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Use of UK Biobank Genetics and Genomics in Drug Discovery and Development

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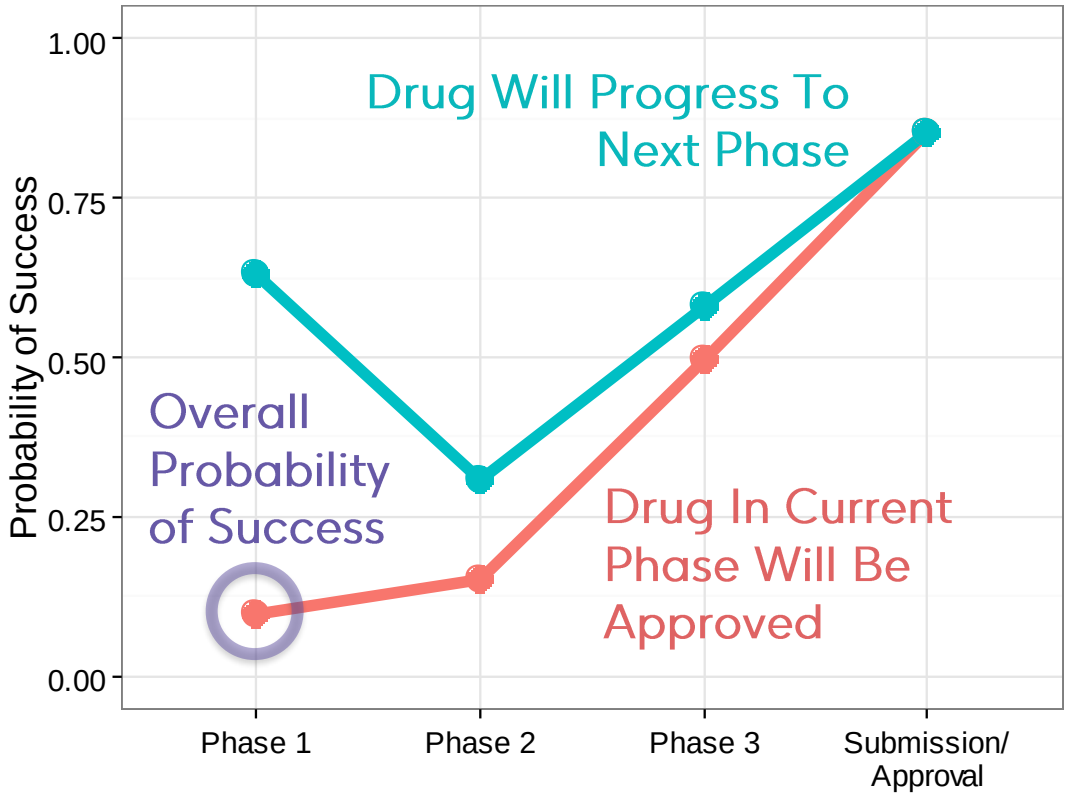
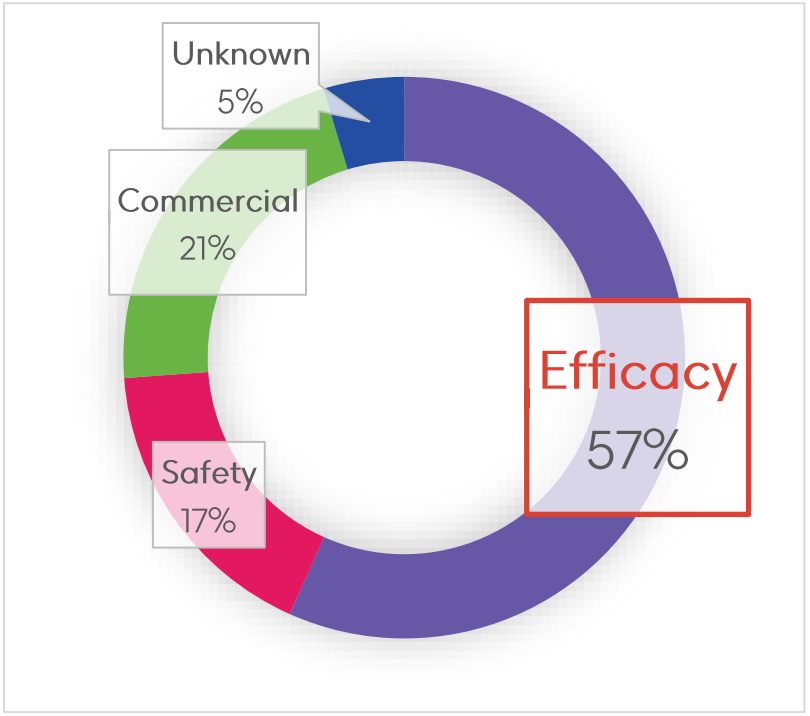
Failure Due to Lack of Efficacy is a Major Challenge in Drug Development

Clinical Development Success Rates for Investigational Drugs



Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. *Nat. Biotechnol.* **32**, 40–51 (2014).

Reasons for Failure of Late-Stage Clinical Development of Experimental Agents (344 Drugs)

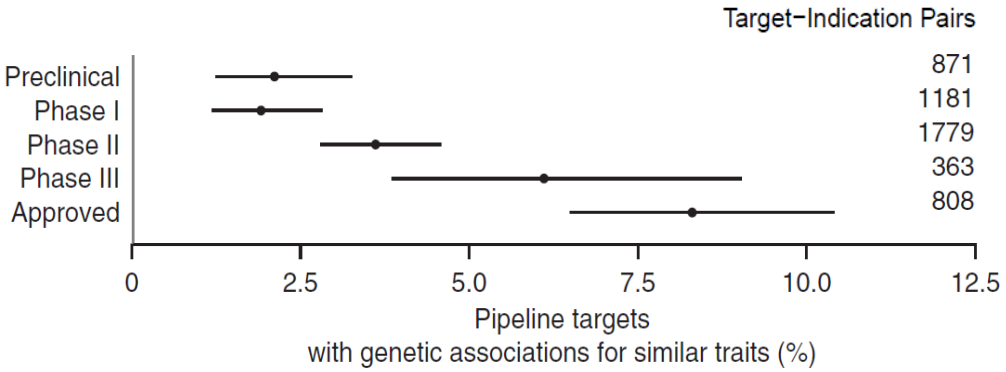


Thomas D. et al. *Clinical Development Success Rates and Contributing Factors 2011–2020* (Biotechnology Innovation Organization, 2021); https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

~$2.6bn in R&D costs per drug

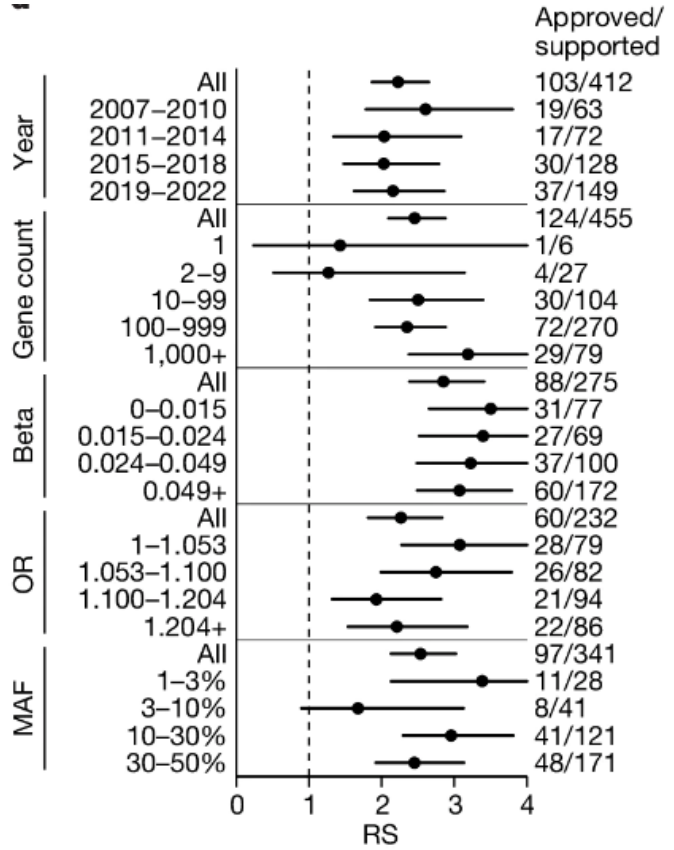
Most Drugs in Clinical Development Fail to Become Medicines

Evidence to Increase our Probability of Success is Much Needed



Drugs with human genetic evidence >2x more likely to be successful.

Nelson MR, Tipney H, Painter JL, et al. The support of human genetic evidence for approved drug indications. Nat Genet. 2015;47(8):856-860. doi:10.1038/ng.3314

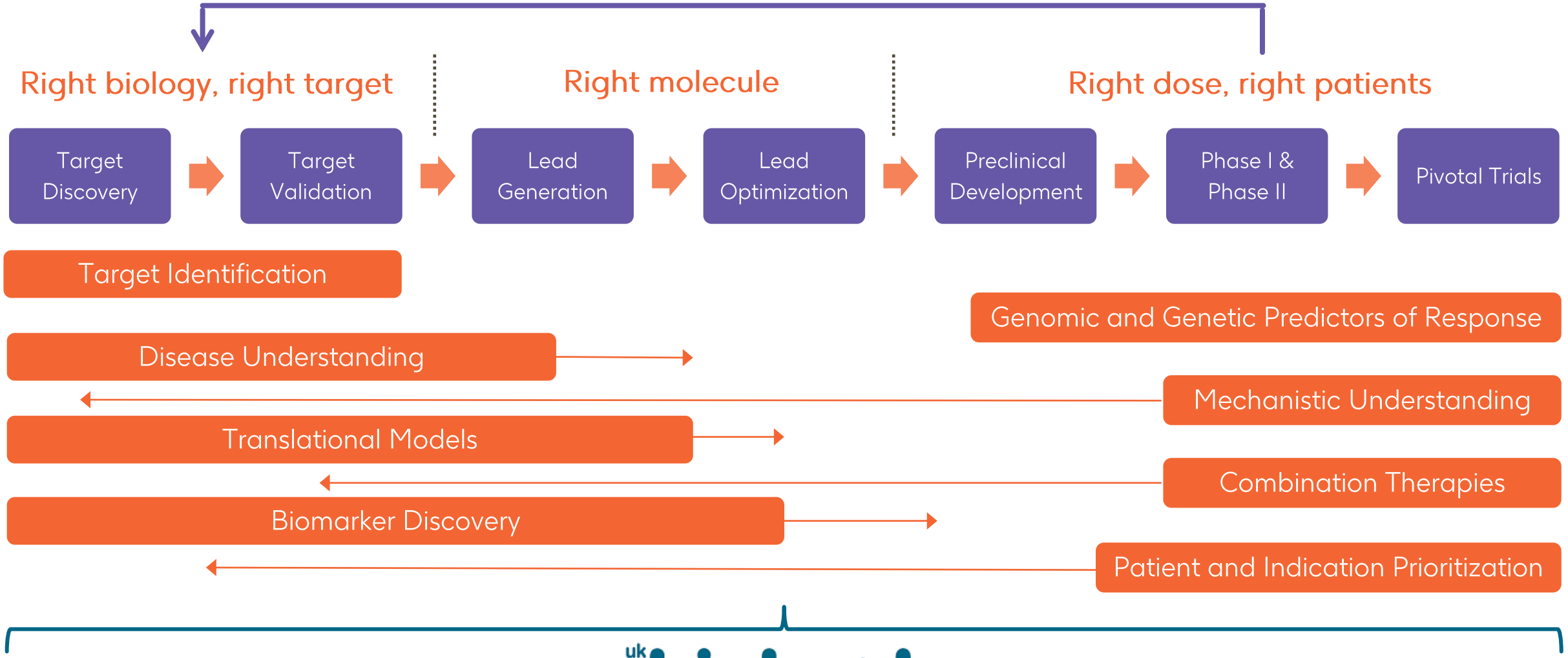


Minikel, E.V., Painter, J.L., Dong, C.C. *et al.* Refining the impact of genetic evidence on clinical success. *Nature* **629**, 624–629 (2024). https://doi.org/10.1038/s41586-024-07316-0

- Relative Success:
  - Varies among therapy areas and development phases
  - Improves with increasing confidence in the causal gene
- Largely unaffected by:
  - Genetic effect size
  - Minor allele frequency
  - Year of discovery

Genetics and Genomics From Discovery to Development

UK Biobank Provides Key Insights Across All Phases of GSK R&D



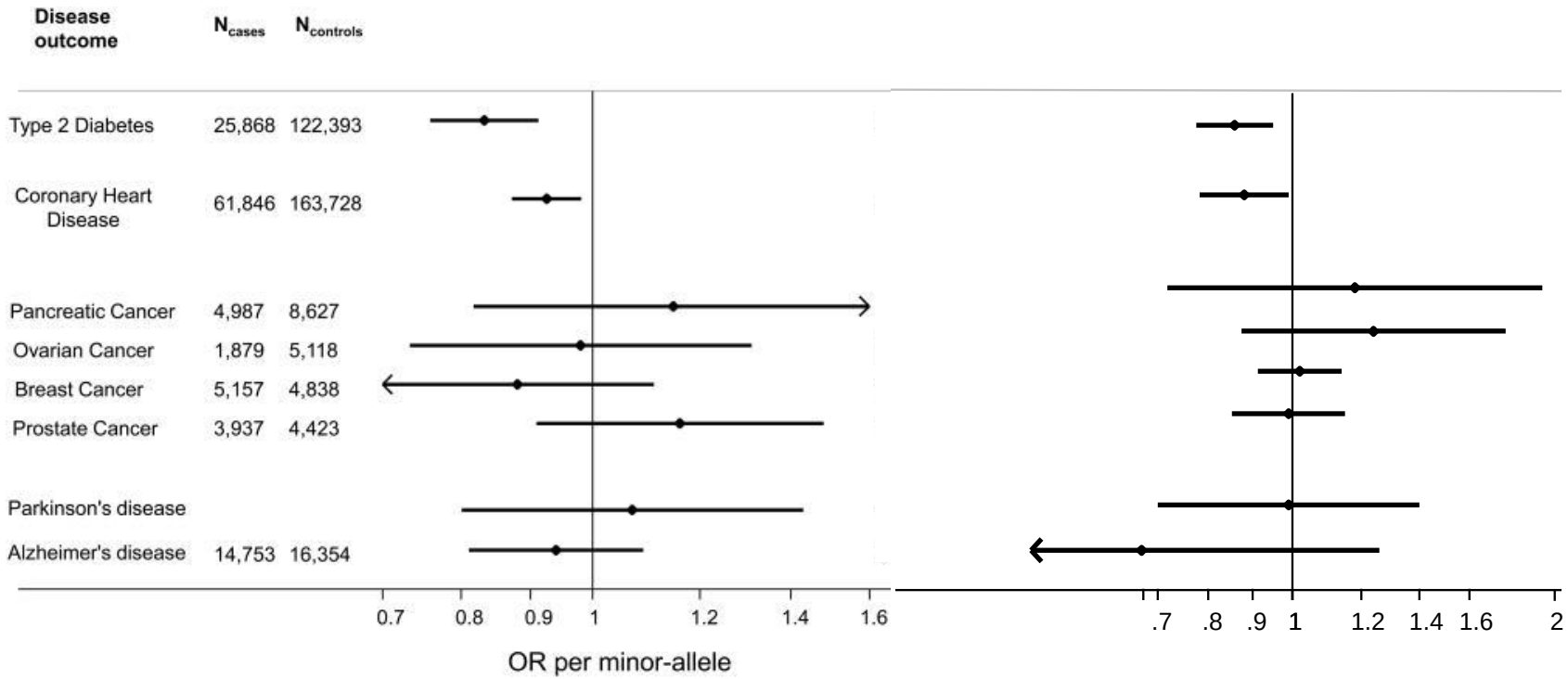
Our Ability to Bring Genetic Insights to Drug Development Has Transformed

A low frequency glucose lowering variant in GLP1R associated with type 2 diabetes and cardiovascular protection

Could we use GLP1R variant to recapitulate efficacy, identify potential indications or safety flags for GLP1R-agonists?

18 Months > 1,000 E-mails

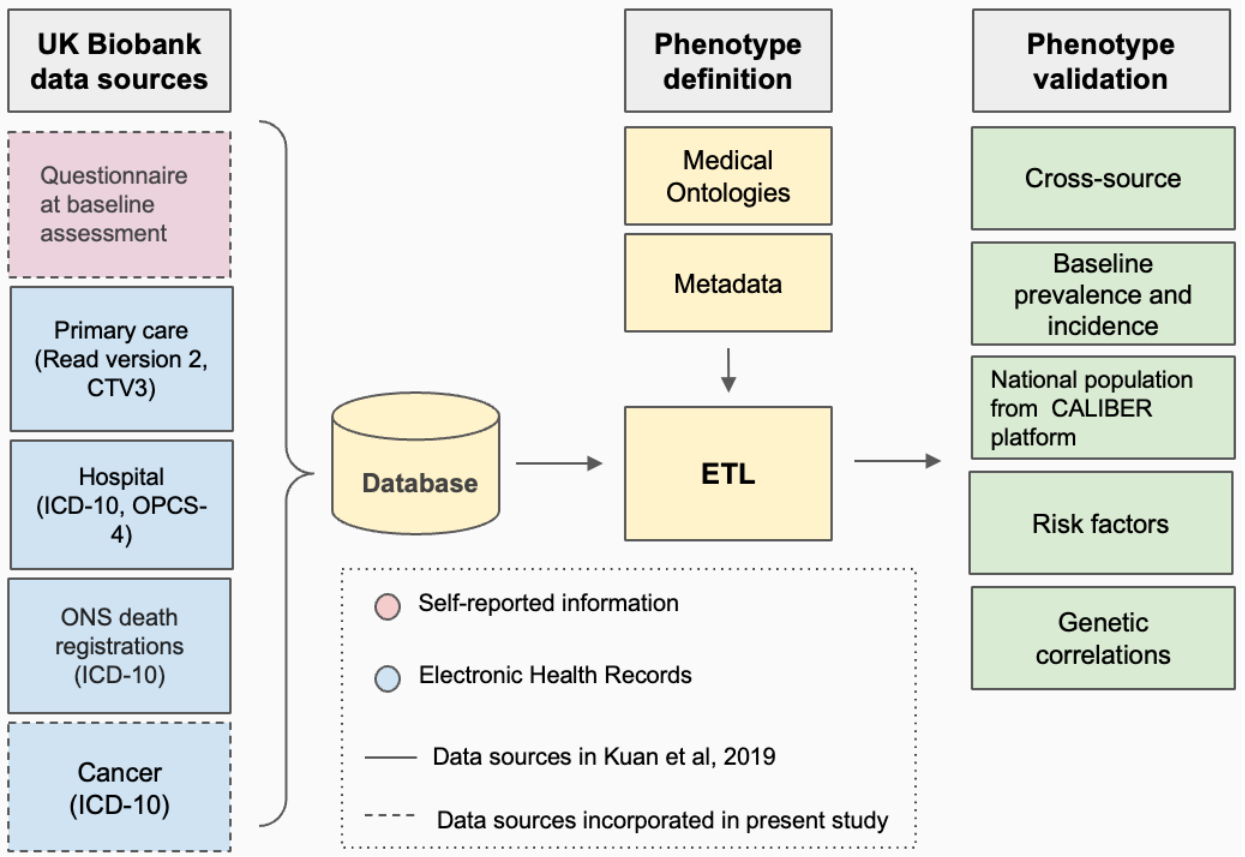
2 Minutes and a Teams Message



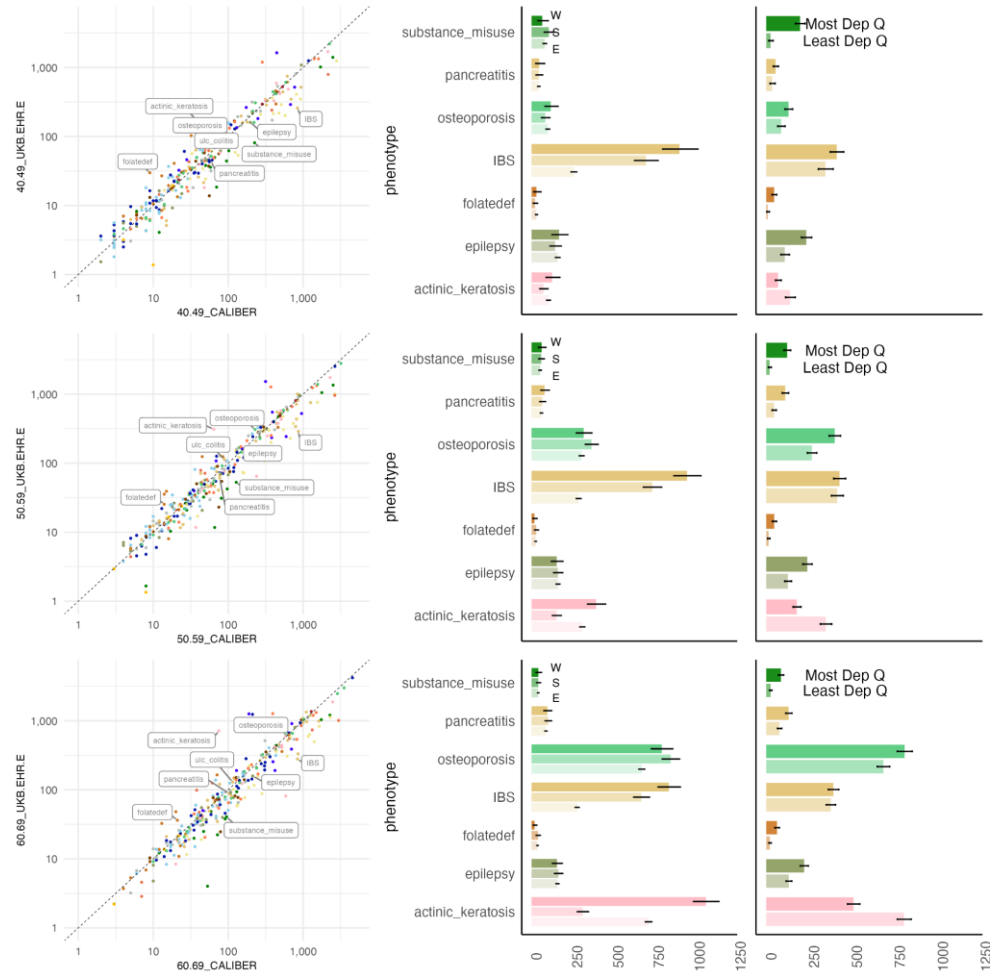
Scott RA, Freitag DF, Li L, et al. A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. Sci Transl Med. 2016;8(341):341ra76. doi:10.1126/scitranslmed.aad3744

At-Scale Phenomics

Defining and Validating Reproducible Phenotyping for 313 Diseases in UKB

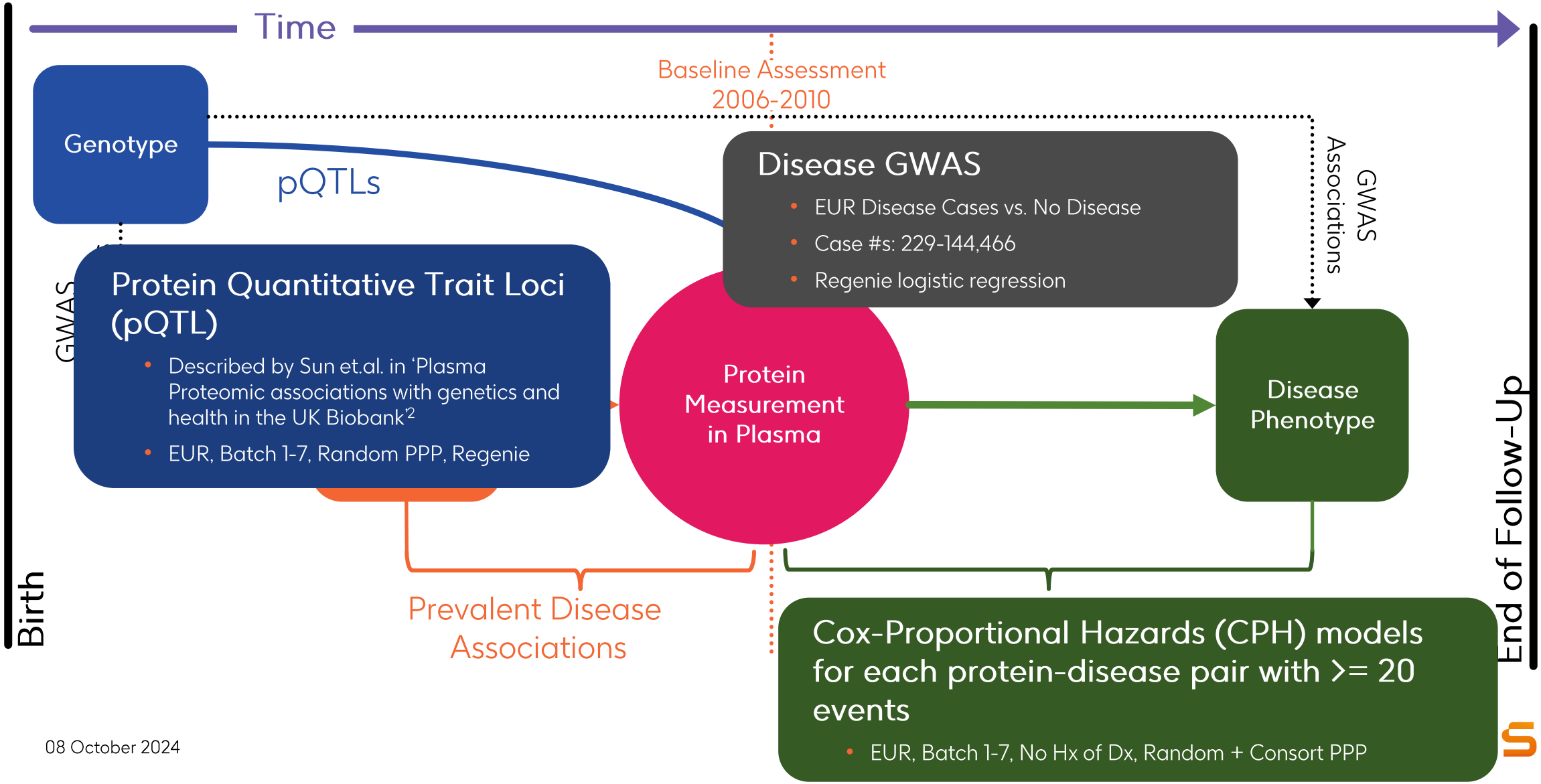


Log_{10}-transformed sex-standardised period prevalence for UKB vs. CALIBER; Prevalence by Country; Prevalence by Economic Deprivation



Epidemiology in Action

Integration of Genetics and Observational Epidemiology using Plasma Proteomics



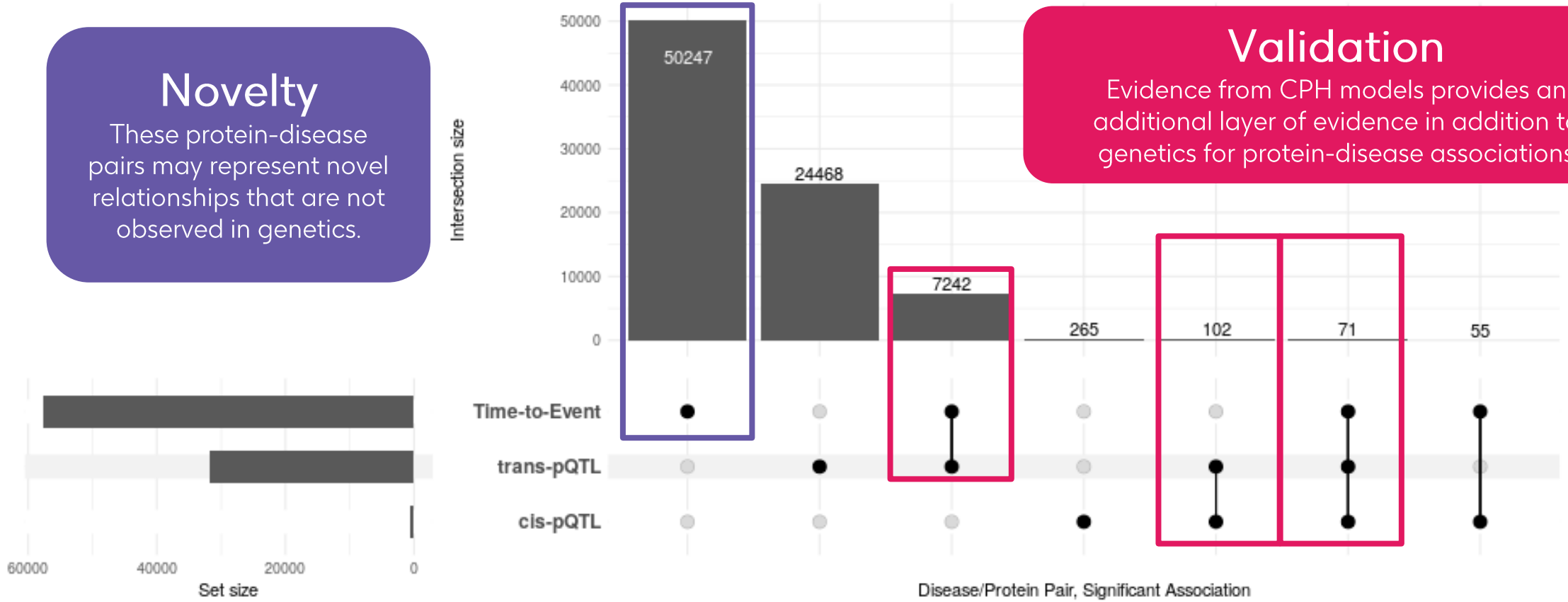
Time Makes a Difference in Understanding Disease

Novelty

These protein-disease pairs may represent novel relationships that are not observed in genetics.

Validation

Evidence from CPH models provides an additional layer of evidence in addition to genetics for protein-disease associations

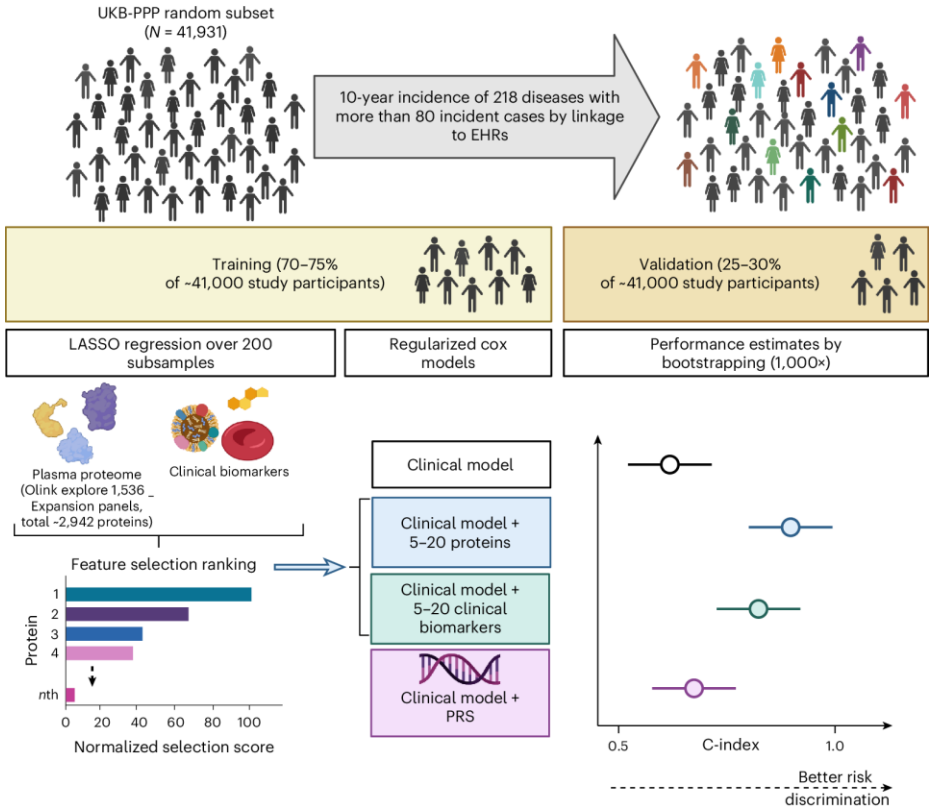


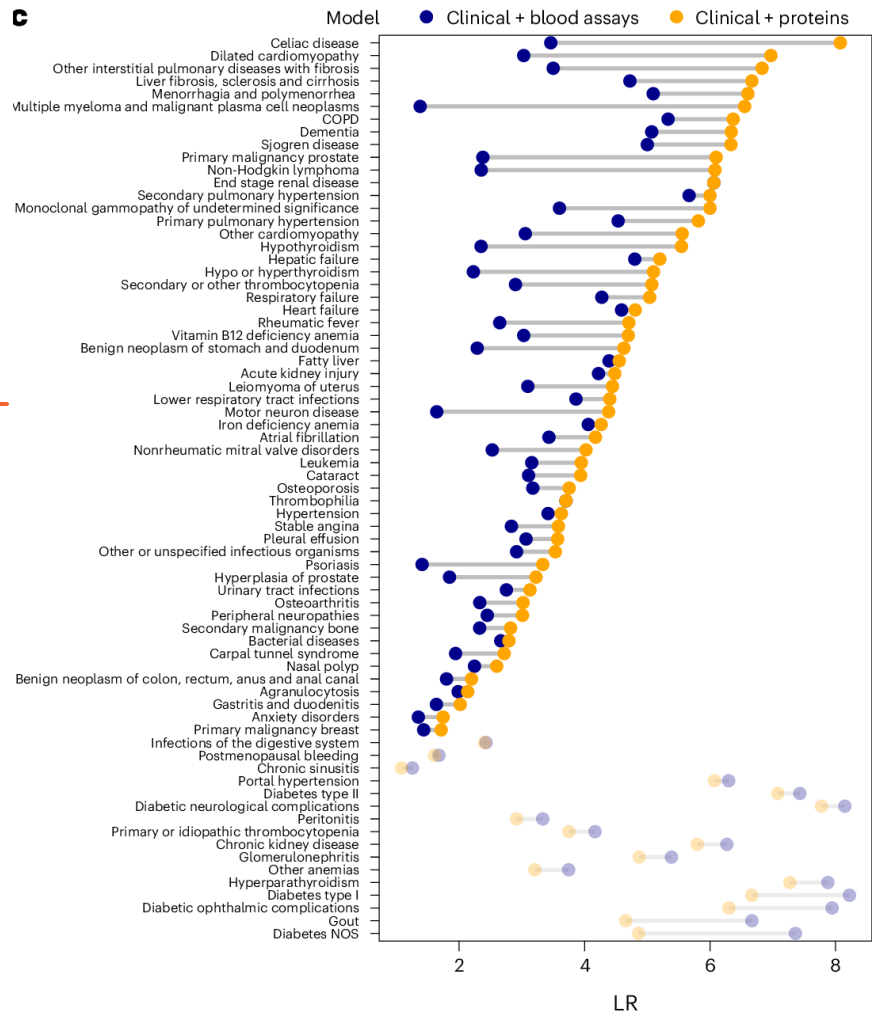
Integration of time-to-event evidence provides a **new layer of information** not easily investigated in genetics:

> ... knowledge that the protein is associated **not just with susceptibility** to the disease, but that the protein is associated with the **rate at which individuals develop new disease**

Disease Prediction and Potential Patient Selection

Proteomic Signatures Improve Risk Prediction for Common and Rare Diseases





"For 52 of 218 diseases, adding proteins was the single best prediction model, not only superior to commonly used patient characteristics, but also to a large array of blood assays in clinical use and PGS."

Carrasco-Zanini J, Pietzner M, Davitte J, et al. Proteomic signatures improve risk prediction for common and rare diseases. *Nat Med*. Published online July 22, 2024. doi:10.1038/s41591-024-03142-z

Key Takeaways

- UK Biobank is one of the world's foremost biomedical resources, enabling cutting-edge research to improve our understanding of the determinants of health and disease

- We leverage the entirety of UK Biobank data to accelerate diverse research activities across the Research and Development pipeline

- Insights obtained from UK Biobank greatly improve our ability to discover and develop safe, effective medicines to patients worldwide

Acknowledgements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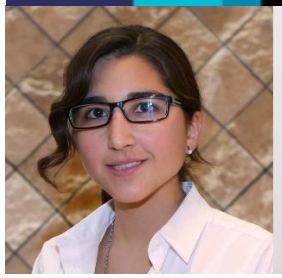
... and many others across our Human Genetics and Genomics organization!

MRC Epidemiology Unit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