Multi-omic studies at population scale: opportunities and challenges

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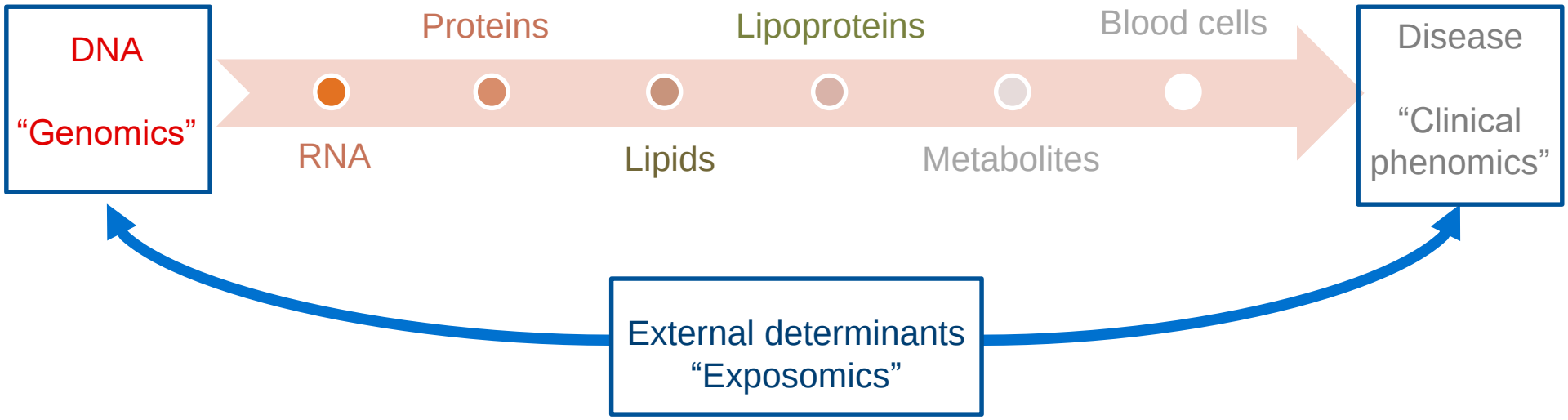
What are ‘omics?

Extensive (or even complete) measurement of a particular domain, eg:



What is the potential value of molecular ‘omics?

To offer new insights into:

- Biology
- Disease aetiology / subclassification
- Risk prediction
- Therapeutic targeting

Some key challenges to enable robust inference from ‘omics

Need to:

- Validate assays in population studies
- Understand complexities in interpreting assays
- Control for technical artefacts
- Address statistical and computational challenges

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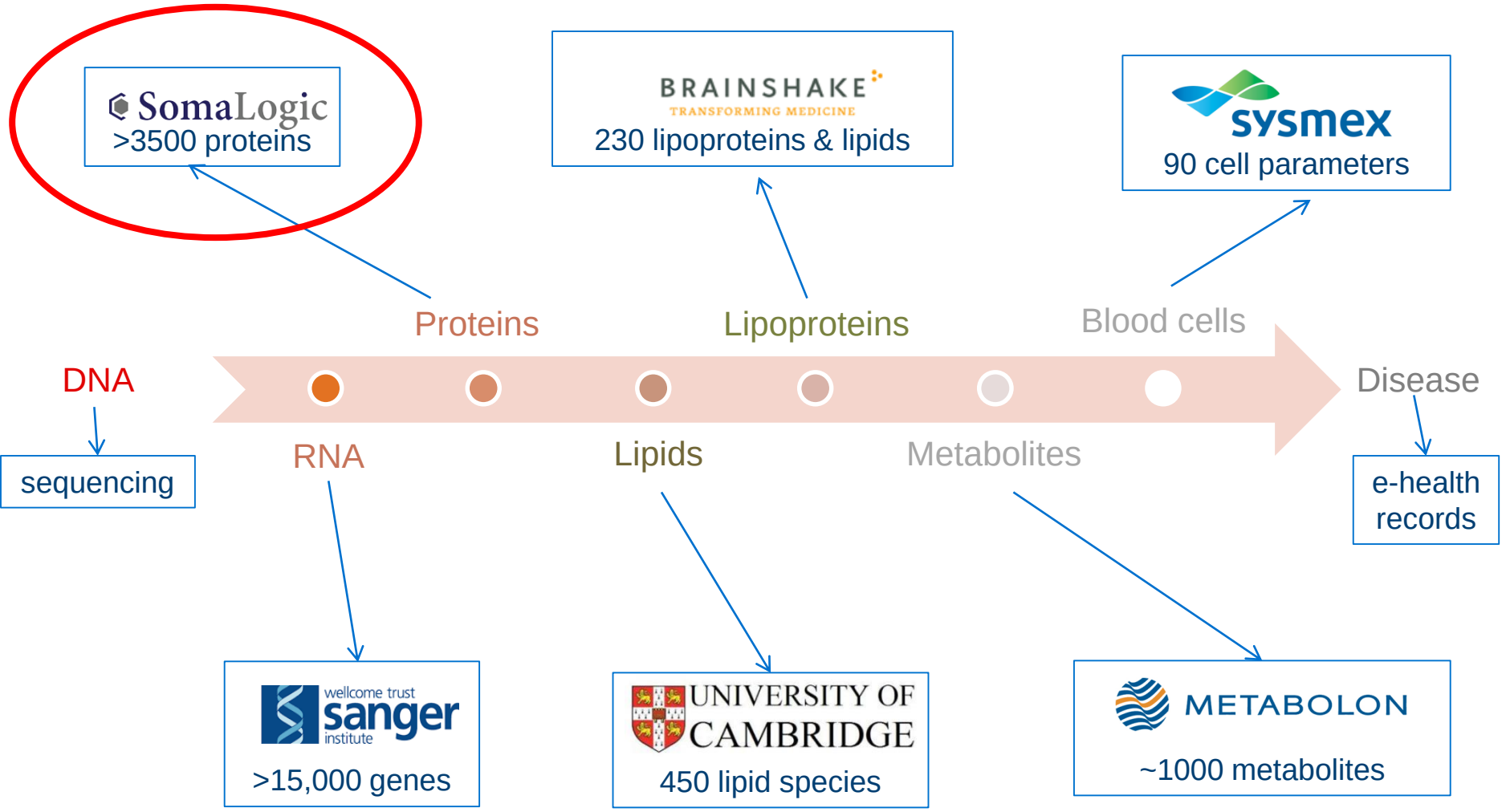
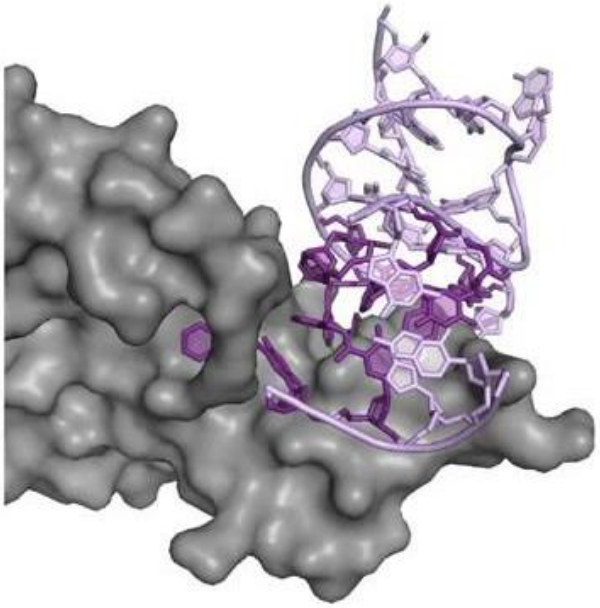
INTERVAL: a proof-of-concept study of 50,000 people

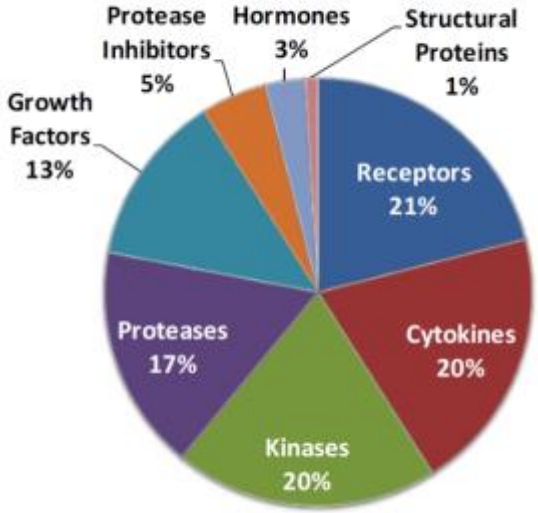


SomaScan plasma proteomics

~5000 proteins across 8 orders of magnitude of abundance



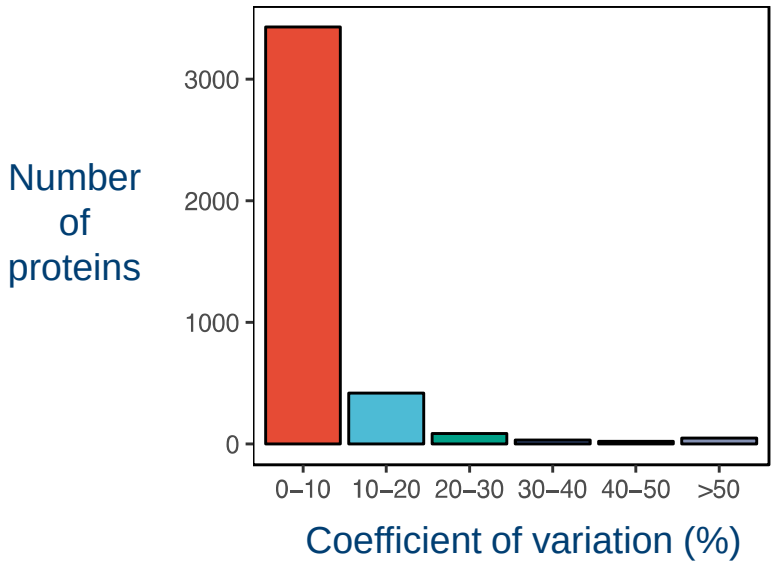
High-specificity aptamer-based approach



Diverse set of proteins, with a bias towards clinical and pharmaceutical relevance

Population-scale validation of the SomaScan assay

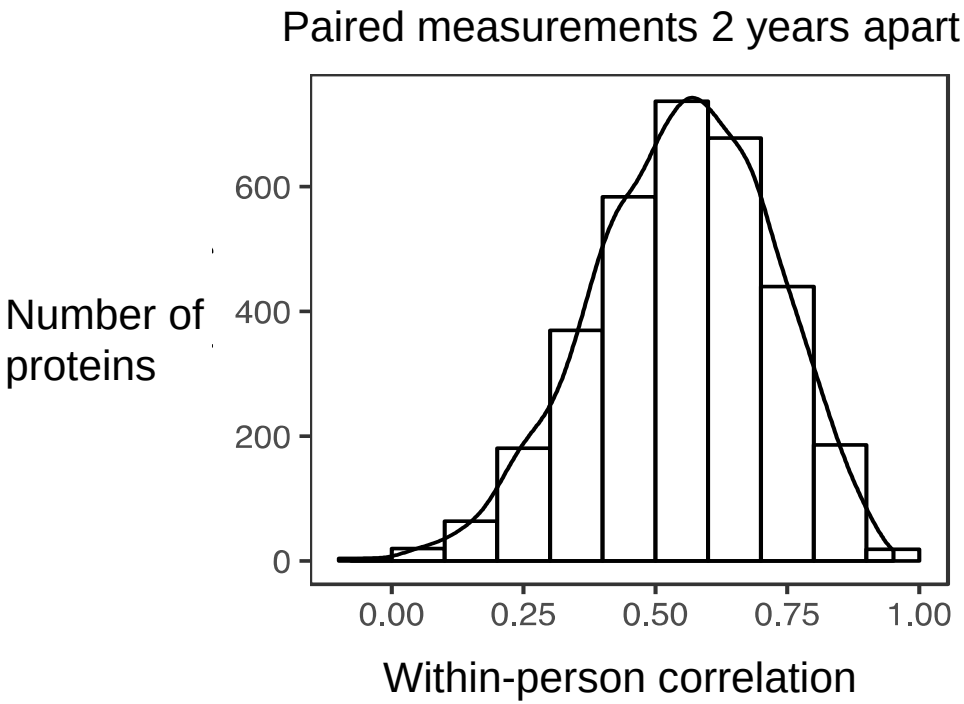
- What is the variability between assays run with the same samples?
  - More than 90% of proteins had CVs less than 20%



Sun *et al.*, *Nature* (in press)

Population-scale validation of the SomaScan assay

- What is the variability between assays run in the same samples?
- How stable are protein levels within participants over time?



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Population-scale validation of the SomaScan assay

- What is the variability between assays run in the same samples?
- How stable are protein levels within participants over time?
- Can well-known associations of proteins with phenotypes be reproduced?

For example,

- cystatin C and beta-2-microglobulin were associated with eGFR, a marker of renal function
- leptin, insulin and ghrelin were associated with body-mass index, a marker of obesity

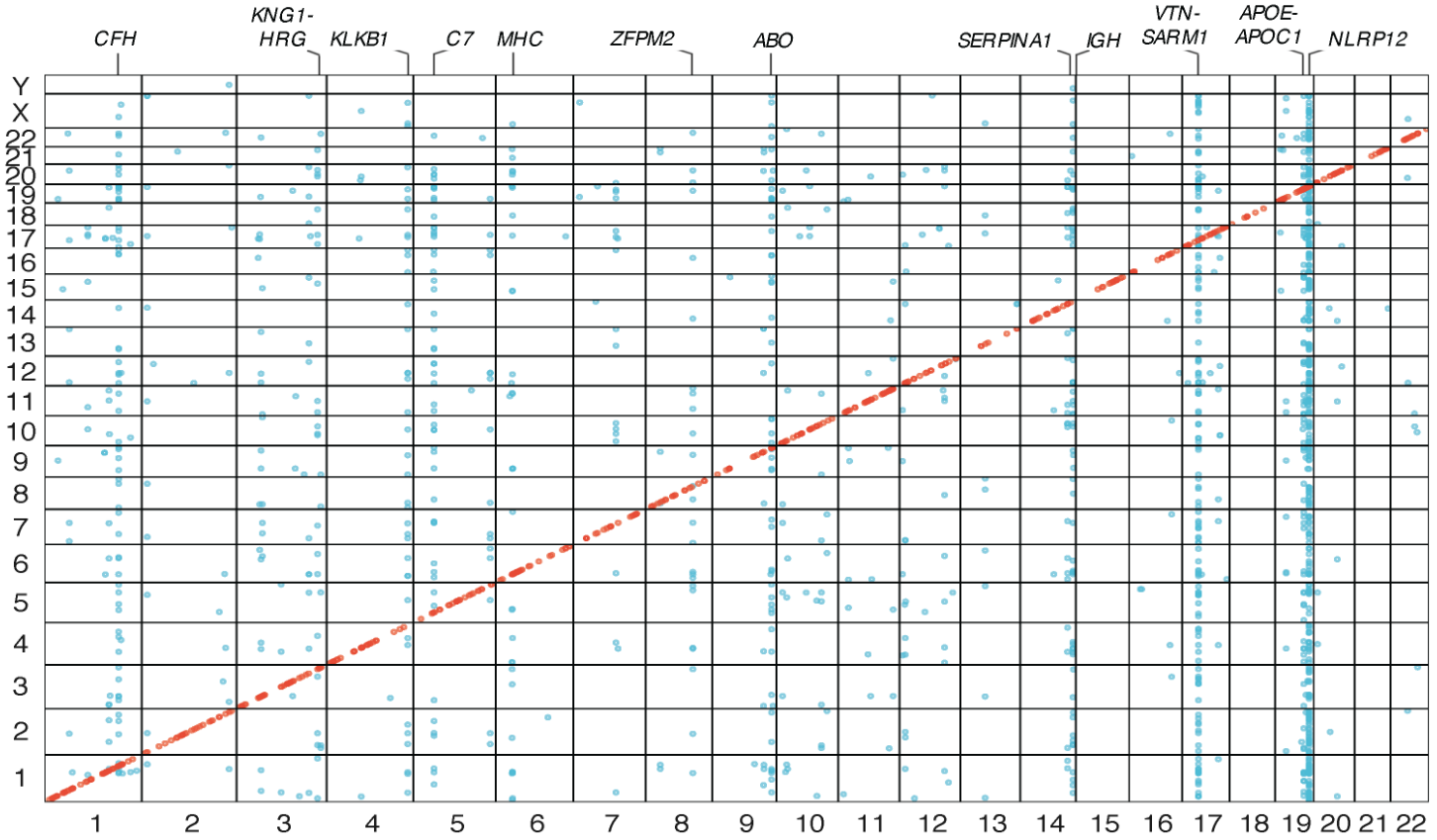
Sun *et al., Nature* (in press)

Population-scale validation of the SomaScan assay

- What is the variability between assays run in the same samples?
- How stable are protein levels within participants over time?
- Can well-known associations of proteins with phenotypes be reproduced?
- Can biologically plausible genetic associations be detected?

“Genetic validation” of the assay

Genes encoding target proteins

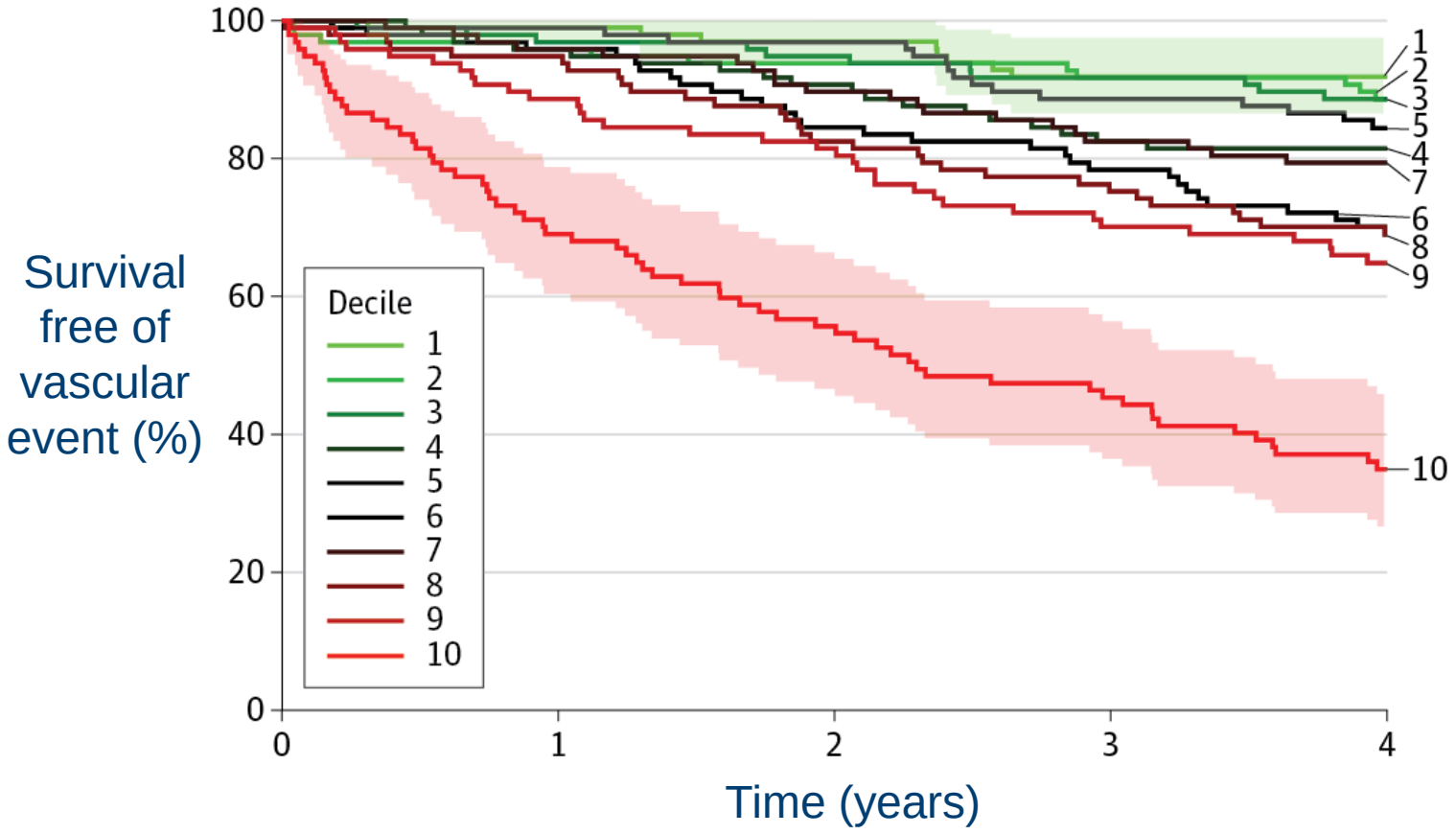


Genetic variants

Sun *et al.*, *Nature* (in press)

Predictive inference is enabled by such population scale validation

Adding 9 proteins from the SomaScan could enhance conventional vascular risk prediction



Ganz *et al.*, *JAMA* 2016

Some key challenges to enable robust inference from ‘omics

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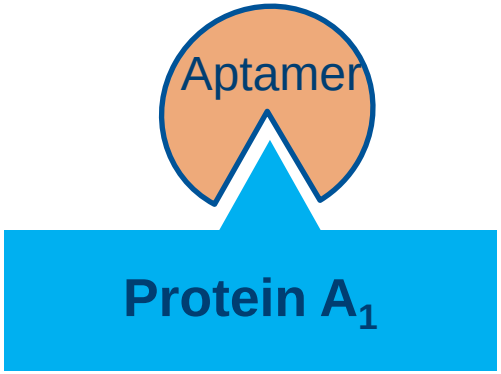
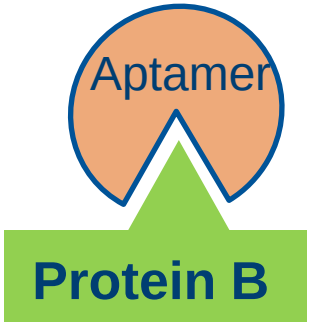
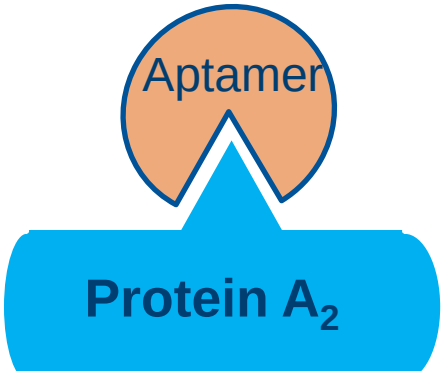
Aetiological inference for protein assays involves additional considerations

- Does the measurement reflect only one protein?





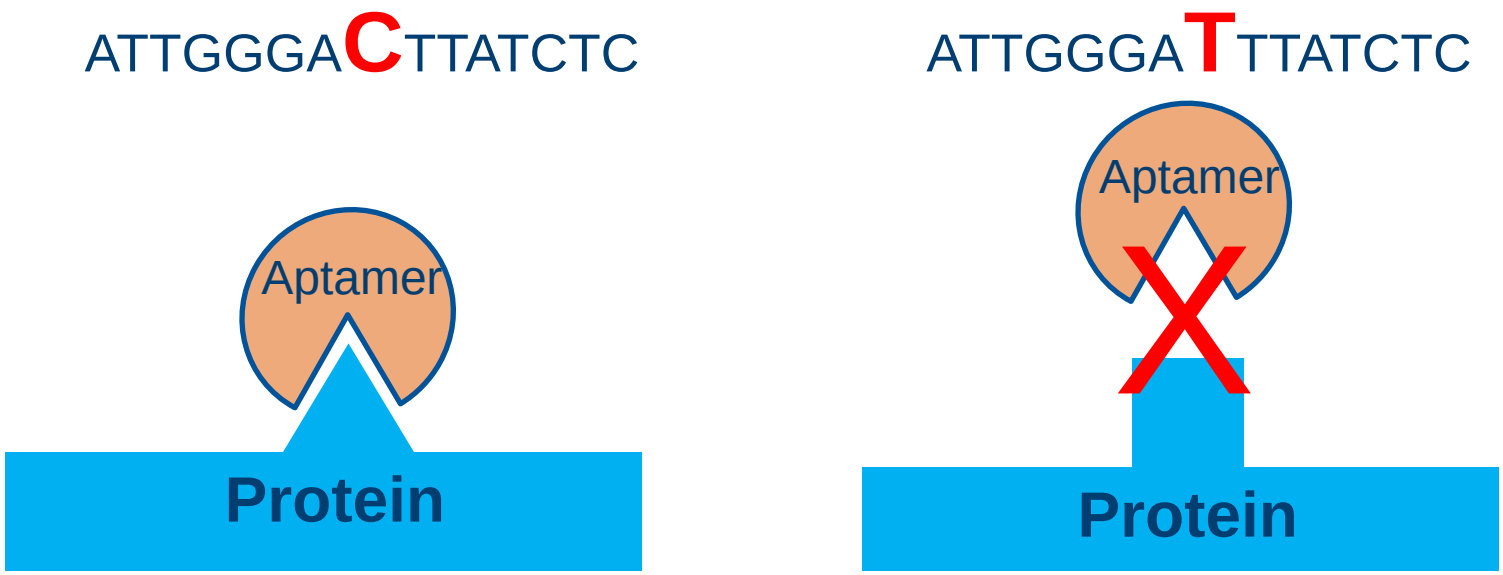


However, 87% of ~1000 SomaScan aptamers tested reflected only one protein

Sun *et al.*, *Nature* (in press)

Aetiological inference for protein assays involves additional considerations

- Does the measurement reflect only one protein?
- Does the measurement reflect different versions of the same protein rather than differences in protein levels?



Aetiological inference for protein assays involves additional considerations

- Does the measurement reflect only one protein?
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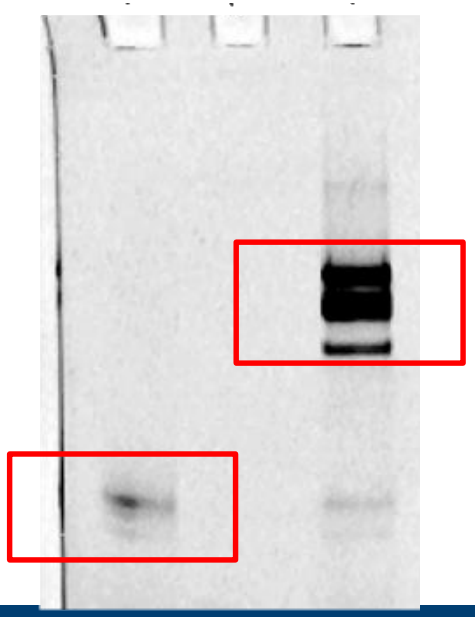
- Does the measurement reflect free protein or a “protein complex”?

Mass-spec ‘pull-down’ of proteinase-3 (PR3) aptamer



Strong binding to PR3:A1AT complex

Weak binding to free PR3

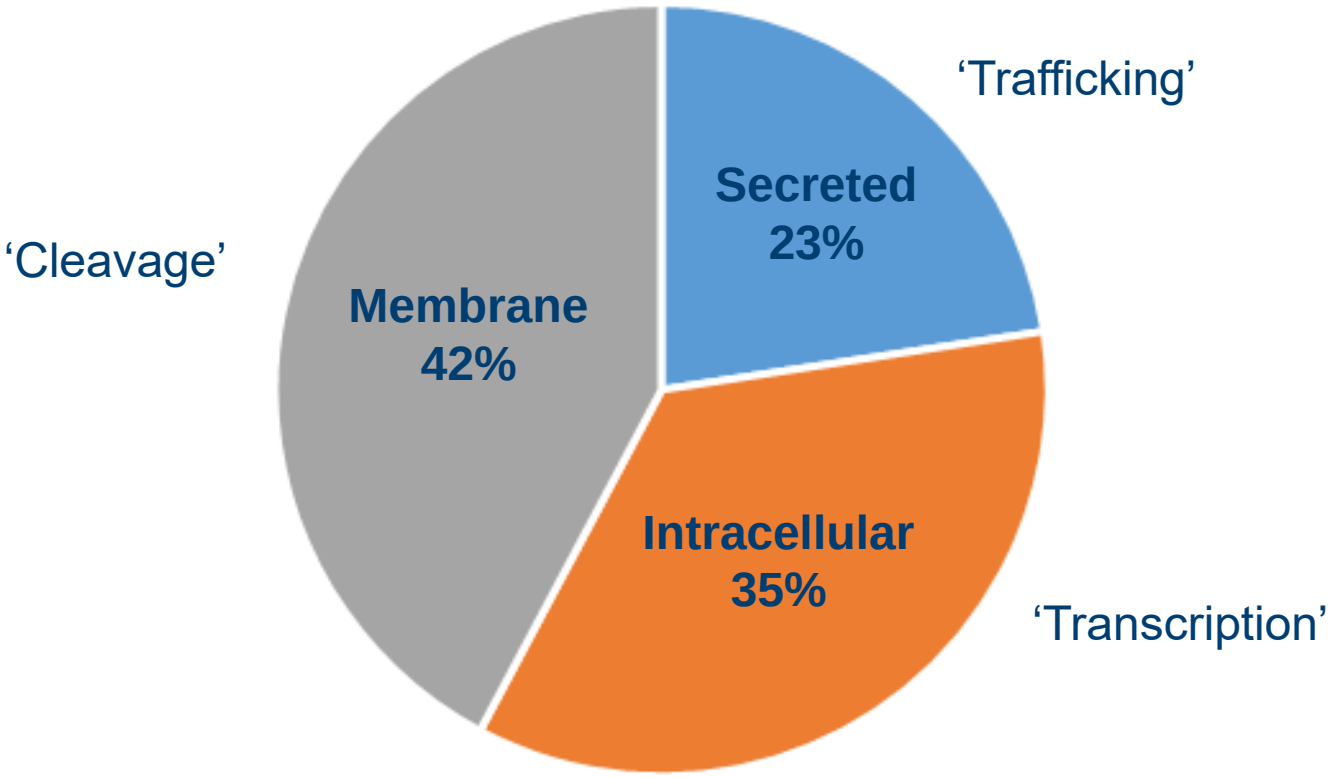
Sun *et al.*, *Nature* (in press)

Aetiological inference for protein assays involves additional considerations

- Does the measurement reflect only one protein?
- Does the measurement reflect different versions of the same protein rather than differences in protein levels?
- Does the measurement reflect free protein or a “protein complex”?
- What do protein levels in plasma reflect?

Protein concentrations in plasma may not reflect cell- or tissue-specific concentrations

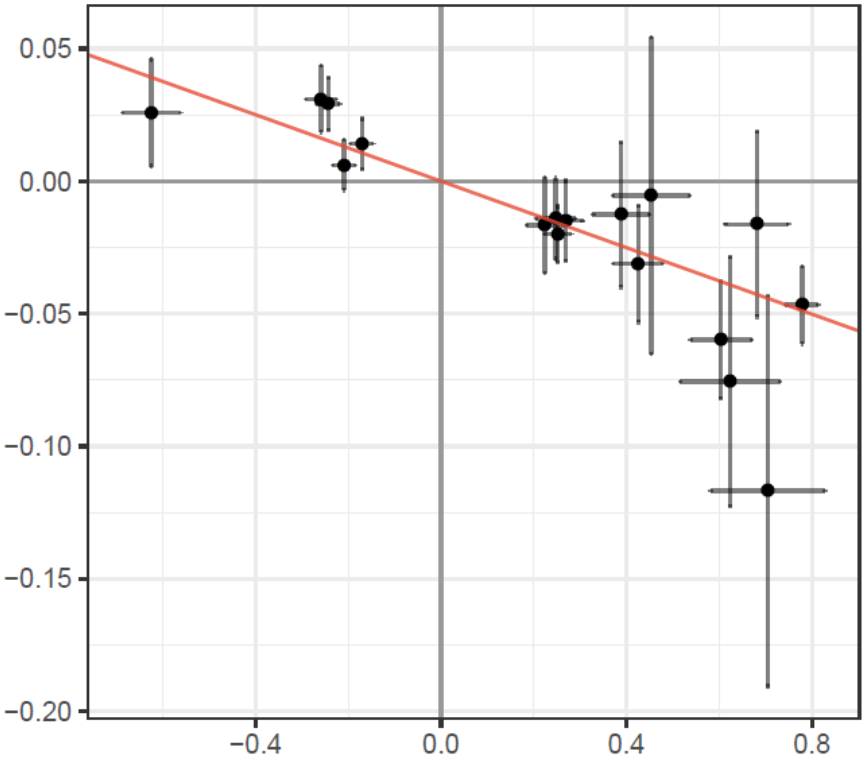
Proteins measured by the SomaScan assay
are influenced by different processes



Sun *et al.*, *Nature* (in press)

Plasma proteomics can help yield potential causal insight into disease

Mendelian randomisation suggests a causal role for matrix metalloproteinase-12 in coronary disease



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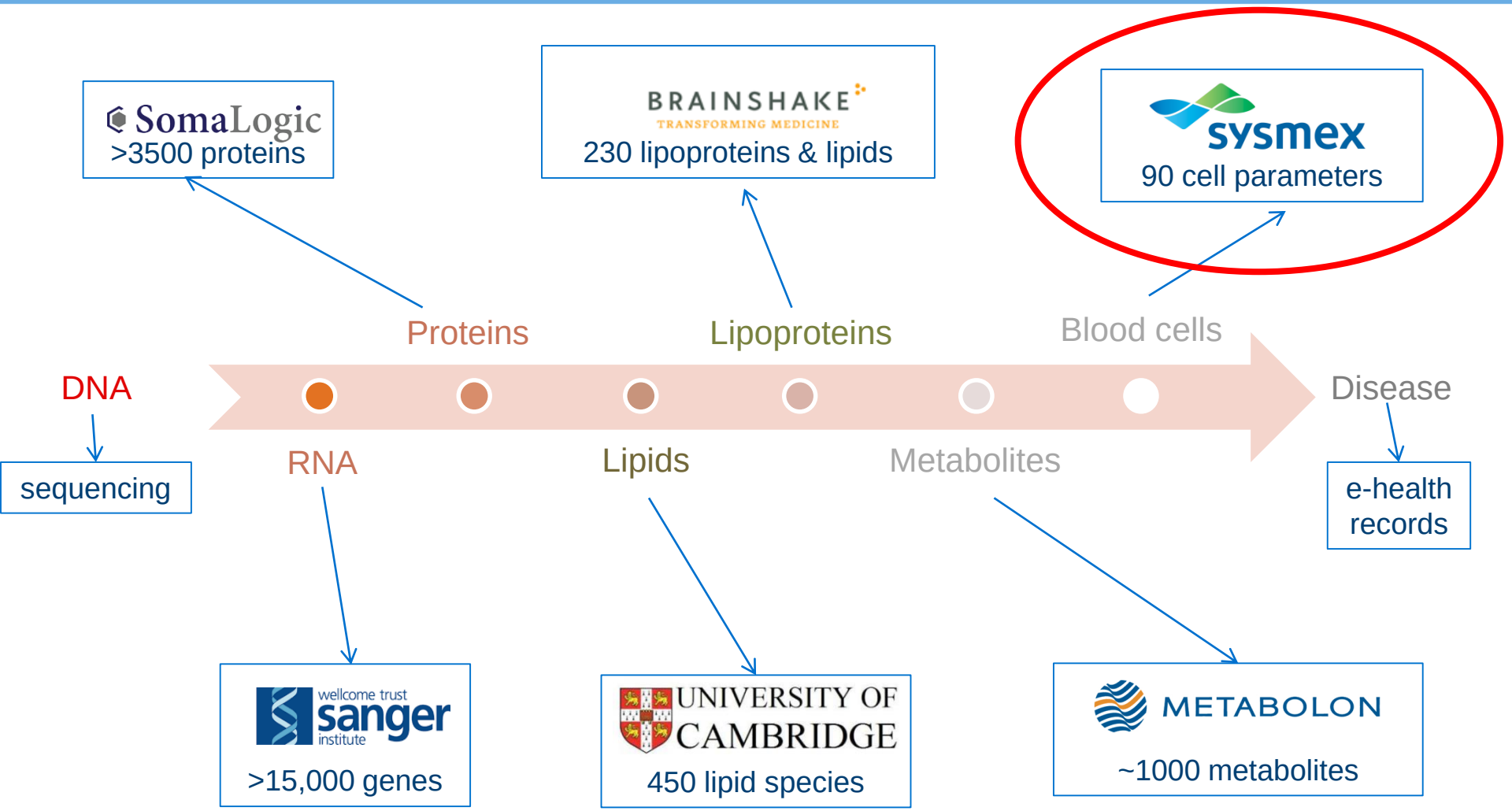
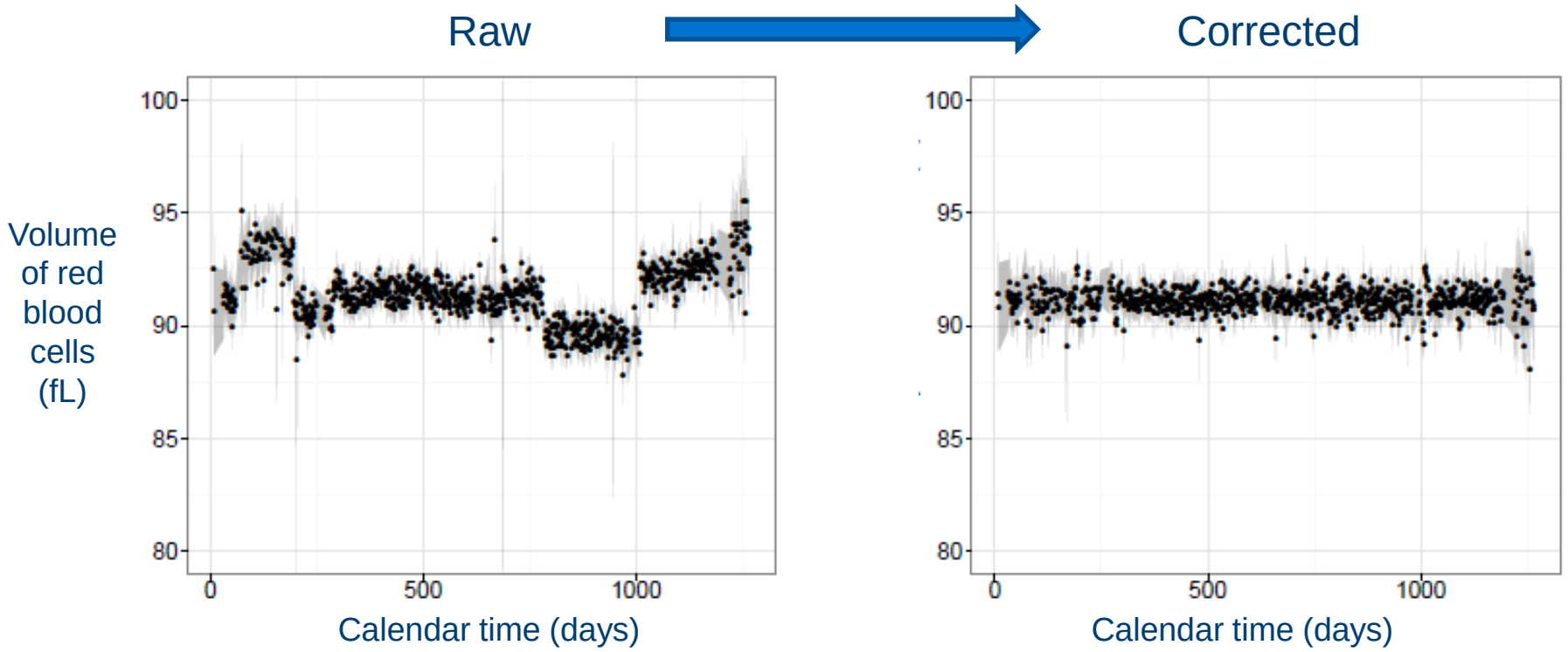


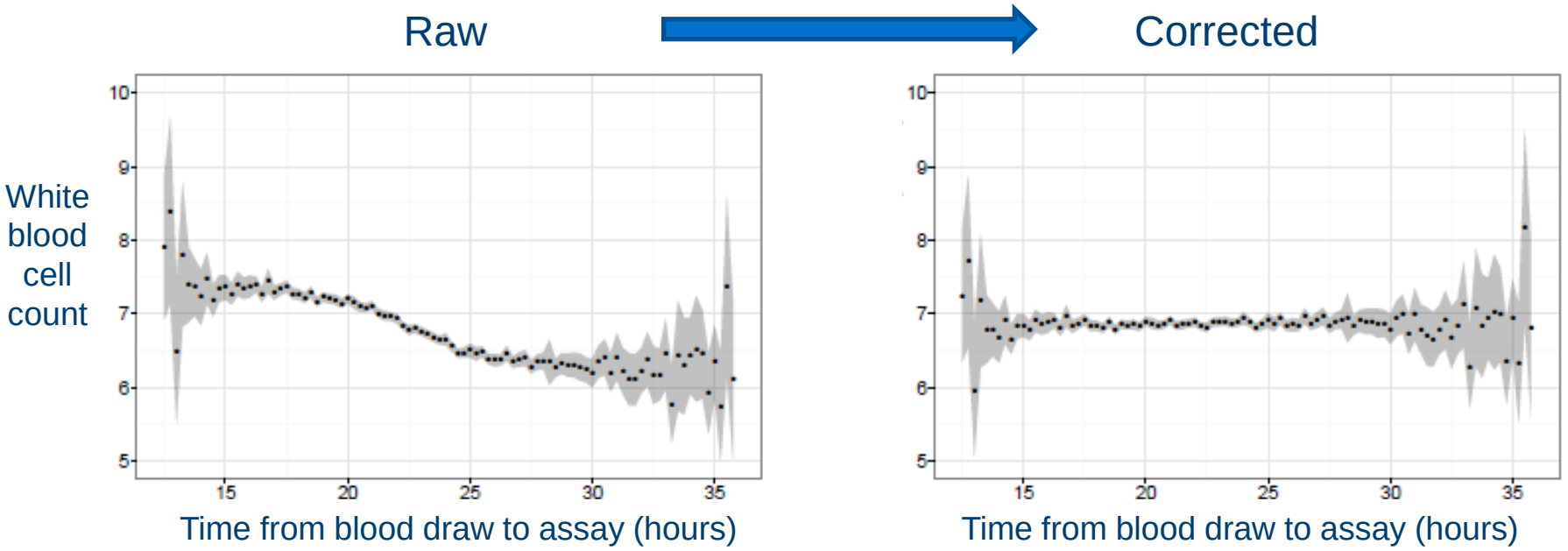
Non-biological variation is not always identified but is potentially correctable

- Batch effects due to lengthy periods of assay



Technical artefacts are important but correctable sources of variability

- Batch effects due to lengthy periods of assay
- Subtle distortions due to operational effects



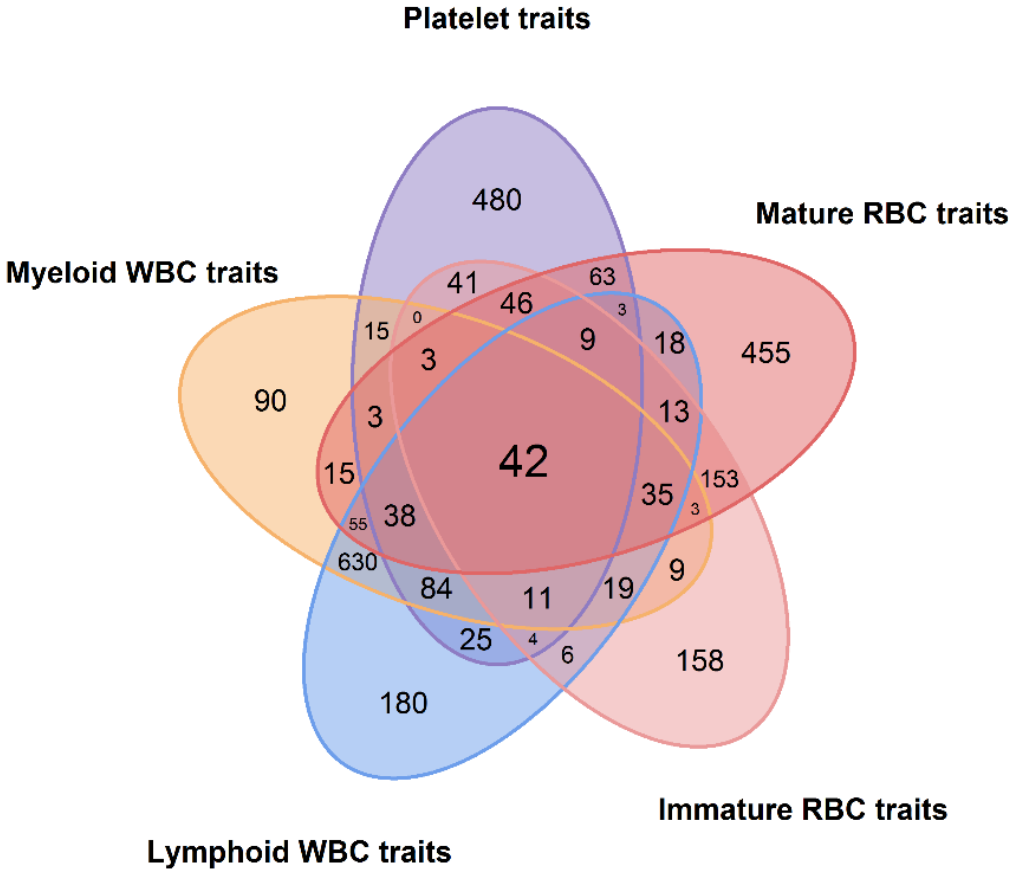
Discovery power can be substantially enhanced after correction for non-biological variation

	Uncorrected	→	Corrected
Number of RBC loci discovered with n=50,000	10		36

RBC = red blood cell count

Blood cell ‘omics can help yield biological insight

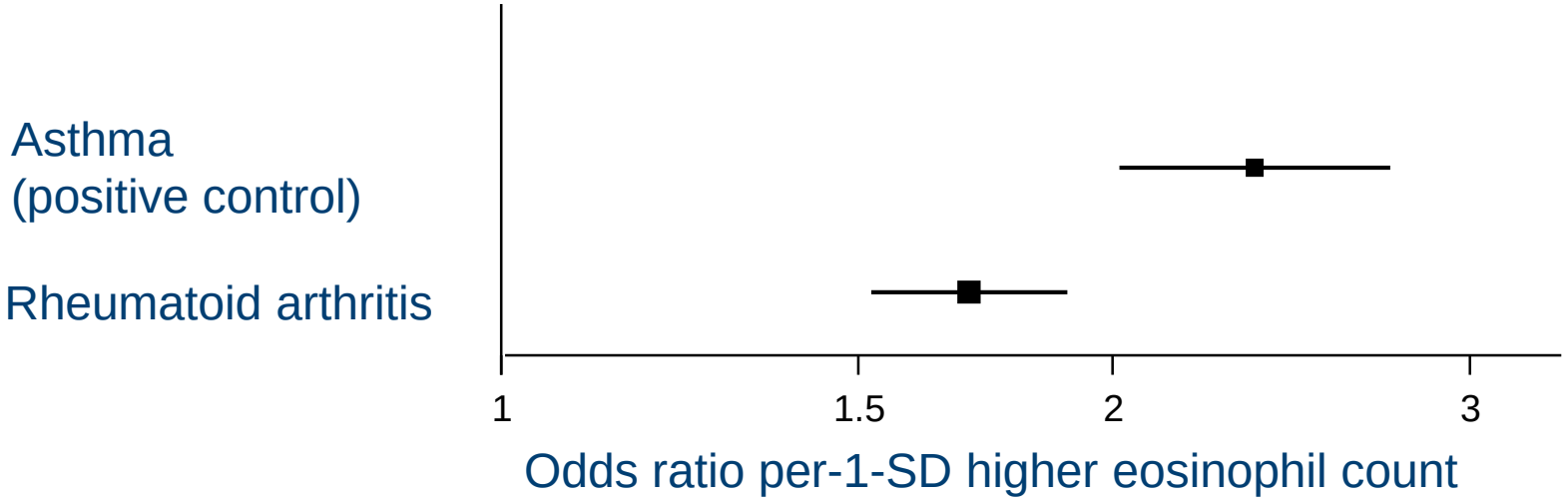
Discovery of the genetic architecture of blood cell traits: 2700 variants



Astle *et al.*, *Cell* 2016

Blood cell ‘omics can help yield potential causal insights into disease

Mendelian randomisation suggests a causal role for eosinophils in rheumatoid arthritis



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Non-trivial computational challenges of combining multi-omic data

~ 50,000 participants

~ 1600 distinct lipids / metabolites (plus ratios/combinations)

~ 80 million genotypes

➔ ~ 130 billion calculations

High-performance computing is essential

	Time to achieve ~130 billion calculations
Conventional computing	~1300 days
High-performance computing*	~4 days

* Cambridge University Peta 5 HPC

Conclusions

- Multi-omics can help address the post-GWAS grand challenge of bridging molecular gaps from genotype to disease

- ‘Omic assays have common and assay-specific technical and interpretive challenges

- Several assays are being used at population scale, with results being pooled across cohorts

“Progress in science depends on new techniques, new discoveries and new ideas, probably in that order.”

- Sydney Brenner

Acknowledgements

Ben Sun

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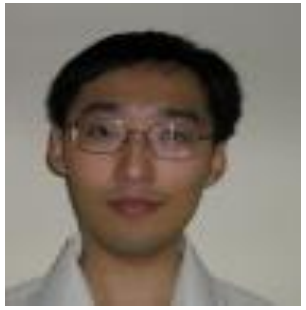

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SEVENTH FRAMEWORK
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MERCK
INVENTING FOR LIFE

Examples of Cambridge-led 100K+ cohorts

UK blood donor cohorts (consented for recall)

Today: 100K participants

Recruiting 250K further participants

South Asian cohorts (enriched for autozygosity)

Today: 95K participants

Recruiting 150K further participants