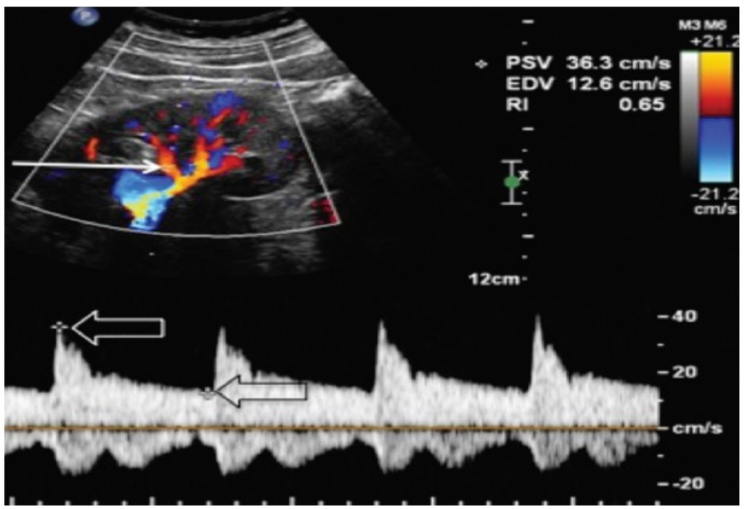
Ultrasound is widely available | Enabling access to patients who could otherwise not be imaged in trial settings



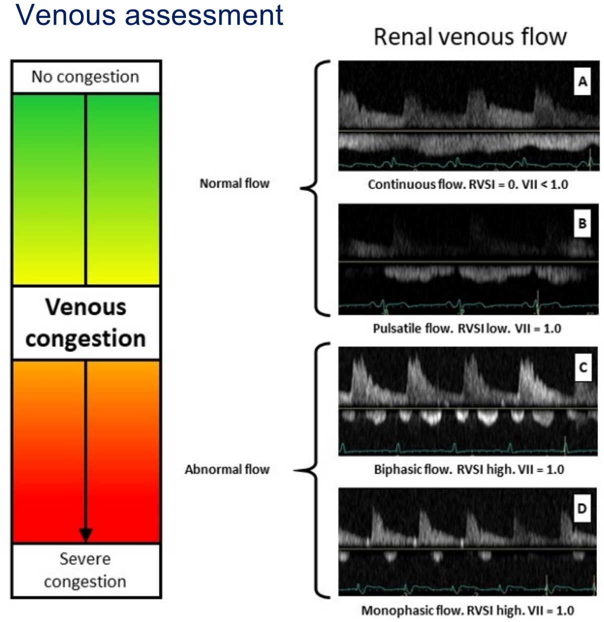
Source: MA- emergency ultrasound, www.healthmanagement.org

Doppler ultrasound measurements to asses renal perfusion

Arterial assessment: resistive index



Venous assessment



Source: Hermansen. Nat. ScRe 2021

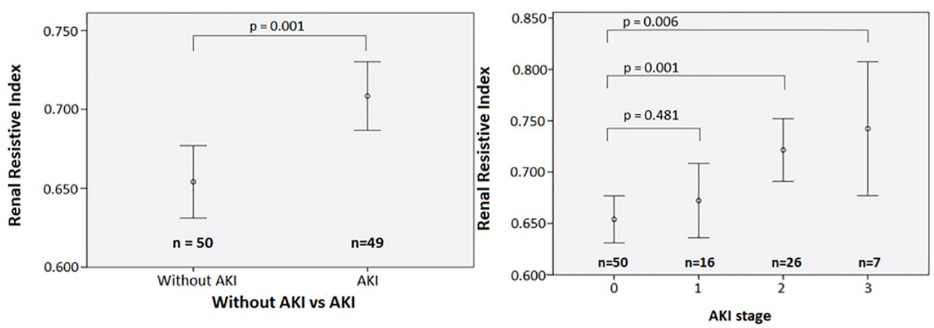
Perioperative ultrasound predicts AKI | ready for clinical trials?

89 patients with open-heart surgery | postoperative ultrasound | AKI developed within 4 days

Ultrasound indices 1st postoperative day	Univariate analyses OR	Univariate analyses 95% CI	Univariate analyses P-value	Multivariate analyses OR	Multivariate analyses 95% CI	Multivariate analyses P-value
Renal venous flow pattern						
Normal	1.0 (Ref)			1.0 (Ref)		
Abnormal	2.83	(1.18; 6.80)	0.020*	1.69	(0.60; 4.80)	0.32
RVSI						
Low (0–0.30)	1.0 (Ref)			1.0 (Ref)		
High (0.31–1.00)	3.19	(1.31; 7.78)	0.011*	1.70	(0.58; 4.94)	0.33
Resistive index	1.21	(1.10; 1.34)	< 0.001*	1.23	(1.09; 1.40)	0.001*
Portal pulsatility fraction	1.02	(1.00; 1.05)	0.08	1.01	(0.98; 1.03)	0.55

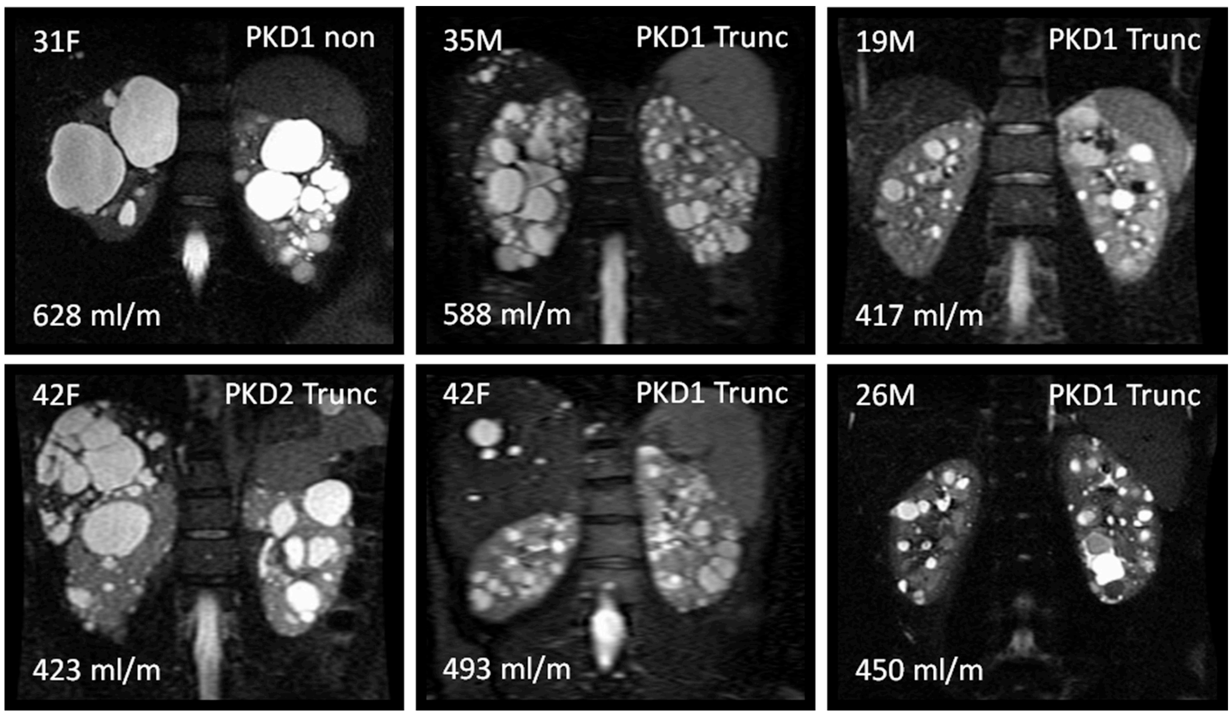
Source: Hermansen. Nat. ScieRep 2021

100 patients admitted to ICU for shock | ultrasound on admittance | AKI developed within 1 week



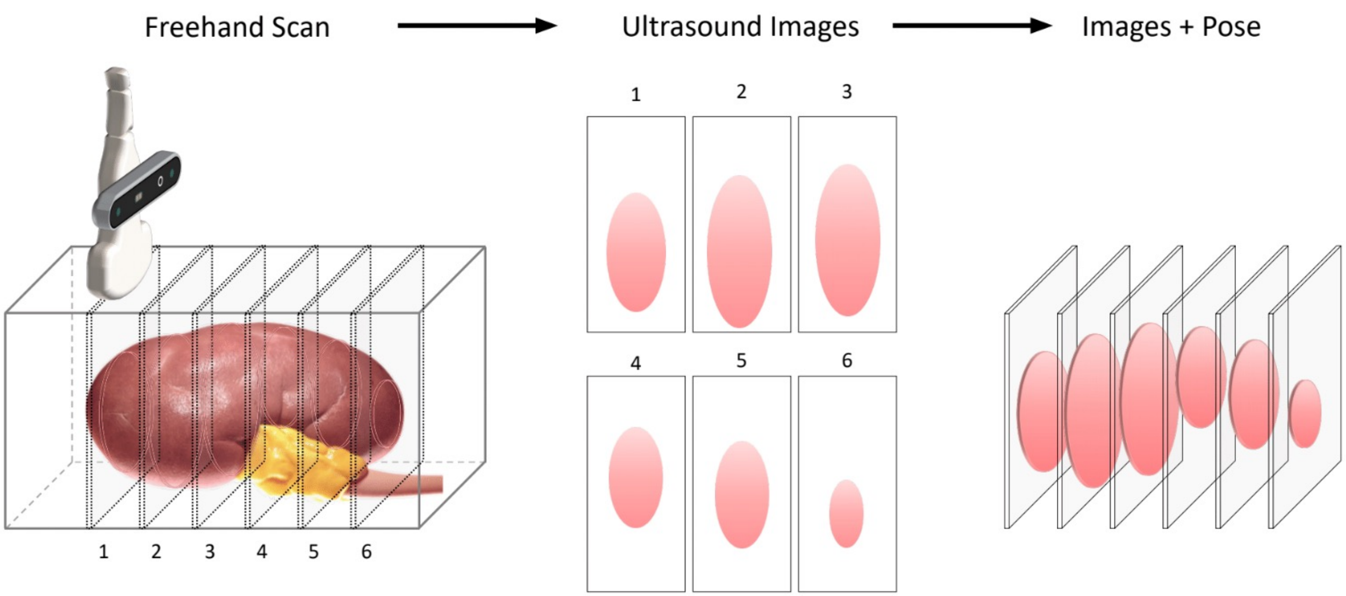
Source: Mulier. Plus One 2018

Volumetric changes | gold standard for assessing therapeutic response in polycystic kidney disease



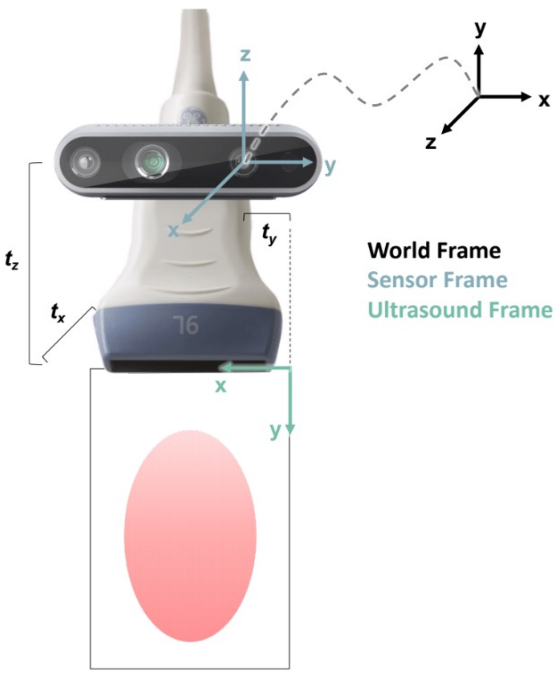
Source: Kidney-international.org

Creating 3D volume from 2D ultrasound scan



Source: Chen, dissertation 2022

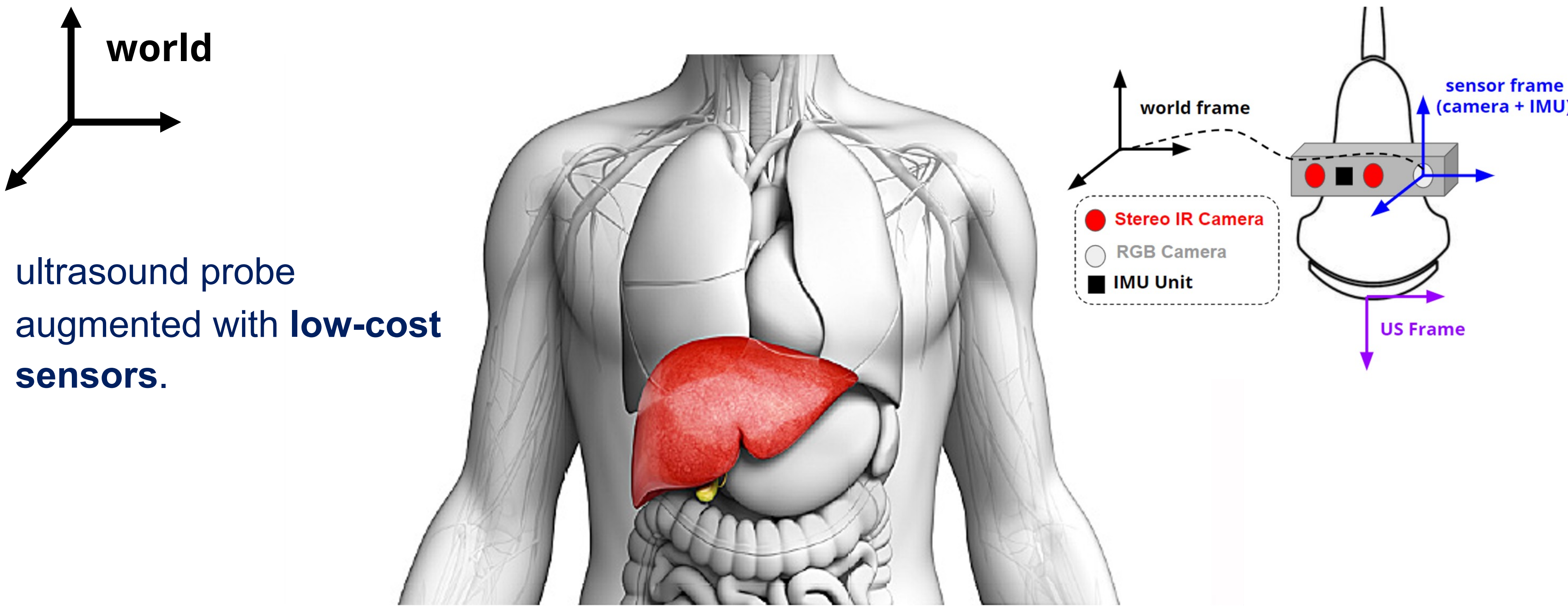
Coordinate system alignment

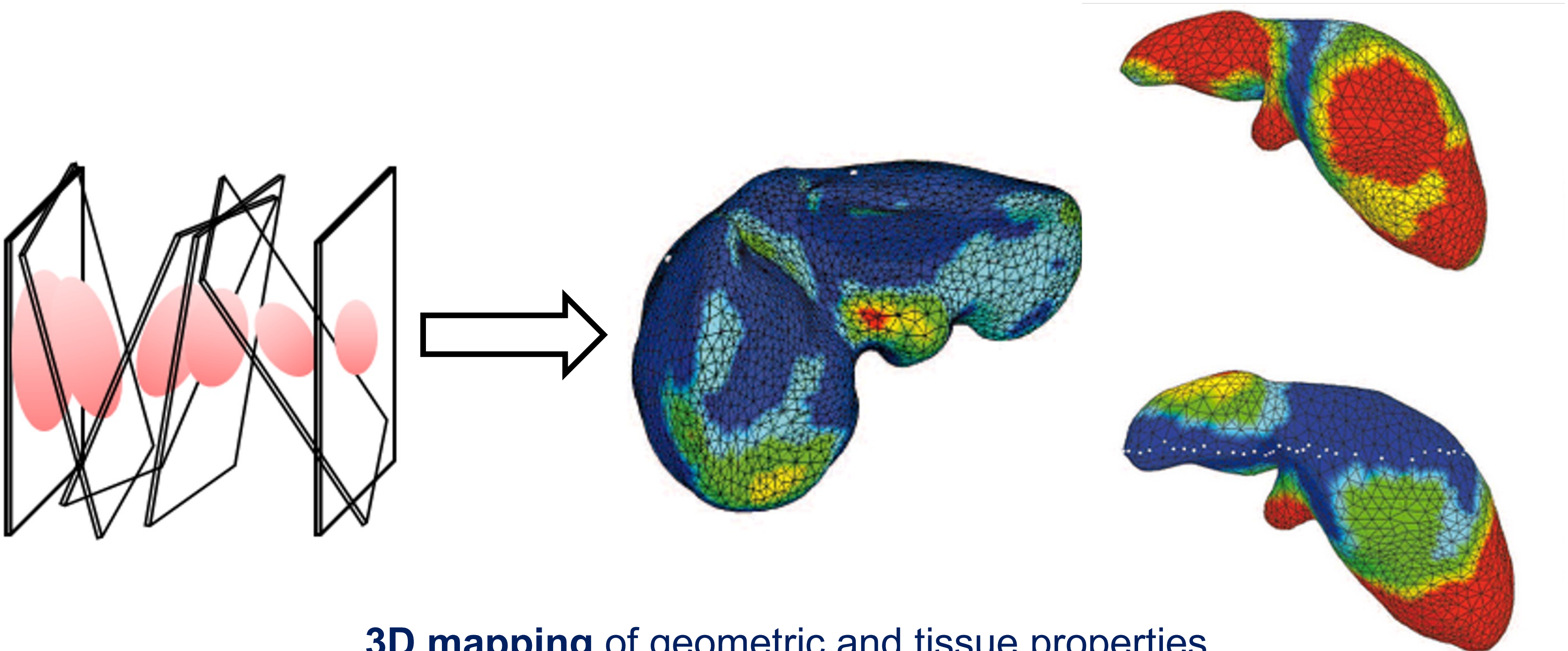


$$\begin{bmatrix} X \\ Y \\ Z \end{bmatrix} = [S]\,[T_{\text{sensor}}^{\text{world}}]\,[T_{\text{US}}^{\text{sensor}}]\begin{bmatrix} u \\ v \\ 1 \end{bmatrix}$$

- $\begin{bmatrix} X \\ Y \\ Z \end{bmatrix}$: Image pixel coordinates in the world frame
- $[T_{\text{sensor}}^{\text{world}}]$: Pose of the sensor relative to world coordinates
- $\begin{bmatrix} u \\ v \\ 1 \end{bmatrix}$: Image pixel coordinates in the US frame
- $[S]$: Scale Factor
- $[T_{\text{US}}^{\text{sensor}}]$: Transformation between the US and sensor

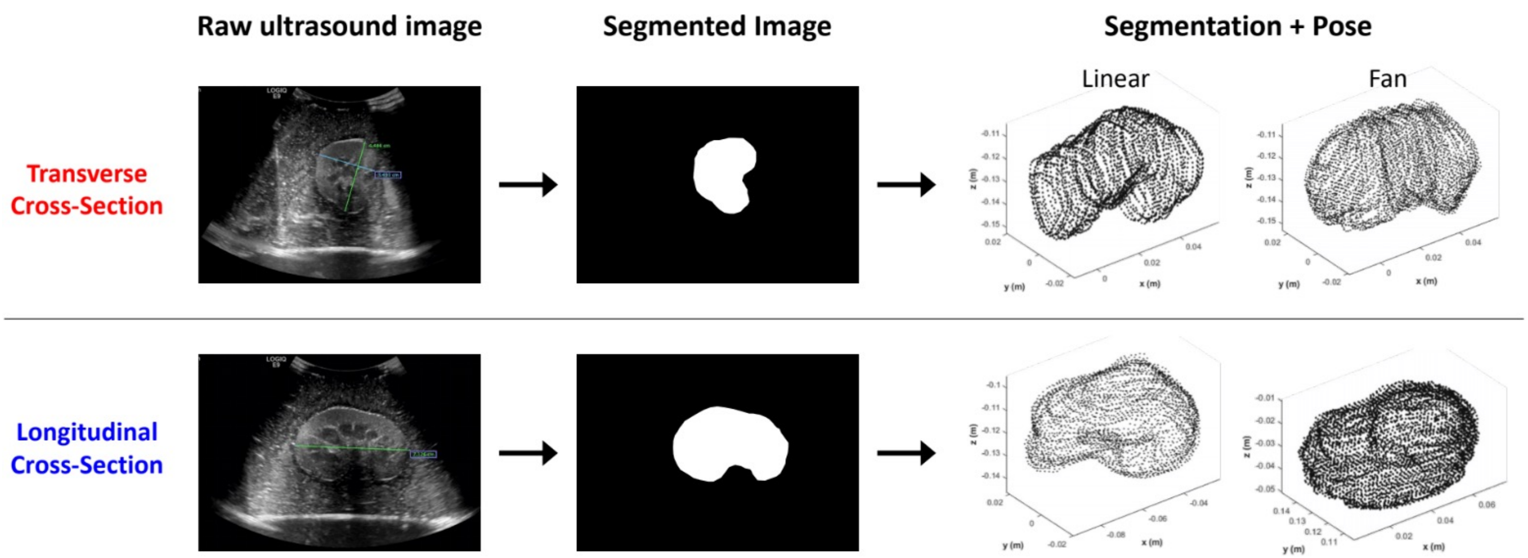
Source: Chen, dissertation 2022


world
ultrasound probe augmented with **low-cost sensors**.
world frame
sensor frame
(camera + IMU)
Stereo IR Camera
RGB Camera
IMU Unit
US Frame



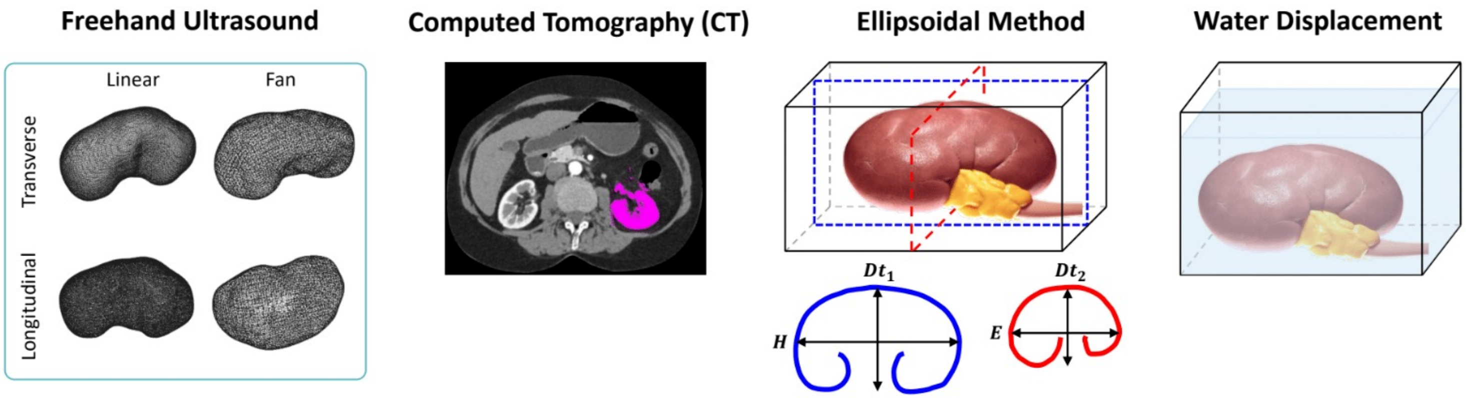
3D mapping of geometric and tissue properties

Freehand ultrasound volumes



Benjamin, A., Chen, M. (UMB, 2020)

Ultrasound derived volumes are comparable with gold standard



$$Volume = \frac{\pi}{12} \times H \times E \times (Dt_1 + Dt_2)$$

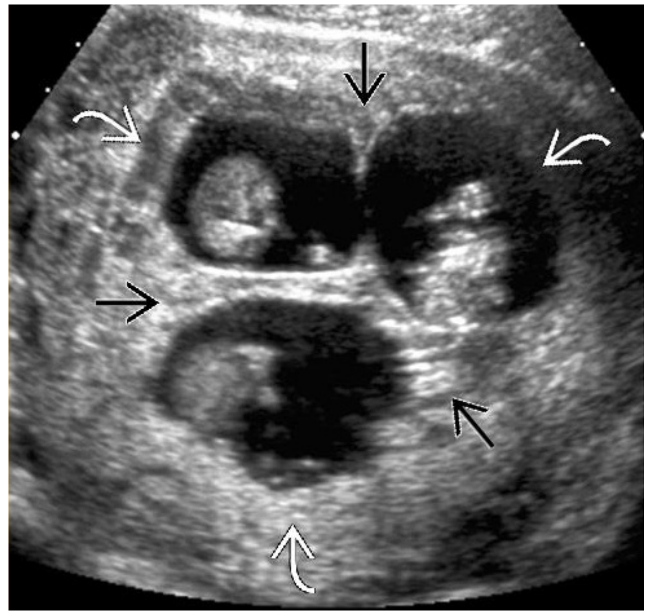
Kidney No.	Measurement	Freehand US (mL)	CT (mL)	Ellipsoid (mL)	Water Displacement (mL)
1	Volume	64.08	63	57.49	66
	Error (%)	2.90	4.54	12.90	0
2	Volume	65.25		60.15	66.2
	Error (%)	1.40		9.130	0

Benjamin, A., Chen, M. (UMB, 2020)

A. Esophagus

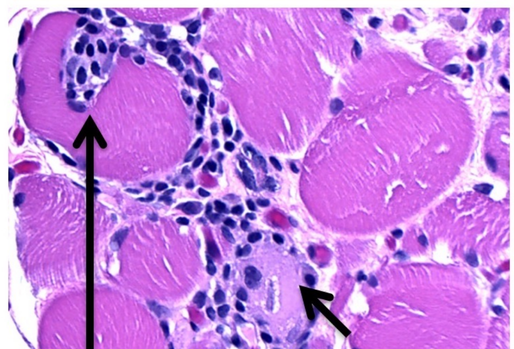
B. Gallstones

C. Triplets

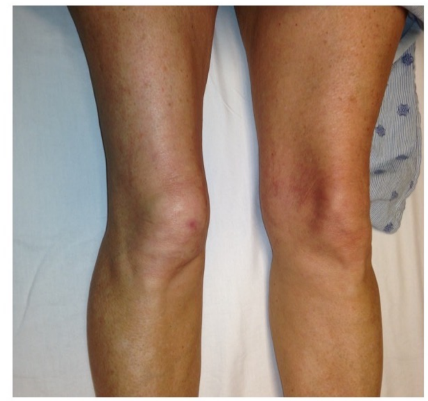


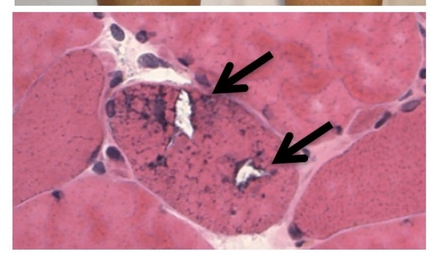
Multiparametric MRI to go beyond structure | sporadic inclusion body myositis

- A rare progressive and currently untreatable muscle disorder causing severe disability
- Muscle biopsies show both inflammatory and degenerative changes (protein aggregates)



Autoinvasion of Mononuclear Cells **Myofiber Degeneration**



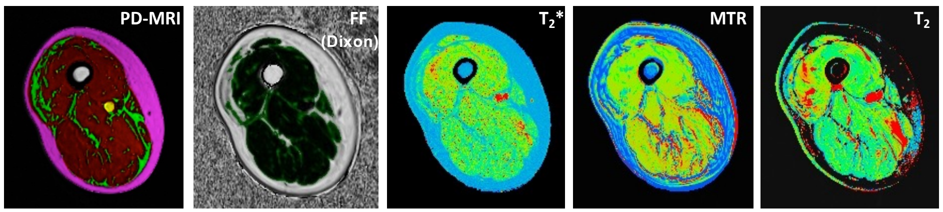


Rimmed vacuoles (RVs) and protein aggregates

Source: https://lloydlab.jhmi.edu/IBM.html

Quantitative MRI findings | Correlation with observed functional, mobility and strength outcomes

Early-stage patient



75% TMV
24% IMAT

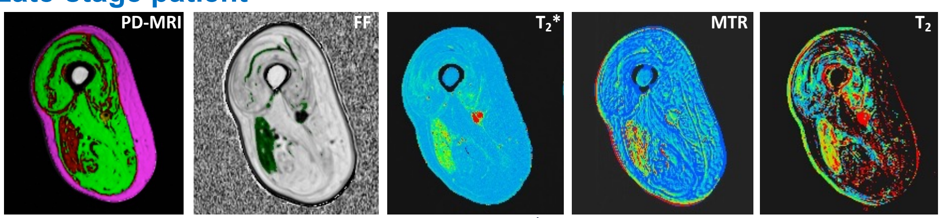
FF 12.9%

0.1% IMCT-T_2*
10.9% IMAT-T_2*

31.8% MTR

T_2 35.7 ms

Late-stage patient



25% TMV
75% IMAT

FF 37.1%

3.7% IMCT-T_2*
82.7% IMAT-T_2*

12.0% MTR

T_2 28.8 ms

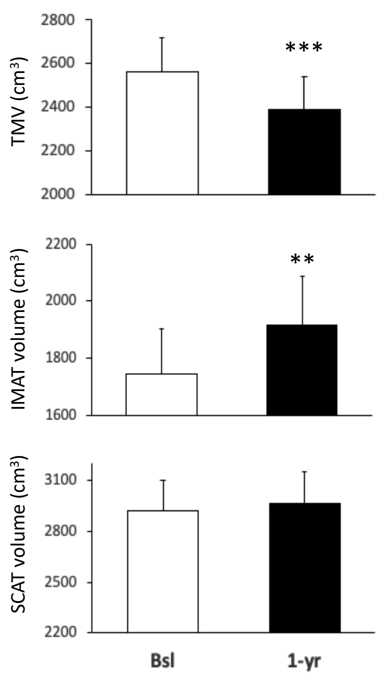
Atrophy | *Fat infiltration* | *Connective tissue* | *Protein organization* | *Oedema*

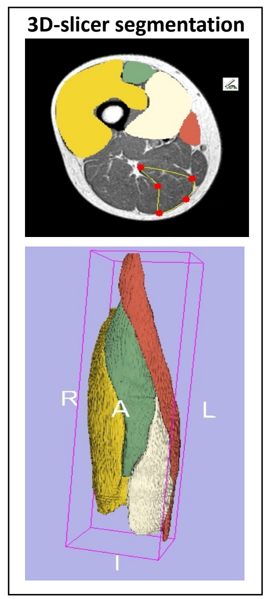
Source: Laurent, Neurology 2022

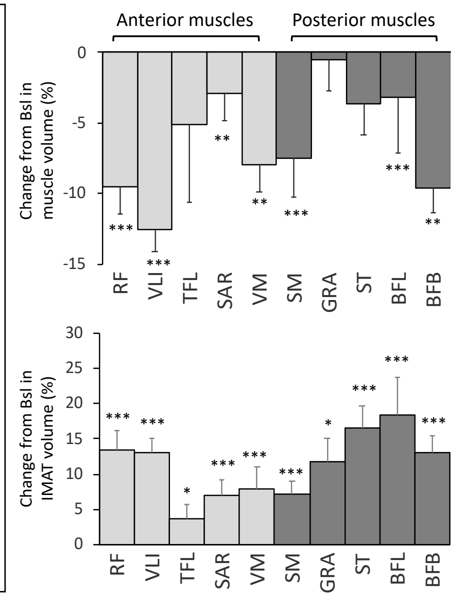
	%TMV (ml)	%IMAT (ml)	T_2 (ml)	FF (%)	T_2*-IMCT (%voxels)	T2*-IMAT (%voxels)	MTR (%)
sIFA (score)	-0.32 (p=0.088)	0.19 (p=0.319)	0.25 (p=0.174)	**0.53*** (p=0.002)	0.25 (p=0.185)	0.33 (p=0.079)	-0.27 (p=0.144)
6MWD (m)	**0.52*** (p=0.003)	**-0.54*** (p=0.003)	0.23 (p=0.230)	**-0.66*** (p<0.001)	-0.36 (p=0.054)	**-0.52*** (p=0.004)	0.34 (p=0.068)
QMT (lbs)	**0.65*** (p<0.001)	**-0.41*** (p=0.025)	0.12 (p=0.546)	**-0.68*** (p<0.001)	**-0.53*** (p=0.003)	**-0.57*** (p=0.001)	**0.43*** (p=0.019)

SIFA: sIBM physical fucntional assessment
6MWD: 6-min walking distance
QMT: Quantitative muscle testing

Sporadic inclusion body myositis | changes after 1 year



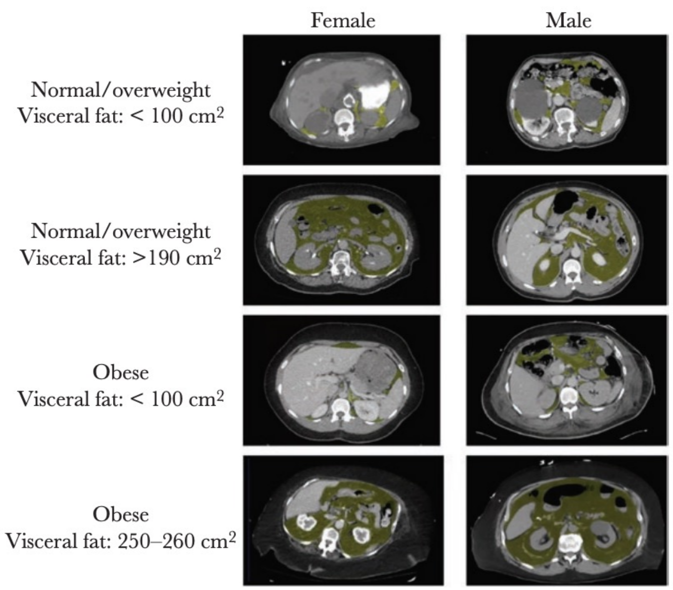


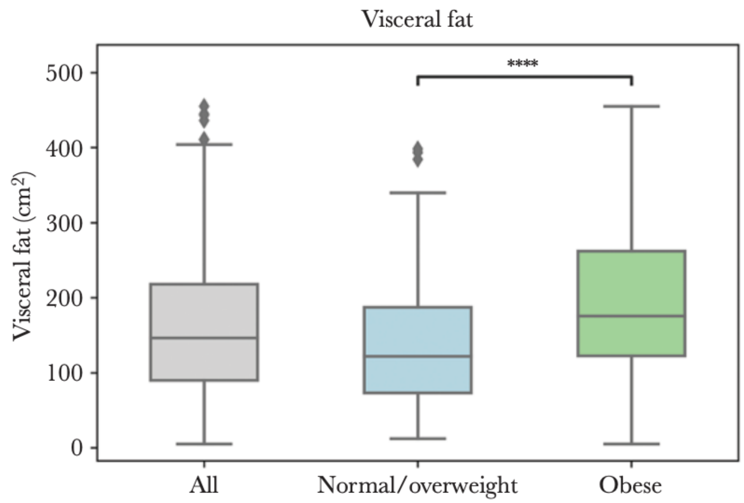


- Volume loss ranging from <1% (*gracilis*) to -12.6% (*vastus lateralis & intermedius*)
- More prominent IMAT deposition in posterior (+13.4%) *vs* anterior muscles (+8.5%)

Source: Laurent, Neurology 2022

Risk stratifying COVID patients | opportunistic use of available information from chest CT data*





* 2019 MGH COVID registry: 410/866 (47.3%) had chest CT during our before hospitalization

Source: Goehler, OFID 2021

Visceral fat quantified on chest CT | correlation with 28 day mortality or intubation independent of BMI

	VAT Only	BMI + VAT	BMI Only
	aHR + 95% CI	aHR + 95% CI	aHR + 95% CI
VAT ≥100 cm^2	2.00 (1.32–3.02)	1.97 (1.24–3.09)	—
Age, y	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Male	1.21 (0.85–1.72)	1.22 (0.85–1.76)	1.51 (1.07–2.13)
Diabetes	1.27 (0.93–1.74)	1.20 (0.87–1.66)	1.21 (0.88–1.67)
BMI			
Normal	—	Reference	Reference
Overweight	—	0.76 (0.47–1.21)	0.95 (0.61–1.49)
Obese	—	1.14 (0.71–1.82)	1.57 (1.02–2.40)
Race			
White	Reference	Reference	Reference
Hispanic	1.05 (0.67–1.63)	1.07 (0.69–1.68)	1.09 (0.70–1.70)
Black	1.88 (1.08–3.27)	1.95 (1.11–3.40)	1.67 (0.97–2.90)
Other	1.05 (0.71–1.54)	1.03 (0.70–1.52)	1.01 (0.68–1.49)

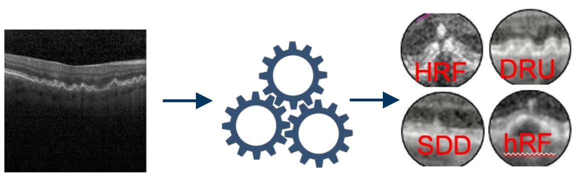
Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; VAT, visceral adipose tissue.

Source: Goehler, OFID 2021

Imaging AI can address a broad range of applications

Scope depends on the context of use

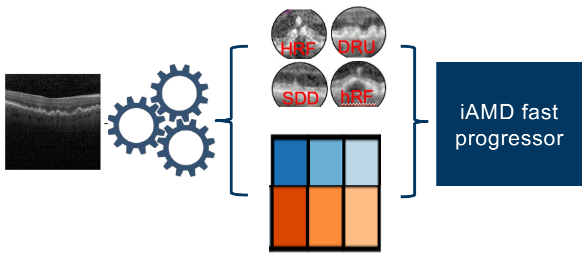
Enabling feasibility: **Automate established endpoint to reduce variability / increase scalability**



Pfizer | Iterative Scopes – AI driven colonoscopies for trial inclusion, primary/secondary endpoints[1]

Biogen | AI2 – FDA-listed AI algorithm to identify and classify Amyloid-related imaging abnormality (ARIA)[2]

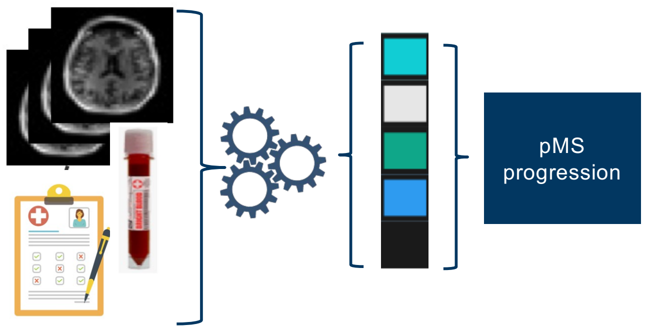
Novel feature association: **Going beyond what the human eye can see**



Roche – macular thickness quantification from color fundus photography (ph 3, RIDE/RISE)[3]

J&J | Neutrogena | FitSkin – AI driven app for skin analyses and product recommendations[4]

Multimodal integration: **Leveraging the full spectrum of information across imaging & non-imaging data**



Merck | Perceiv AI – imaging & molecular & clinical & blood for Alzheimer's progression prediction[5,6]

Sources: (1) https://www.businesswire.com/news/home/20220208005529/en/Iterative-Scopes-Announces-AI-Driven-Data-Sharing-Agreement-with-Pfizer-to-Advance-IBD-Clinical-Trials. (2) https://www.biogen.com/science-and-innovation/biogen-digital-health/portfolio.html (3) https://www.ophthalmologytimes.com/view/deep-learning-predicts-oct-measures-diabetic-macular-thickening. (4) https://www.biogen.com/science-and-innovation/biogen-digital-health/portfolio.html. (5) https://www.perceiv.ai/ (6) https://www.newswire.ca/news-releases/merck-selects-perceiv-ai-for-inaugural-digital-sciences-studio-cohort-853646627.html

Conclusion

- Imaging is a key component of many overall biomarker strategies
- Imaging modalities and methodologies come at different levels of complexity and maturity which affects their utility in later stage studies
- AI assisted imaging analysis provides opportunities for broader use of data; early engagement with health authorities is important to ‘learn together’

Acknowledgments

- Andrea Wiethoff, PhD
- Didier Laurent, PhD
- Alex Benjamin, PhD
- Melinda Chen, PhD
- Andre da Costa, PhD
- Denise Yates, PhD
- Imtiaz Hossain, PhD
- Jonathan Ziegler, PhD
- Roman Zeleznik, PhD
- Jay Patel
- Prateek, Katiyar, PhD

Questions

Feel free to contact me at alexander.goehler@novartis.com