

DL in Healthcare Research: Proteomics, Genomics, and Medical Imaging

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Topics in Deep Learning
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Outline

- General overview
- Proteomics
- Genomics
- Radiomics

DL in Healthcare Research

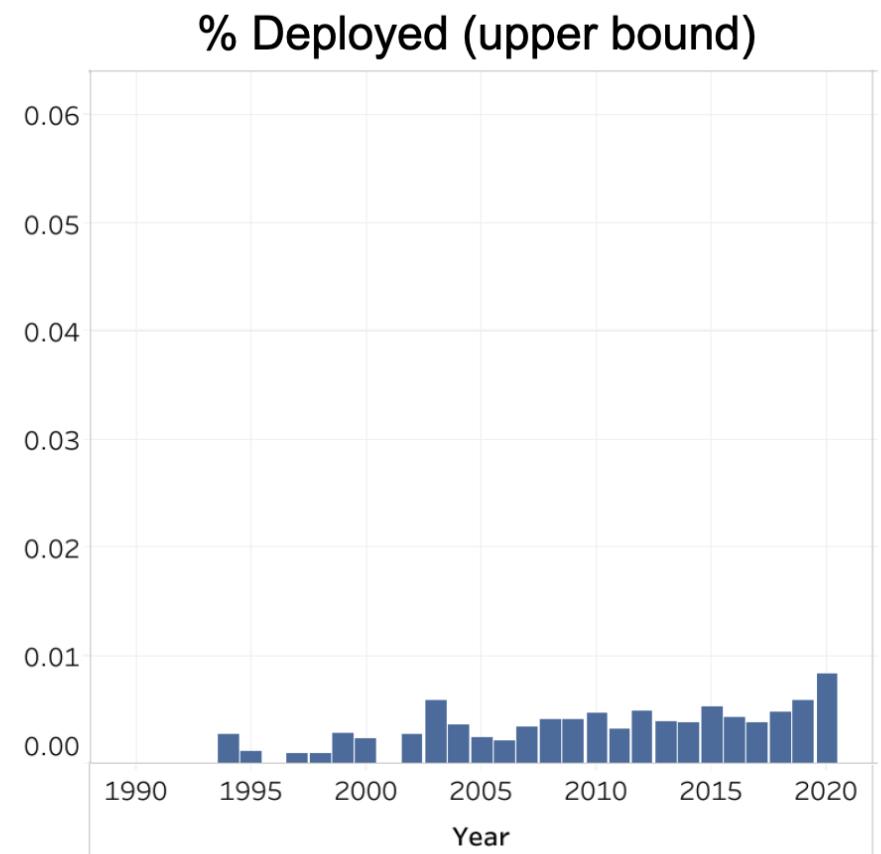
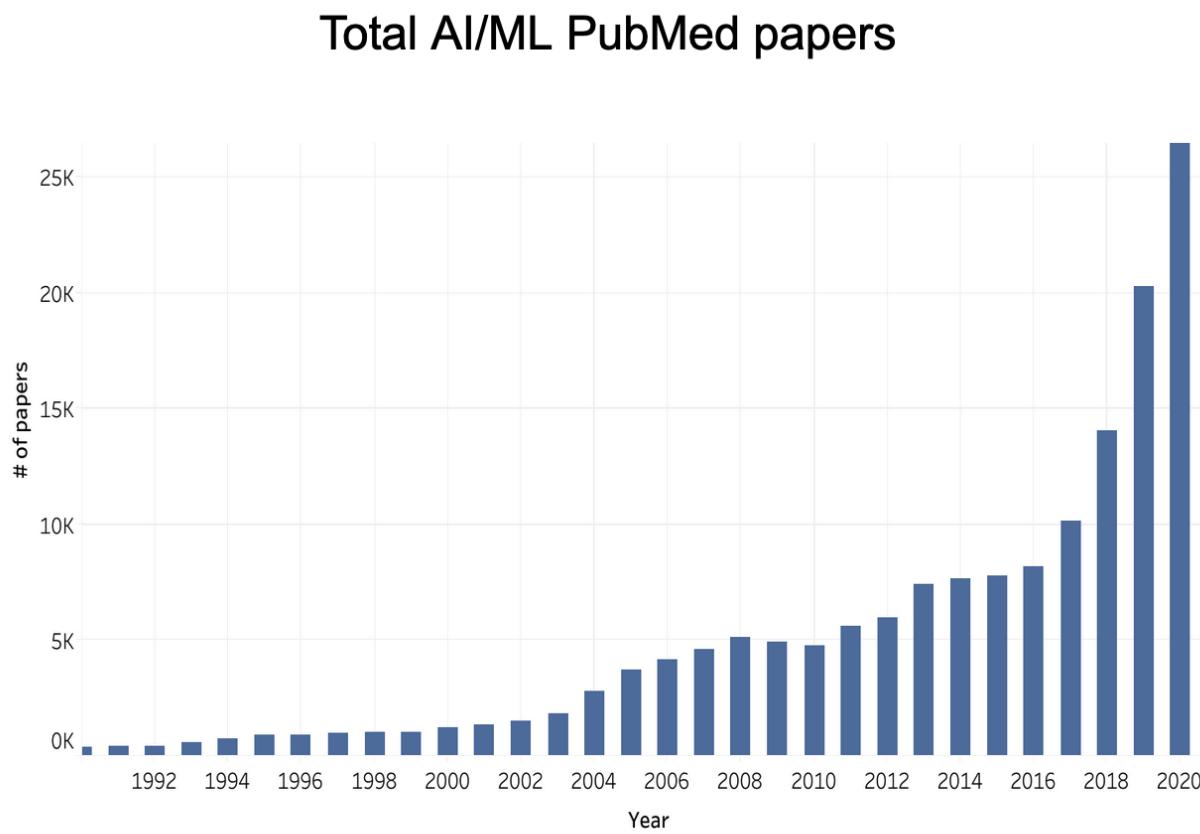
Vast amounts of healthcare data

- Over the past couple of decades, technological advances in data collection have led to an abundance of digital health data.
 - Genome sequencing
 - Wearable sensors
 - High resolution 3D imaging
 - Electronic health records
- Analyzing these types of data can prove very challenging, given their sheer size and complexity.

DL as an analytical tool

- DL offers several advantages over alternative data analysis tools when dealing with large volumes of data:
 - Ability to model highly complex relationships
 - Ability to handle noisy data
 - Adaptability to diverse data types (e.g., text, images, time series)
 - Scalability
- Given the complexity of human health, and the large amounts of health data now available, AI methods like DL have become increasingly popular in healthcare research ¹

DL in healthcare research over the years

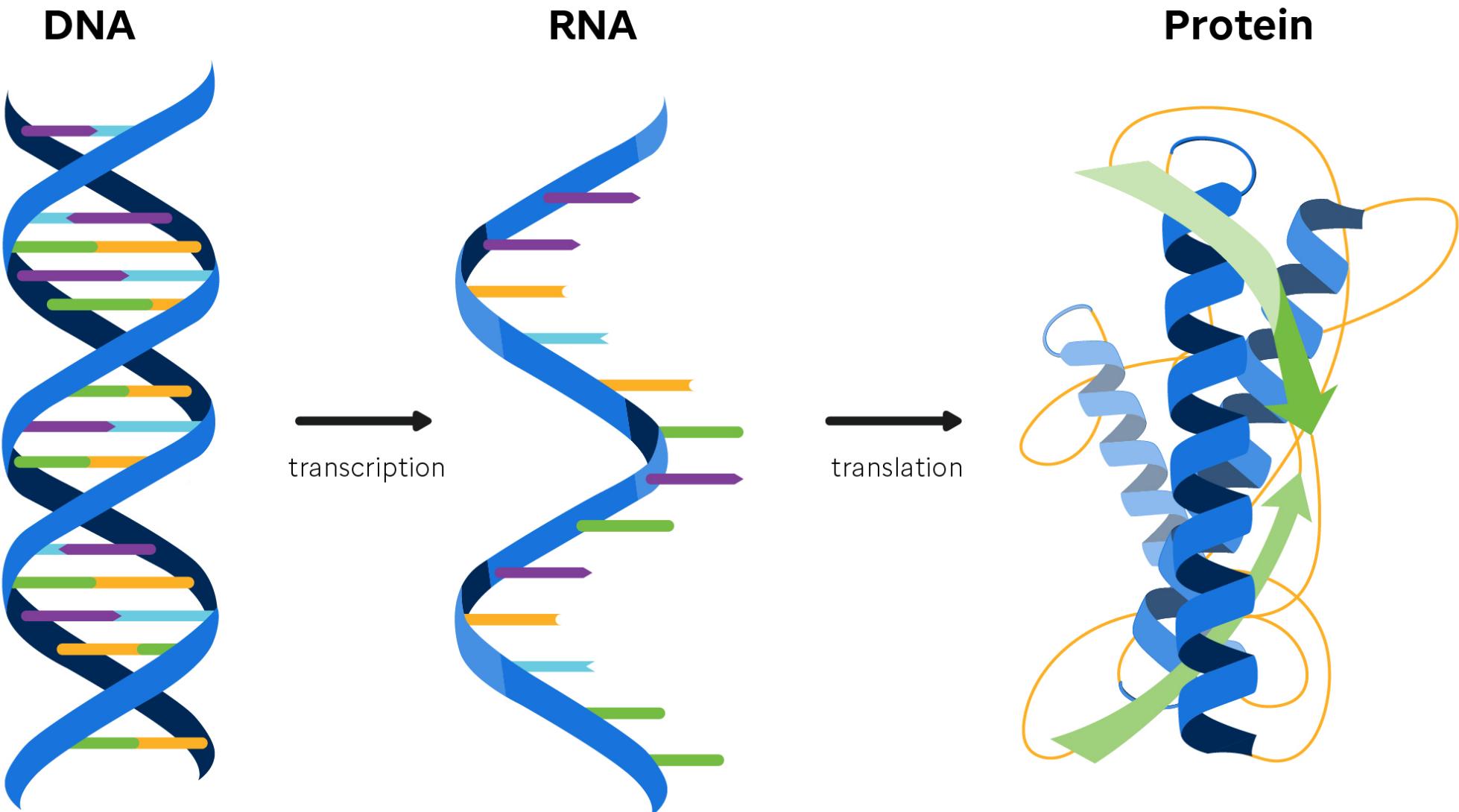


Breakout #1

Why is DL particularly powerful for data modalities like images, text, EKG voltage, etc?

Proteomics

Proteins 101



Proteins 101

mRNA: The Starting Point of Translation

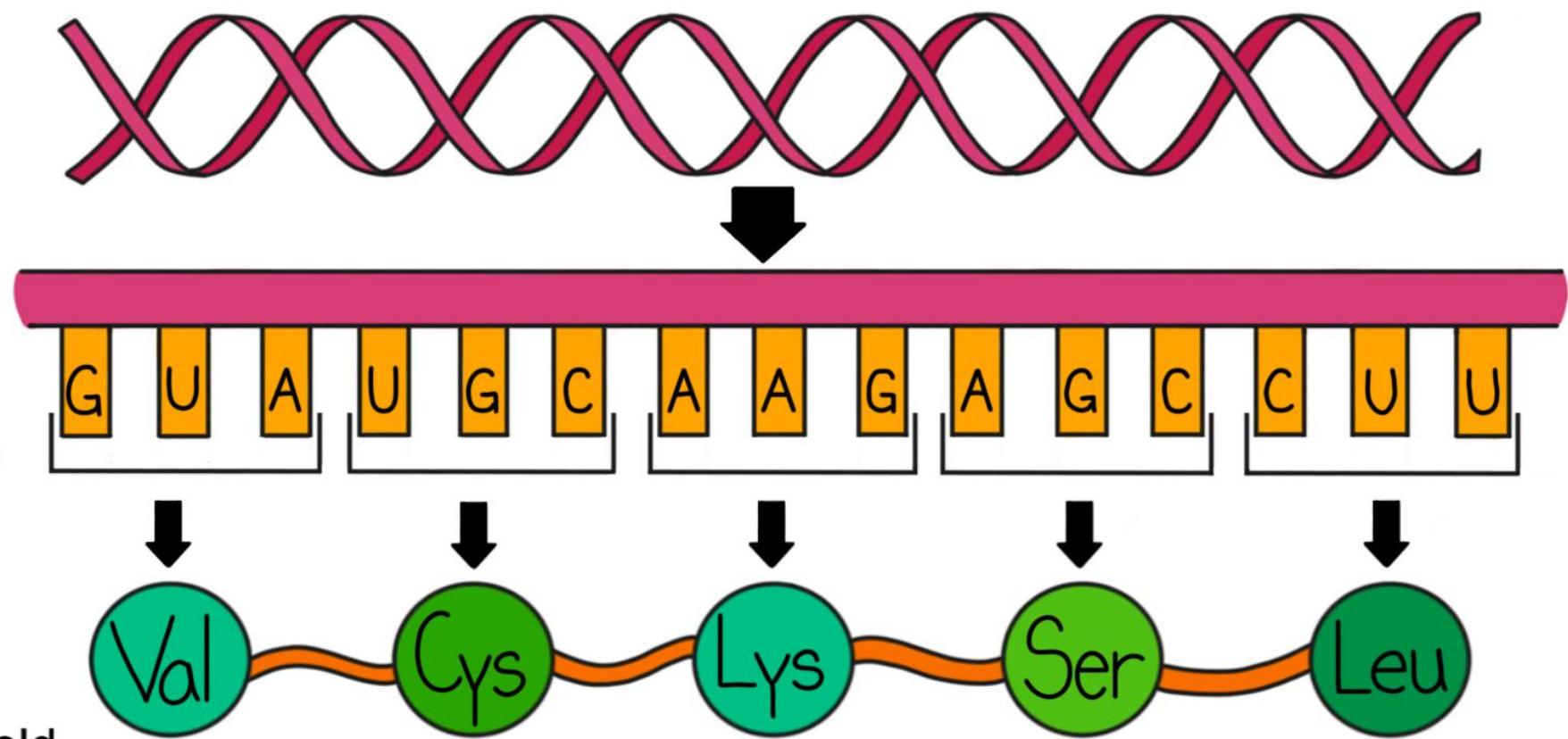
DNA is transcribed into mRNA.

mRNA is translated into amino acids.

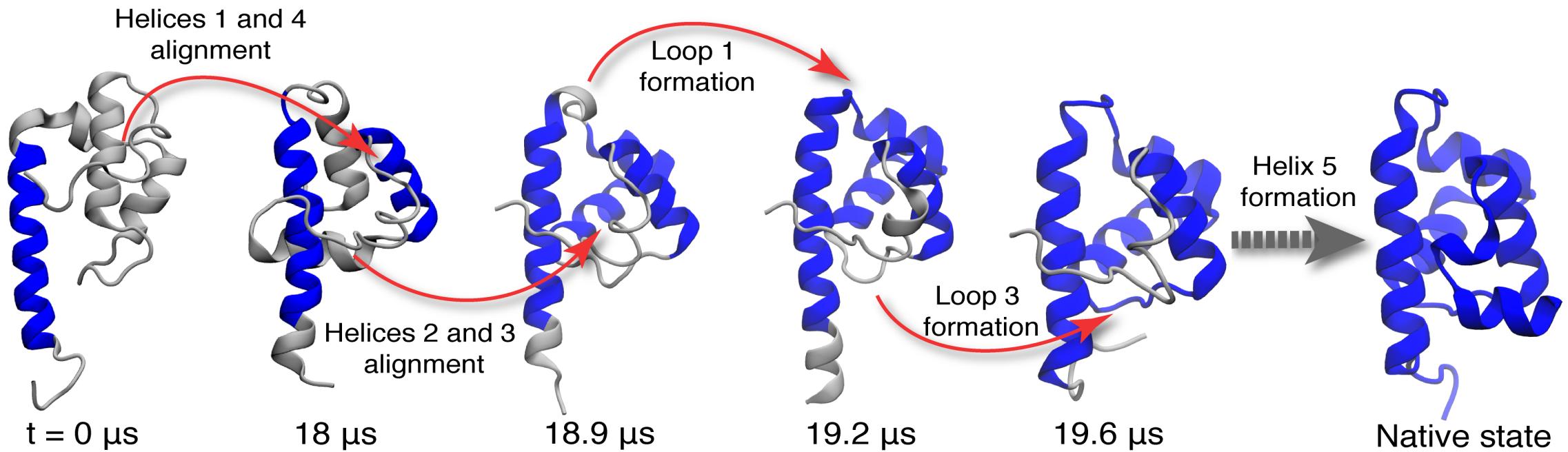
Each codon corresponds to one amino acid.

Amino acids form polypeptide chains.

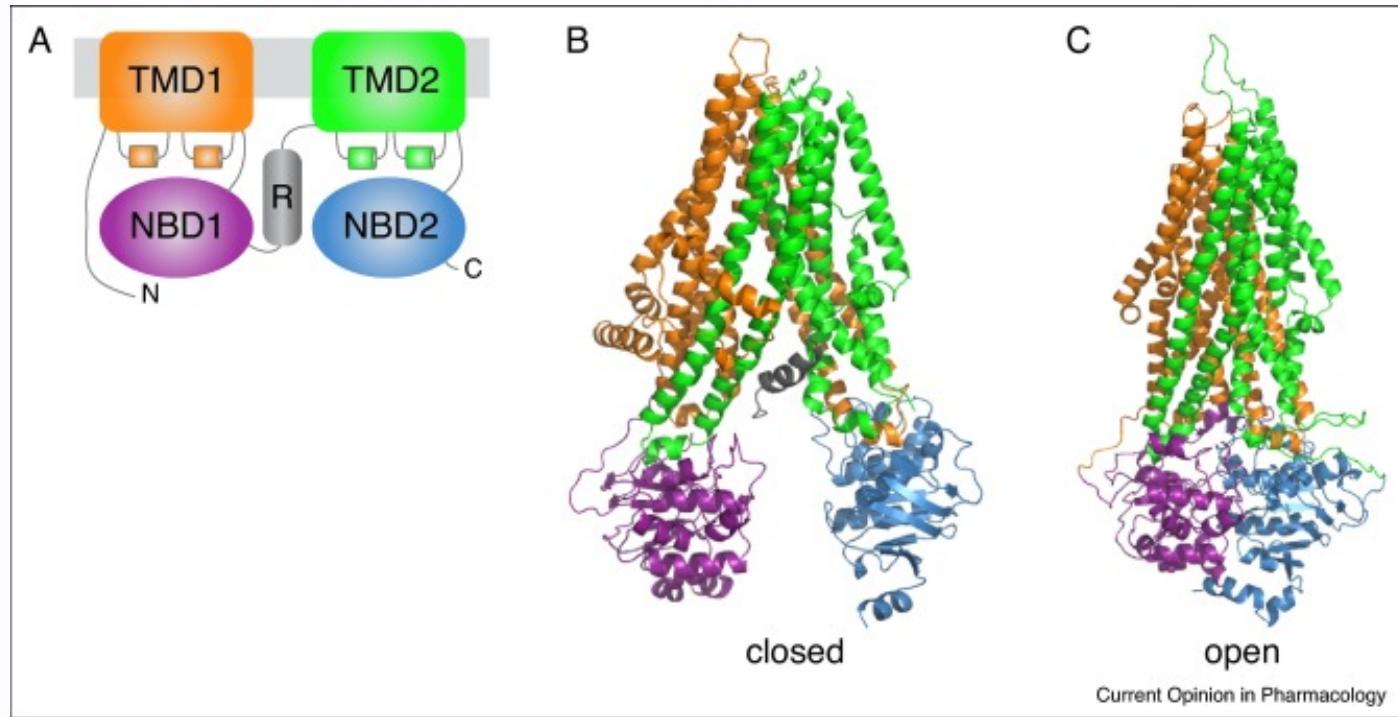
Polypeptide chains fold into proteins.



Proteins 101

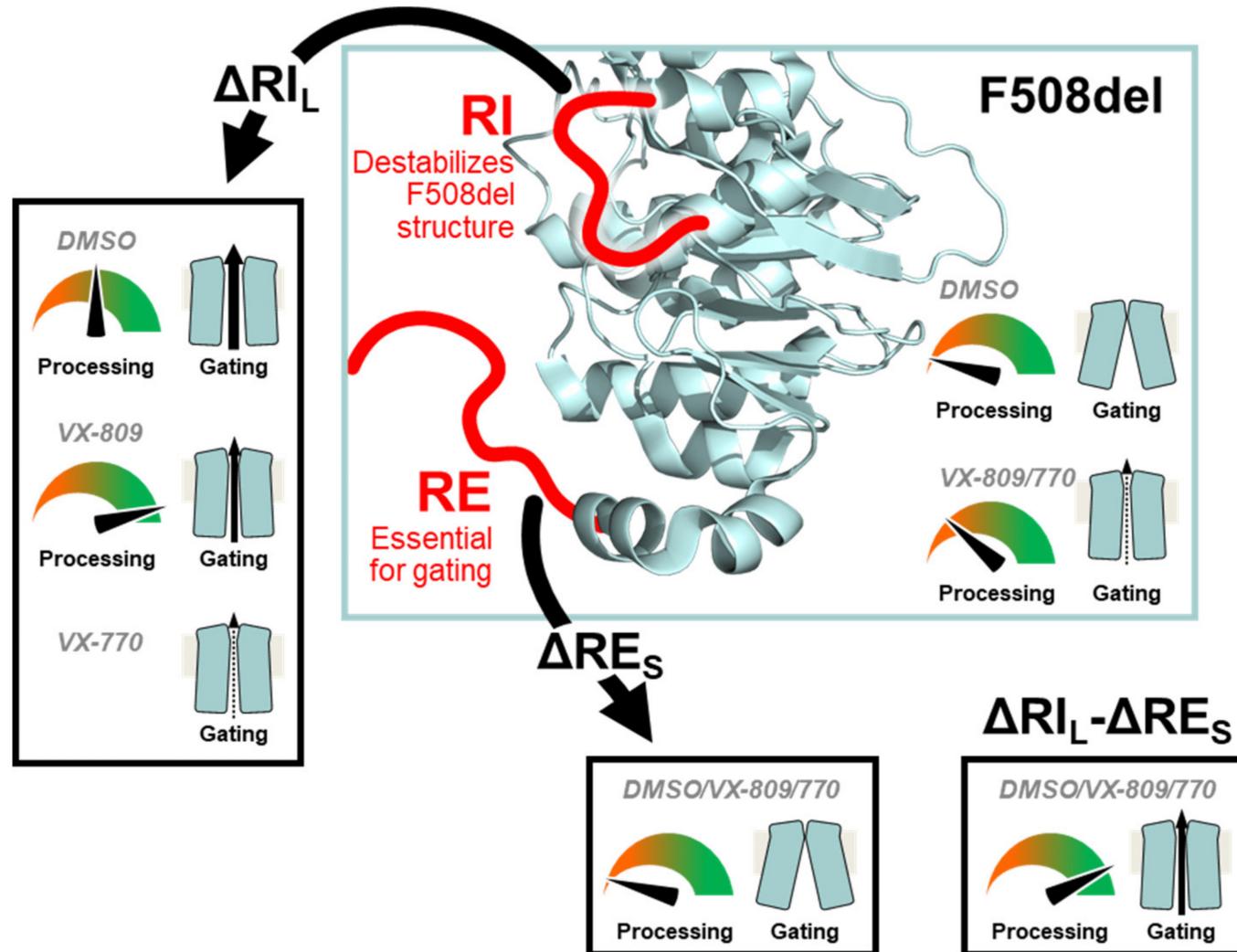


Proteins behaving well (CFTR)



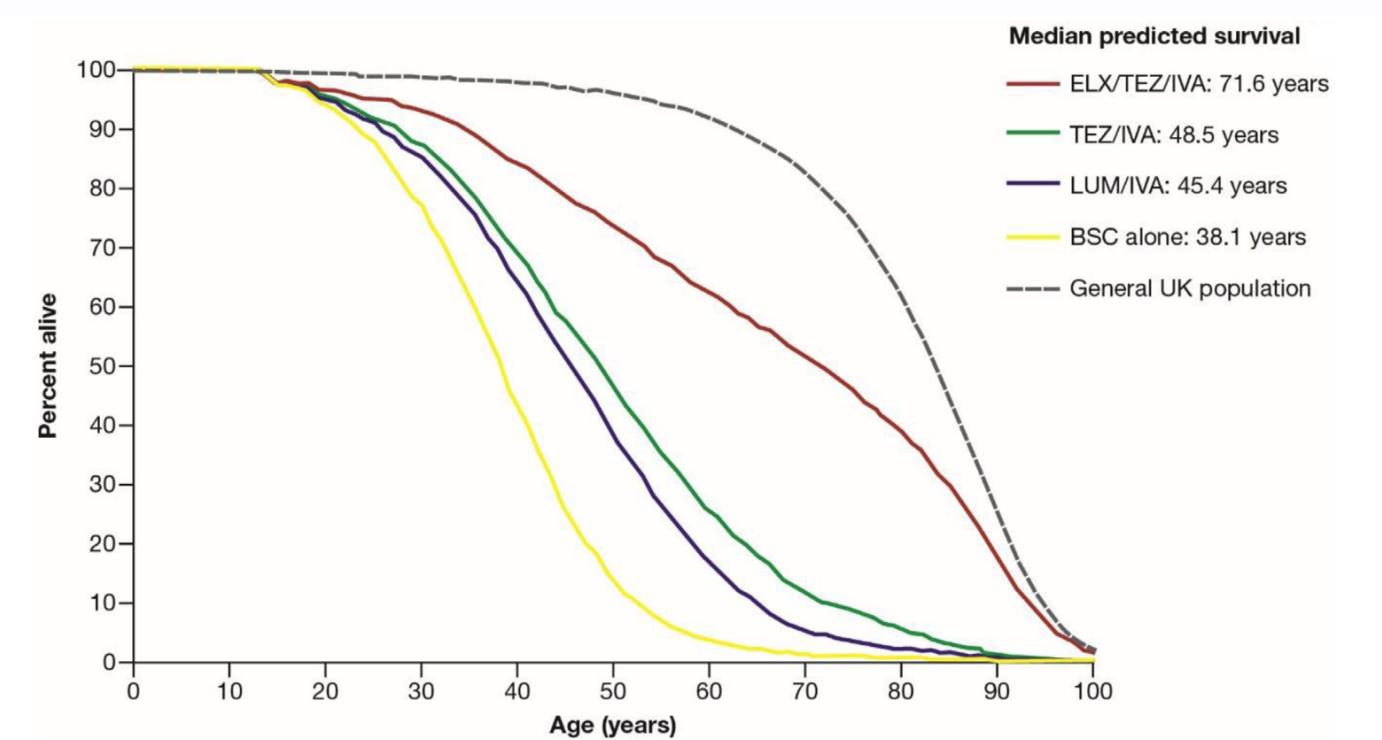
Source: Mijnders et. al (2017)

Proteins behaving badly (CFTR)



Source: Uliyakina et. al (2020)

CFTR protein corrected (modulator therapy)



Source: Lopez et. al (2022)

Protein structure research

- Protein structure and function are inherently linked
 - Knowing a protein's structure helps elucidate its interactions with other molecules.
 - For this reason, protein structure research is extremely important for fields like pharmacology, biochemistry, and immunology
- **The problem:** discovering new protein structures has historically proven to be a very time-consuming and expensive process

The Protein Data Bank (PDB)

- The Protein Data Bank (PDB) contains a comprehensive archive of experimentally determined three-dimensional protein structures
- Currently, it houses around 186,000 known protein structures
 - This number pales in comparison to the billions of known protein sequences

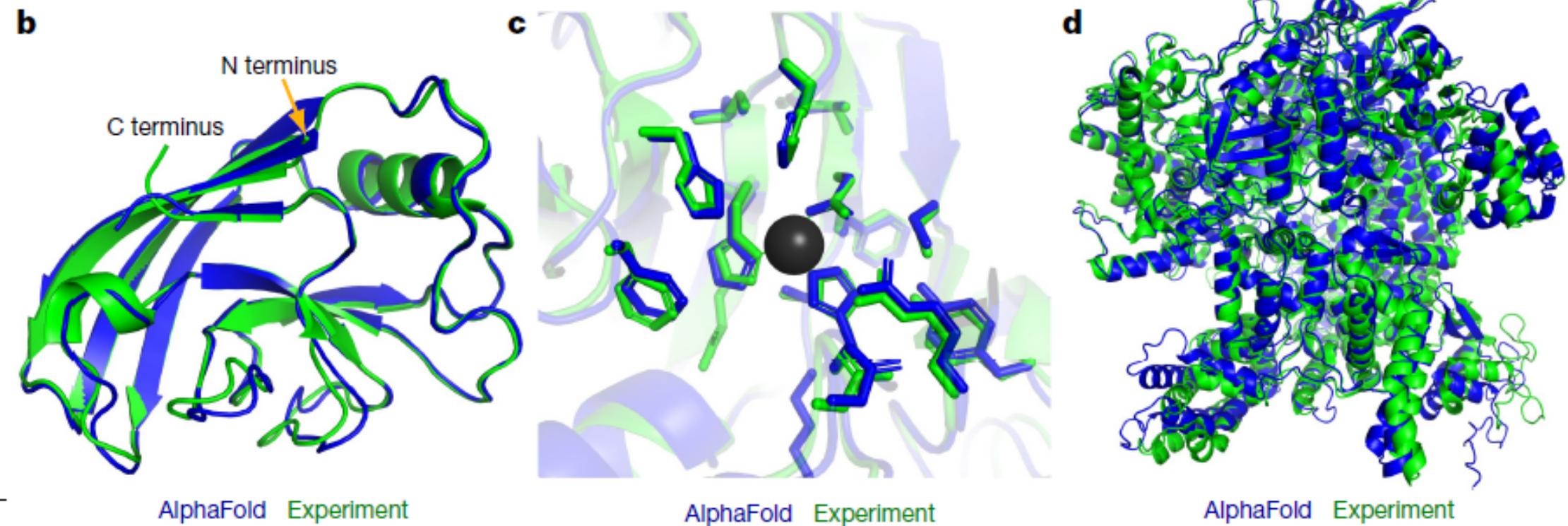
DL in protein structure research

- Protein folding patterns are governed by a variety of different factors, including evolutionary, physical, and geometric constraints
- There exist large databanks from which these factors can be modeled, such as the PDB with its genetic and structural databases
- By leveraging these data, various research groups have recently succeeded in developing DL models capable of predicting folding patterns based on amino acid sequences.

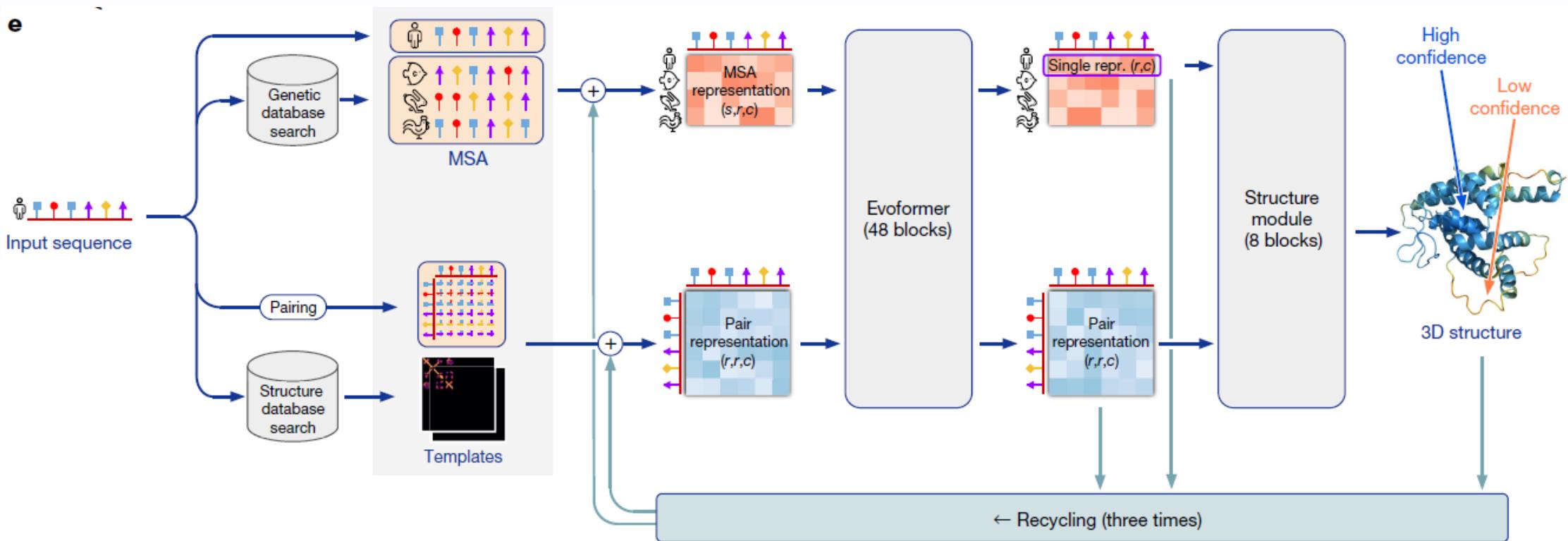
AlphaFold

- AlphaFold is a DL system using advanced neural network architectures and training algorithms to predict protein structures with atomic accuracy²
- This model won the **Critical Assessment of Structure Prediction (CASP)** competition in 2020, a biennial event where international research groups compete to predict protein structures
 - This was the first time that a DL model outperformed all other experimental methods in this competition, with the potential of revolutionising protein structure research with more time- and resource-effective methods

Example of AlphaFold's predicted structures



AlphaFold's architecture



Breakout #2

Besides the 3D structure of the protein, what other "labels" would we want to predict with an (amino acid) input sequence?

Genomics

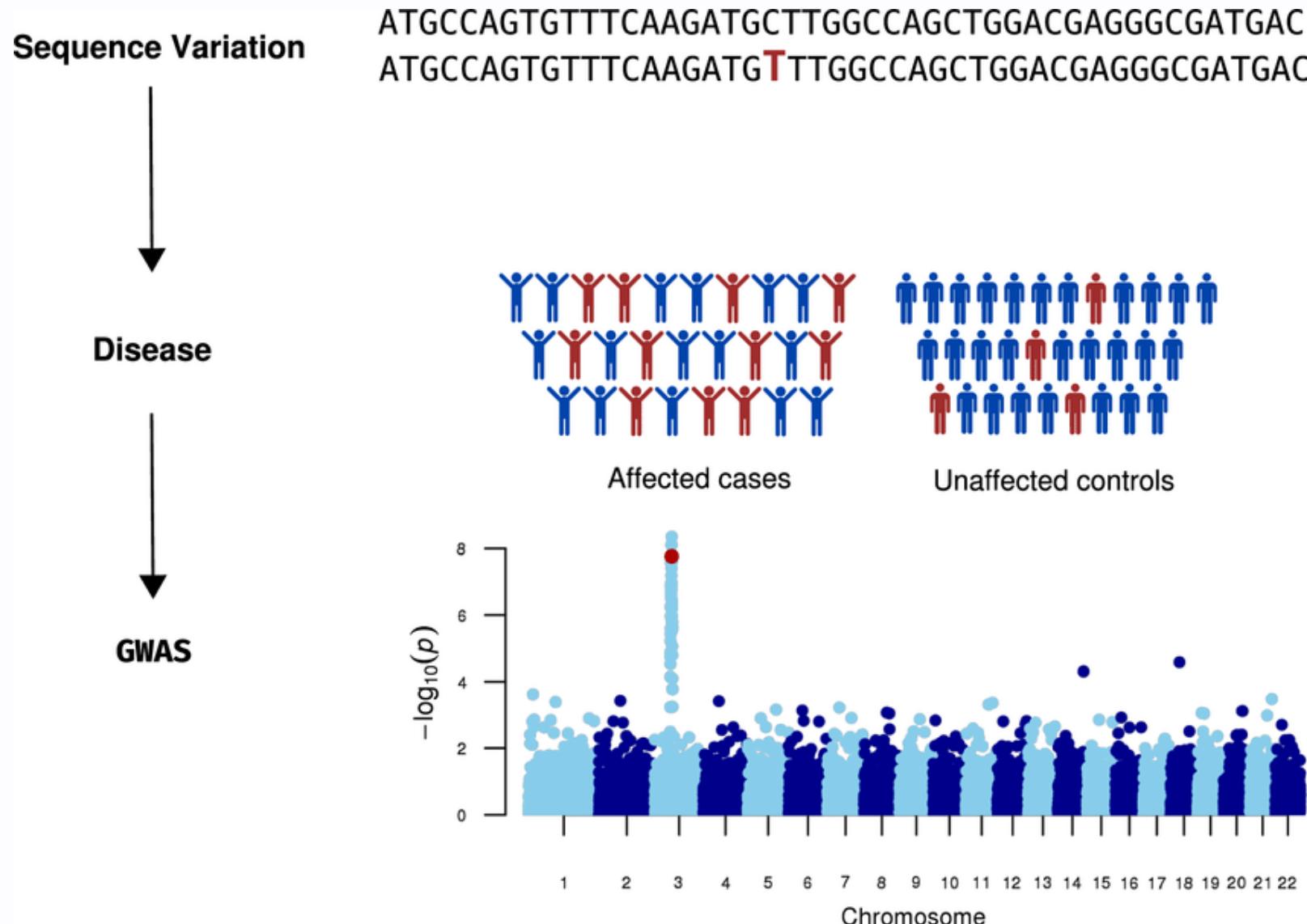
Genetics and health

- Most common diseases have a genetic component
- Genetic research in healthcare has traditionally focused on identifying rare monogenic mutations that are individually associated with a high risk of disease
- However, in most cases, polygenic risk factors, involving many common genetic variants of small individual impact, play a greater role in disease risk than rare monogenic mutations³

Genome-wide association studies (GWAS)

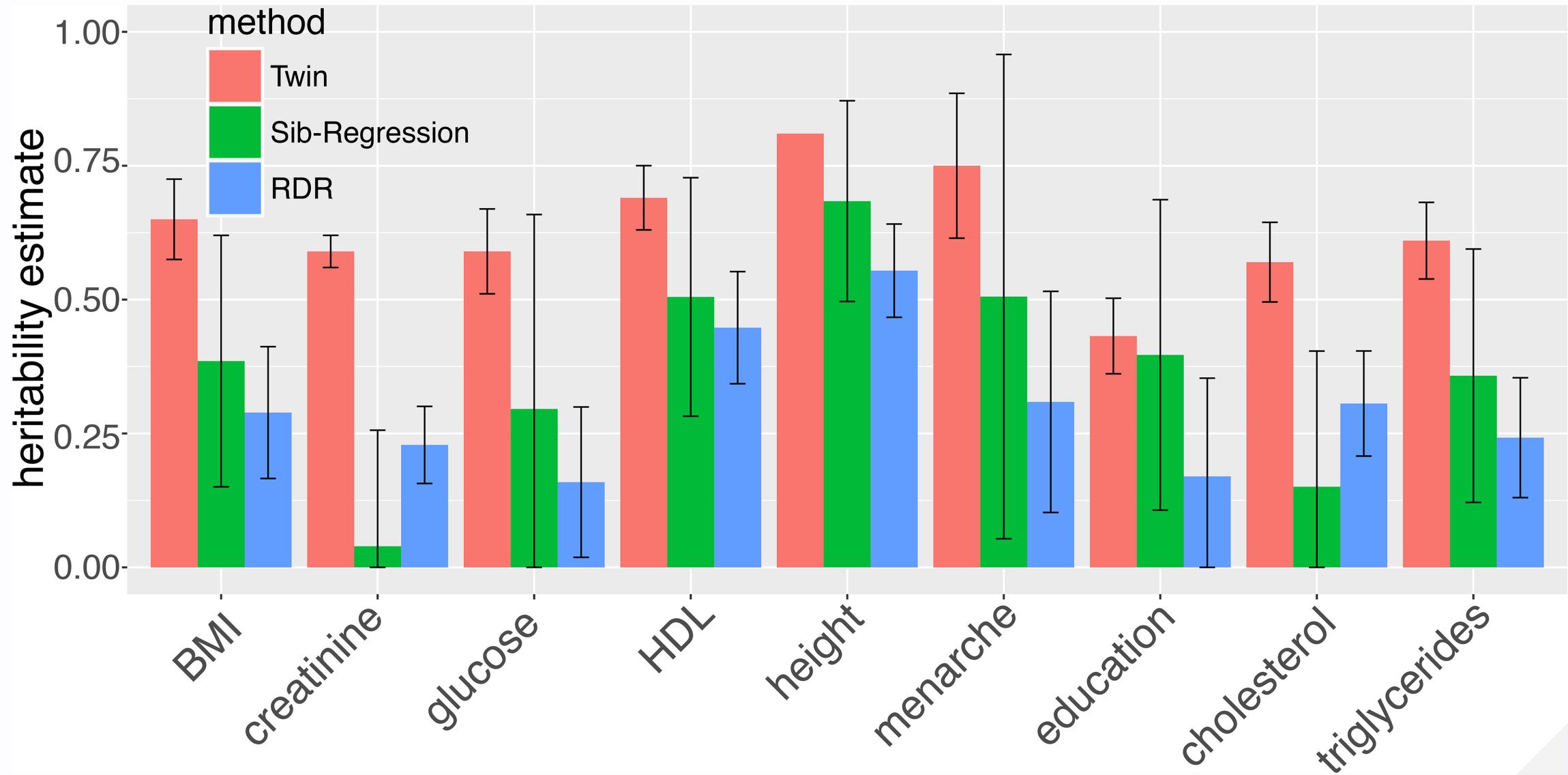
- GWAS involve leveraging genetic data from large and diverse populations to identify genetic variants whose presence is significantly associated with a particular trait or disease of interest
- These studies became increasingly popular in the mid-2000s mainly due to the rise of high-throughput genotyping technologies and to the development of large, publicly available genetic databases
- Associated genetic variants identified via GWAS are typically large in number and most often found in non-coding DNA
 - Downstream analyses are required to properly assess their impact on disease risk

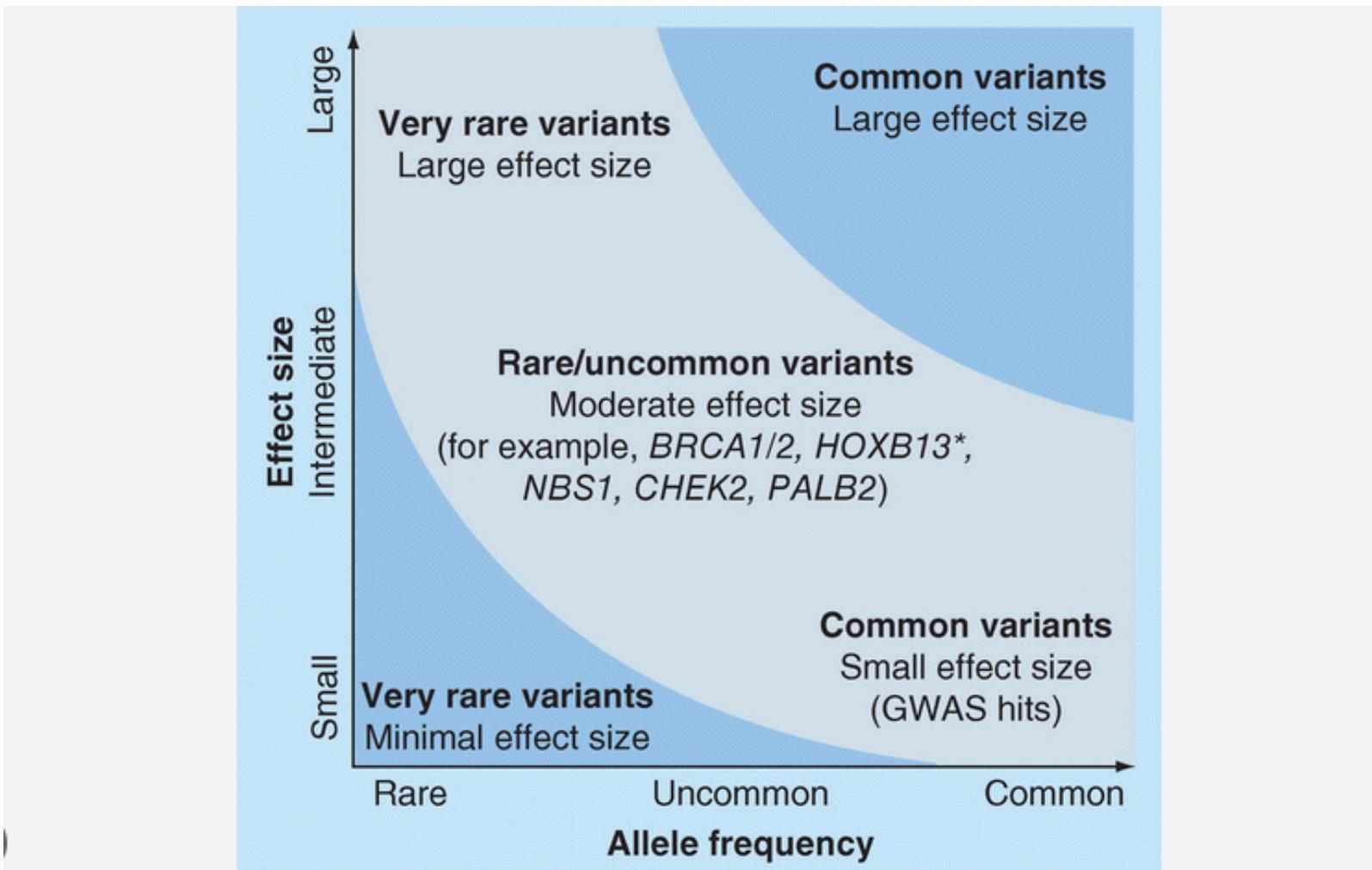
Genome-wide association studies (GWAS)



Source: Palsson et. al (2019)

Missing heritability (Source: Young (2019))





Modeling polygenic risk

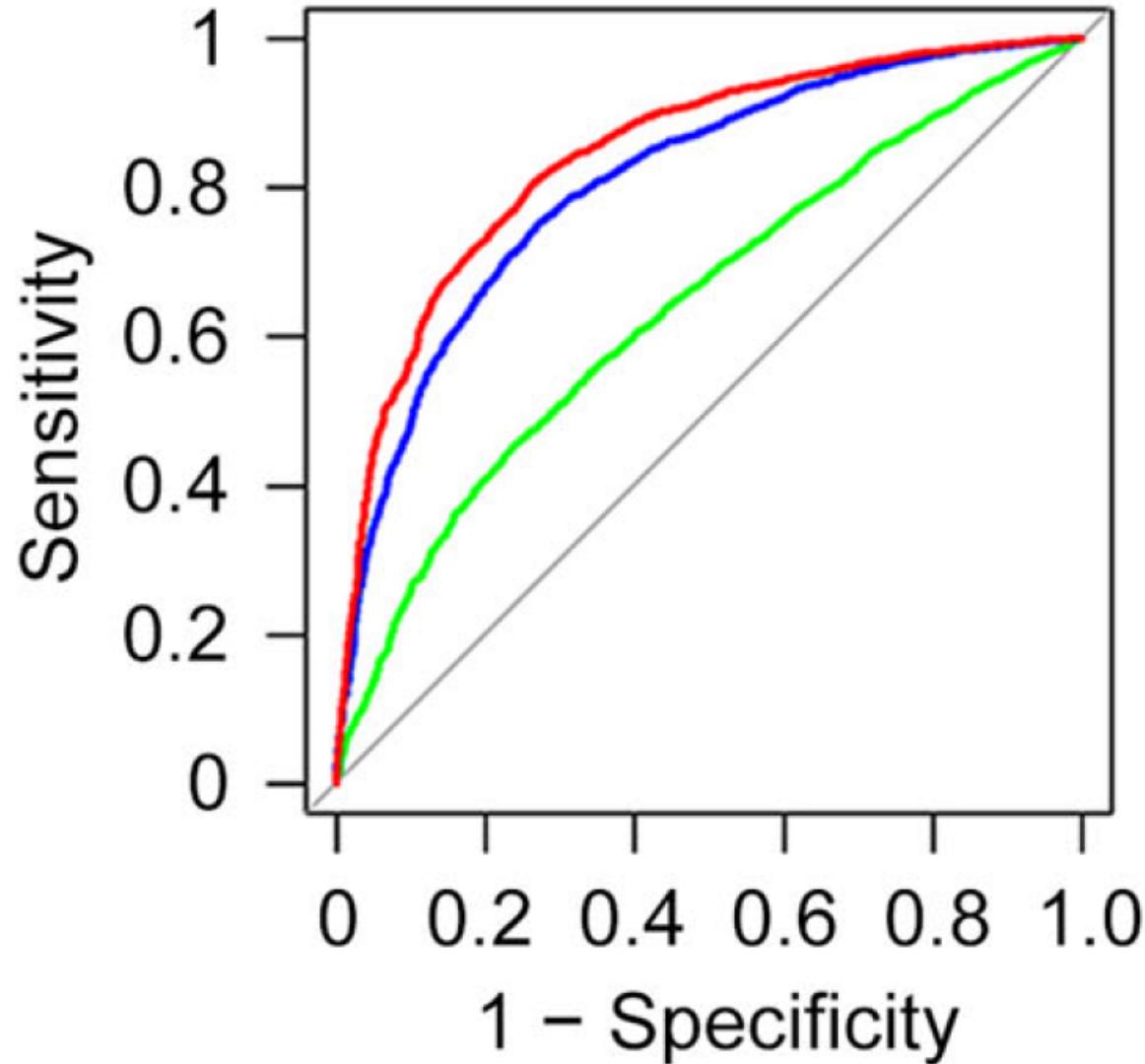
- A popular model of polygenic risk is the weighted polygenic risk score (wPRS)
 - wPRS involves assigning weights to genetic variants based on their effect sizes from GWAS and linearly combining them to generate a risk score based on an individual's genetic makeup
- **The problem:** wPRS is prone to bias given its reliance on GWAS effect sizes. It also assumes that the effects of variants are additive while being incapable of modeling non-linear effects or interactions between variants

DL in polygenic risk modeling

- Unlike wPRS, DL models have the capacity to describe complex relationships between GWAS genetic variants and a disease of interest, adapting well to high-dimensional genomic data
- Because polygenic risk is comprised of multiple genetic variants that are more common than high-risk monogenic mutations, better polygenic risk scoring methods enabled by DL could enable early interventions and improved outcomes for a wider variety of diseases and populations

Polygenic risk for Alzheimer's disease (AD)

- Previous GWAS have revealed that multiple genetic variants contribute to the risk of developing AD
 - Individually, most of these variants have small effects on AD risk, hinting at the need for polygenic risk modeling
- In 2023, Zhou et al. developed a fully connected neural network capable of ingesting thousands of genetic variants associated with AD
 - Their polygenic risk score largely outperformed wPRS, achieving AUROC scores of 0.84 and 0.64, respectively⁴



Model:



wPRS

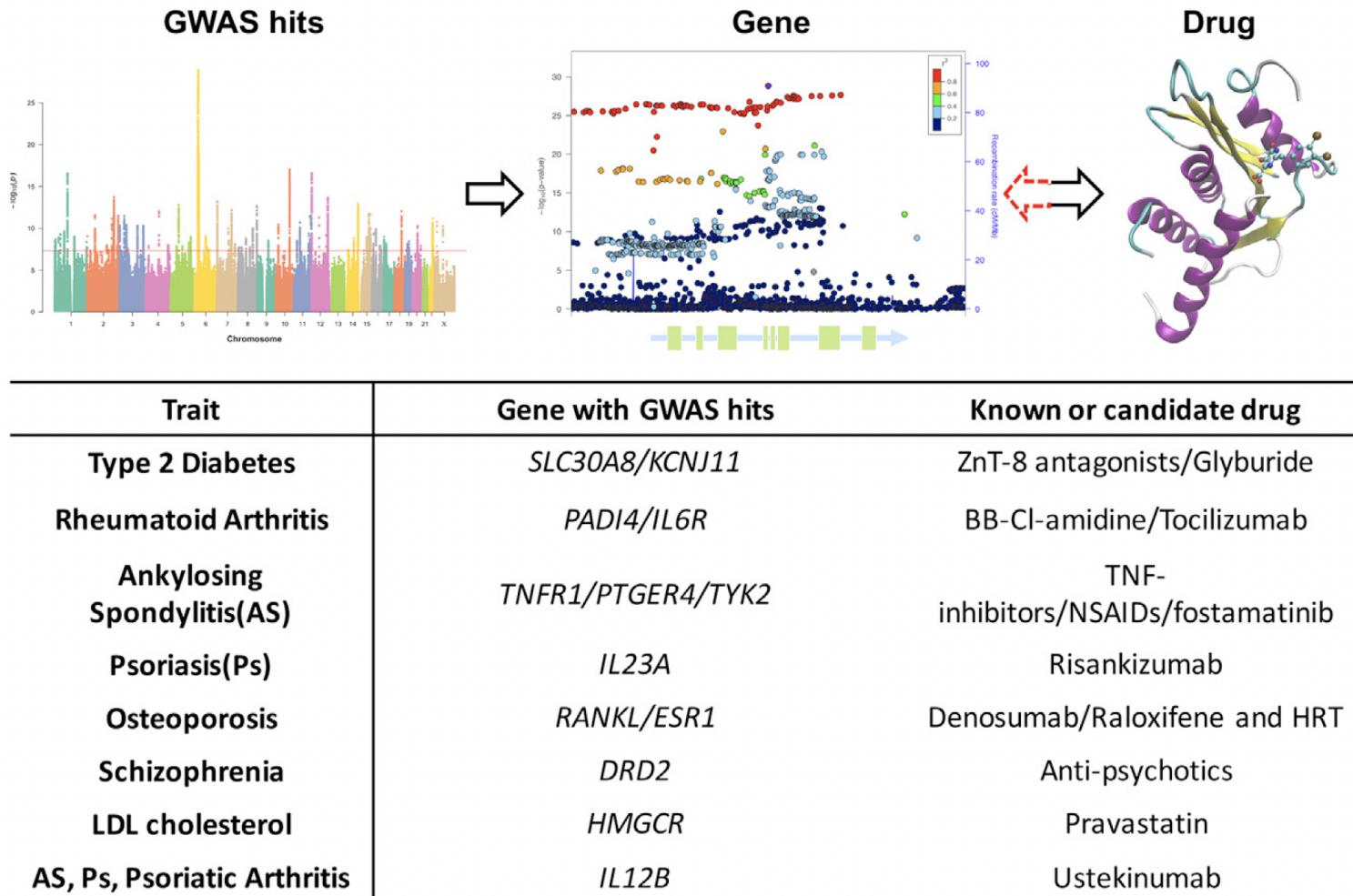


Lasso



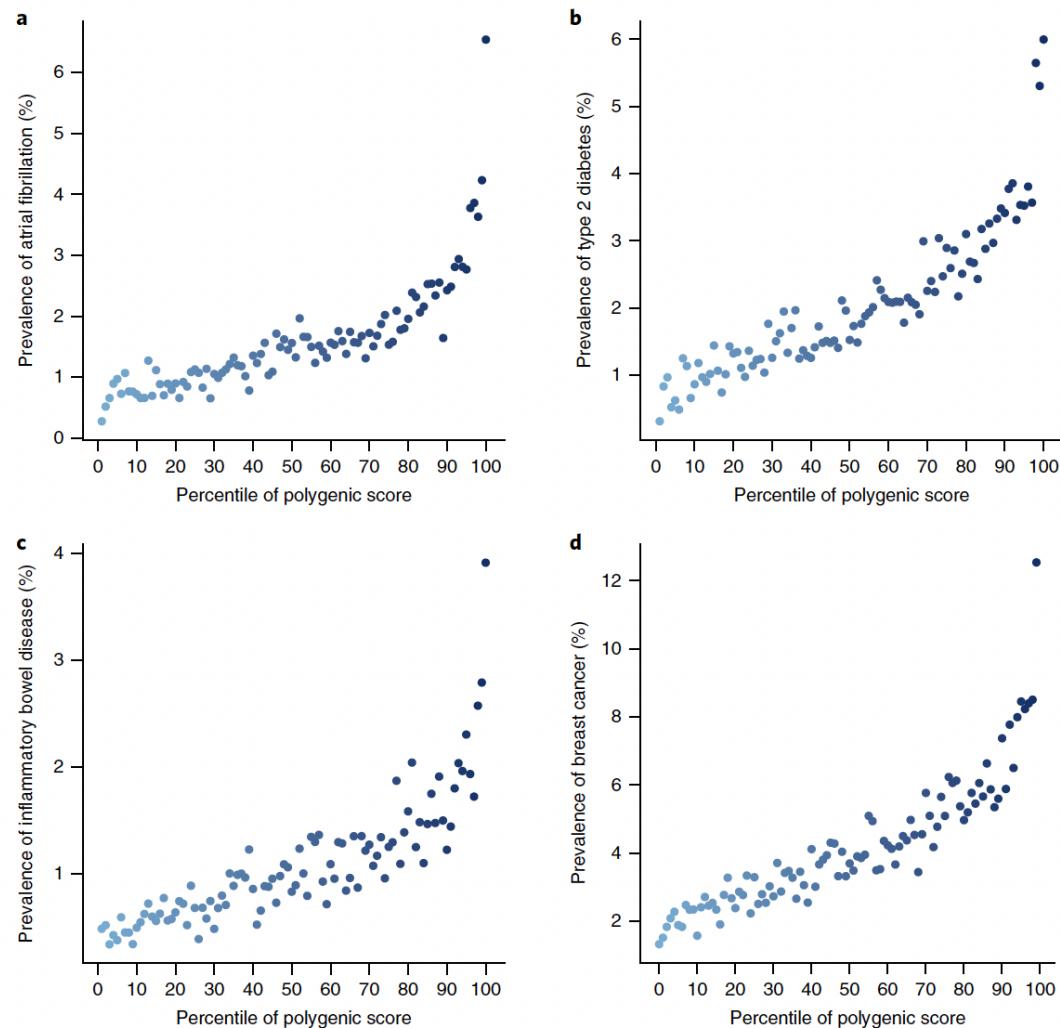
NN

It's all connected



Source: Visscher et. al (2017)

GWAS == Gattaca?



Source: Khera et. al (2018)

Breakout #3

Besides ethical concerns, why haven't GWAS been used more often in clinical care (e.g. pre-diabetes)?

Medical imaging/Radiomics

Medical imaging and healthcare

- Medical imaging provides clinicians with non-invasive or minimally-invasive tools to visually inspect internal anatomy and function
 - X-ray imaging
 - Nuclear imaging (e.g., PET scans)
 - Ultrasound
 - Magnetic resonance imaging (MRI)
 - Optical coherence tomography (OCT)
- In many cases, these techniques enable the early detection, diagnosis, and treatment of many diseases that could otherwise be fatal or incur high morbidity

Recent advances in medical image acquisition

- Given the value of medical imaging for disease detection and management, there is continued interest in advancing medical imaging acquisition techniques
 - This includes improvements in digitisation, resolution, portability, acquisition times, and variety
- Simultaneously, efforts have been led to establish vast, open-source imaging databanks to accelerate research in various disease contexts

Medical image analysis

- In clinic, for many disease contexts, visual inspections performed by a radiologist remain the gold standard for medical image analysis
- **The problem:** these conventional reads fail fully to exploit modern medical image acquisition technologies. Subtle signals captured in high resolution images may not be appreciated by the naked eye, but may represent consistent markers of disease

DL and its success in radiomics

- Radiomics is a field that applies advanced computational methods to extract quantitative features from medical images to ultimately characterise tissue properties
- DL tools, in particular convolutional neural networks (CNNs), have seen increasing popularity in radiomics research given their excellent track record in natural image processing and analysis over the last decade

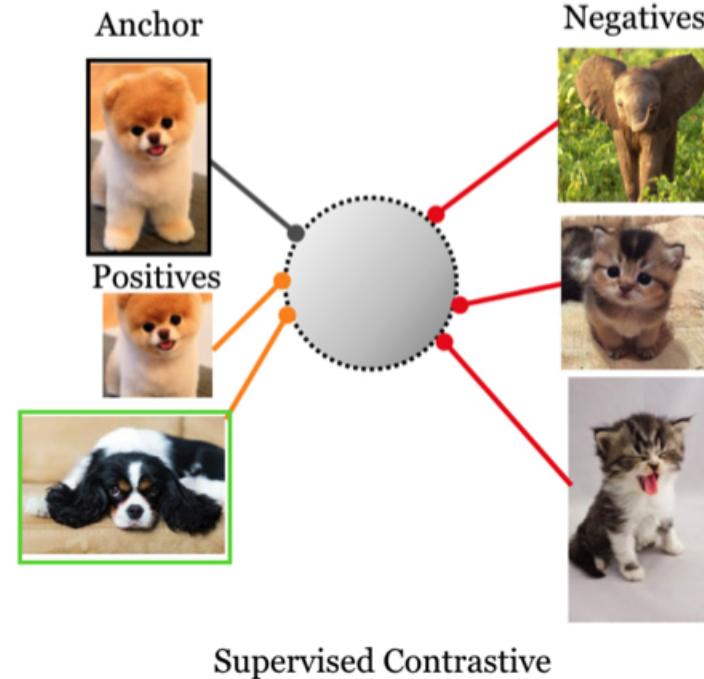
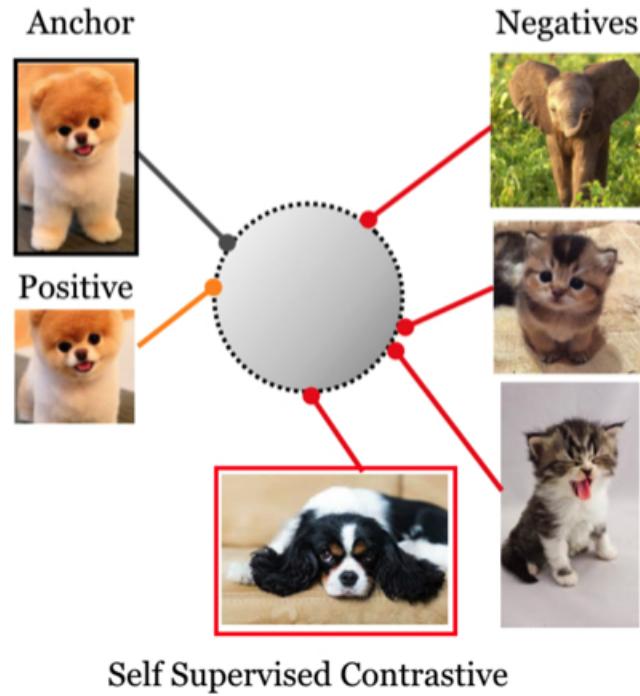
Case study: neuropsychiatric lupus (NPSLE)

- Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease that can affect the nervous system
 - Manifestations of neuropsychiatric lupus (NPSLE) are highly heterogeneous, ranging from mild headaches to psychosis
- Underlying mechanisms of this rare disease are unknown, and recommended diagnostic protocols involve a lengthy, costly, subjective, and non-specific ruling out process
 - Part of this workup involves a conventional read of a structural T1-weighted MRI scan, which fails to identify brain abnormalities in over 50% of lupus patients with neuropsychiatric symptoms

Self-supervised CNN for NPSLE classification

- In 2022, Inglese et al. developed a self-supervised CNN for NPSLE classification⁵
- Given the rarity of this disease, the group faced data scarcity challenges, having access to just 163 T1-weighted MRI images
- Despite these low numbers and the lack of abnormal signals in the MRI scans as probed by the naked eye, their rather simple CNN reached an average classification performance of 83%
 - This was possible due to their use of contrastive learning and augmentation methods

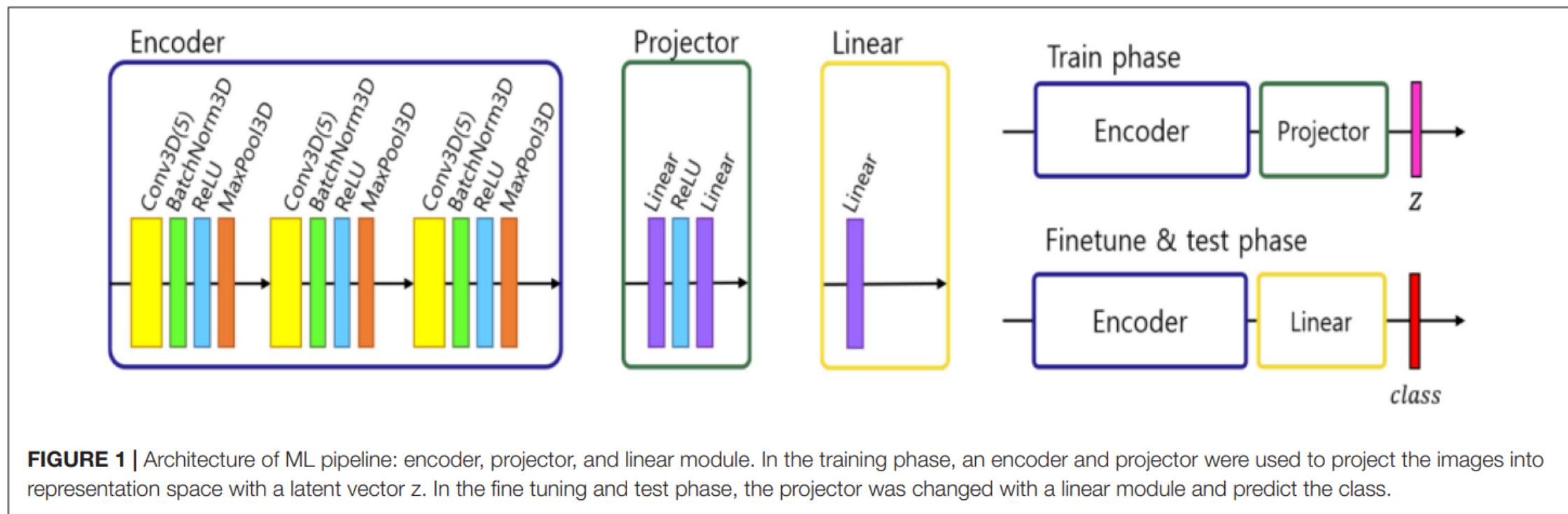
Self-supervised contrastive learning



$$\mathcal{L}^{self} = \sum_{i \in I} \mathcal{L}_i^{self} = - \sum_{i \in I} \log \frac{\exp(z_i \cdot z_{j(i)}/\tau)}{\sum_{a \in A(i)} \exp(z_i \cdot z_a/\tau)} \quad (1)$$

Source: Khosla et. al (2020)

Inglese's self-supervised CNN architecture

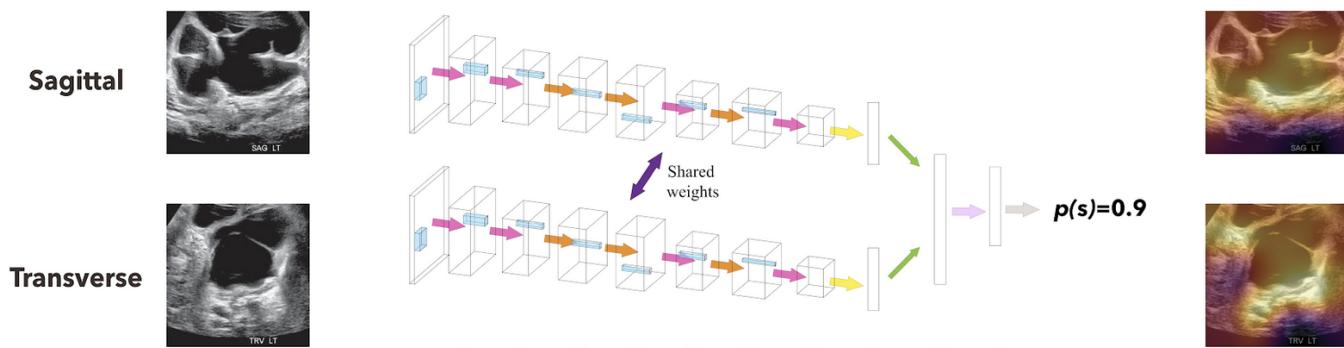
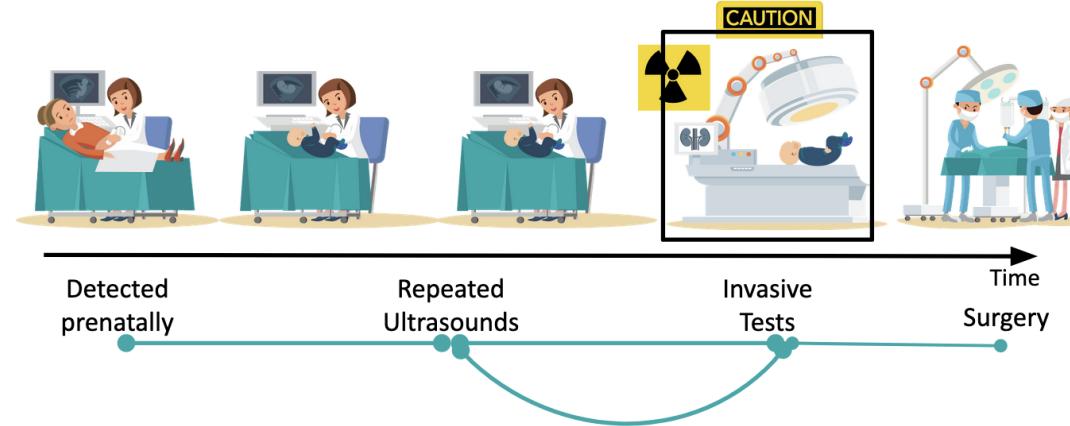


Hydronephrosis

- Prenatal hydronephrosis (PHN) is when the kidney dilates during pregnancy (20% of pregnancies)
- Children born with PHN comprise approximately 20-30% of patients seen in pediatric urology clinics
- All children will be monitored up to 36 months unless there is a spontaneous resolution, meaning many invasive ultrasounds
- Up to 30% of PHN infants will require surgery
- **Could AI help predict earlier when patients need surgery using ultrasound images?**

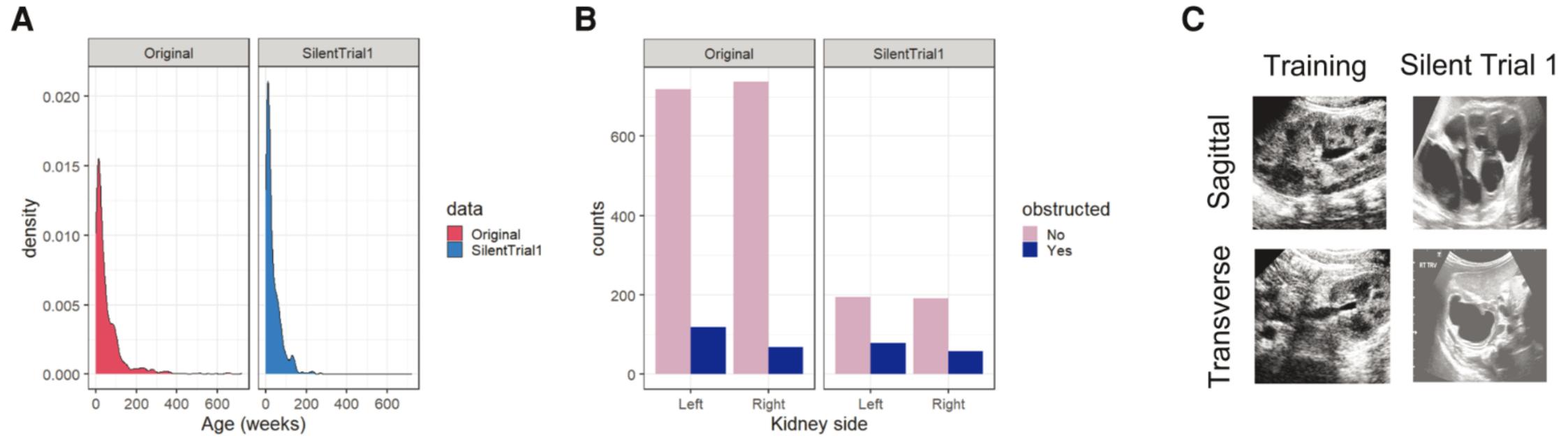
Hydronephrosis

Current clinical management of prenatal hydronephrosis



Source: Erdman et. al (2021)

Hydronephrosis (silent trial)



Source: Kwong et. al (2022)

Hydronephrosis (clinical implementation)

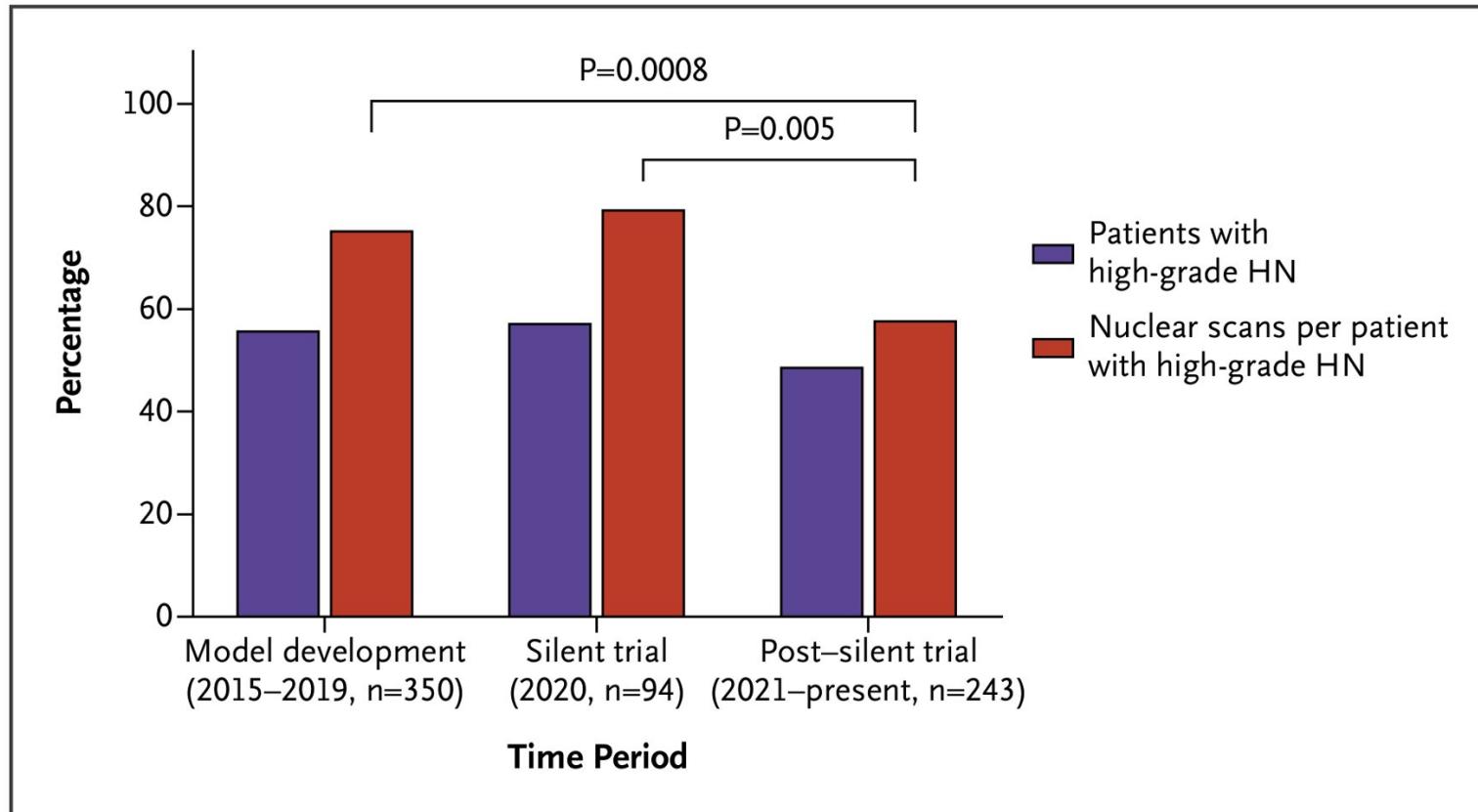


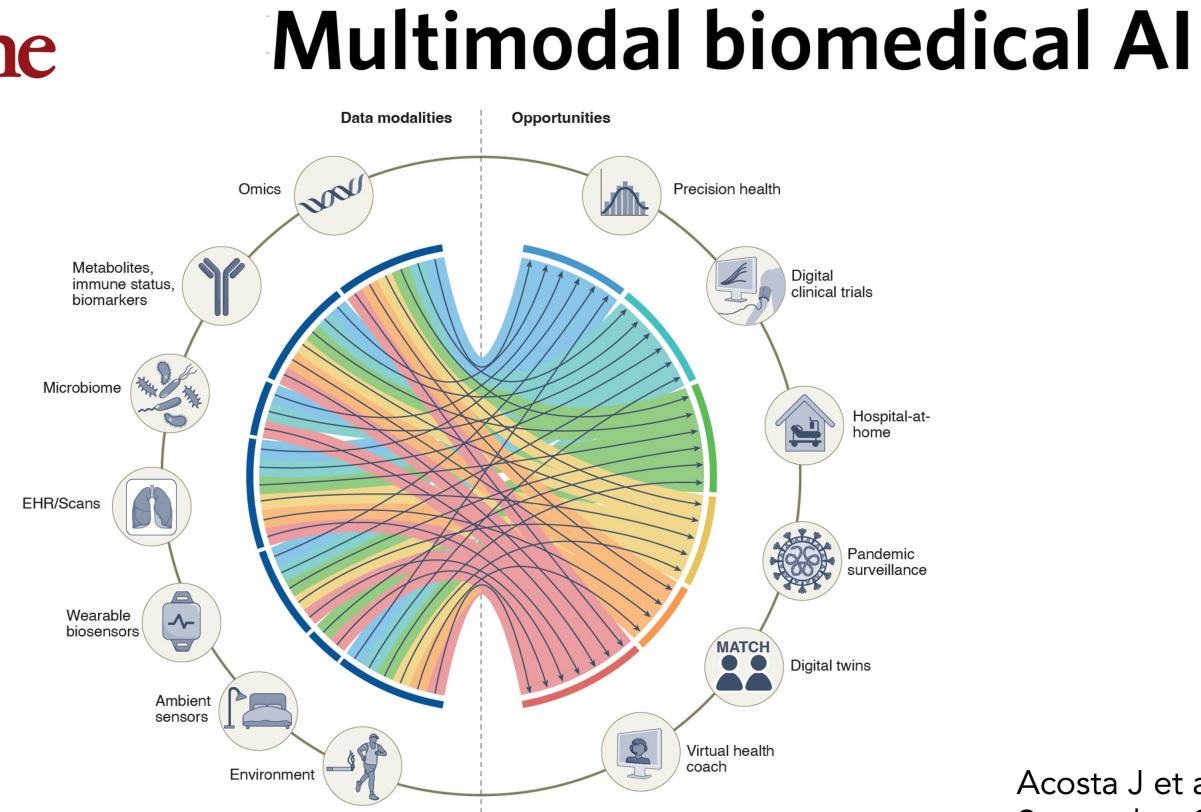
Figure 2. Change in Proportion of Nuclear Scans over Time.

Source: Kwong et. al (2024)

Conclusion

Multimodal utopia (v1)?

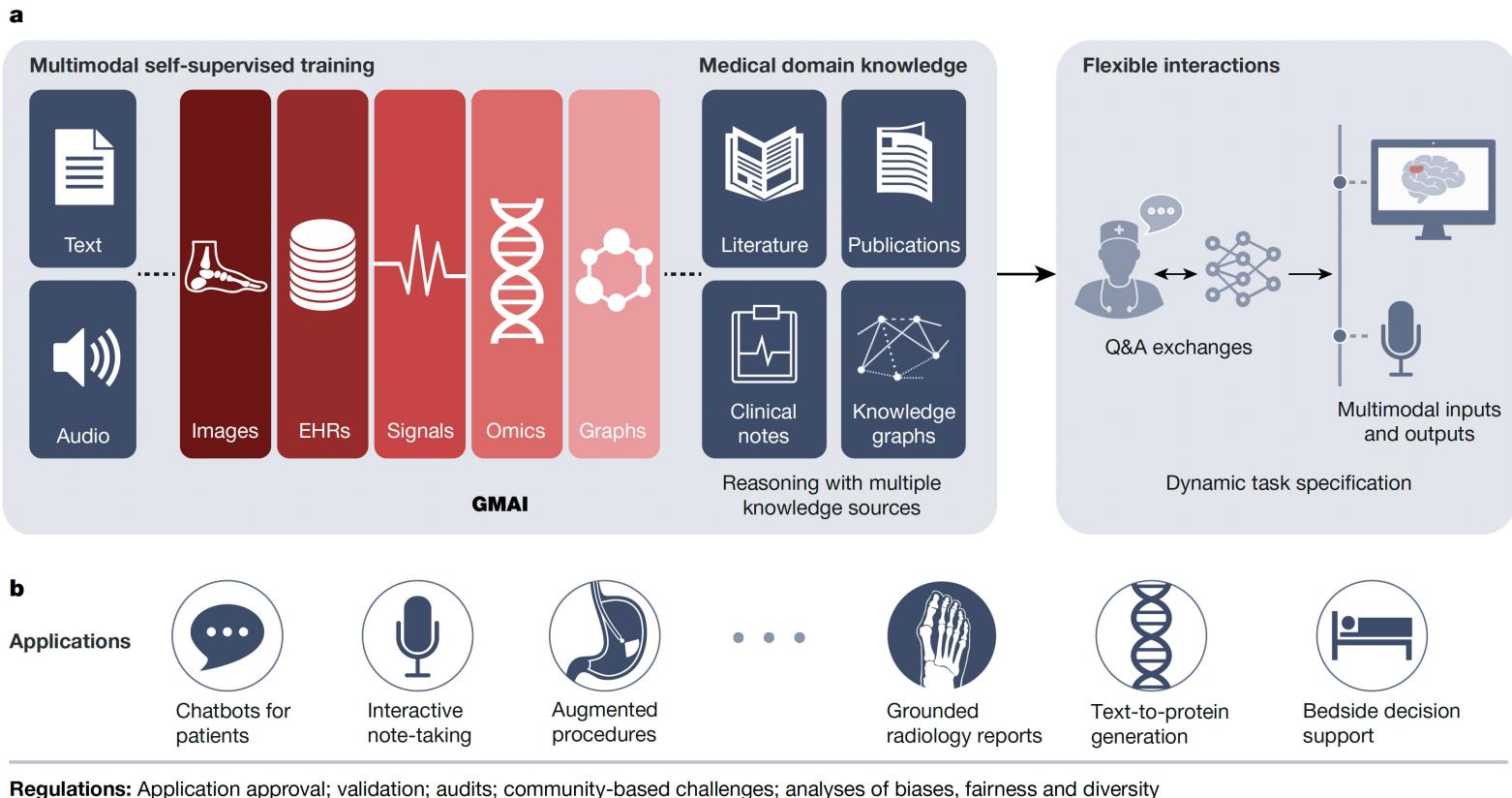
nature
medicine



Acosta J et al,
September 2022

Source

Multimodal utopia (v2)?



Source

Breakout #4

How would we combine different data modality types in a deep learning model? For example, an EKG with genetic information?

Popularity and success of DL in healthcare research

- As depicted by the previous examples, DL has become a popular tool in healthcare-research across a variety of contexts
- With recent advances in health-related data collection and the establishment of vast digital data repositories, it was only a matter of time before DL started to outshine alternative data analysis methods, given its complex modeling and scaling capabilities
- Next, we will examine how institutions and businesses are working to turn these research tools into commerçiable applications

References

- (1) Jimma, B. L. (2023). Artificial intelligence in healthcare: A bibliometric analysis. *Telematics and Informatics Reports*, 9, 100041-.
<https://doi.org/10.1016/j.teler.2023.100041>
- (2) Jumper, J., Evans, R., Pritzel, A. et al. Highly accurate protein structure prediction with AlphaFold. *Nature* 596, 583–589 (2021).
<https://doi.org/10.1038/s41586-021-03819-2>
- (3) Khera, A.V., Chaffin, M., Aragam, K.G. et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 50, 1219–1224 (2018).
<https://doi.org/10.1038/s41588-018-0183-z>
- (4) Zhou, X., Chen, Y., Ip, F.C.F. et al. Deep learning-based polygenic risk analysis for Alzheimer's disease prediction. *Commun Med* 3, 49 (2023). <https://doi.org/10.1038/s43856-023-00269-x>

(5) Inglese, F., Kim, M., Steup-Beekman, G. M., Huizinga, T. W. J., van Buchem, M. A., de Bresser, J., Kim, D.-S., & Ronen, I. (2022). MRI-Based Classification of Neuropsychiatric Systemic Lupus Erythematosus Patients With Self-Supervised Contrastive Learning. *Frontiers in Neuroscience*, 16, 695888–695888.
<https://doi.org/10.3389/fnins.2022.695888>