AI in Medicine: Transforming the landscape of Tissue-based Diagnostics

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Disclosures

Behzad Najafian, M.D.

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Learning OBJECTIVES

At the conclusion of this activity, participants will be able to:

1. List some of the applications of AI in Pathology
2. Describe the importance of robust sampling in quantitative tissue analysis
3. Recognize the potentials of AI in standardization and accessibility of specialized tissue assays in rare diseases


University of Washington, Seattle
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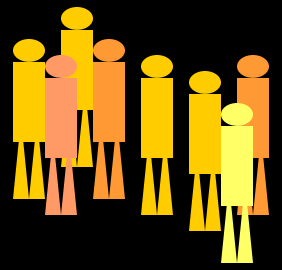
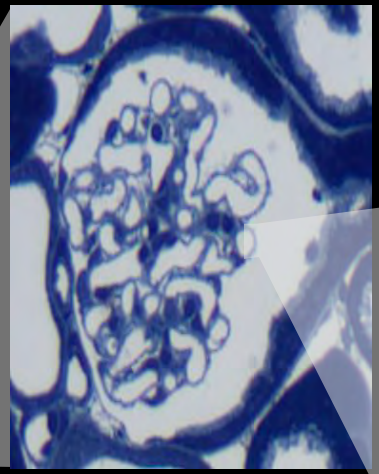
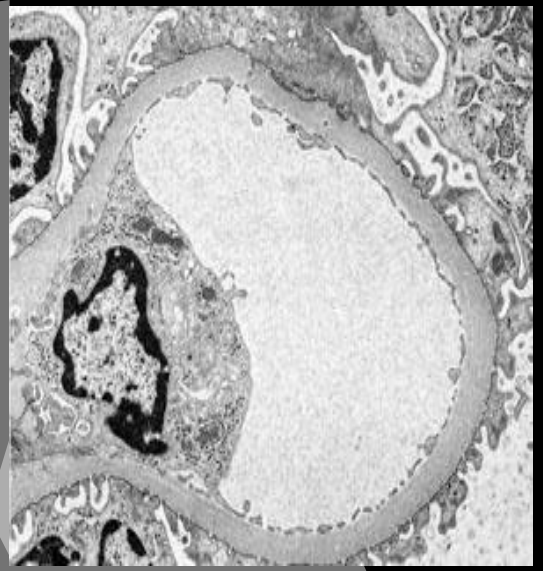


Biopsy
(1 cm)

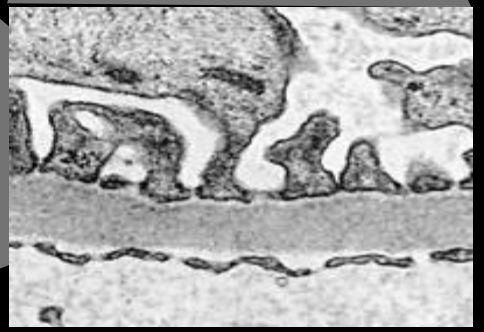
400x



5,000x



60,000X



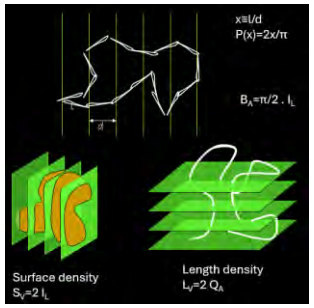
12,000x

Lord Kelvin

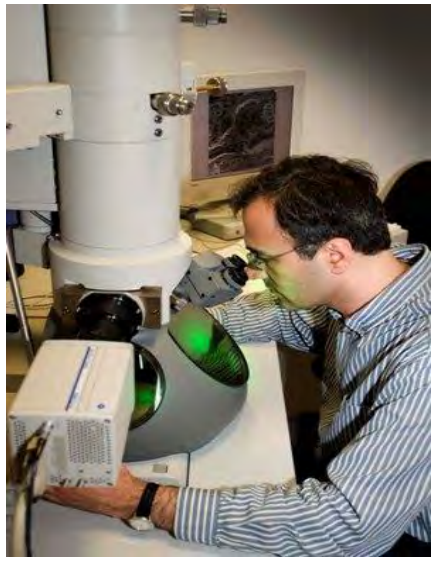
I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind.

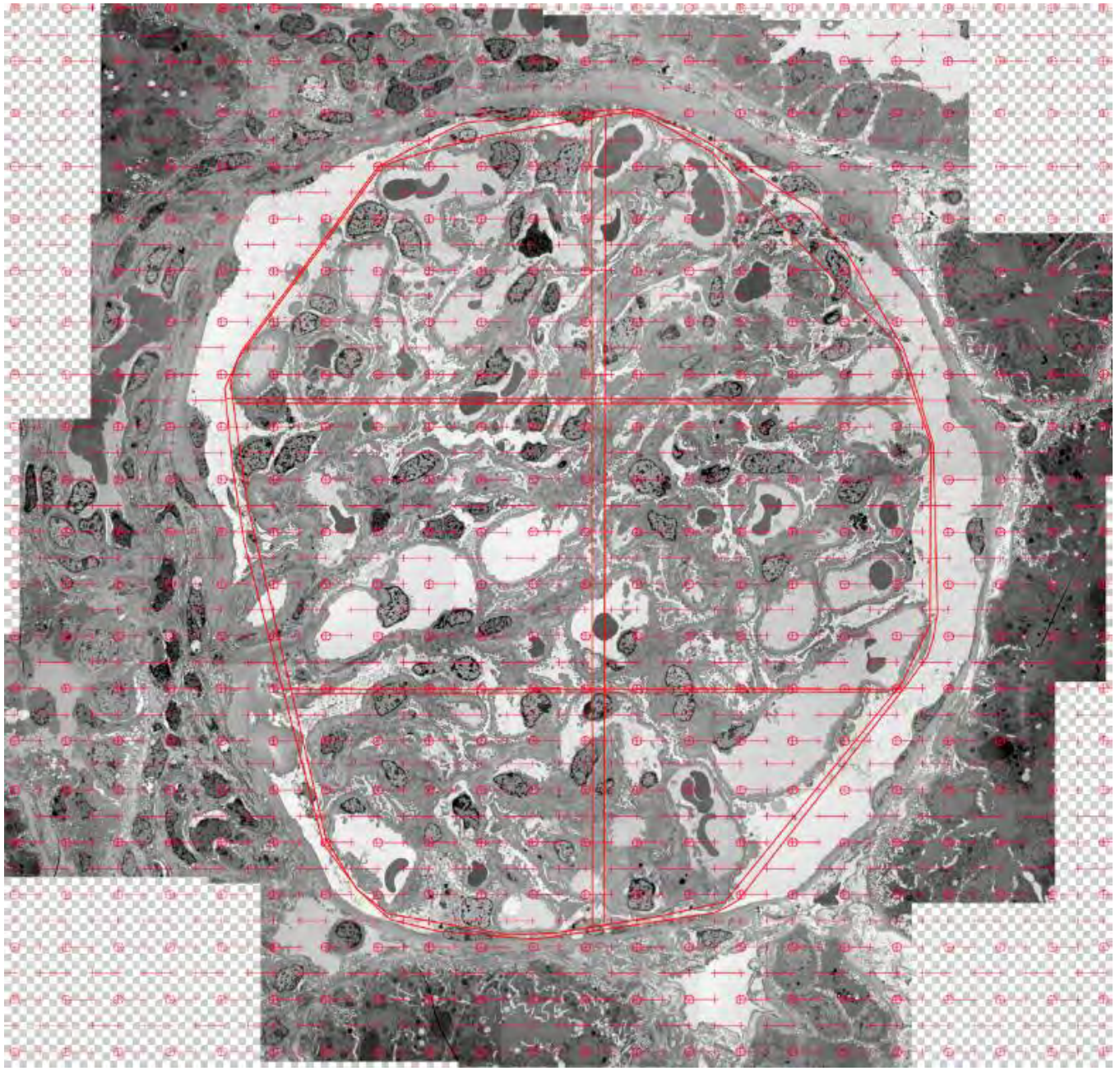
AZ QUOTES

Stereology is a body of mathematical methods relating three-dimensional parameters defining the structure to two-dimensional measurements obtainable on sections of the structure.



Coefficient of error for line length	$CE(\hat{L}\|L) = \frac{\sqrt{VAR_{SRS}}}{\sum_{i=1}^{n} I_i}$
Variance of systematic random sampling (VAR_{SRS})	$VAR_{SRS} = \frac{3g_0 - 4g_1 + g_2}{12}$ $g_k = \sum_{i=1}^{n-k} L_i L_{i+k}$





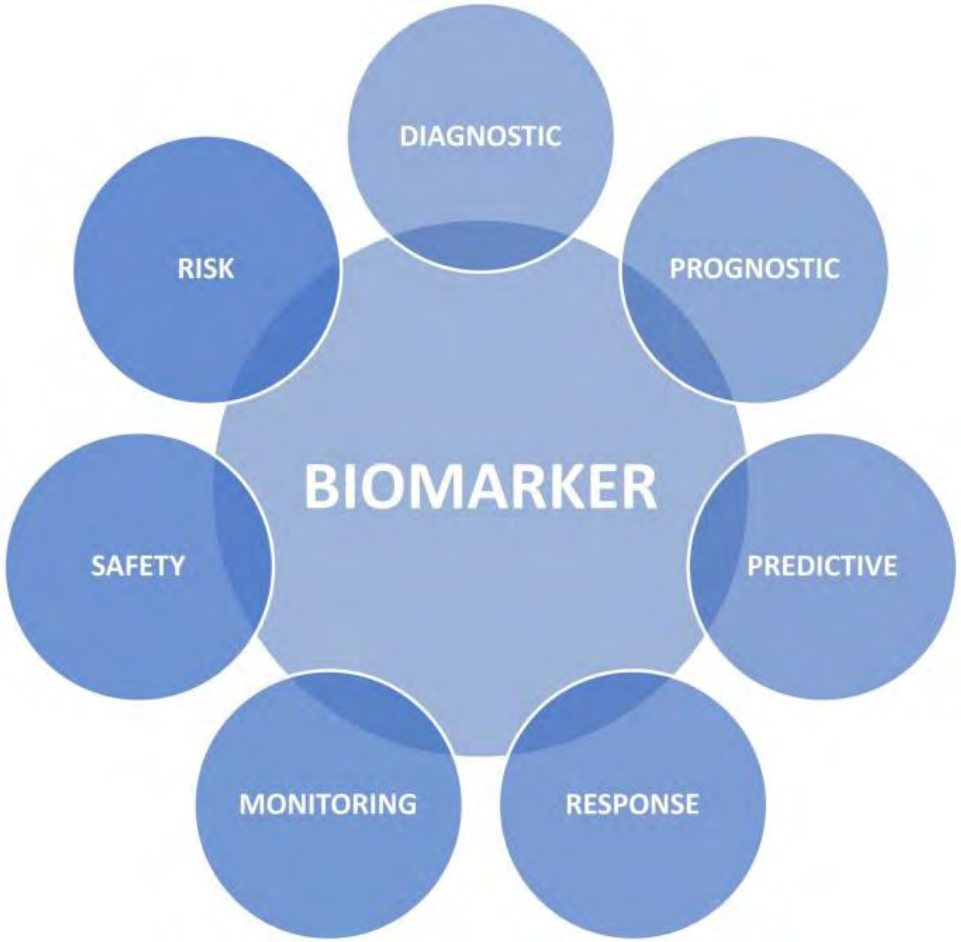
Biomarkers

Definition: A defined characteristic that is measured (objectively) as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.

Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics.

A biomarker **is not** a measure of how an individual feels, functions, or survives.

Biomarker categories according to the BEST resource (FDA)



https://www.ncbi.nlm.nih.gov/books/NBK326791/
Journal of Neurology•Volume 270, pages 4157–4178, (2023)

Biomarker Categories

Susceptibility/risk biomarkers

Associated with the chance of developing a disease or condition

Diagnostic biomarkers

Confirms or establishes diagnosis.

Monitoring biomarker

Detects the change in degree or extent of disease.

Prognostic biomarker

Identifies the likelihood of a clinical event or progression

Enriches clinical trials with patients who have a higher likelihood of experiencing an event and therefore increase statistical power.

Predictive biomarker

Indicates the likelihood of benefiting from a treatment

Pharmacodynamic (response) biomarker

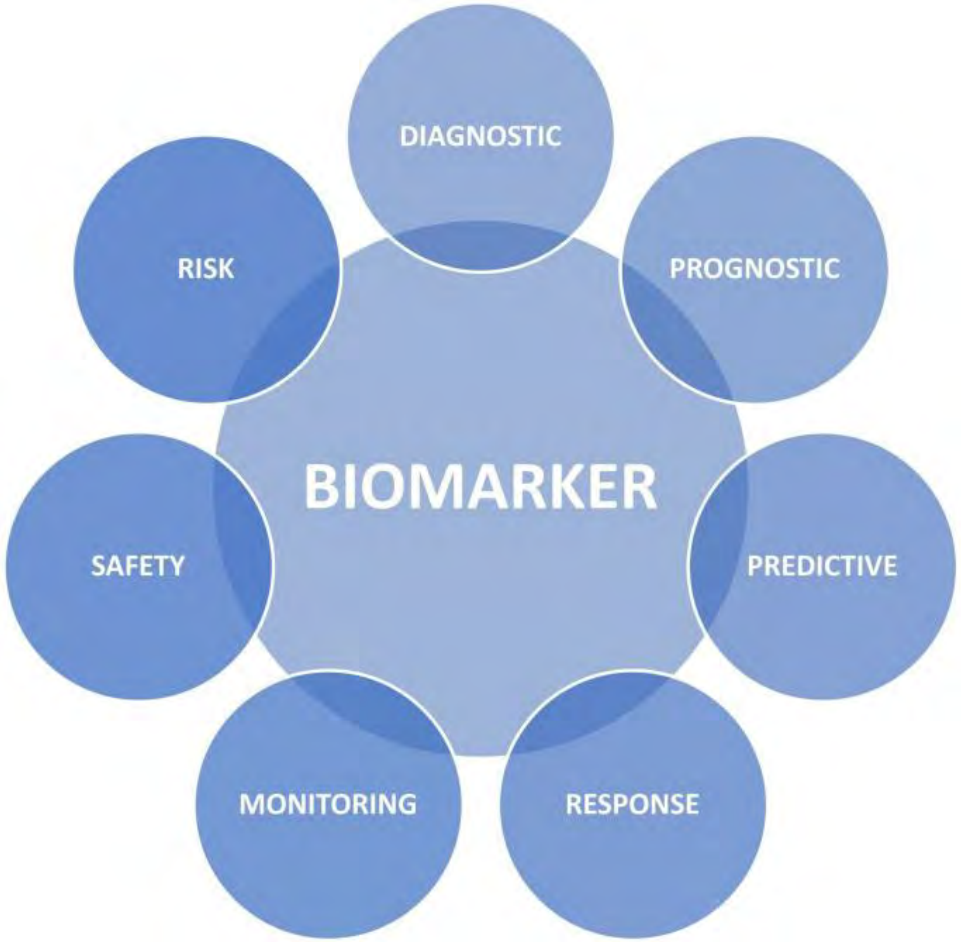
Shows biological response to a treatment

May act as a surrogate clinical endpoint (also known as efficacy response biomarker) in a clinical trial when validated.

Safety biomarker

Monitors adverse effects of the therapy.

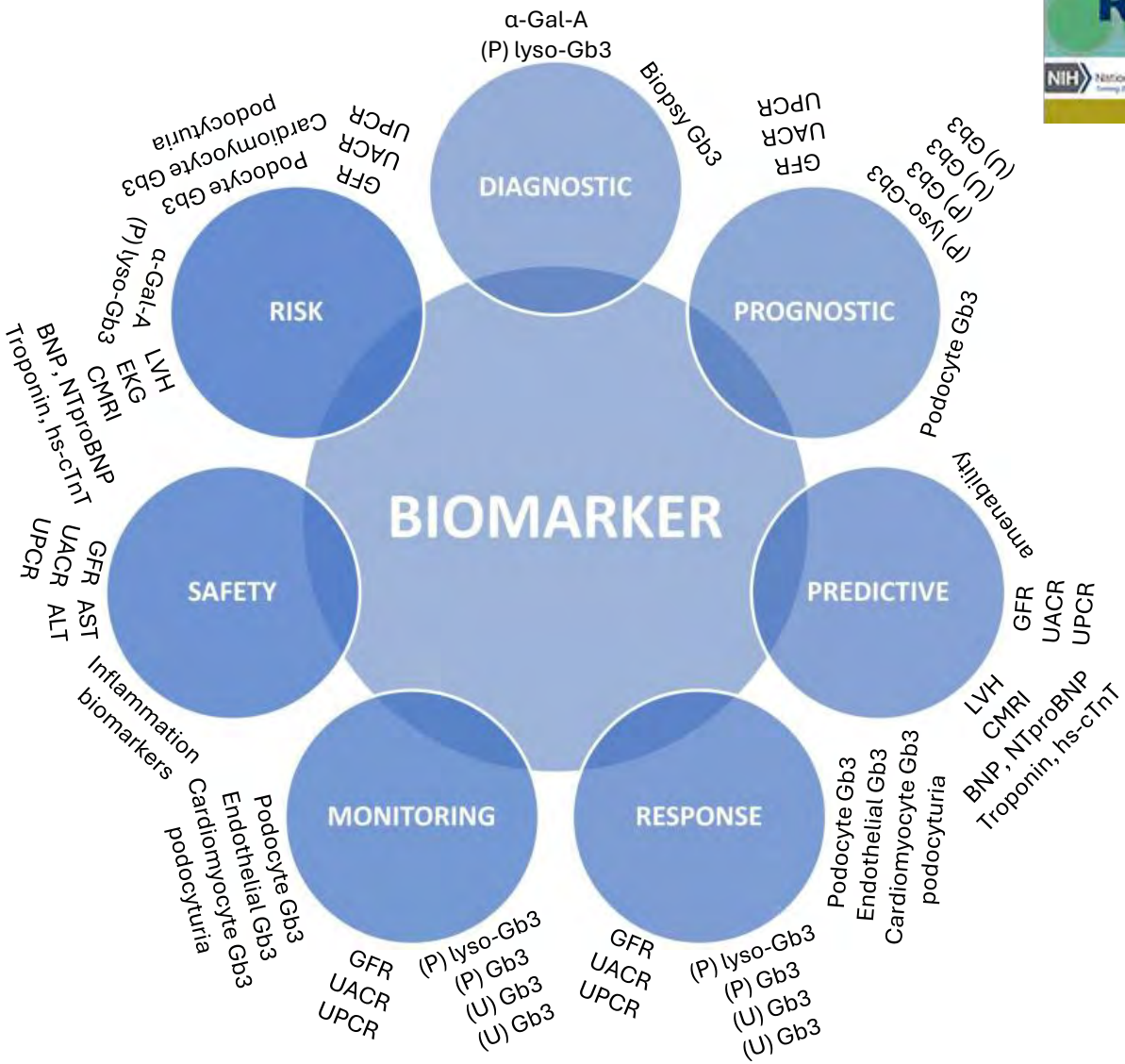
Biomarker categories according to the BEST resource (FDA)



https://www.ncbi.nlm.nih.gov/books/NBK326791/
Journal of Neurology•Volume 270, pages 4157–4178, (2023)

Fabry Biomarker considerations

- It is critical to carefully specify the intention of use for a biomarker.
- A biomarker may report useful information on multiple categories, but may not be an ideal choice for all of them.
- Commonly we need multiple biomarkers for a given condition. Careful selection is the key. The more is not always the better.
- Biobanking, careful annotation, and democratic use of biospecimens are essential, especially when dealing with rare conditions.



https://www.ncbi.nlm.nih.gov/books/NBK326791/
Journal of Neurology•Volume 270, pages 4157–4178, (2023)

Types of Biomarkers

Systemic Biomarkers: measurable indicators of a biological state or condition that reflects a broader, whole-body process, rather than being localized to a specific tissue or organ

- Plasma Gb3, plasma lyso-Gb3, plasma a-Gal-A activity, inflammatory biomarkers, etc.

Organ-specific Biomarkers: reflect the status of function, anatomy, or overall involvement of an organ by a disease or condition.

Non-invasive:

- **Chemical:**

kidney: GFR, UACR, UPCR, urine Gb3 (?)

Heart: troponin, BNP, NT-proBNP

- **Imaging:**

Heart: LVH, CMRI, Non-contrast T-1 mapping,

Invasive (Biopsy):

Kidney: fibrosis, global glomerulosclerosis, kidney tissue Gb3

Heart: fibrosis, heart tissue Gb3

Cell-based Biomarkers: reflect the status of injury, function, accumulation, or morphology of specific cell types

Non-invasive:

- **Chemical:**

Heart: troponin, BNP, NT-proBNP, hs-cTnT, leukocyte α-Gal-A activity

- **Microscopy, cytometry:**

Kidney: podocyturia, podocyte Gb3, EVs

Invasive (Biopsy):

Kidney: Gb3 in various kidney cell types, podocyte number, podocyte foot process width

Heart: Gb3 in various cardiac cell types

How does Fabry disease affect the kidneys?

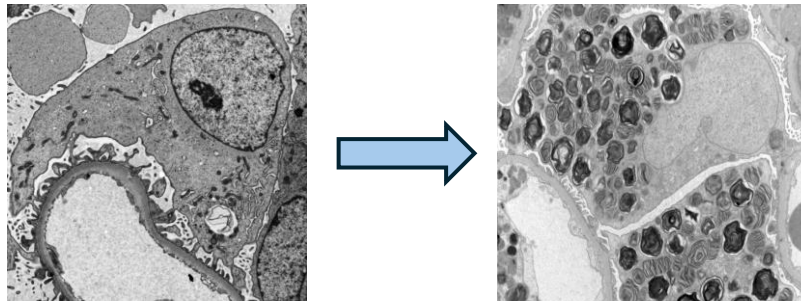
GLA mutation

↓

α-Galactosidase A deficiency

↓

Intracellular accumulation of the enzyme substrates (Gb3)



Normal podocyte

Fabry podocyte

Effective prevention of disease progression

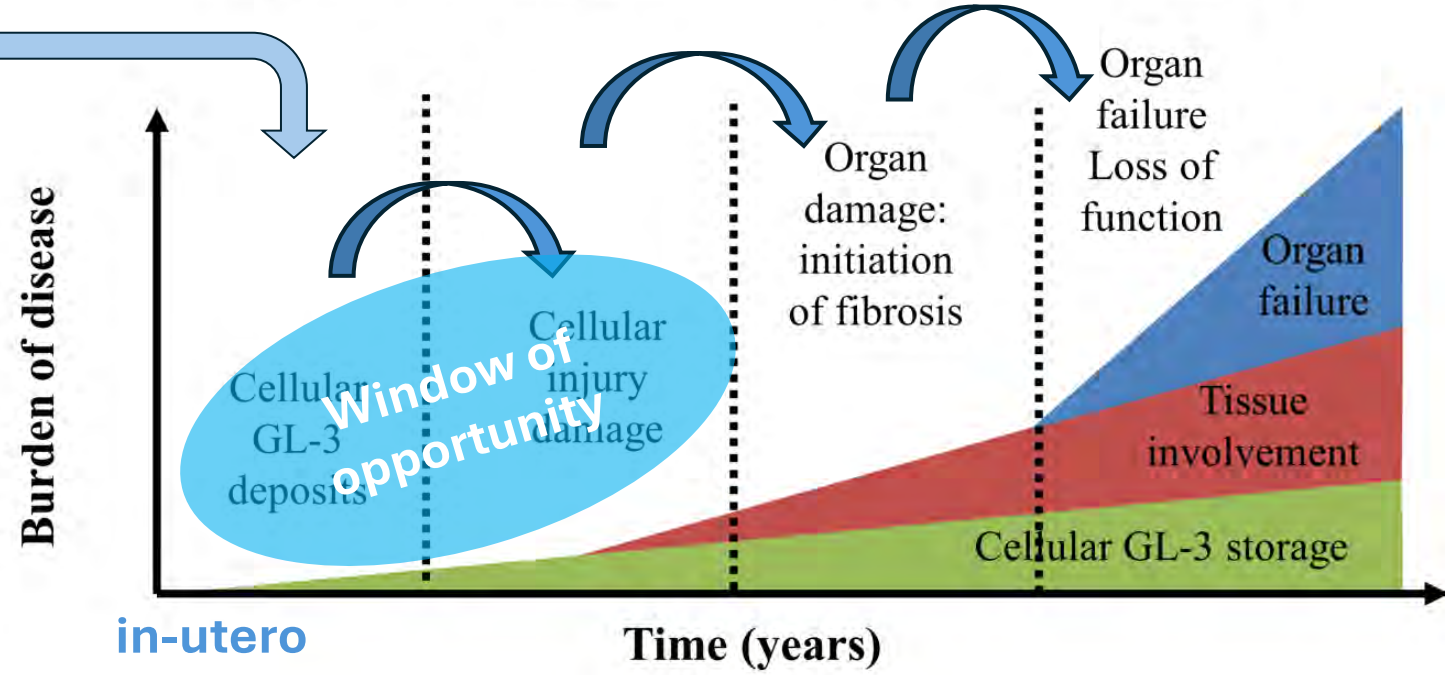
UACR↑
UPCR ↑
GFR↓

Sub-clinical Stage

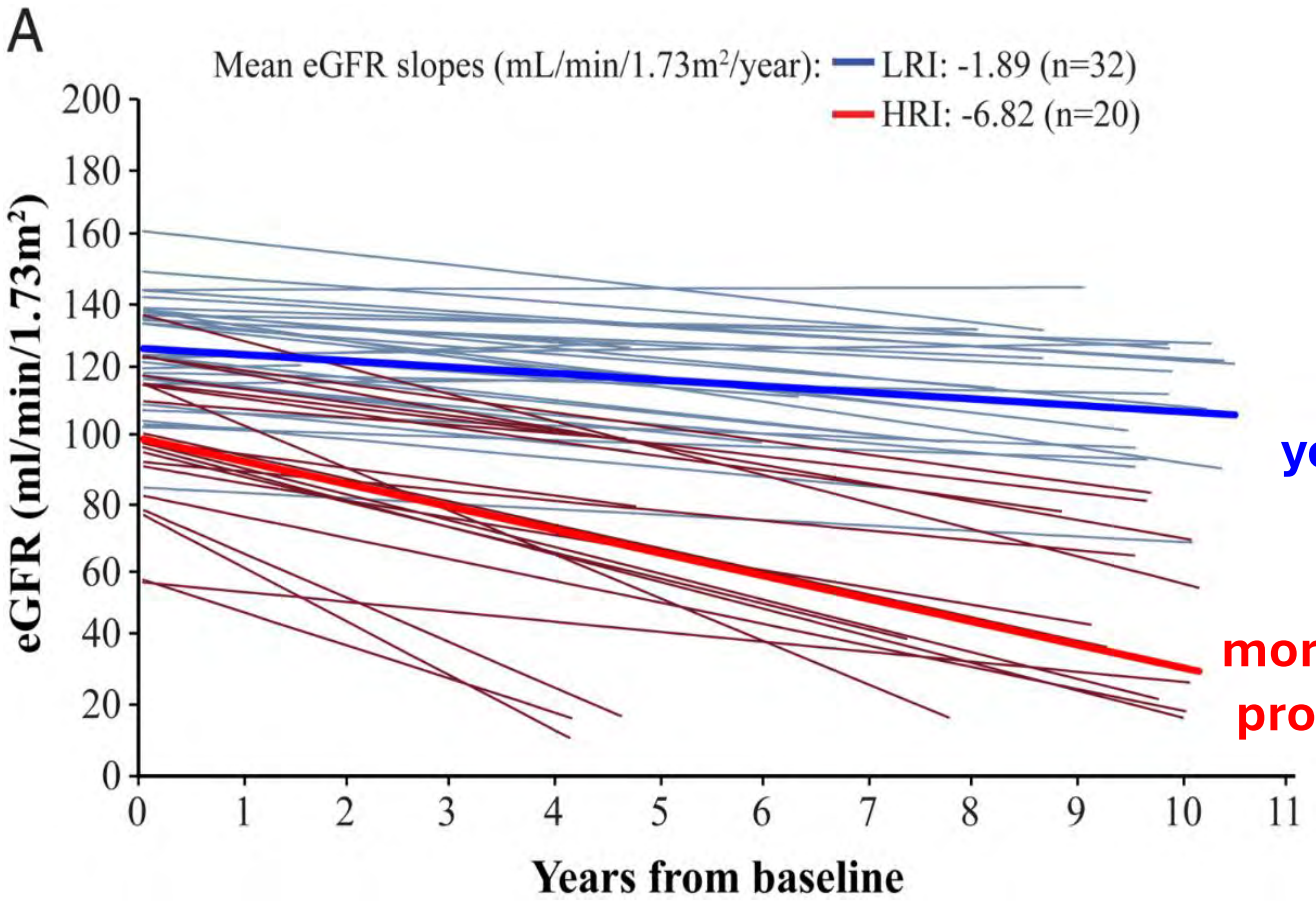
Stage 1 Stage 2

Clinical Stage

Stage 3 Stage 4



Late initiation of ERT may not stop progressive GFR loss in Fabry patients. This may at least in part be related to podocyte loss with age.



13 years younger on average

more severe proteinuria

Aging

Podocyte injury

Low renal involvement (LRI): UPCR ≤0.5 g/g and <50% sclerotic glomeruli

High renal involvement (HRI): UPCR >0.5 g/g or ≥50% sclerotic glomeruli

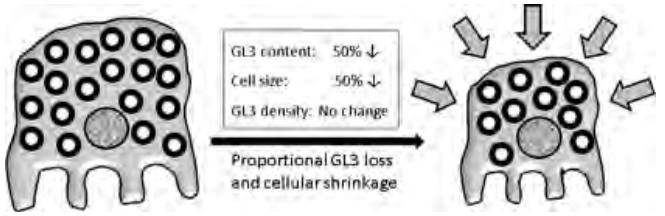
ERT, enzyme replacement therapy

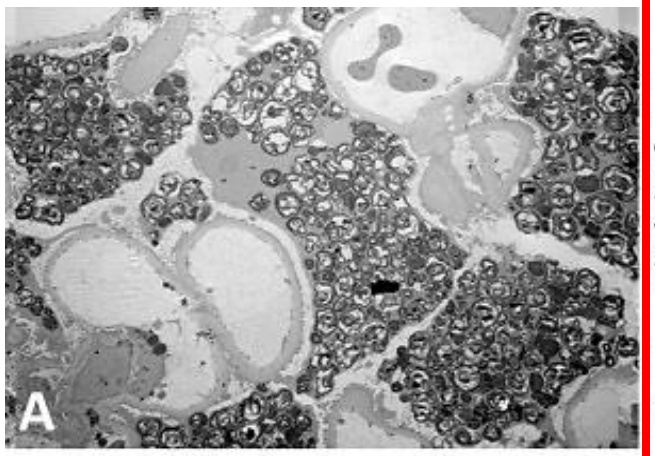
Germain DP *et al. J Med Genet* 2015;52:353–8

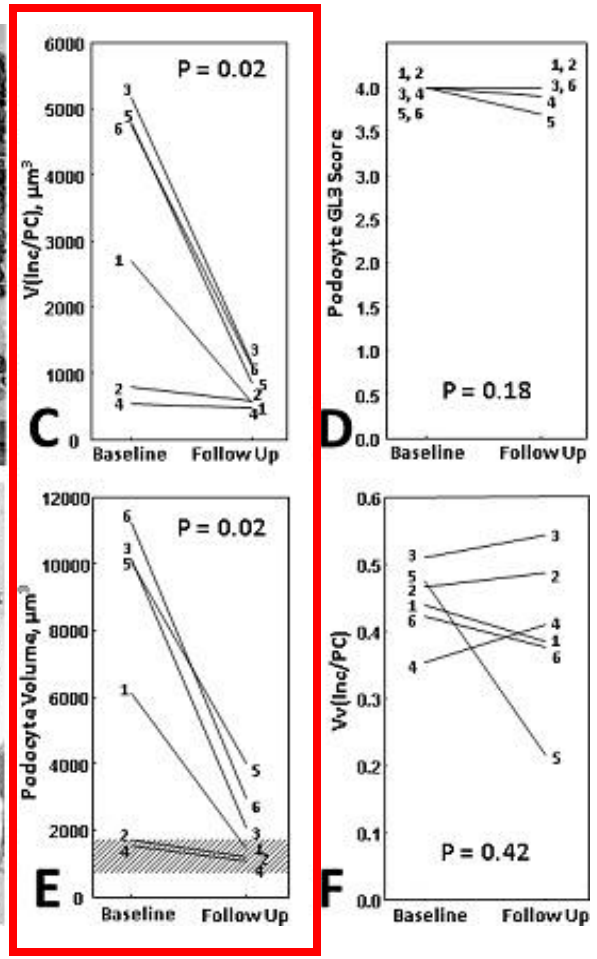
PLOS ONE 11(4): e0152812, 2016

One Year of Enzyme Replacement Therapy Reduces Globotriaosylceramide Inclusions in Podocytes in Male Adult Patients with Fabry Disease

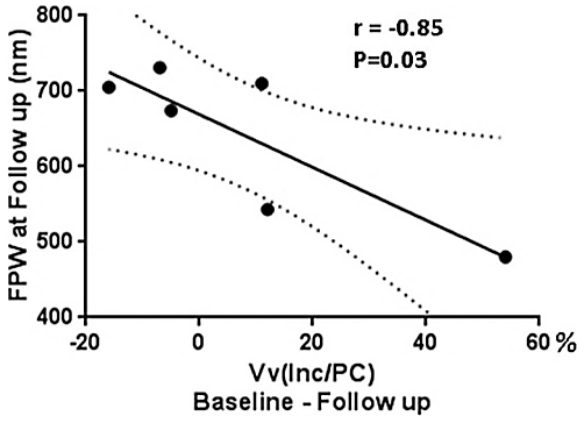
Behzad Najafian[1]*, Camilla Tøndel[2,3], Einar Svarstad[2,4], Alexey Sokolovkiy[1], Kelly Smith[1], Michael Mauer[5]





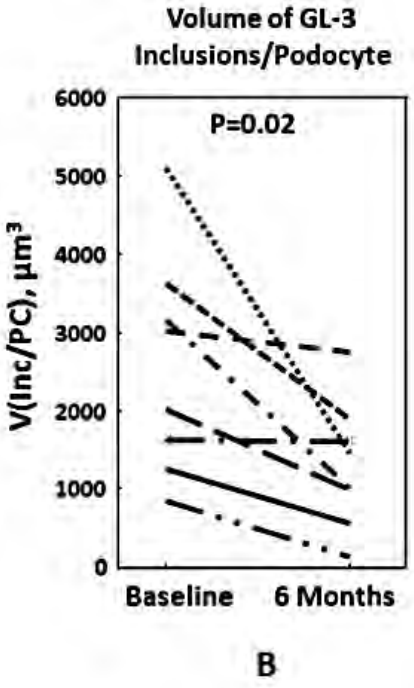


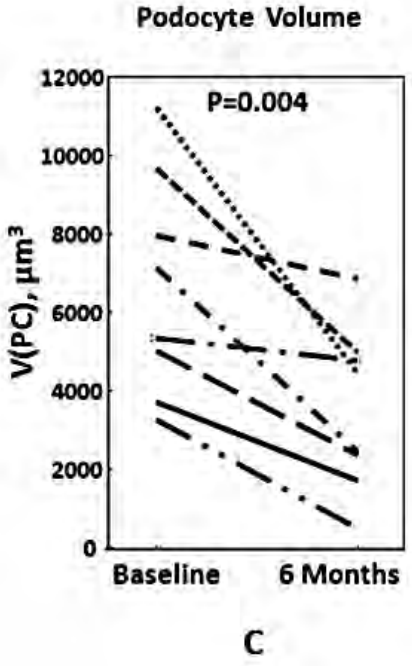
Reduction in GL-3 density in podocytes inversely correlated with foot process width at follow up

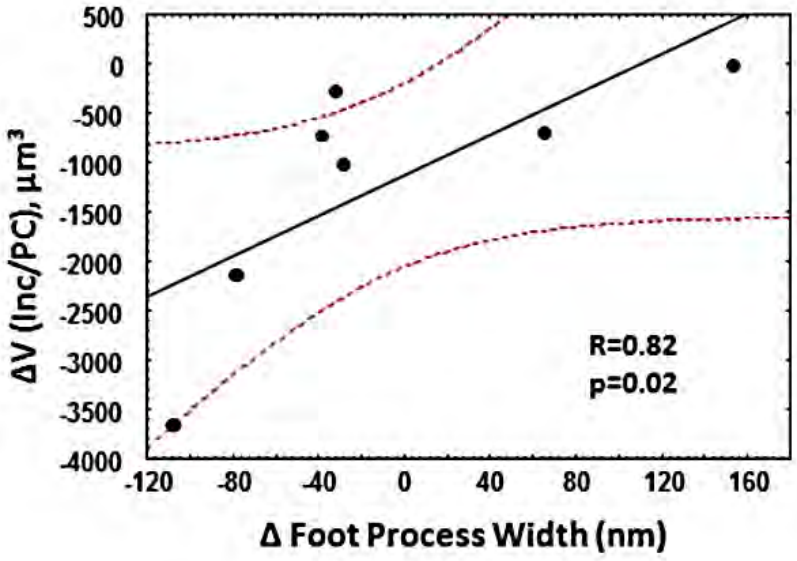


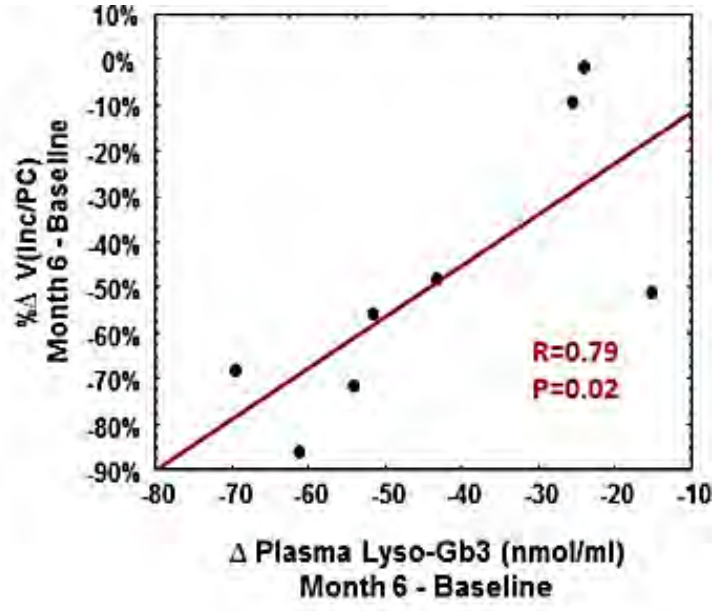
Reduction of podocyte globotriaosylceramide content in adult male patients with Fabry disease with amenable *GLA* mutations following 6 months of migalastat treatment

- Total volume of GL3 inclusions was reduced in podocytes after 6 months.
- Podocytes became smaller and foot process widening was improved parallel to GL3 clearance.









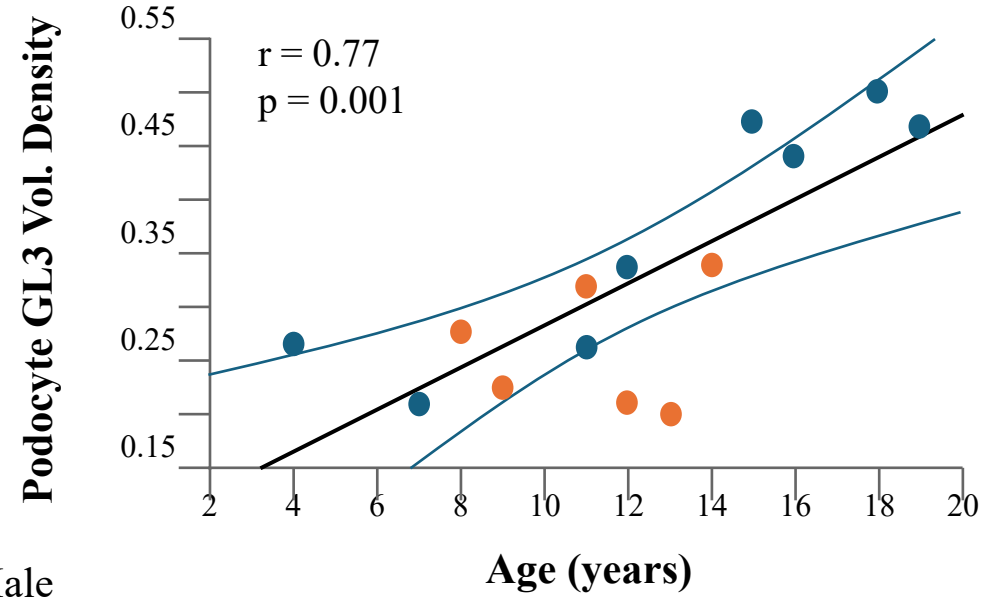
Mauer M, et al. J Med Genet 2017;54:781-786

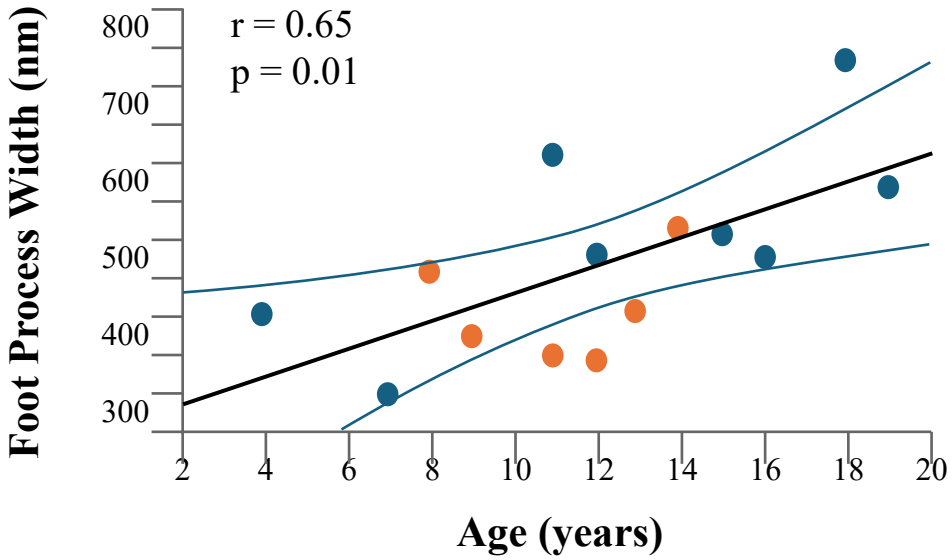
Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease

Behzad Najafian[1], Einar Svarstad[2,3], Leif Bostad[4,5], Marie-Claire Gubler[6], Camilla Tøndel[3,7], Chester Whitley[8] and Michael Mauer[8,9]

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
(2011) 79, 663–670; doi:10.1038/ki.2010.484;

Age < 20 years





- Male
- Female

Podocyte GL3 volume density and foot process width progressively increase with age in young Fabry patients with normal GFR and normal albuminuria

FPW, foot process width; Vv (Inc/EC), GL-3 inclusion fractional volume per endothelial cell; Vv (Inc/MC), GL-3 inclusion fractional volume per mesothelial cell; Vv(INC/PC), GL-3 inclusion fractional volume per podocyte cytoplasm

230 A. M. TURING

ON COMPUTABLE NUMBERS, WITH AN APPLICA
THE ENTSCHEIDUNGSPROBLEM

By A. M. TURING.

[Received 28 May, 1936.—Read 12 November, 1936.]

The "computable" numbers may be described briefly
numbers whose expressions as a decimal are calculable by fi
Although the subject of this paper is ostensibly the computal
it is almost equally easy to define and investigate computab
of an integral variable or a real or computable variable,
predicates, and so forth. The fundamental problems in
however, the same in each case, and I have chosen the computa
for explicit treatment as involving the least cumbrous techniq
shortly to give an account of the relations of the computab
functions, and so forth to one another. This will include a d
of the theory of functions of a real variable expressed in ter
putable numbers. According to my definition, a number is
if its decimal can be written down by a machine.

In §§ 9, 10 I give some arguments with the intention of show
computable numbers include all numbers which could n
regarded as computable. In particular, I show that certain
of numbers are computable. They include, for instance, the
all algebraic numbers, the real parts of the zeros of the Bess
the numbers π, e, etc. The computable numbers do not, howe
all definable numbers, and an example is given of a defina
which is not computable.

Although the class of computable numbers is so great, a
ways similar to the class of real numbers, it is nevertheless
In § 8 I examine certain arguments which would seem to prove t
By the correct application of one of these arguments, con
reached which are superficially similar to those of Gödel†. T

† Gödel, "Über formal unentscheidbare Sätze der Principia Mathem
wandter Systeme, I", *Monatshefte Math. Phys.*, 38 (1931), 173–198.

Turing, A.M. (1950). Computing machinery and intelligence. Mind, 59, 433-460.

COMPUTING MACHINERY AND INTELLIGENCE

By A. M. Turing

1. The Imitation Game

I propose to consider the question, "Can machines think?" This should begin with definitions of the meaning of the terms "machine" and "think." The definitions might be framed so as to reflect so far as possible the normal use of the words, but this attitude is dangerous, If the meaning of the words "machine" and "think" are to be found by examining how they are commonly used it is difficult to escape the conclusion that the meaning and the answer to the question, "Can machines think?" is to be sought in a statistical survey such as a Gallup poll. But this is absurd. Instead of attempting such a definition I shall replace the question by another, which is closely related to it and is expressed in relatively unambiguous words.

The new form
terms of a game which we
call the 'imitati
ople, a man (A), a
woman (B), an
f either sex. The
interrogator sta
vo. The object of the
game for the in
the other two is the man
and which is th
X and Y, and at the end
of the game he
'X is B and Y is A." The
interrogator is
thus:

C: Will X plea
ir?

Now suppose X
. It is A's object in the
game to try and
fication. His answer might
therefore be:

I propose to consider the question, "Can machines think?" This should begin with definitions of the meaning of the terms "machine" and "think."

have a teleprinter communicating between the two rooms. Alternatively the question and answers can be repeated by an intermediary. The object of the game for the third player (B) is to help the interrogator. The best strategy for her is probably to give truthful answers. She can add such things as "I am the woman, don't listen to him!" to her answers, but it will avail nothing as the man can make similar remarks.

We now ask the question, "What will happen when a machine takes the part of A in this game?" Will the interrogator decide wrongly as often when the game is played like this as he does when the game is played between a man and a woman? These questions replace our original, "Can machines think?"

2. Critique of the New Problem

1956 Dartmouth Conference: The Founding Fathers of AI


John MacCarthy


Marvin Minsky


Claude Shannon


Ray Solomonoff


Alan Newell


Herbert Simon


Arthur Samuel


Oliver Selfridge

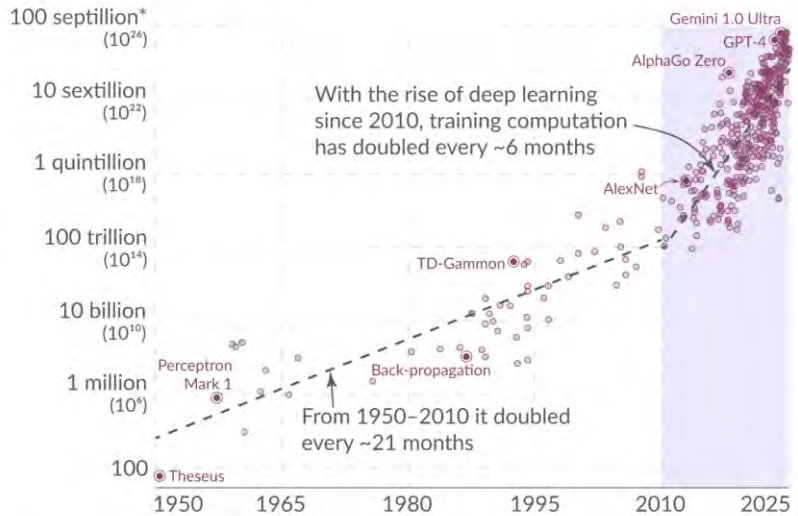

Nathaniel Rochester


Trenchard More

The computation used to train notable AI systems has doubled every ~6 months since 2010

Our World in Data

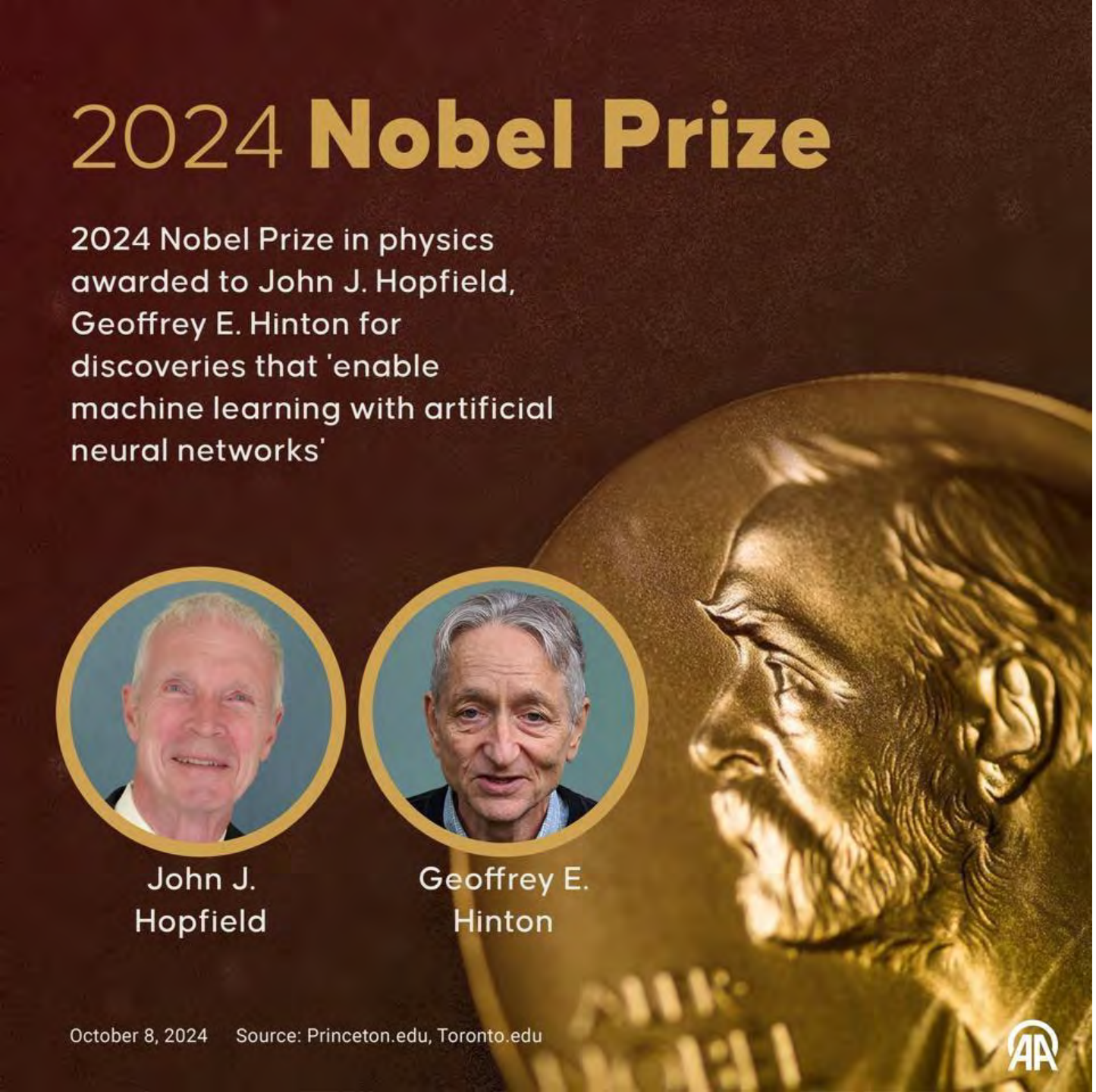
Training computation is measured in total floating-point operations (FLOP). Each FLOP represents a single arithmetic calculation, such as multiplication. Shown on a logarithmic scale.



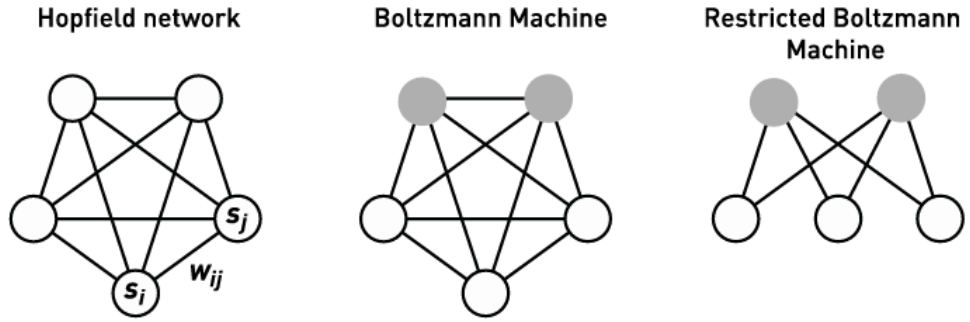
*For comparison, 1 septillion (1,000,000,000,000,000,000,000,000) is the estimated number of stars in the universe.

Data source: Epoch (2024)

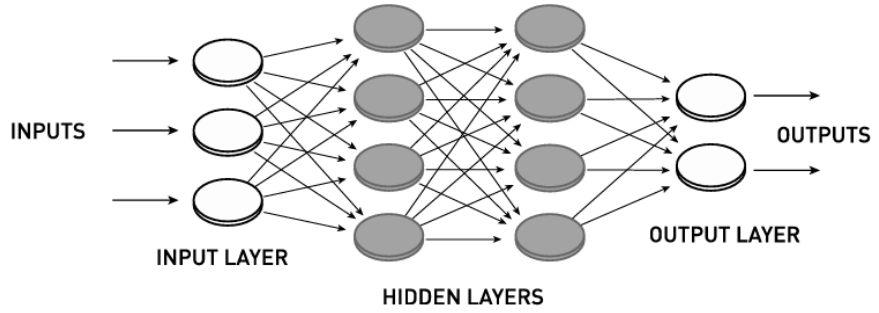
CC BY

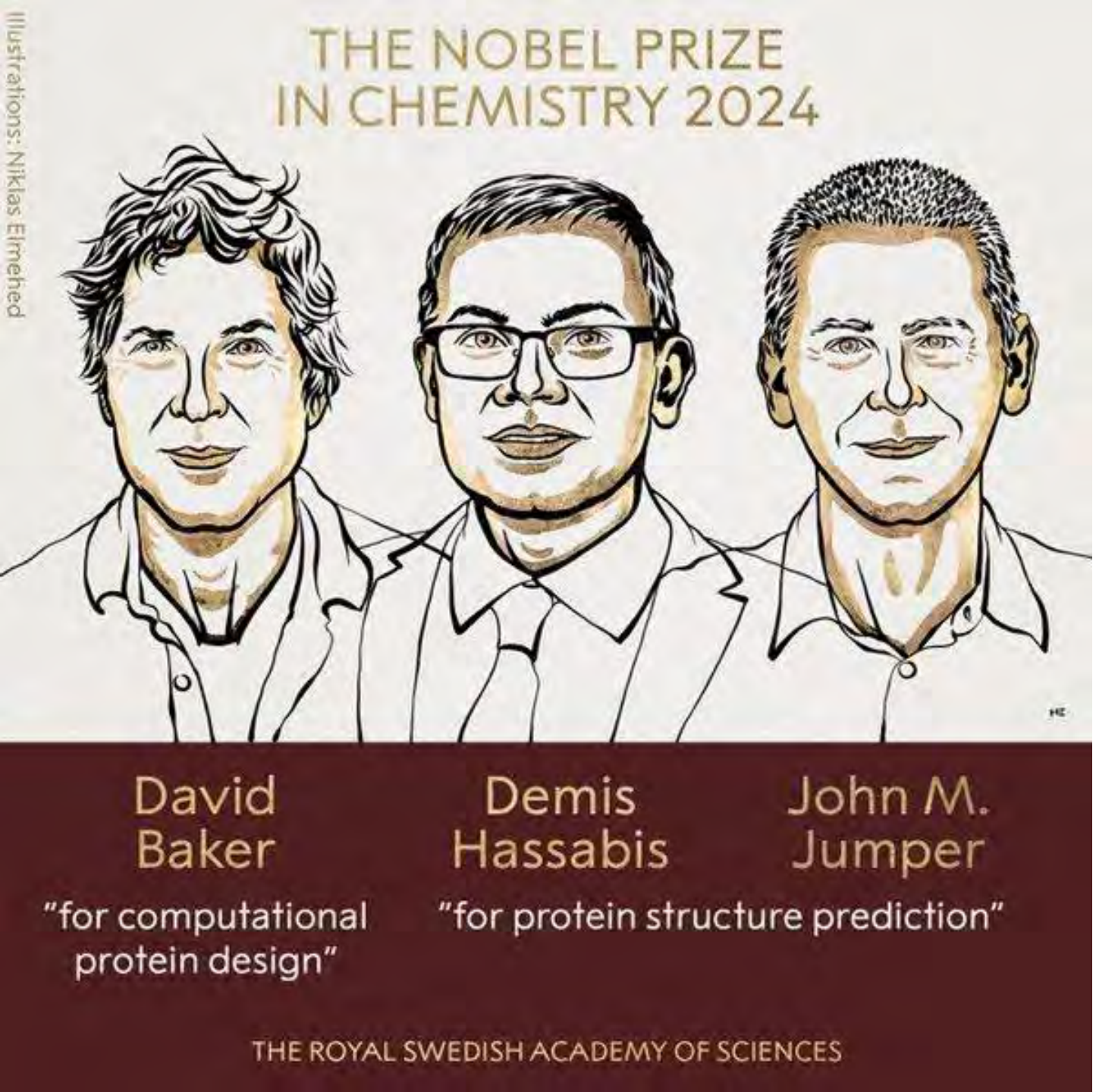


In 1982, Hopfield published a dynamical model for an associative memory based on a simple recurrent neural network

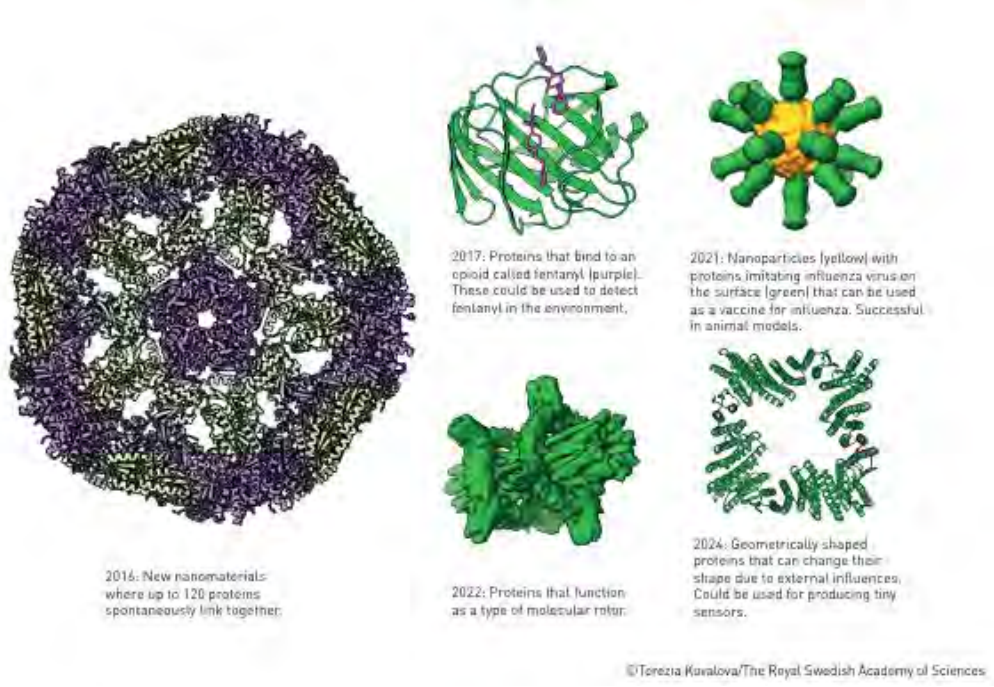


In 1983–1985 Geoffrey Hinton, together with Terrence Sejnowski and other coworkers, developed a stochastic extension of Hopfield's model from 1982, called the Boltzmann machine





The Nobel Prize in Chemistry 2024 is about proteins, life's ingenious chemical tools. David Baker has succeeded with the almost impossible feat of building entirely new kinds of proteins. Demis Hassabis and John Jumper have developed an AI model to solve a 50-year-old problem: predicting proteins' complex structures. These discoveries hold enormous potential.



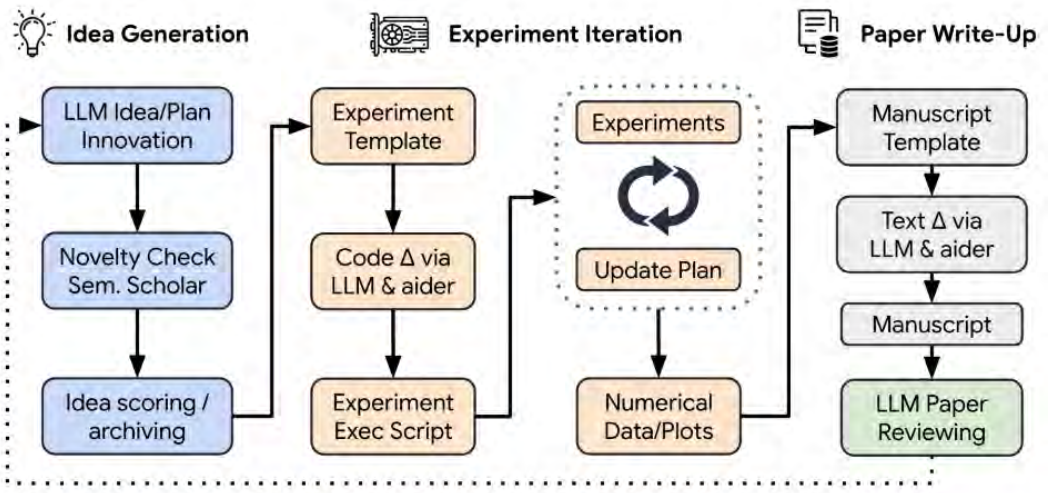
The AI Scientist: Towards Fully Automated Open-Ended Scientific Discovery

Chris Lu[1,2,*], **Cong Lu**[3,4,*], **Robert Tjarko Lange**[1,*], **Jakob Foerster**[2,†], **Jeff Clune**[3,4,5,†] **and David Ha**[1,†]
[*]Equal Contribution, [1]Sakana AI, [2]FLAIR, University of Oxford, [3]University of British Columbia, [4]Vector Institute, [5]Canada CIFAR AI Chair, [†]Equal Advising

We developed methods to automatically merge the knowledge of multiple LLMs. In more recent work, we harnessed LLMs to discover new objective functions for tuning other LLMs.

This led us to dream even bigger: Can we use foundation models to automate the entire process of research itself?

Conceptual illustration of The AI Scientist.



https://github.com/SakanaAI/AI-Scientist

Examples of papers that were entirely autonomously generated by The AI Scientist.

AI-Scientist Generated Preprint

DUALSCALE DIFFUSION: ADAPTIVE FEATURE BALANCING FOR LOW-DIMENSIONAL GENERATIVE MODELS

Anonymous authors
Paper under double-blind review

ABSTRACT

This paper introduces an adaptive dual-scale denoising approach for low-dimensional diffusion models, addressing the challenge of balancing global structure and local detail in generated samples. While diffusion models have shown remarkable success in high-dimensional spaces, their application to low-dimensional data remains crucial for understanding fundamental model behaviors and addressing real-world applications with inherently low-dimensional data. However, in these spaces, traditional models often struggle to simultaneously capture both macro-level patterns and fine-grained features, leading to suboptimal sample quality. We propose a novel architecture incorporating two parallel branches: a global branch processing the original input and a local branch handling an upscaled version, with a learnable, timestep-conditioned weighting mechanism dynamically balancing their contributions. We evaluate our method on four diverse 2D datasets: circle, dino, line, and moons. Our results demonstrate significant improvements in sample quality, with KL divergence reductions of up to 12.8% compared to the baseline model. The adaptive weighting successfully adjusts the focus between global and local features across different datasets and denoising stages, as evidenced by our weight evolution analysis. This work not only enhances low-dimensional diffusion models but also provides insights that could inform improvements in higher-dimensional domains, opening new avenues for advancing generative modeling across various applications.

1 INTRODUCTION

Diffusion models have emerged as a powerful class of generative models, achieving state-of-the-art

Article

An autonomous laboratory for the accelerated synthesis of novel materials

In 17 days of closed-loop operation, the A-Lab performed 355 experiments and successfully realized 41 of 58 (71%) novel inorganic crystalline solids with diverse structures and chemistries.

https://doi.org/10.1038/s41586-02
Received: 16 May 2023
Accepted: 10 October 2023

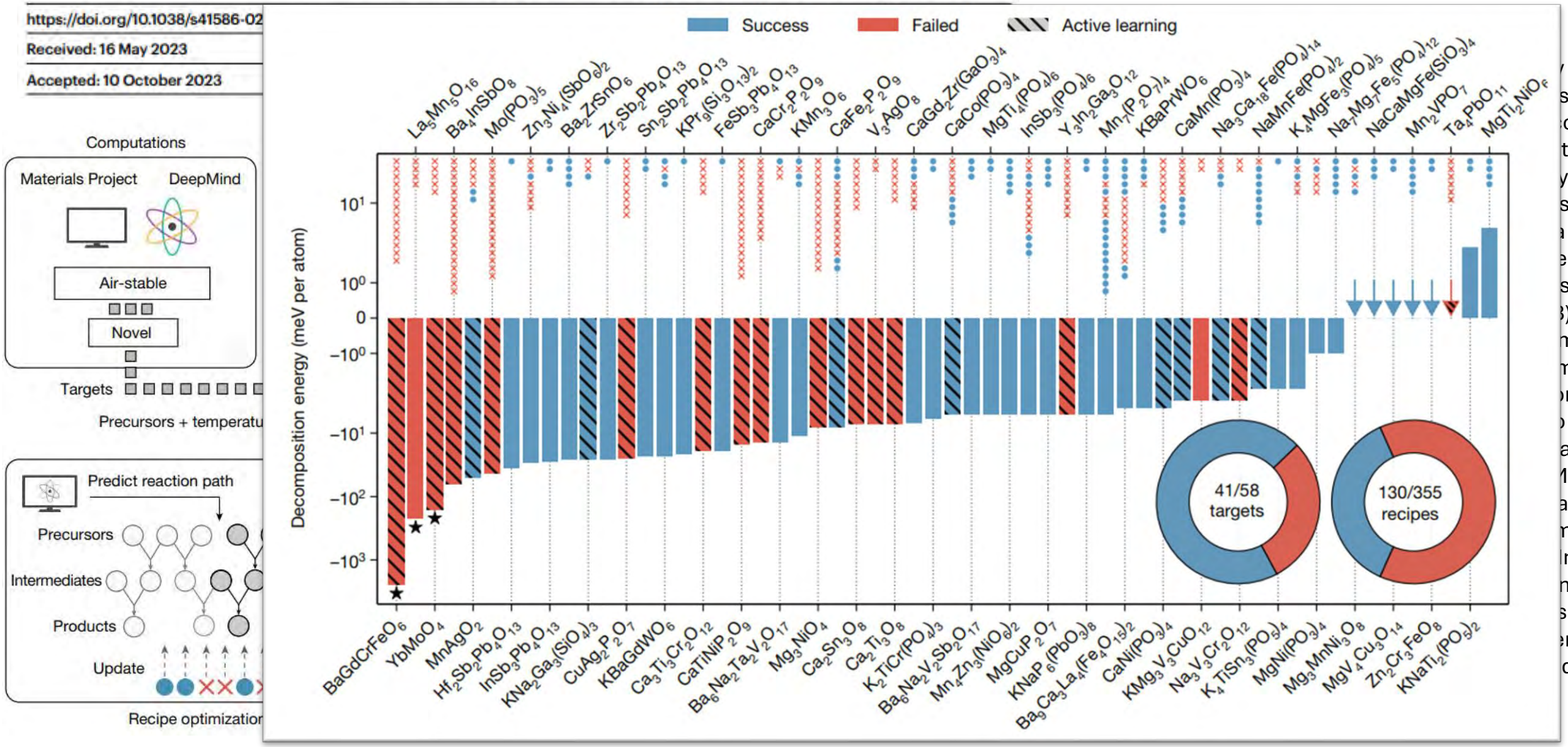


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ILLUSTRATION: ADRIA VOLTA

WILL AI EVER WIN ITS OWN NOBEL PRIZE?

Some researchers predict a science breakthrough by 2050. Others are sceptical. **By Jenna Ahart**

Artificial intelligence models are starting to succeed in science. In the past two years, they have demonstrated that they can analyse data, design experiments and even come up with new hypotheses. The pace of progress has some researchers convinced that artificial intelligence (AI) could compete with science's greatest minds in the next few decades.

In 2016, Hiroaki Kitano, a biologist and chief executive at Sony AI, challenged researchers to accomplish just that: to develop an AI system so advanced that it could make a discovery worthy of a Nobel prize. Calling it the Nobel Turing Challenge, Kitano presented the endeavour as the grand challenge for AI in science[1]. A machine wins if it can achieve a discovery on a par with top-level human research.

That's not something current models can do. But by 2050, the Nobel Turing Challenge envisions an AI system that, without human intervention, combines the skills of hypothesis generation, experimental planning and data analysis to make a breakthrough worthy of a Nobel prize.

npj | Systems Biology and Applications

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PERSPECTIVE OPEN

Check for updates

Nobel Turing Challenge: creating the engine for scientific discovery

Hiroaki Kitano [1]✉

Hiroaki Kitano
SONY CTO, Exec. Deputy President

I propose the Nobel Turing Challenge as a grand challenge for artificial intelligence that aims at "developing AI Scientists capable of autonomously carrying out research to make major scientific discoveries and win a Nobel Prize by 2050"

SEARCH and OPTIMIZATION

Goal: Reprogram Cell to gain Stemness

SEARCH → Search 24 genes from FANTOM DB

24 genes enabled reprogramming

OPTIMIZATION → Leave-one-out experiments

Yamanaka Factors identified

Nobel Prize in Physiology and Medicine 2012

ACCIDENT, SEARCH and OPTIMIZATION

Accidental discovery of thin film formation in polyacetylene polymerization process

ACCIDENT

Goal: Polyacetylene thin film formation condition

OPTIMIZATION → Search optimal thin film formation condition

Prof. Alan MacDiarmid

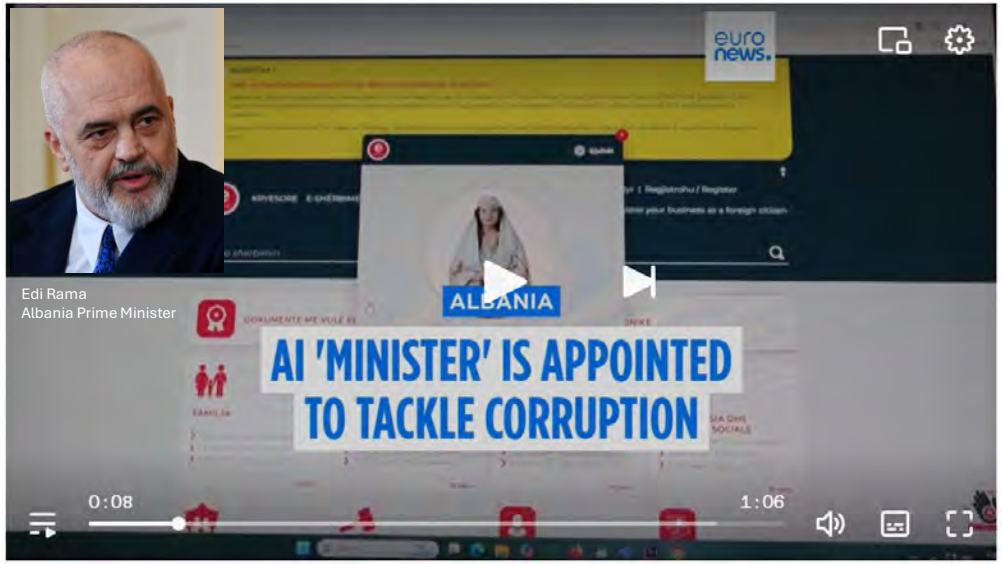
Goal: Conducting polymer

SEARCH & OPTIMIZATION → Prof. Alan Heeger

Conducting polymer thin film

Nobel Prize in Chemistry 2000

Albania appoints world's first AI government 'minister' to root out corruption



The digital assistant, called Diella, is pictured as a woman dressed in traditional Albanian garb.

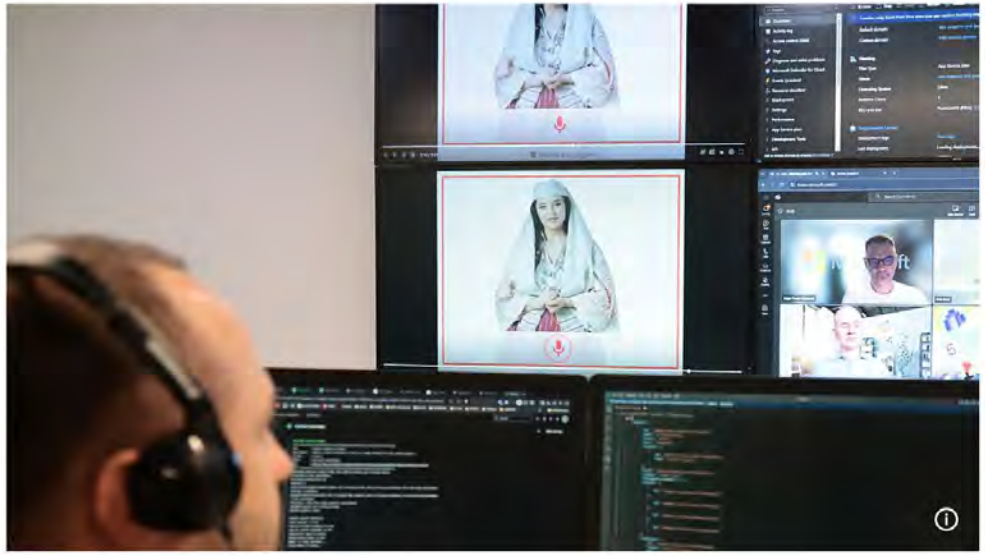
Albania has appointed the world's first artificial intelligence-generated government "minister", aiming to make the country "corruption-free".

The digital assistant is called Diella, meaning Sun, and has been advising people how to navigate government services online since January. On Thursday, Albania's Prime Minister Edi Rama announced the digital minister to his cabinet.

"Diella is the first [government] member who is not physically present, but virtually created by artificial intelligence," Rama said.

Diella will be entrusted with all decisions on public tenders, making them "100 per cent corruption-free," he said, adding that "every public fund submitted to the tender procedure will be perfectly transparent".

Albania's AI minister is 'pregnant' with 83 digital assistants, prime minister says



By **Euronews**
Published on 30/10/2025 - 12:14 GMT+1

Diella, the country's first AI system that is now a minister in Edi Rama's cabinet, will have 83 "children," who will become parliamentary assistants.

Albania's first non-human minister made up entirely by artificial intelligence (AI) is "pregnant" with 83 children that will become parliamentary assistants, according to the country's prime minister.

Albanian Prime Minister Edi Rama **told**the Global Dialogue Forum in Berlin that the parliamentary assistants will participate in parliamentary sessions, keep notes on what goes on and then give advice to members on how they should react to specific pieces of legislation.

"These children will have their mother's knowledge regarding EU legislation and everything else," Rama said.

PERSPECTIVE

Tech's Love Affair with Trump Grows Stronger By the Day

Tech Policy .PRESS

PAUL M. BARRETT / OCT 23, 2025

President Donald Trump and First Lady Melania Trump host business and technology leaders for a dinner in State Dining Room at the White House, Thursday, September 4, 2025. (Official White House photo by Andrea Hanks)

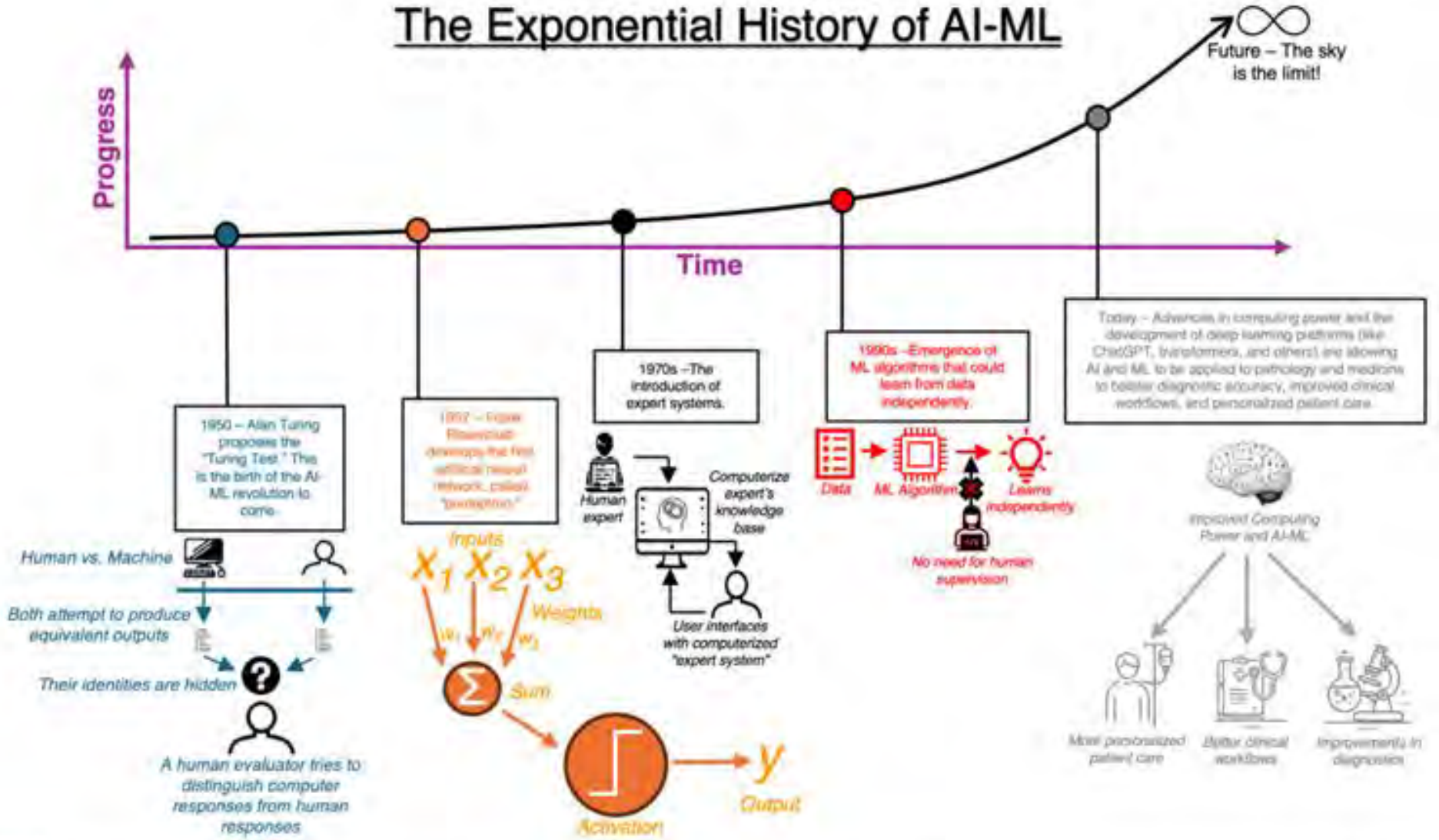
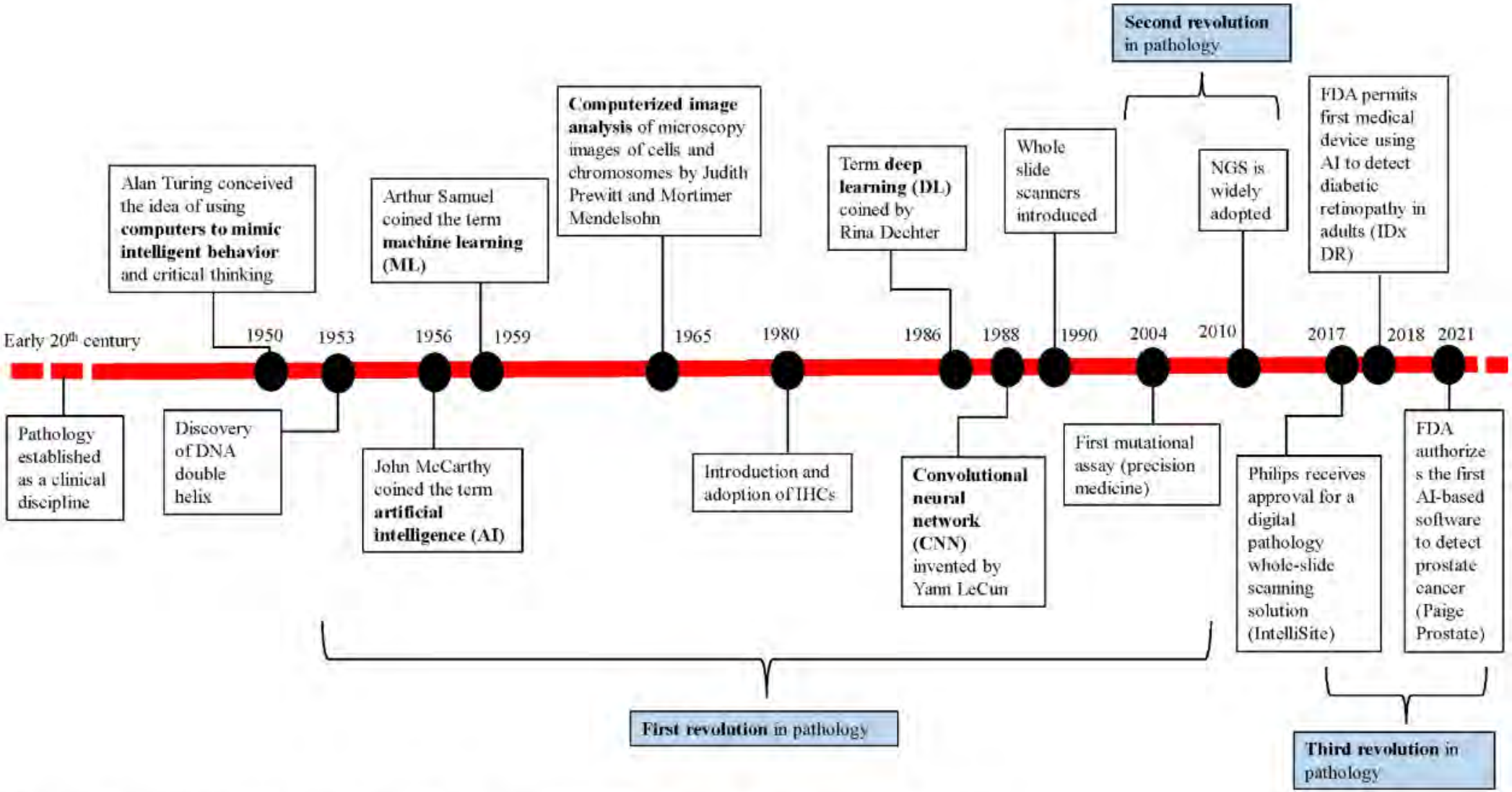


Figure 1.

Timeline of AI-ML history in pathology and medicine. All artworks were drawn by the authors in combination with generated individual embedded images via DALL-E through ChatGPT-4o. AI, artificial intelligence; GPT, generative pretrained transformer; ML, machine learning.

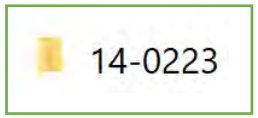


Schematic representation of the how artificial intelligence (AI) can be applied in the practice of pathology

Current Gold Standard for FPW measurement: Unbiased Stereology

Systematic Uniform Random Sampling (SURS)

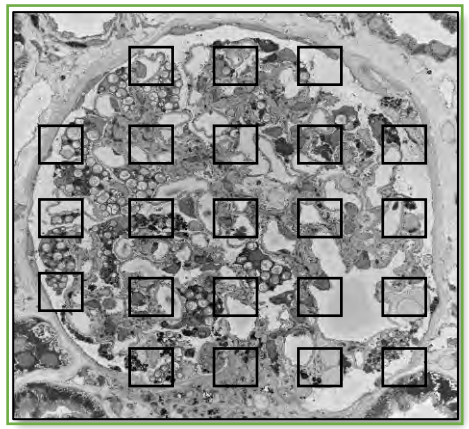
Biopsy



Glomeruli

(~3 gloms/biopsy)

SURS

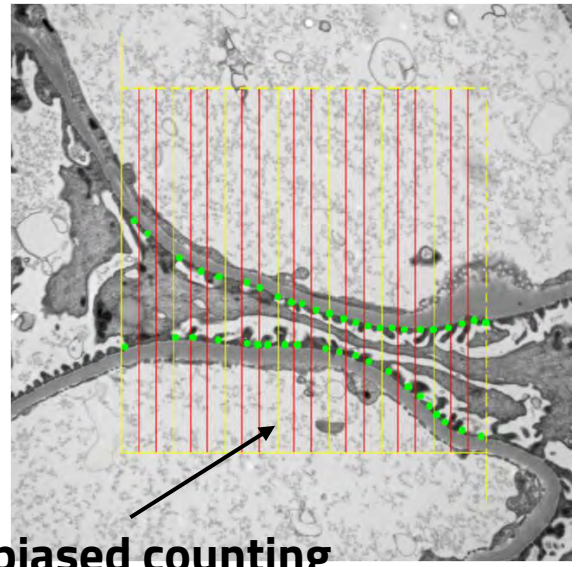


Systematic Uniform Random Sampling

SURS Images (~30,000x mag)

(50-100 images/glom)

FPW Estimate



Unbiased counting frame

$$L_S(Slit/Z) = \frac{\sum Q_{Slit}}{\sum I_{\text{intact FP}} \cdot d}$$

FPW=1/Ls(Slit/Z)

6-8 hours/biopsy by expert technician

Application of deep-learning for FPW measurement

Systematic Uniform Random Sampling (SURS)

Biopsy

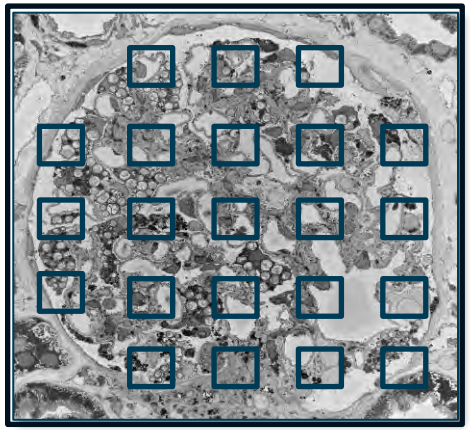
14-0223

Glomeruli

14-0223 blk B1-1
14-0223 blk B1-2
14-0223 blk B1-3

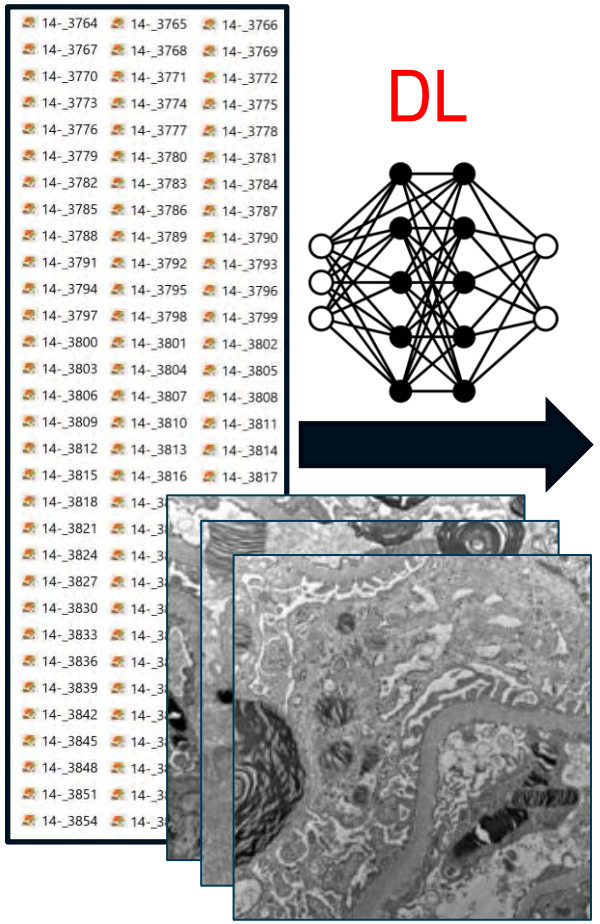
(~3 gloms/biopsy)

SURS



Systematic Uniform Random Sampling

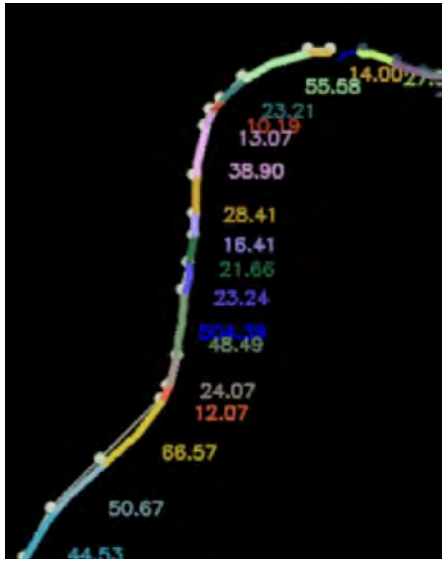
SURS Images (~30,000x)



(50-100 images/glom)

DL

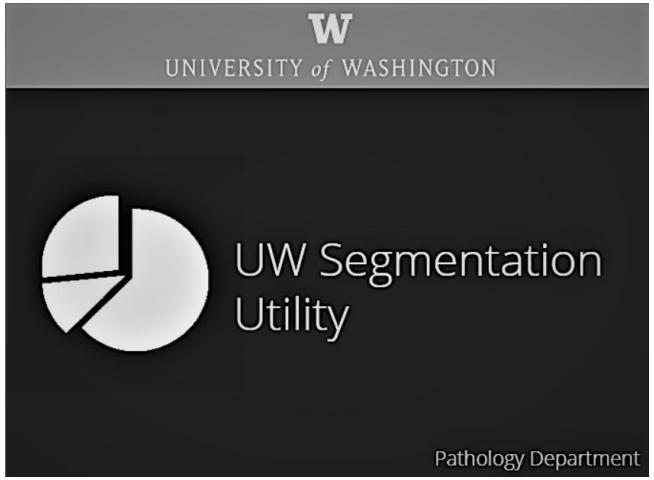
FPW

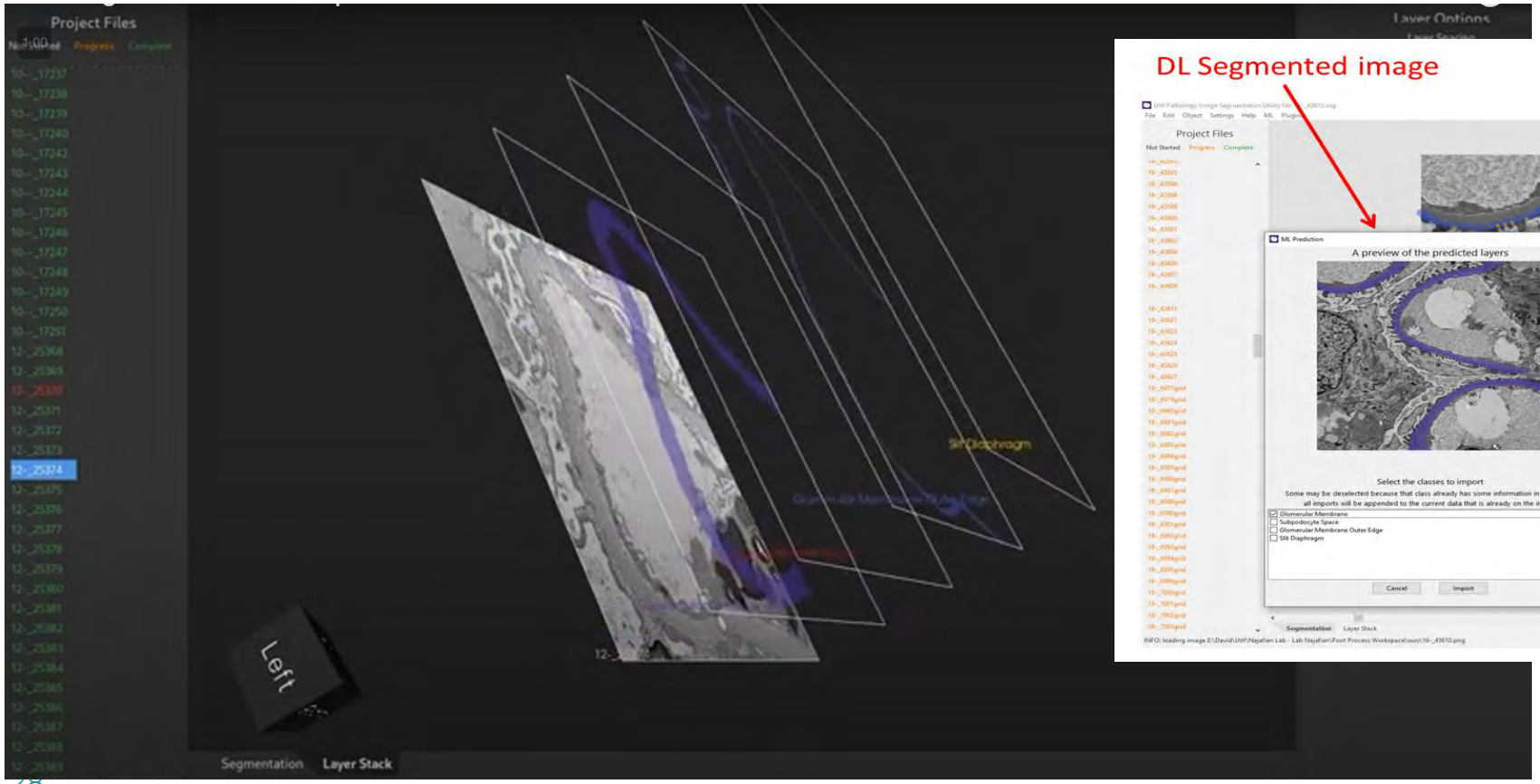


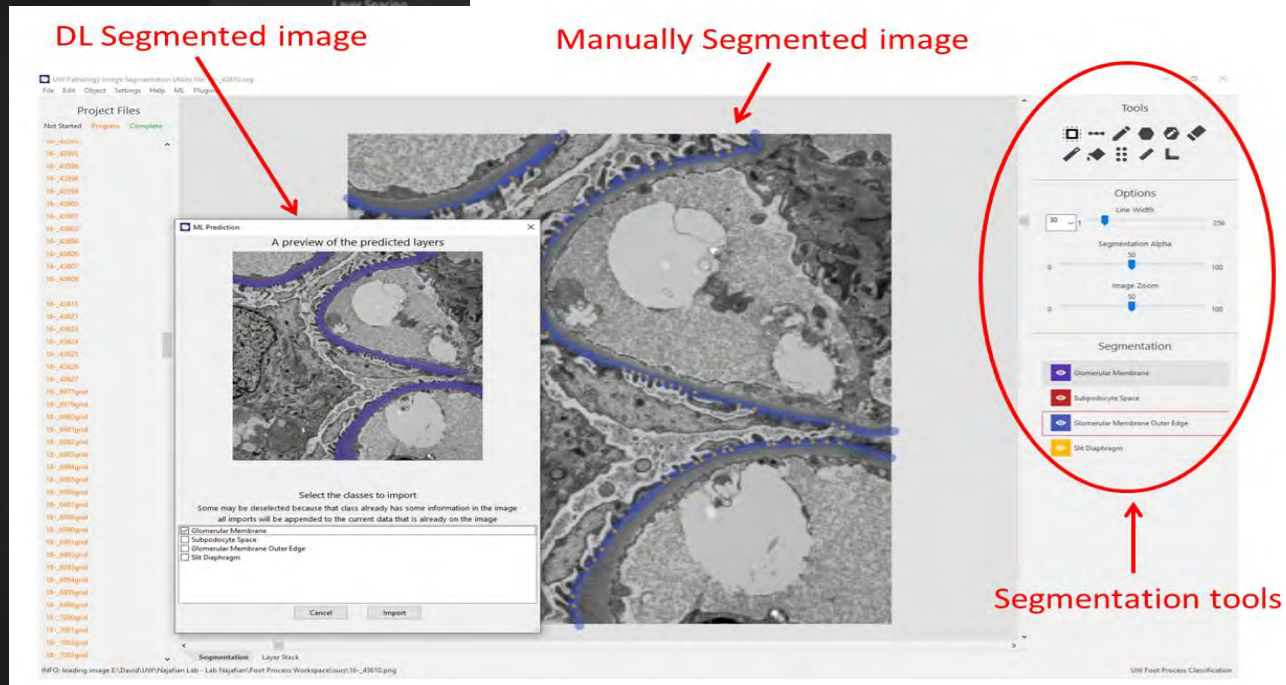
<1 min per biopsy

Segmentation Based Dataset

Custom Segmentation Utility with easy to use overlapping layer and multi-layer tiff support



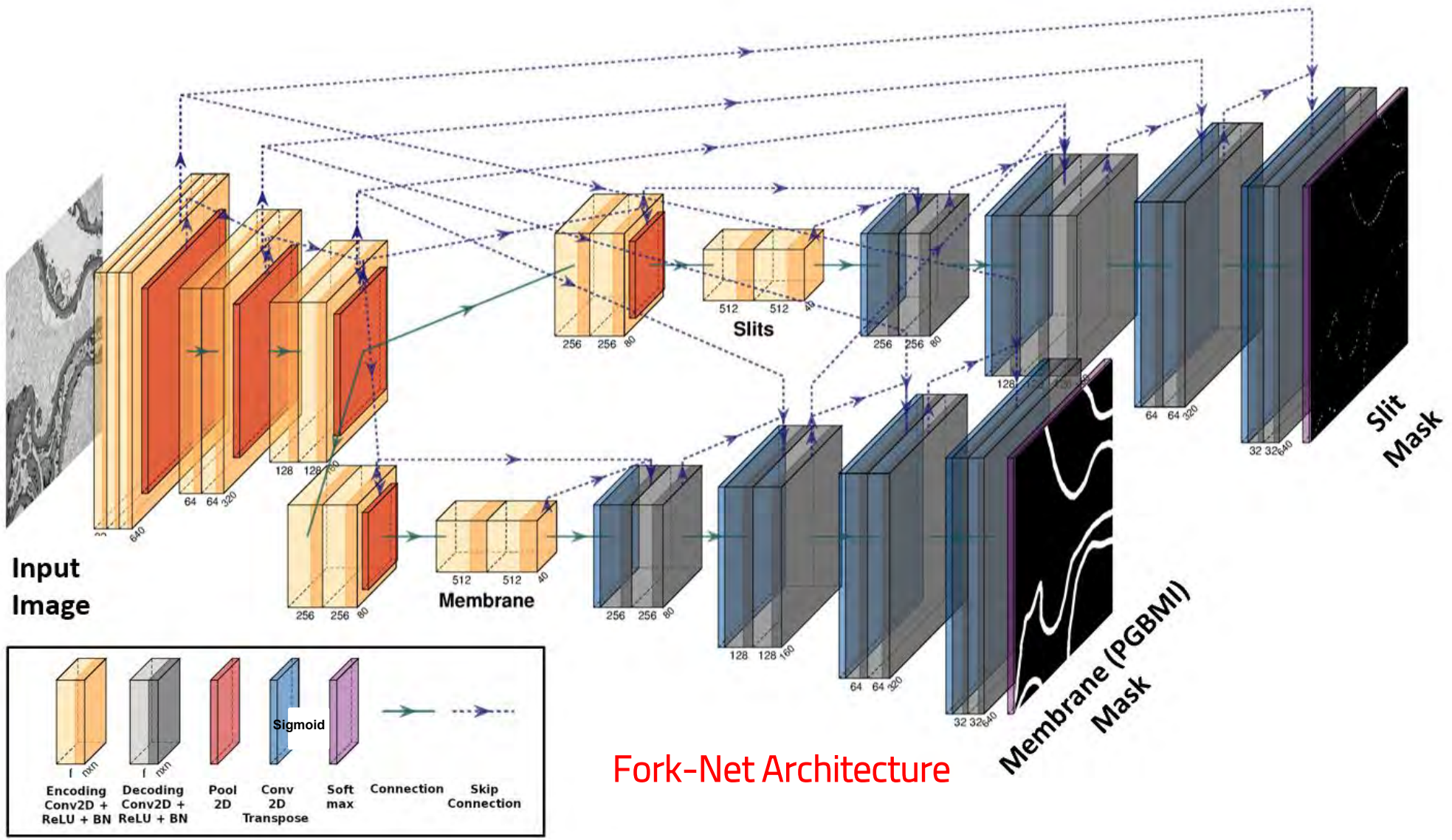




820 GT Images, mixture of normal and diseased

Stage 1: Convolutional Neural Network (CNN)

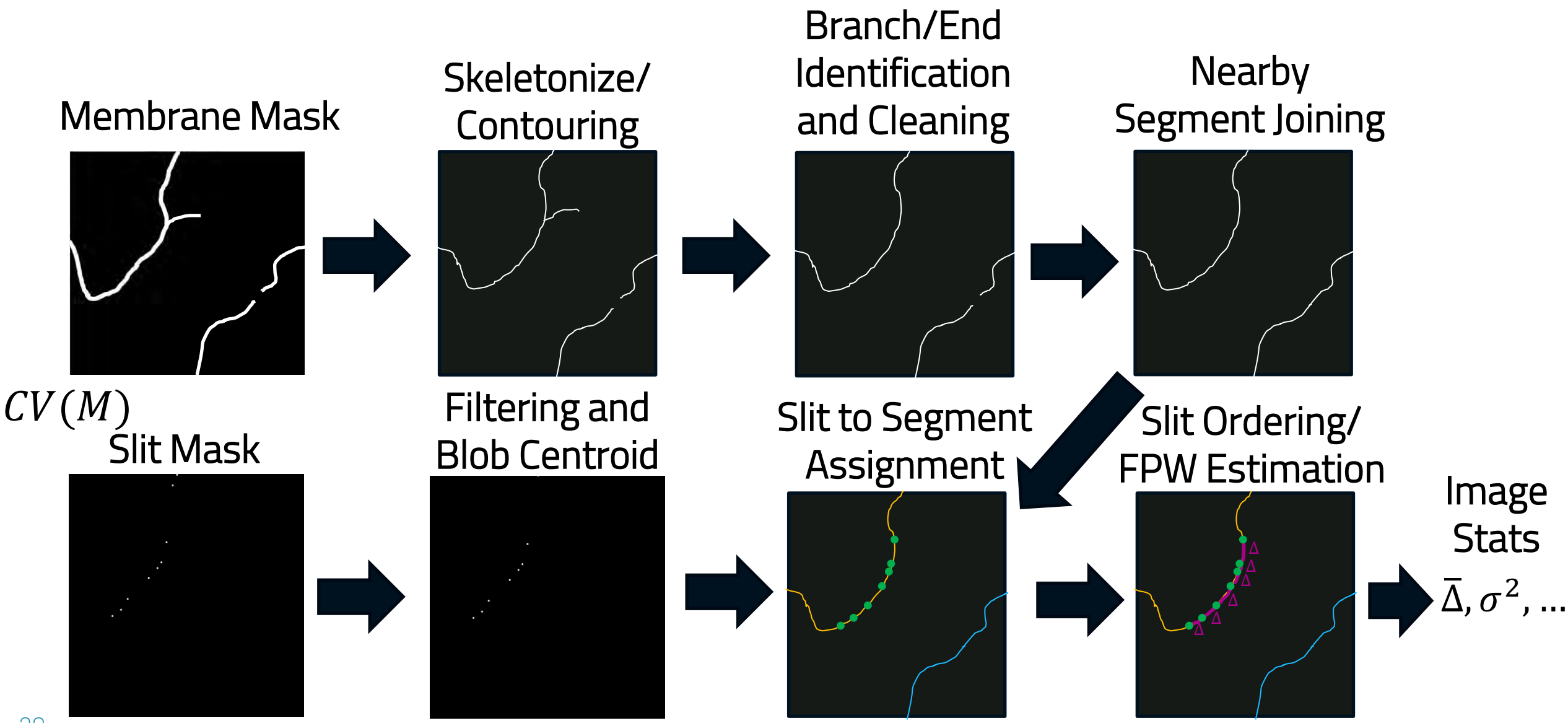
$Seg(I)$



Fork-Net Architecture

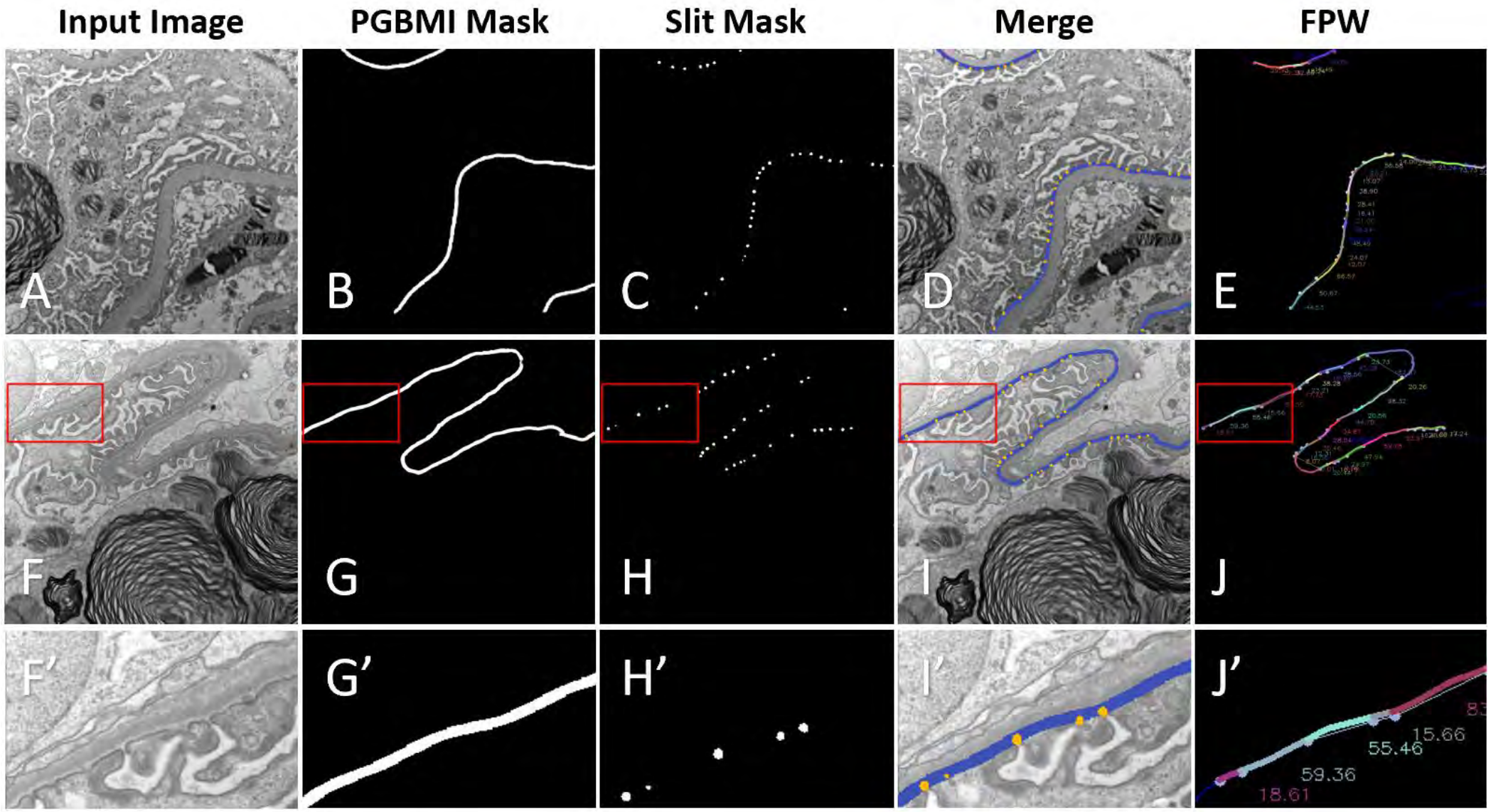
Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

Stage 2: Computer Vision



Note: Most steps shown are visualizations of applied operations

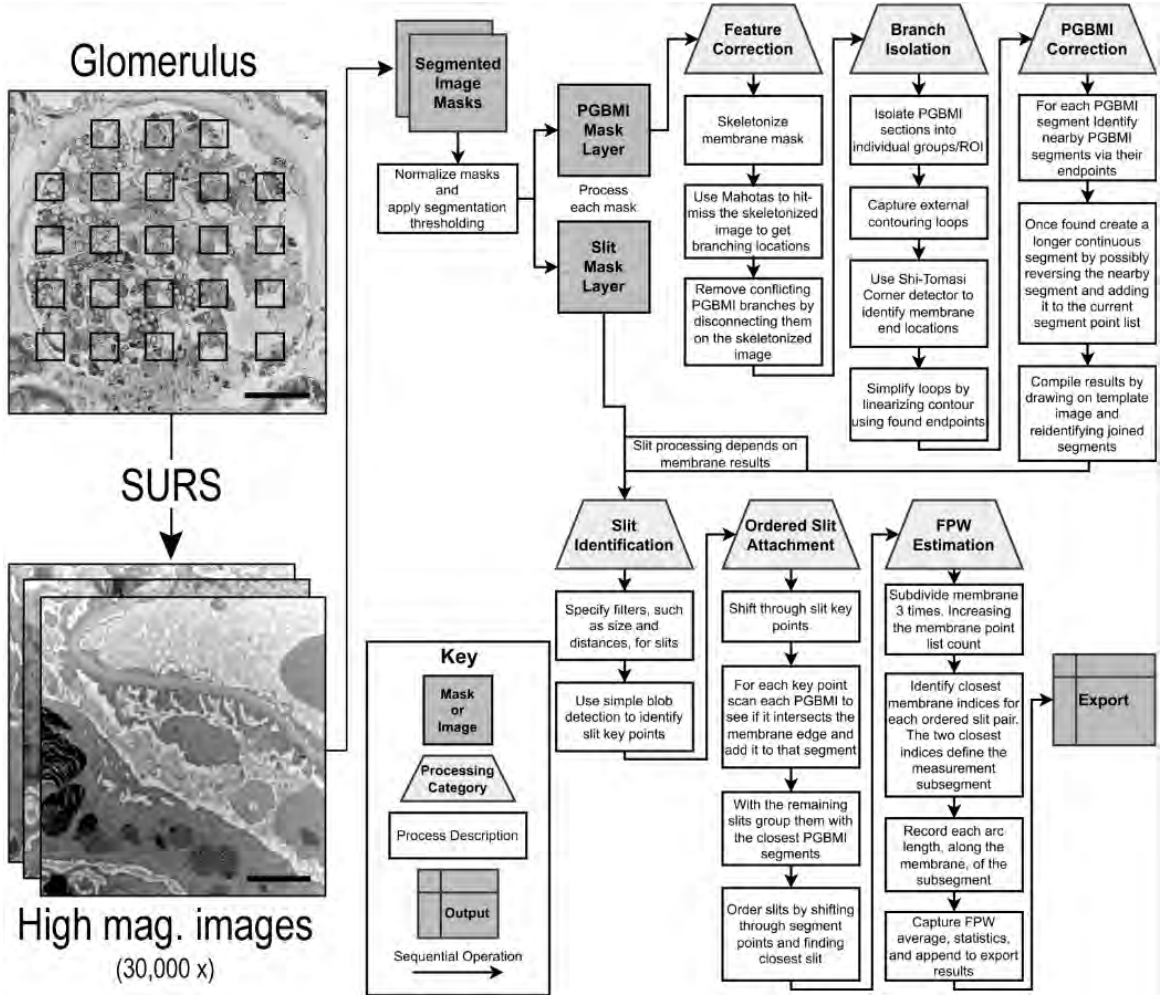
Example Output



PGBMI: podocyte GBM interface

Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

Model Workflow Diagram



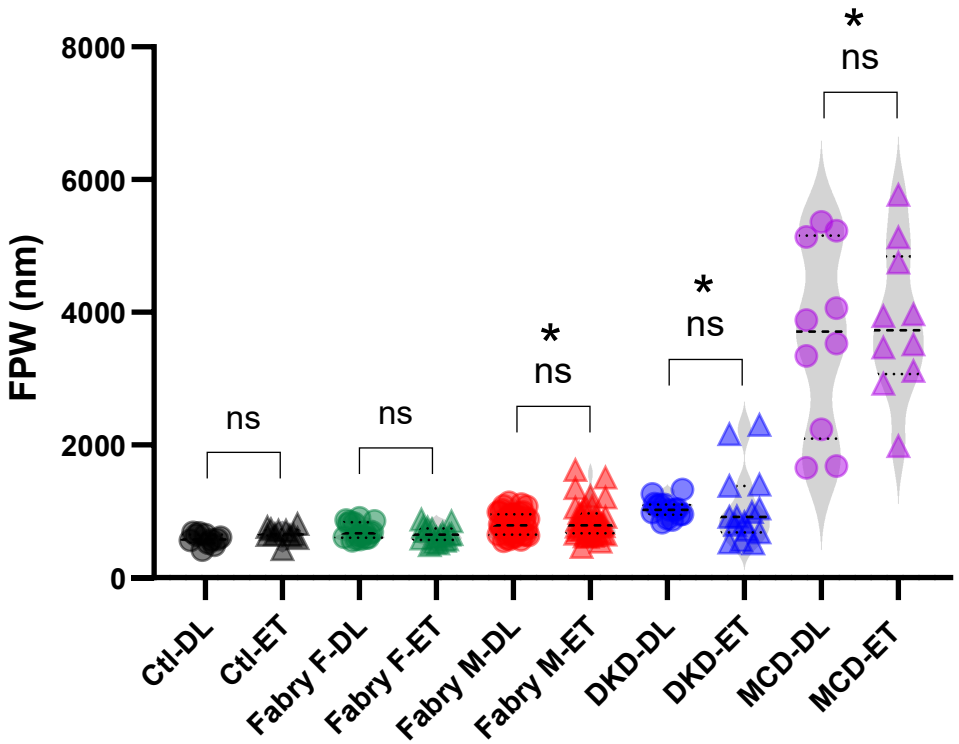
The model training accuracy measured against manual segmentation was 61-67% (15% SD) for slits and 76-86% (7.5% SD) for PGBMI.

Model precision performance on segmentation of 6960 filtration slits (i.e. positive predictive value) was 91%, with a recall (i.e. sensitivity) of 78%, and an F-score (the harmonic mean of precision and recall) of 0.84

Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

Interchangeability of FPW Measured by Deep Learning (DL) and Expert Technician (ET)

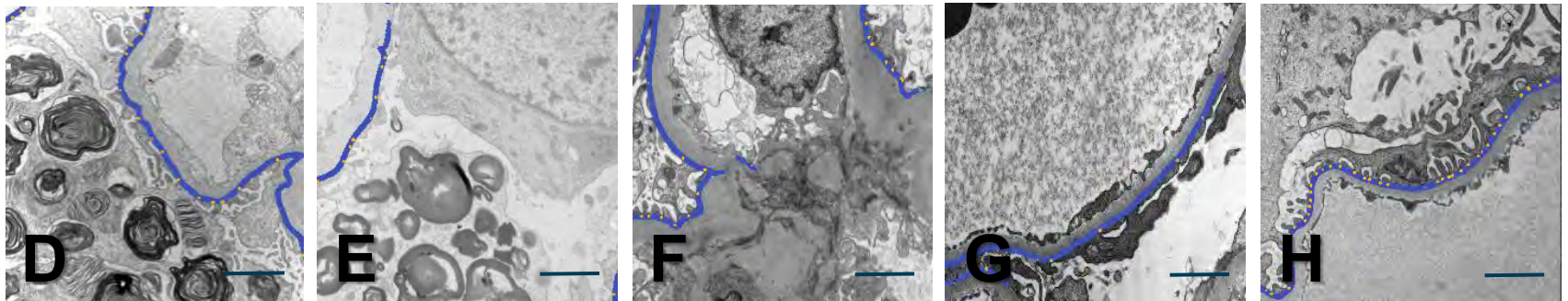
Deep learning and human measurements were not statistically different



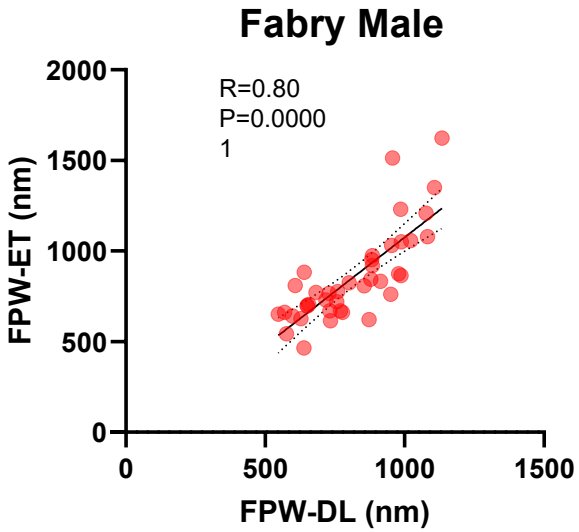
Ctl: control
F: female
M: male
DKD: diabetic kidney disease
MCD: minimal change disease
ns: not significant
*: statistically different from Ctl

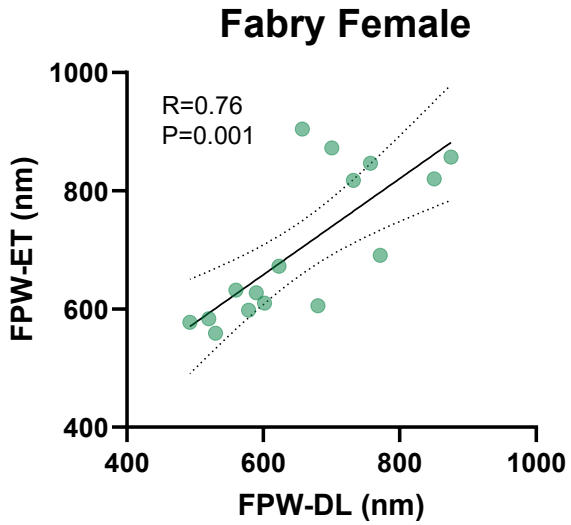
Ctl (living kidney donors): n=17
Fabry-F: n=16
Fabry-M: n= 40
DKD: n=15
MCD: n=10

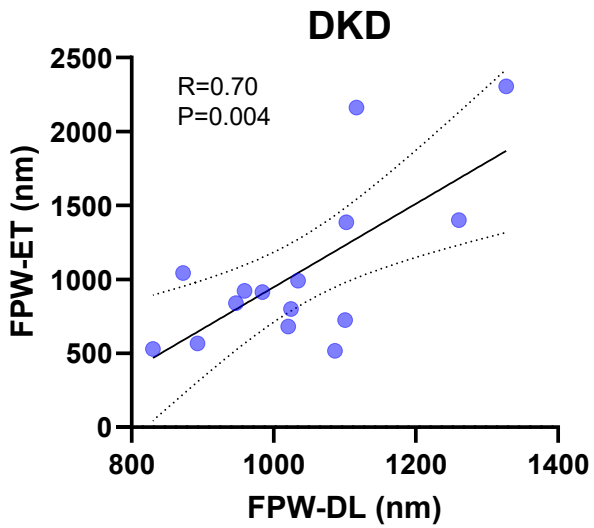
Fabry Male | Fabry Female | DKD | MCD | Control

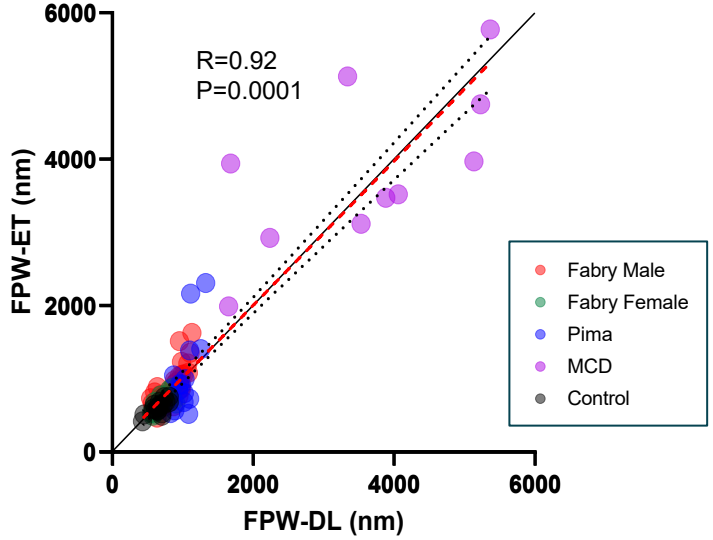


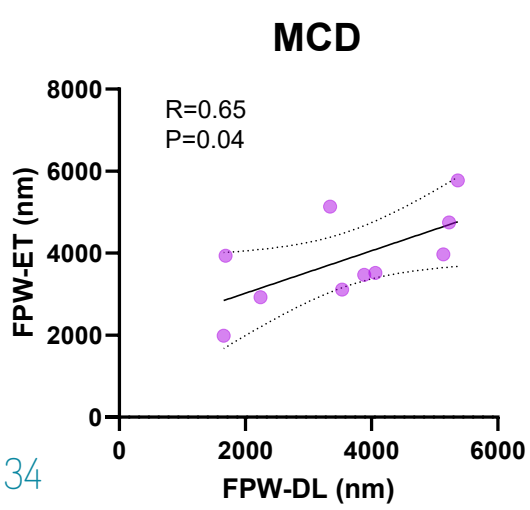
Interchangeability of FPW Measured by Deep Learning (DL) and Expert Technician (ET)

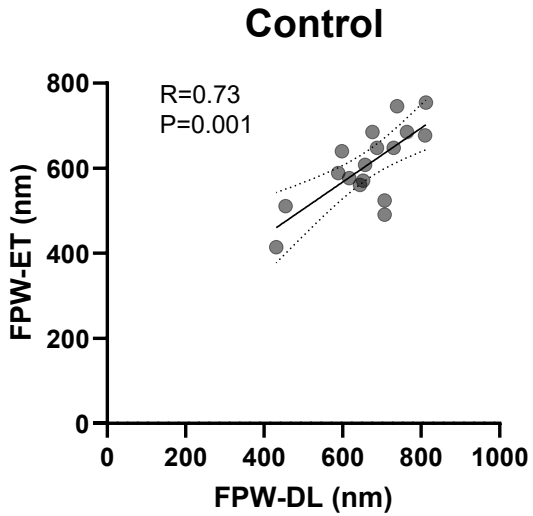


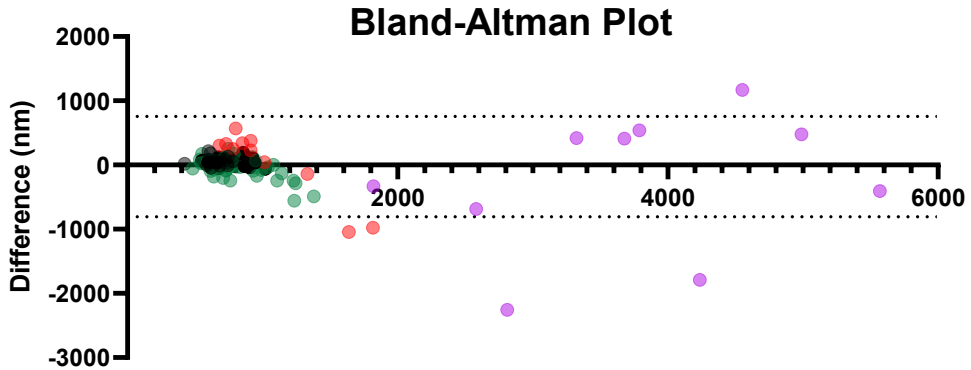












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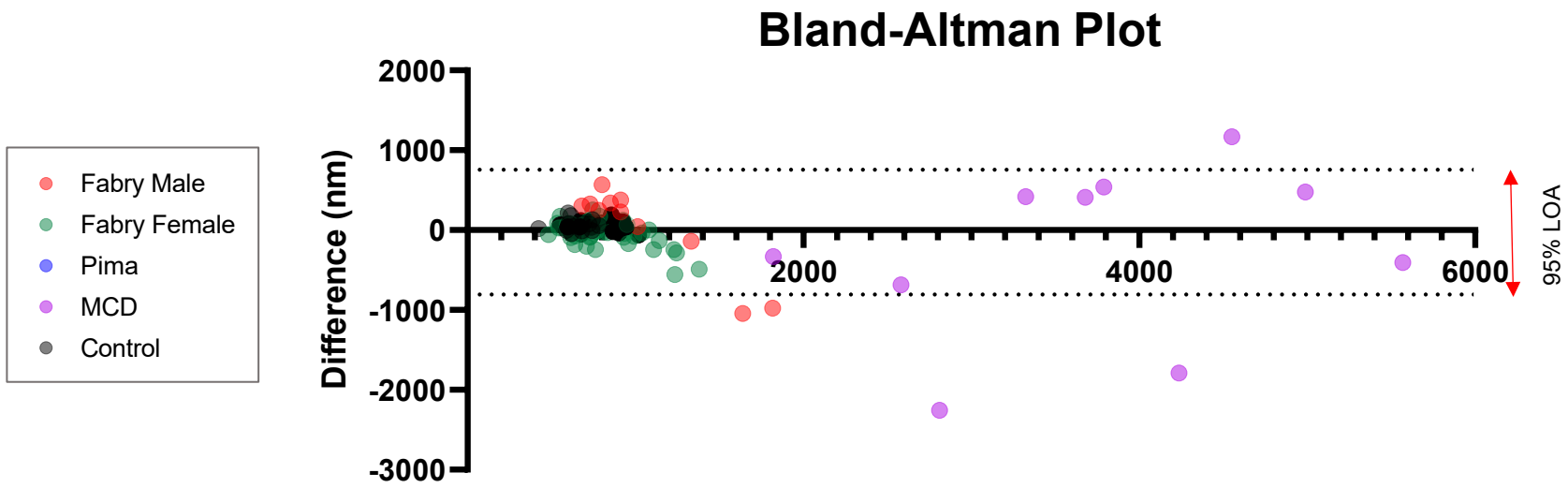
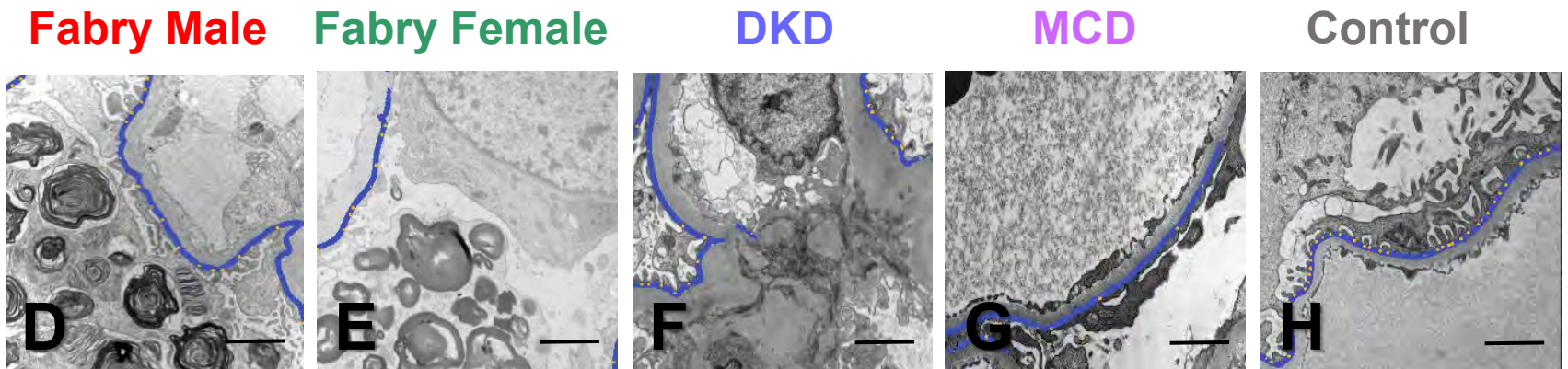
Interchangeability of FPW Measured by Deep Learning (DL) and Expert Technician (ET)

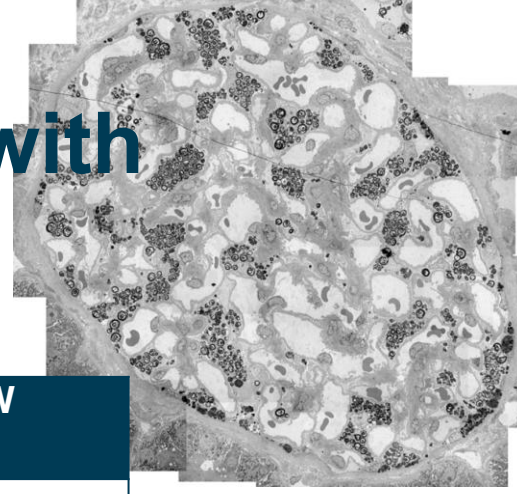


Entire Cohort Combined
Bias: 63 nm
SD of differences: 433 nm
±1.96 SD: 94%

Per Class Comparison
±1.96 class SD: 95% [90-100]
±1 class SD: 88% [70-95]



DL measurements of FPW shows Correlations with Relevant Variables – Fabry Nephropathy

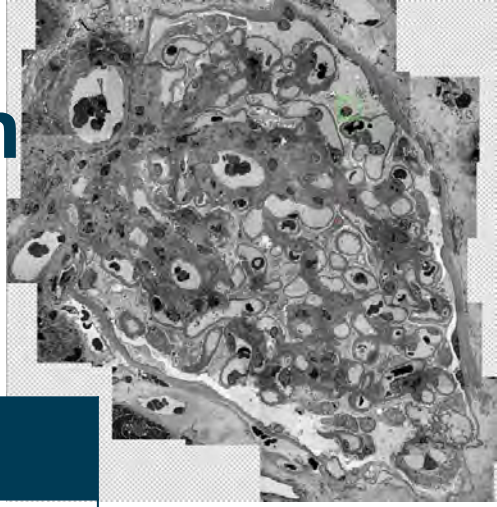


Variable	Correlation with DL- FPW (R; p-value)	Correlation with ET-FPW (R; p-value)
Age (year)	0.40; 0.012	0.36; 0.022
UPCR	0.44; 0.005	0.58; 0.0001
%α-GAL-A activity	-0.22; 0.203	-0.29; 0.091
Plasma GL3	0.40; 0.06	0.26; 0.236
Podocyte number density (1/μm^3)	-0.44; 0.025	-0.38; 0.053
Podocyte GL3 volume fraction	0.32; 0.041	0.15; 0.349
Podocyte volume (μm^3)	0.49; 0.011	0.43; 0.028
Podocyte GL3 volume (μm^3)	0.54; 0.004	0.44; 0.026

DL: deep learning
ET: expert technician
UPCR: urine protein creatinine ratio
GL3: globotriaosylceramide

Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

DL measurements of FPW shows Correlations with Relevant Variables – Diabetic Kidney Disease



Variable	Correlation with DL- FPW (R; p-value)	Correlation with ET-FPW (R; p-value)
UACR	0.51; 0.05	0.30; 0.28
Mesangial fractional volume	0.61; 0.015	0.49; 0.066
Mesangial matrix fractional volume	0.62; 0.015	0.51; 0.051
Glomerular filtration surface density	-0.58; 0.024	-0.38; 0.158
GBM width (µm)	0.25; 0.376	0.36; 0.188
Podocyte volume (μm^3)	0.54; 0.037	0.37; 0.172

DL: deep learning
ET: expert technician
UACR: urine albumin creatinine ratio
GBM: glomerular basement membrane

Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

Sources of Variability in an Experiment

$$\overline{R}_n = \frac{1}{n}.\sum_{i=1}^{n} \widehat{R}_i$$

In general:

$$OVar(\hat{R}) = Var\left(\mathrm{E}\left[\hat{R}|R\right]\right) + \mathrm{E}\left[Var\left(\hat{R}|R\right)\right]$$

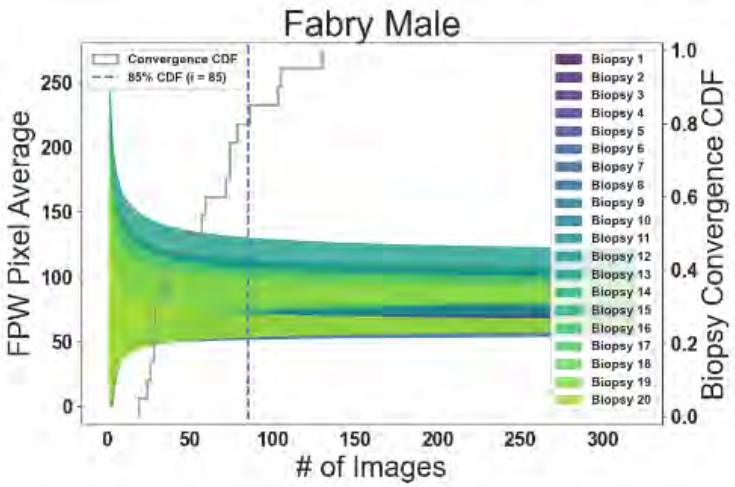
If the method of estimation is unbiased:

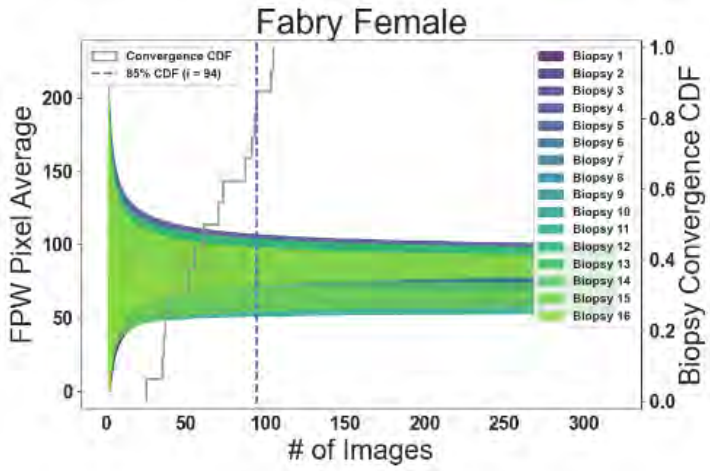
$$OVar(\hat{R}) = Var(R) + \mathrm{E}\left[Var\left(\hat{R}|R\right)\right]$$

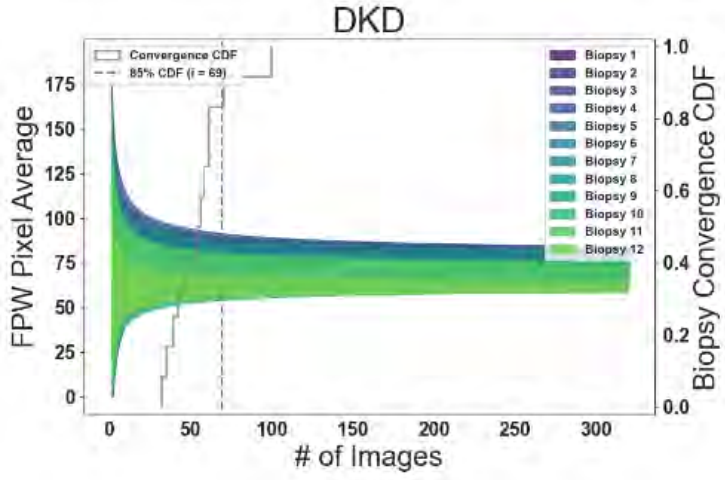
Observed Variance = Biological variation + Sampling Variance

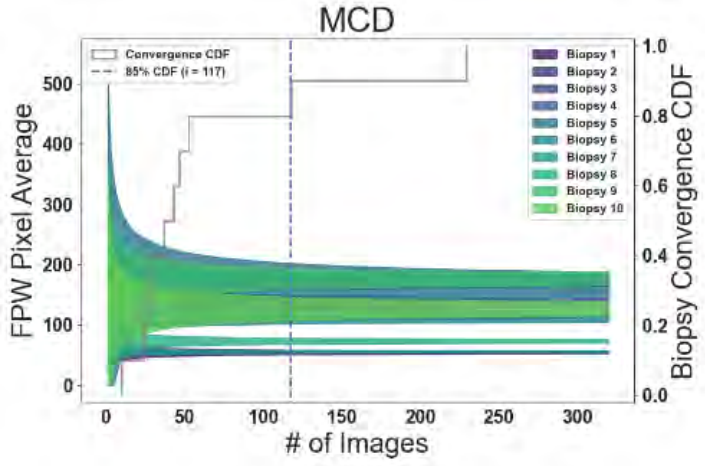
~60 images per biopsy provided reasonably stable average FPW

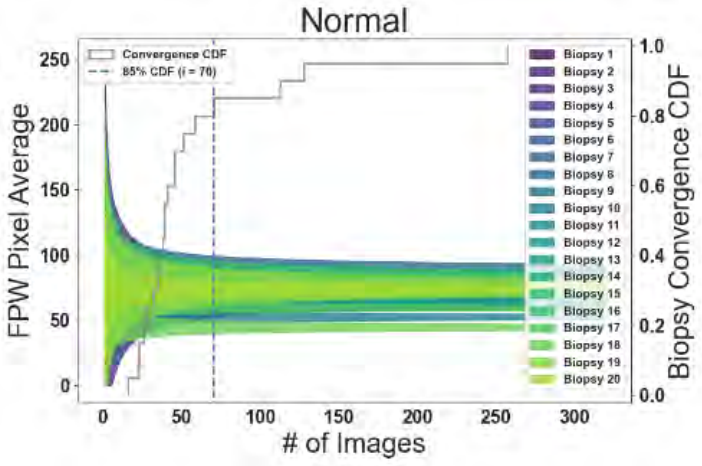
of sampled images required







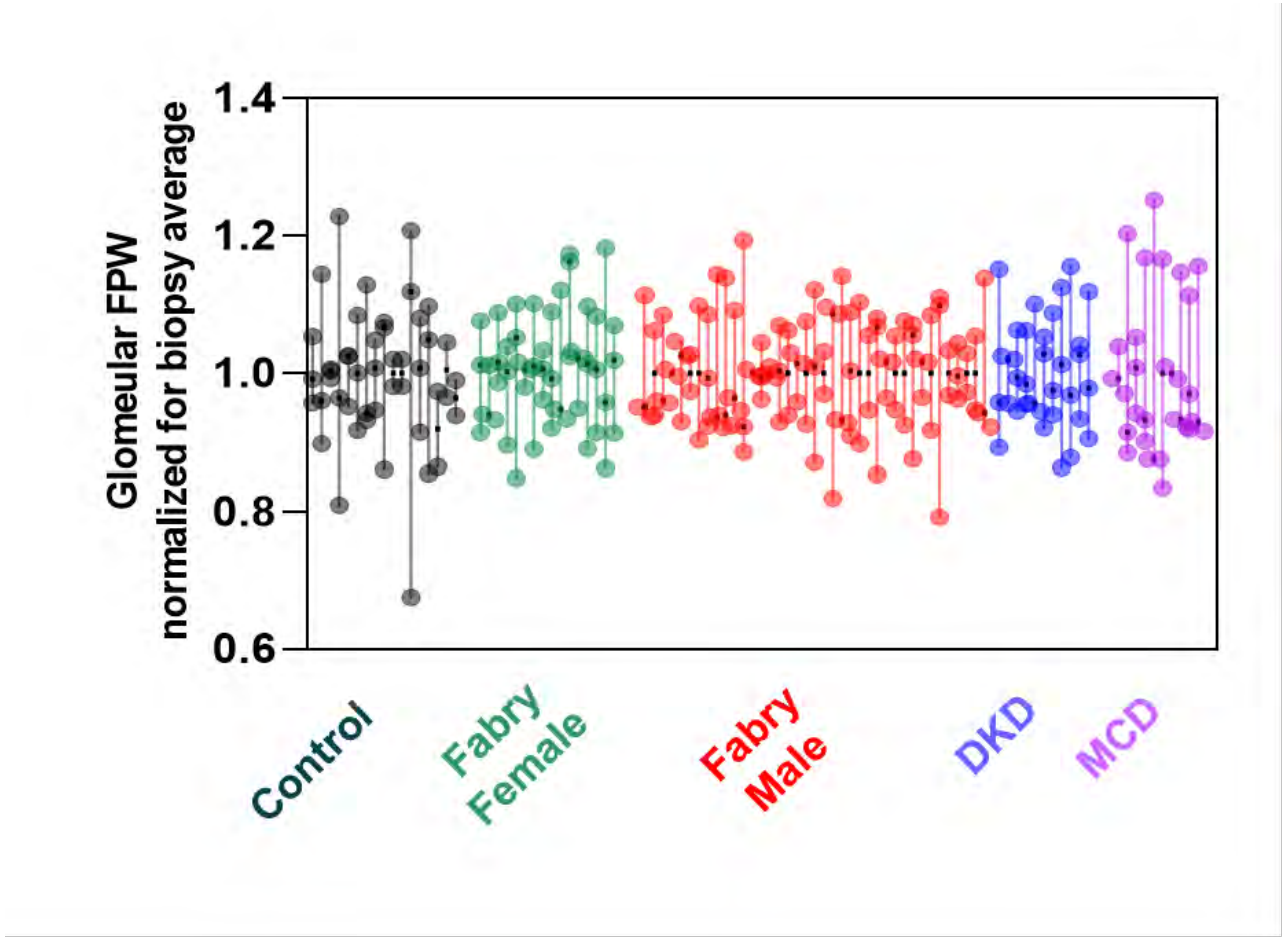


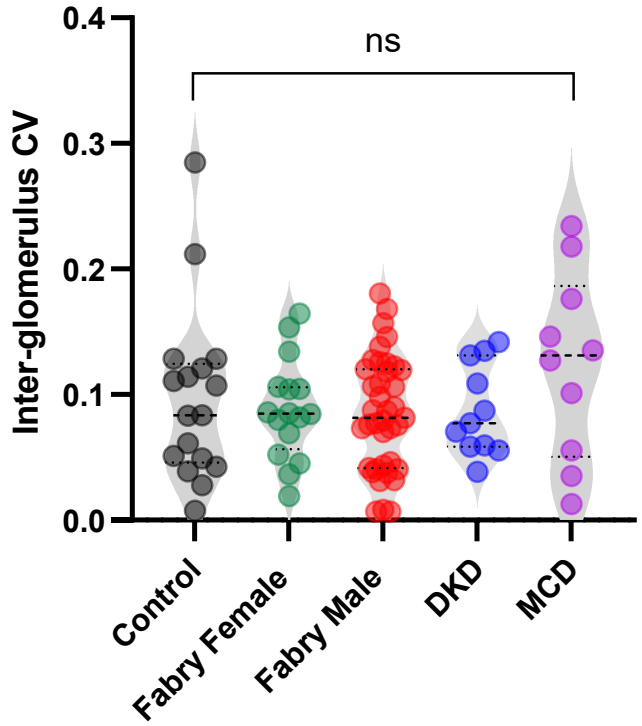


CDF: cumulative distribution function

Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

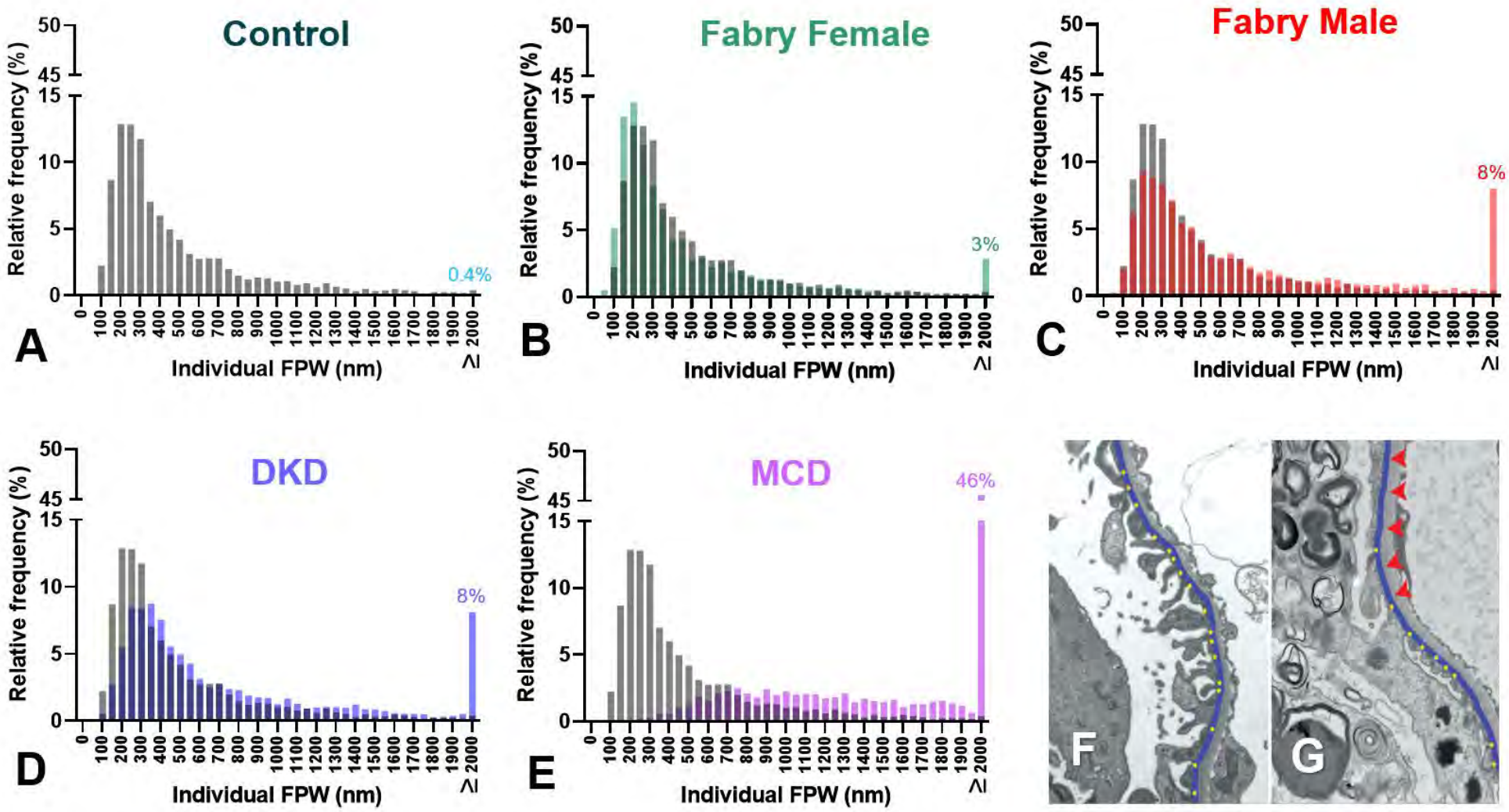
Sampling Strategy: Interglomerular FPW variation?





Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

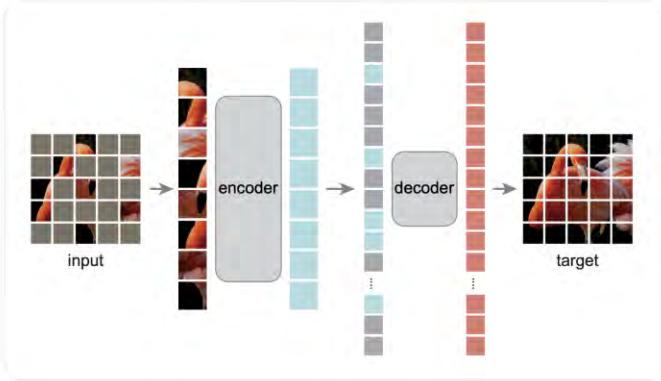
Distribution of individual FPW values: proposing a quantitative approach to segmental vs. diffuse foot process effacement



Smerkous et al. Kidney Int. 2024 Jan;105(1):165-176.

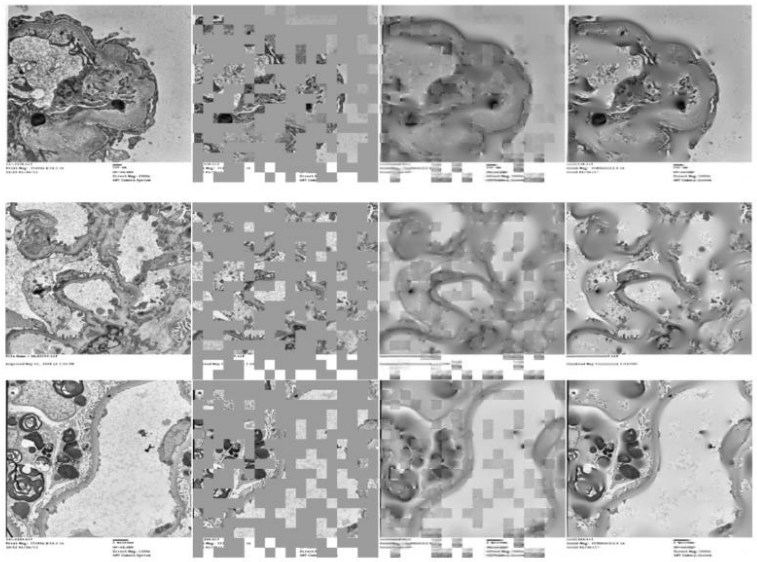
Vision Transformer – Masked Auto-Encoder (MAE)

MAE (masked auto encoding) is a method for self-supervised pre-training of Vision Transformers (ViTs). The pre-training objective is that by masking a large portion (75%) of the image patches, the model must reconstruct raw pixel values.

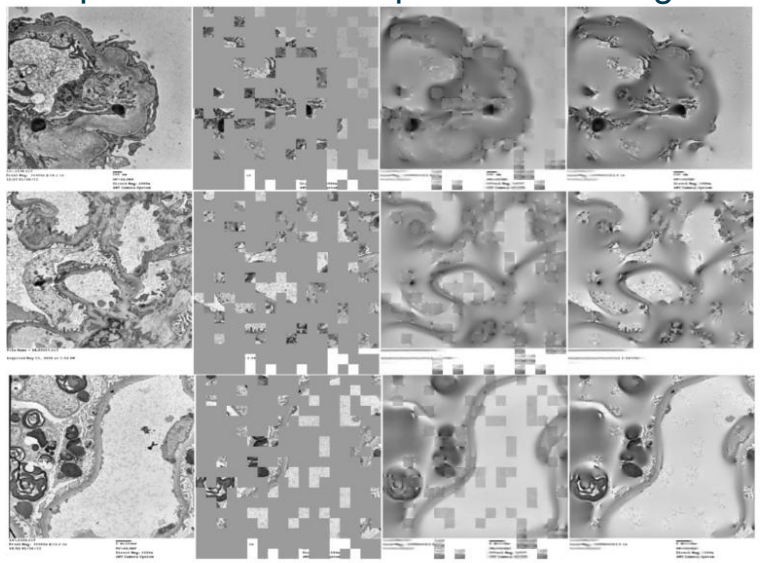


He et al. arXiv:2111.06377v3 [cs.CV] 19 Dec 2021

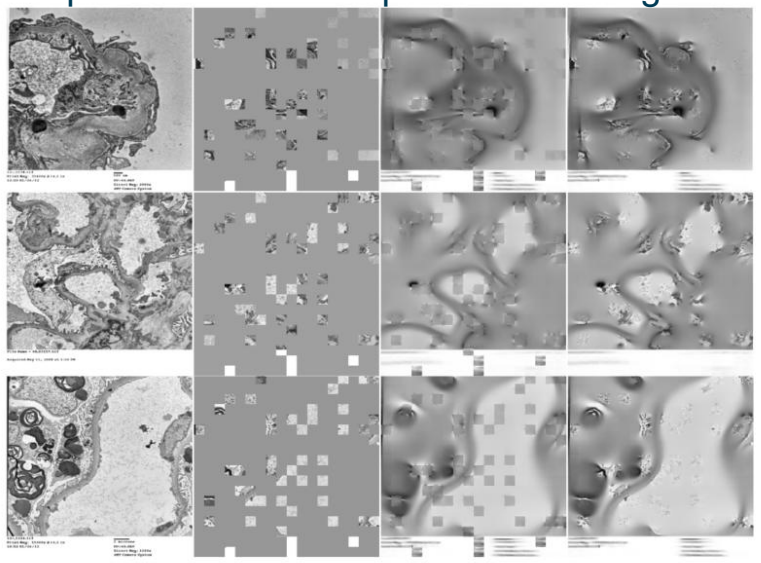
65% of Image Masked



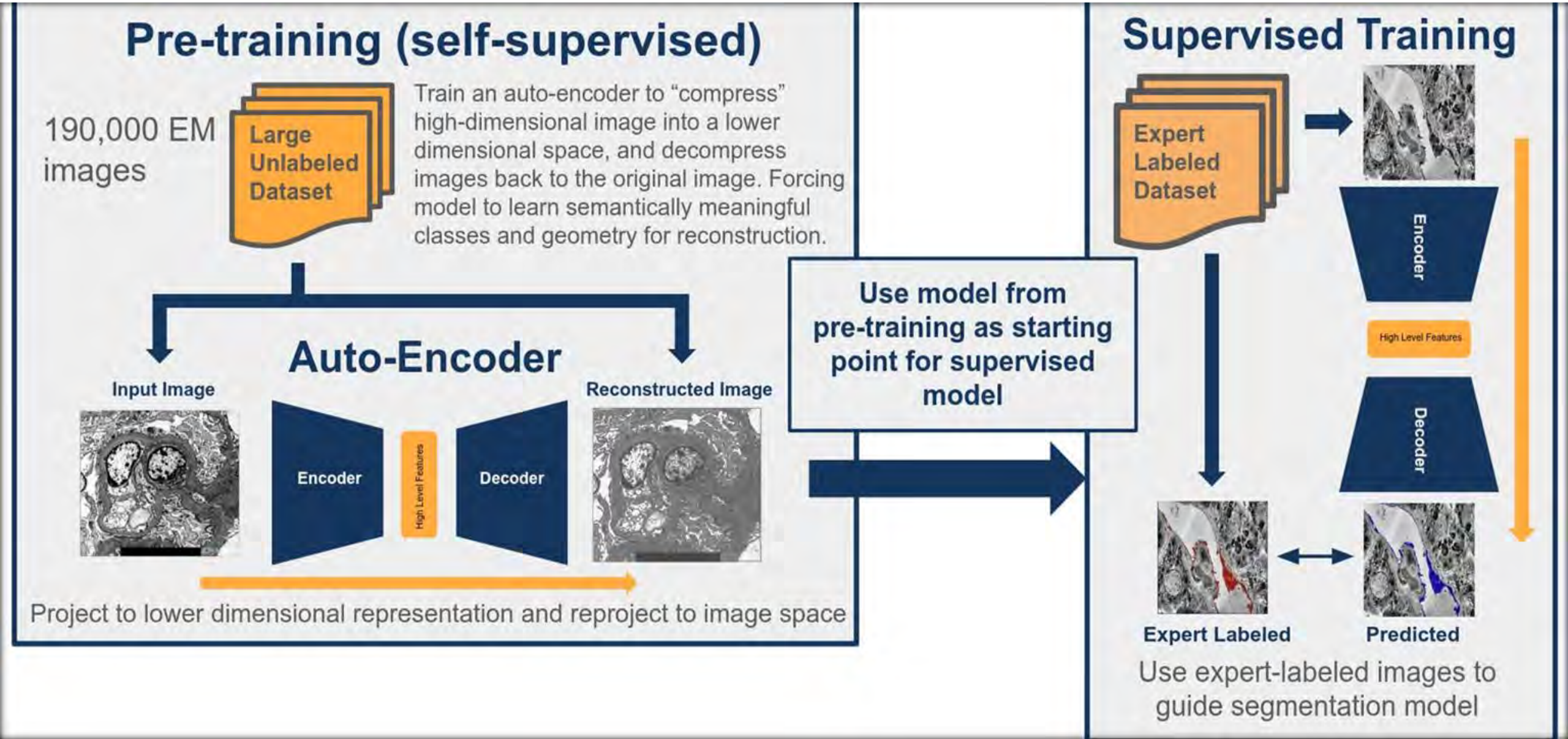
75% of Image Masked



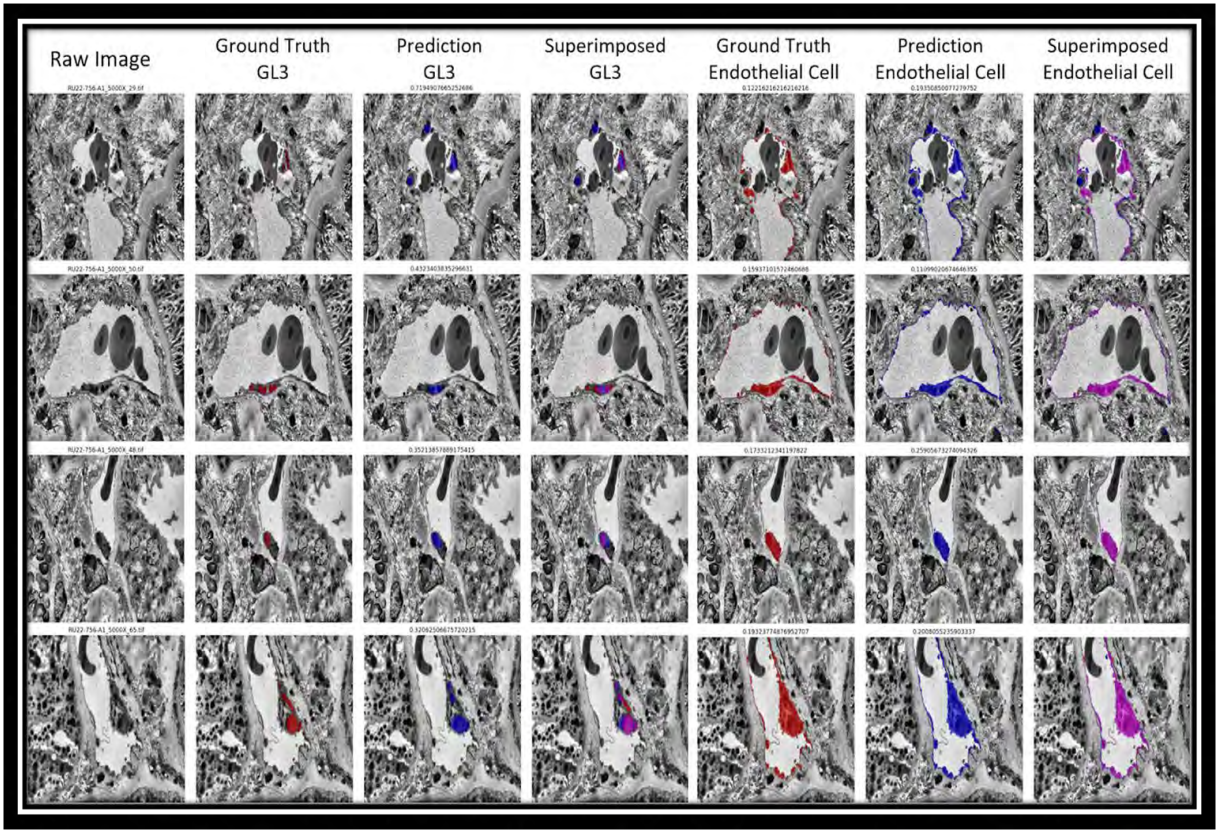
85% of Image Masked

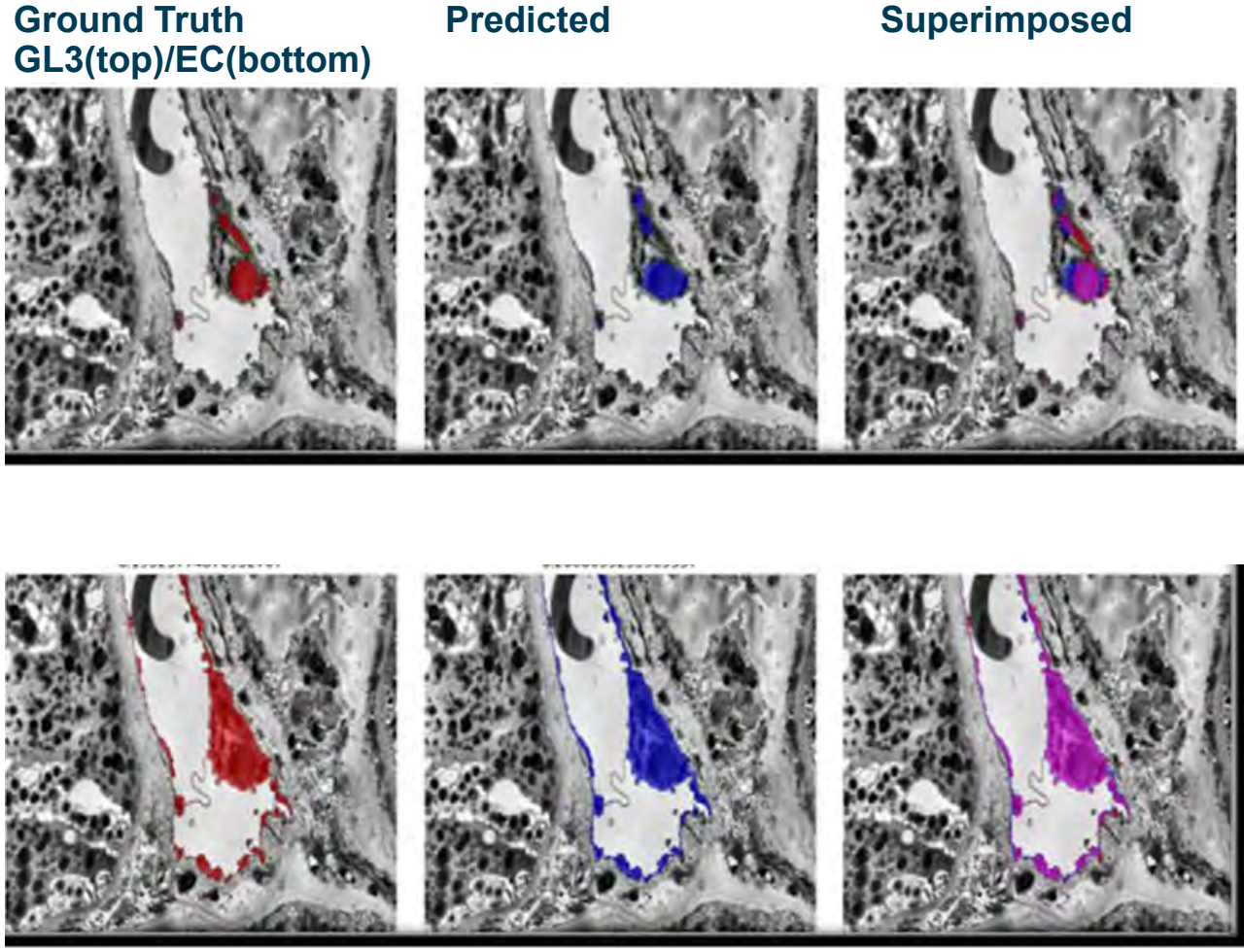


Model Implementation



Results





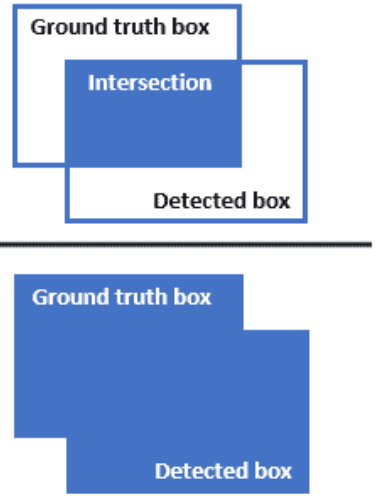
$$Vv(Inc/Endo_{PTC}) = \frac{\sum_{i=0}^{n} A_{GL3}}{\sum_{i=0}^{n} A_{Endo} - \sum_{i=0}^{n} A_{nuc}}$$

$Vv(Inc/Endo_{PTC})$ = fraction of endothelial cells occupied by GL3 inclusions; A = area (pixel); PTC = peritubular capillary

Results

Measurement	All Images (Train + Test)	Train (Fabry + Normal)	Train (Fabry)	Train (Normal)	Test (Fabry + Normal)	Test (Fabry)	Test (Normal)
GL3 **IOU ± STD**	0.8263 ± 0.2895	0.8249 ± 0.2957	0.6153 ± 0.3390	0.9962 ± 0.0000	0.8382 ± 0.2346	0.6101 ± 0.2131	0.9962 ± 0.0000
EC **IOU ± STD**	0.8162 ± 0.1118	0.8179 ± 0.1153	0.8264 ± 0.0750	0.8110 ± 0.1399	0.8020 ± 0.0747	0.8613 ± 0.0507	0.7610 ± 0.0601
Nucleus **IOU ± STD**	0.8401 ± 0.2521	0.8364 ± 0.2628	0.8850 ± 0.1914	0.7967 ± 0.3044	0.8716 ± 0.1276	0.8267 ± 0.1578	0.9027 ± 0.0965
GL3 Inc Ratio Ground Truth	0.0431 ± 0.0916	0.0415 ± 0.0916	0.0922 ± 0.1185	0.0000 ± 0.0000	0.0574 ± 0.0922	0.1403 ± 0.0962	0.0000 ± 0.0000
GL3 Inc Ratio Model Predicted	0.0478 ± 0.1001	0.0437 ± 0.0933	0.0972 ± 0.1193	0.0000 ± 0.0000	0.0833 ± 0.1438	0.2035 ± 0.1635	0.0000 ± 0.0000
Absolute Error	0.0168 ± 0.0428	0.0152 ± 0.0382	0.0338 ± 0.0513	0.0000 ± 0.0000	0.0309 ± 0.0705	0.0755 ± 0.0962	0.0000 ± 0.0000

$$IoU = \frac{\text{Area of Overlap}}{\text{Area of Union}} = \frac{}{}$$



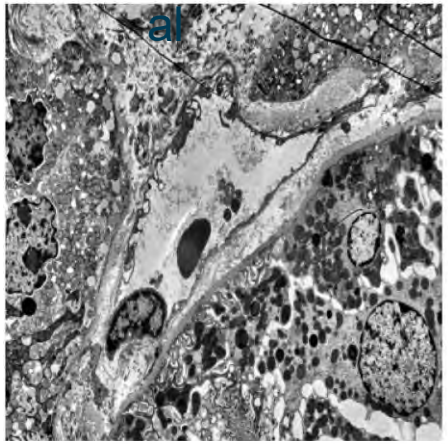
IOU: intersection over union

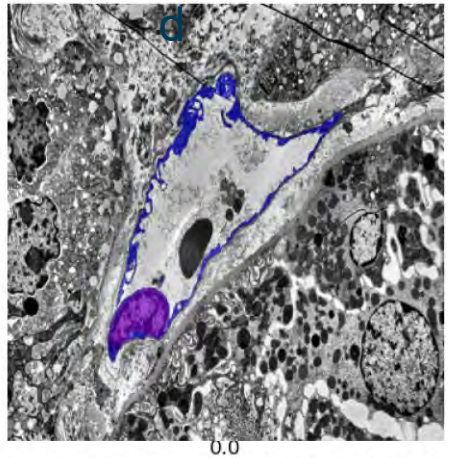
Origin

Predicte

Origin

Predicte





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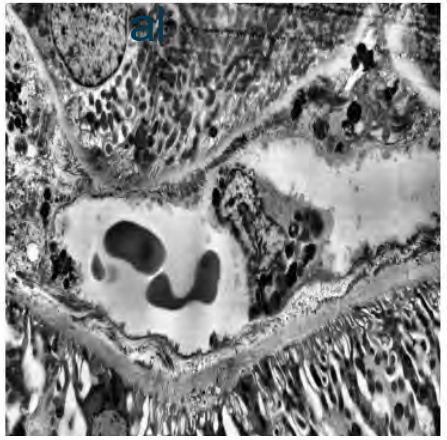

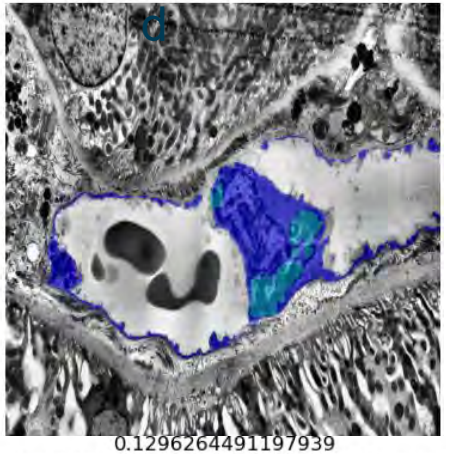

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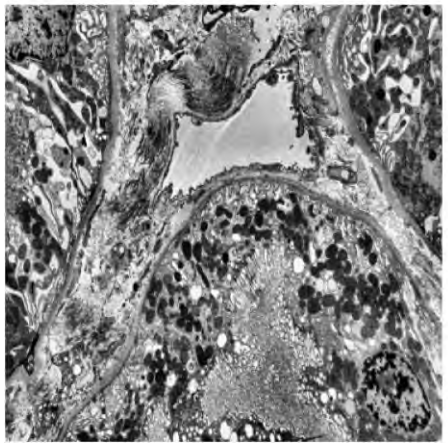

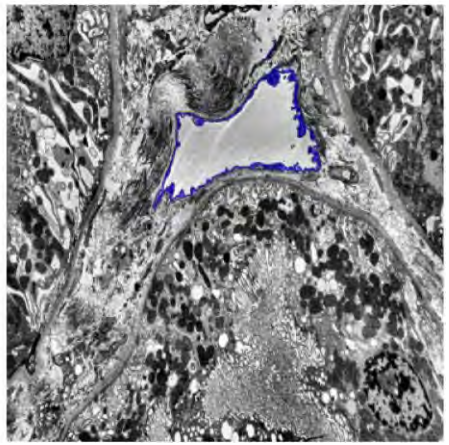

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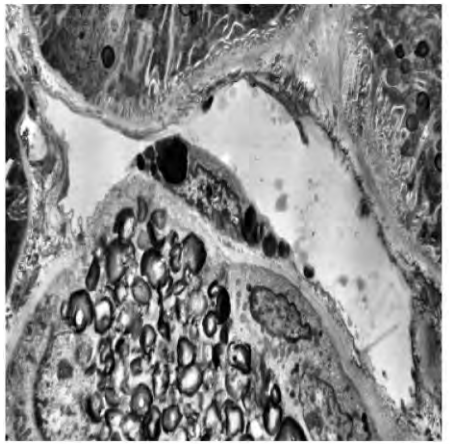

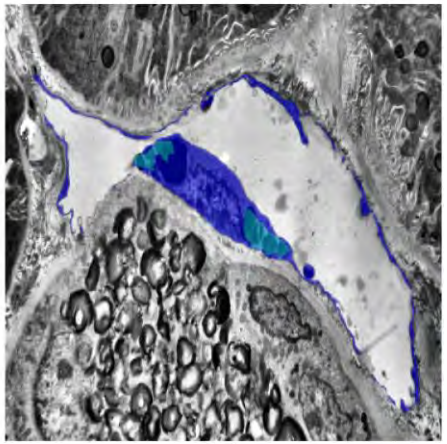

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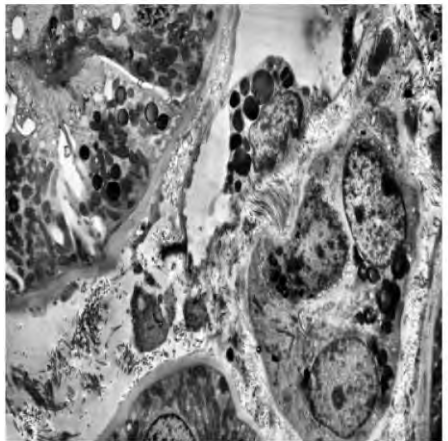

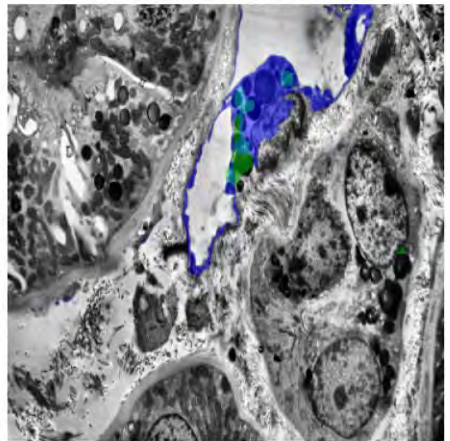

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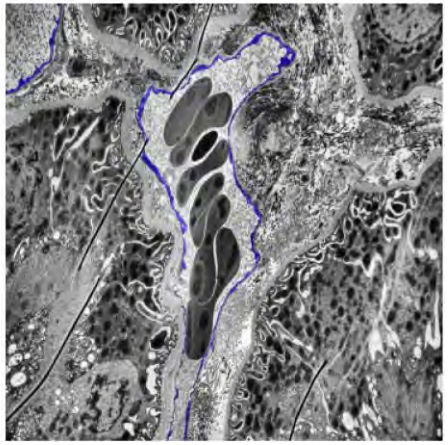

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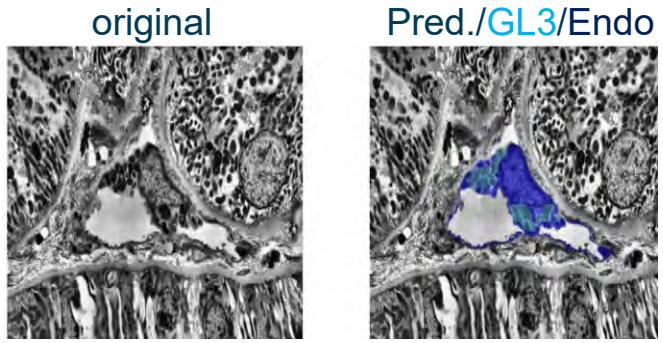
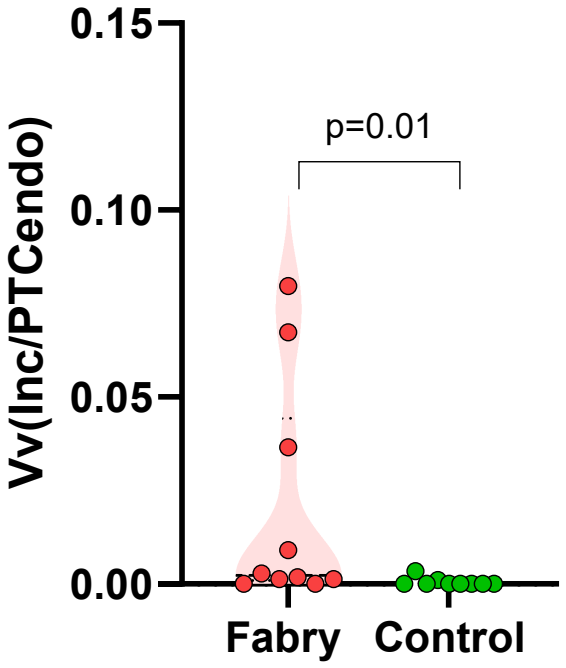
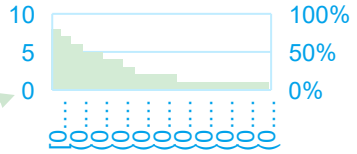
Peritubular Capillary Endothelial GL3 Inclusion Fractional Volume [Vv(Inc/PTCendo)]



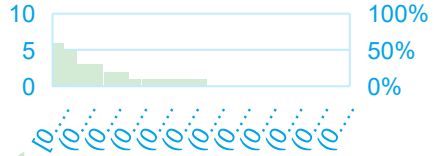


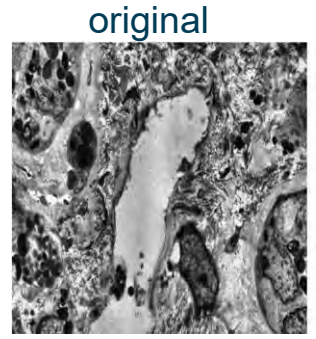
29 y/o male
c.679C>T (R227X)
Nonsense mutation
Classic

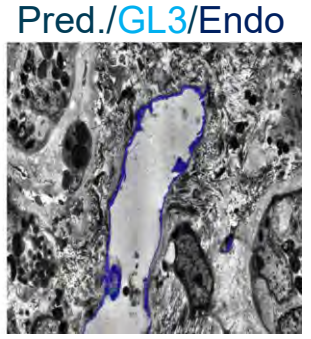


18 y/o male
c.281G>A (C94Y)
Missing mutation
Classic
α-Gal-A: 0.1
Lyso-Gb3: 171

11 y/o male
c.281G>A
903INSG
Classic
α-Gal-A: 0.3

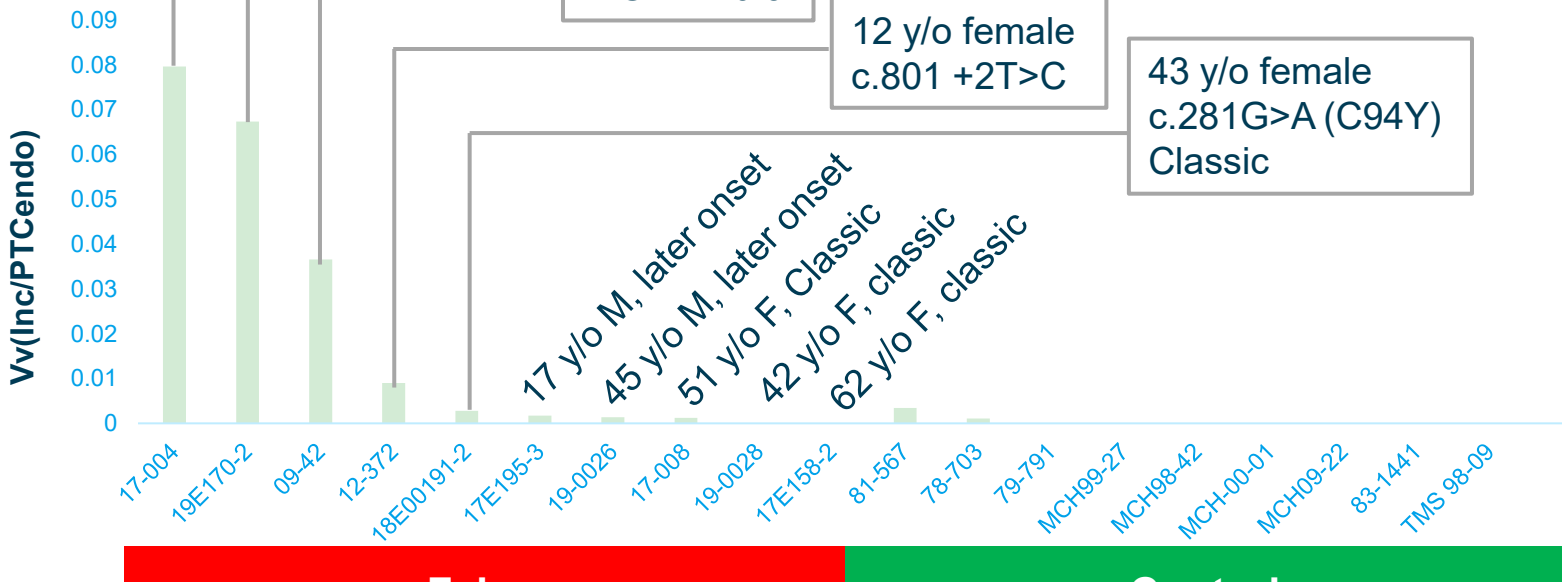




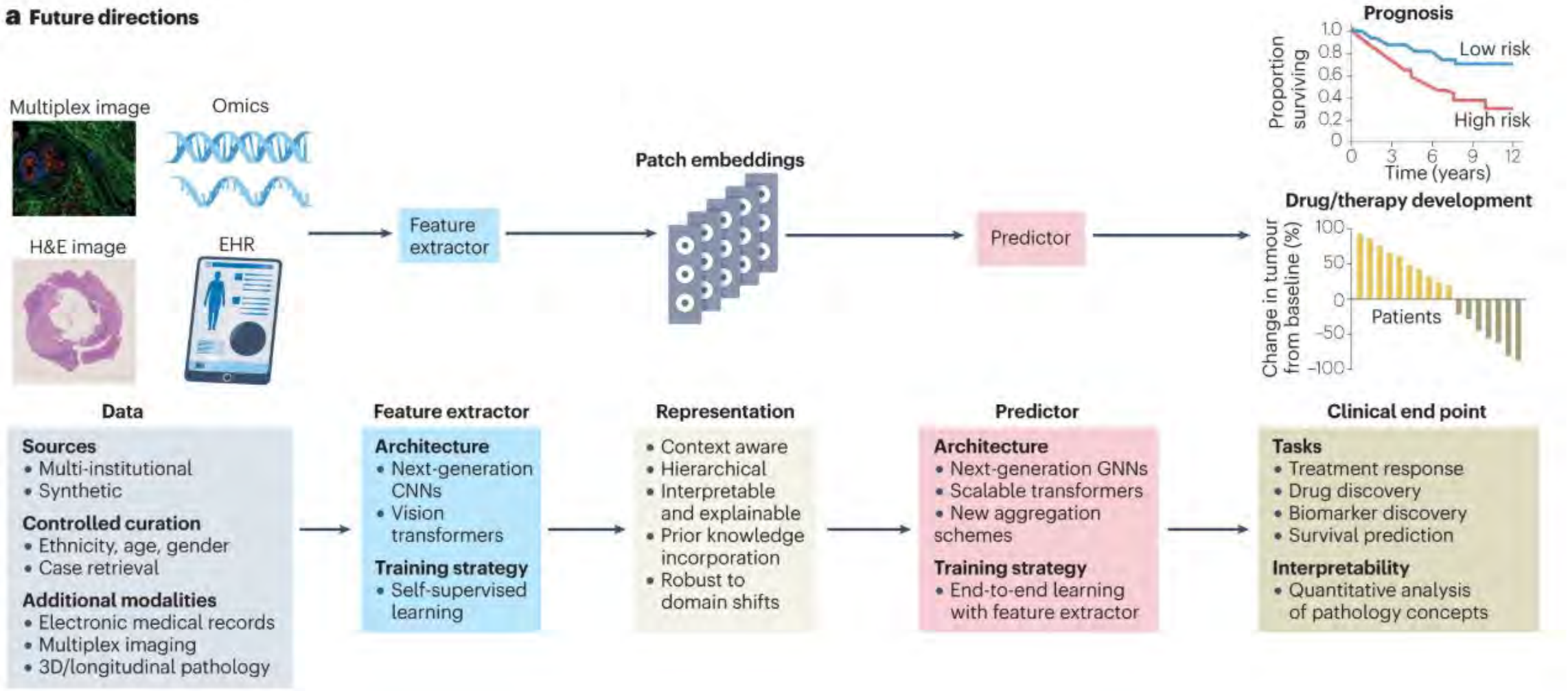


12 y/o female
c.801 +2T>C

43 y/o female
c.281G>A (C94Y)
Classic



Future directions in computational pathology



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Roadblocks and challenges preventing AI application

- Ethical principles and AI
- Validation of algorithms and overfitting
- Interpretability and the ‘black box’ problem
- Quality of data
- Computational system, data storage and cost-benefit ratio
- Technological issues
- Regulation, reimbursement, and clinical adoption
- Pathologists’ dilemma-to use or not to use

Conclusions

- There has a tremendous growth in the development of novel AI approaches in pathology in the last few years.
- AI can improve diagnostic workflows, eliminate human errors, increase inter-observer reproducibility, and make prognostic predictions.
- While there has been an increase in the development of AI tools, the integration into clinical practice has somewhat lagged owing to several issues related to interpretability, validation, regulation, generalizability, and cost.

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University of Washington

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