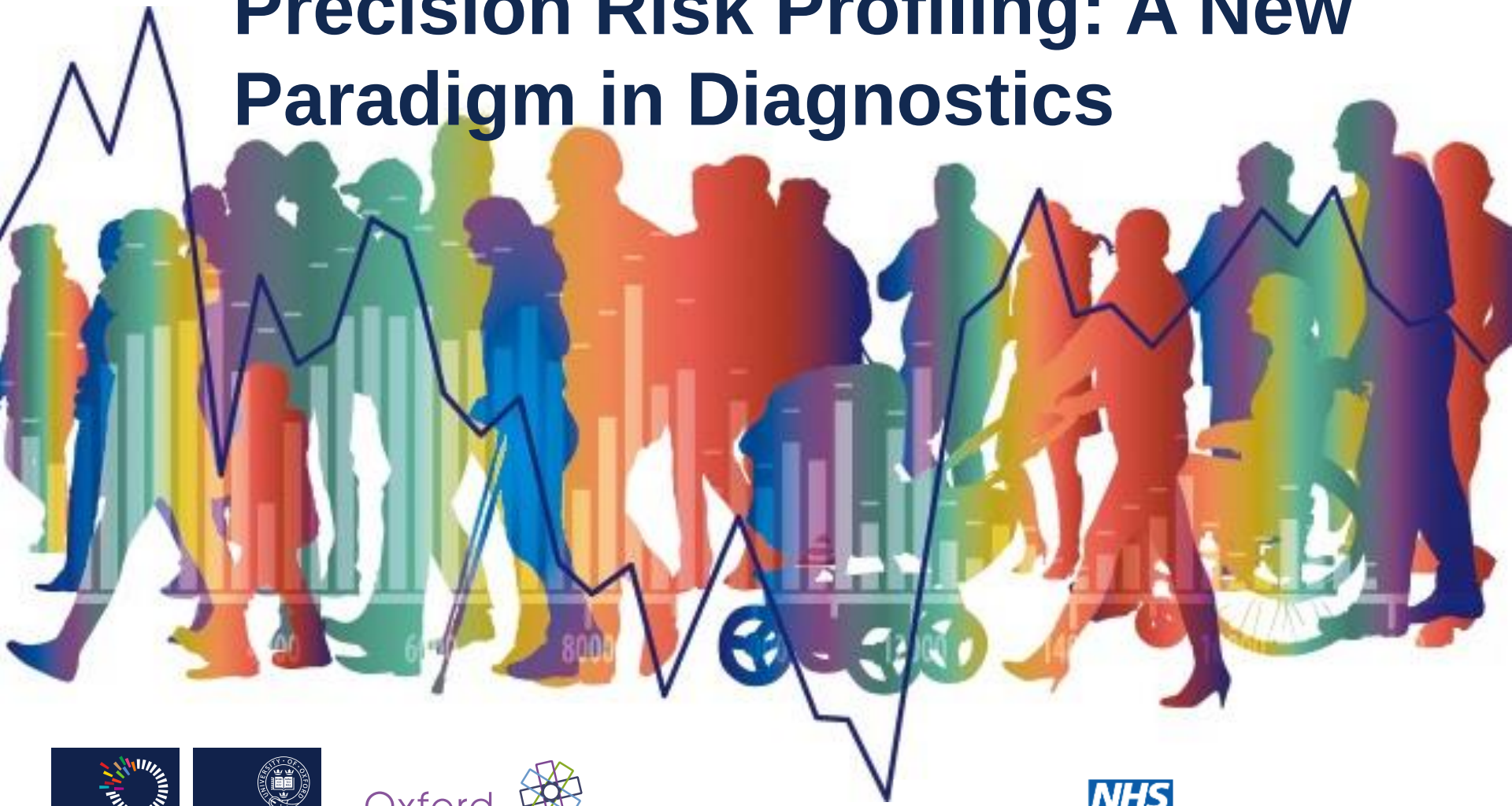
Precision Risk Profiling: A New Paradigm in Diagnostics



OXFORD UNIVERSITY INNOVATION
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Oxford Academic Health Science Network
Oxford Biomedical Research Centre
NHS National Institute for Health Research
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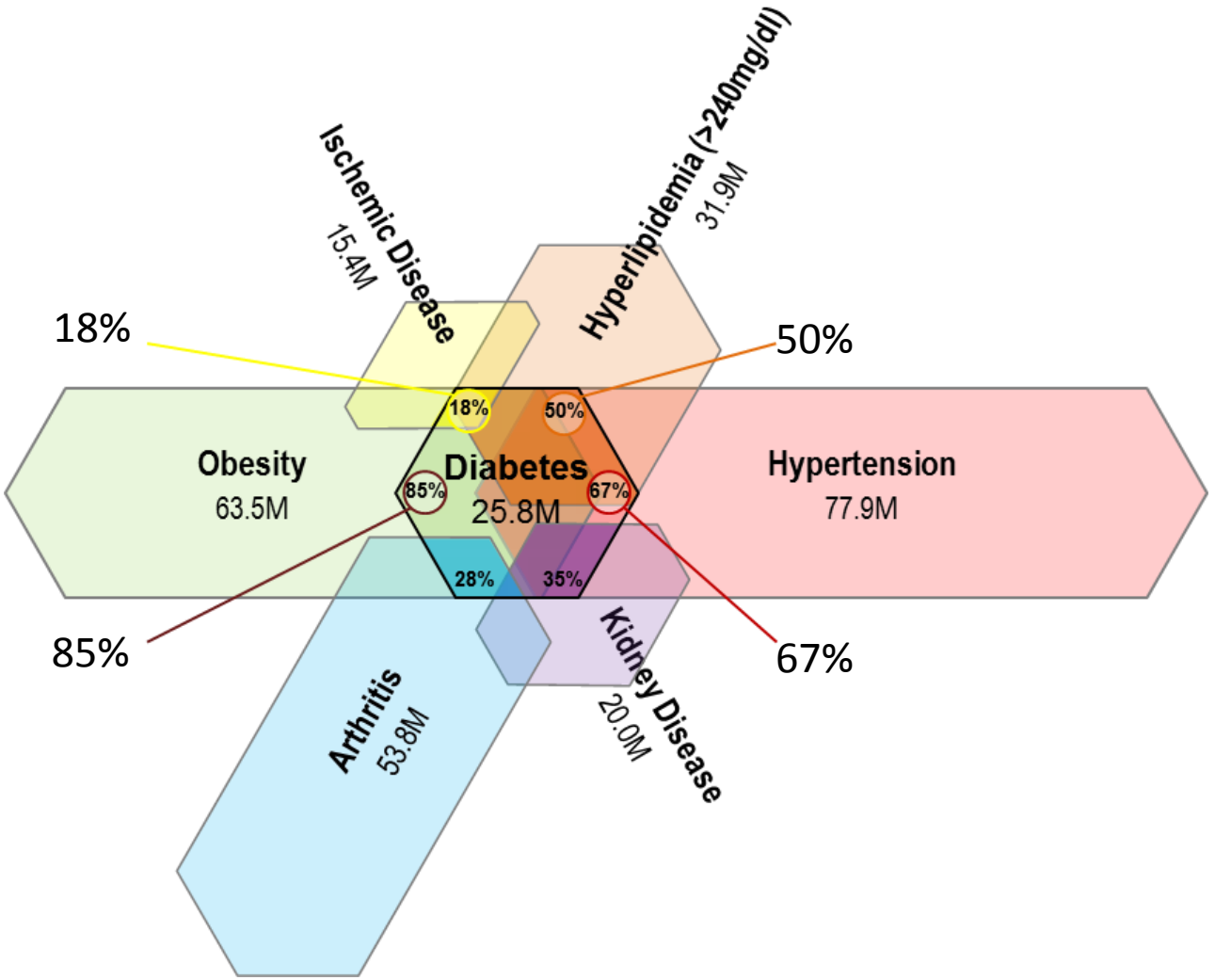
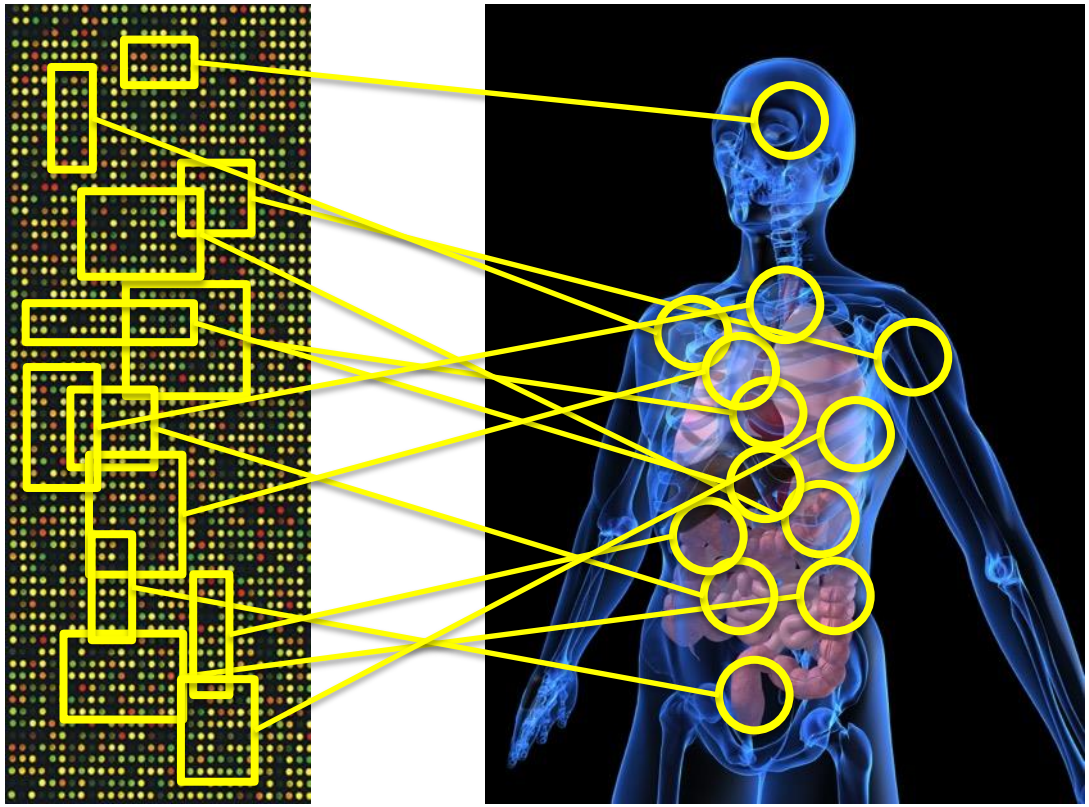
Why do we need a new paradigm?
People are too complex for today's diagnostics



The vision



Features of the new Dx paradigm

- Bet on proteins
- Massively multiplexed measurements
- Biological hypothesis-free
- Utility defined upfront by health system collaborators
- Clear truth standards
- Exploit machine learning and high-powered computing
- Bundle utilities together to manage complex diseases
- Apply validated measures and learn new patterns simultaneously by large scale health system implementation

Why bet on proteins?

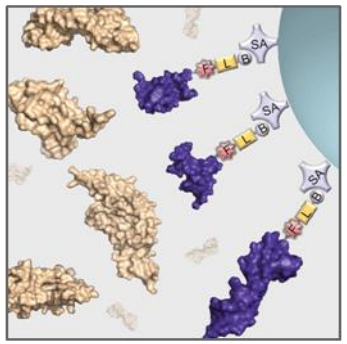
- They change
- Downstream from genetics and environment
- Causal: targets of >95% of all known drugs

But massive multiplexing has not been possible….

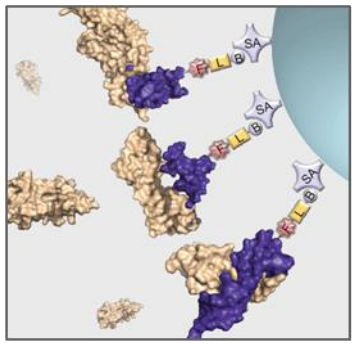
- Proteins cover a 1 billion-fold range of concentrations
- Existing technologies will measure:
  - EITHER: a large number of abundant proteins
    - Shotgun mass spectrometry, 2D Gels
  - OR: a small number of lower abundance proteins
    - Immunoassays, MRM
  - But NOT both
- SomaLogic has overcome this problem

SOMAscan Multiplex Proteomic Assay

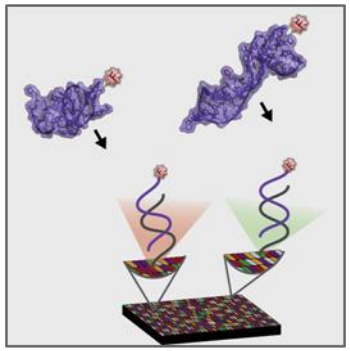
Key assay principle: Turning a **protein measurement** into a **DNA measurement**



Proteins in biologic sample + SOMAmers immobilized on beads



Capture of specific proteins followed by removal of unbound proteins and unbound SOMAmer reagents



Quantification of SOMAmer reagents by hybridization

Gold L. et al (2010) PLoS One
Kraemer S. et al (2011) PLoS One
Rohloff J. et al (2014) Molecular Therapy

Strategies for choosing measurements

Biologically favored list

- Fewer measurements
- Easier control of false discovery rate
- Familiar: psychological acceptance easier
- Uses a-priori evidence – efficient

- Slow: evolution of biological knowledge takes years
- Don't find "black swans" – un-anticipated biology
- Worse performance – uni-dimensional selection process misses complex signals
- A-priori evidence might be wrong: failure to replicate is common

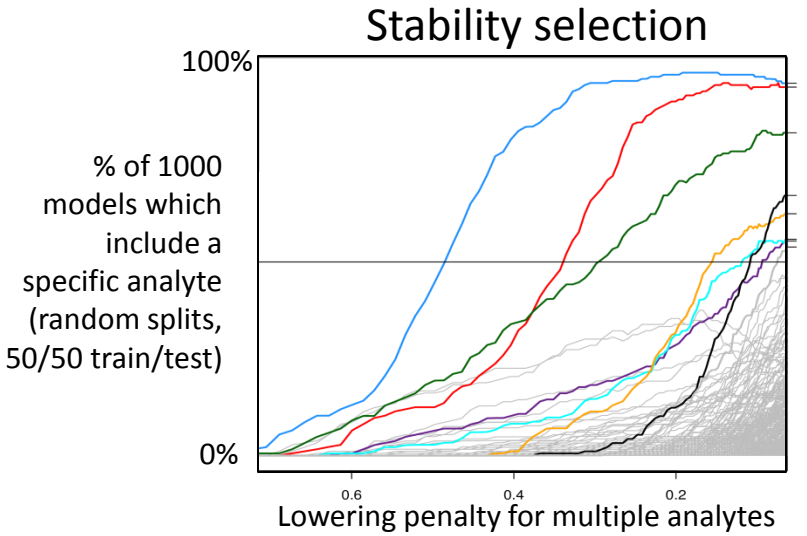
Hypothesis-free

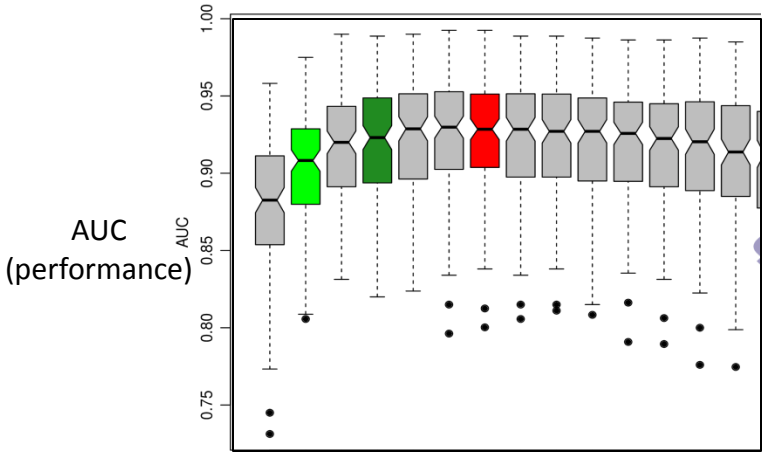
- Fast: does not require biological knowledge
- Objective: does not depend on favorites
- Better performance - Optimal combinations possible
- New Territories - black swans (un-anticipated biology) can be found

- Demands large numbers of precise measurements
- Control of false discovery rate requires more samples/skills
- Psychological barrier to "Fishing Expeditions"

Control of false discovery rate

- Problem:
  - When many measurements are made, eliminate false positives and to include only the best combination of markers in a model
- Sophisticated mathematical strategies:
  - Stability selection process (penalized popularity contest for marker inclusion in models)
  - Multi-dimensional feature selection of stable analytes





Does utility drive or follow biology?

Biology first strategy

- Additional evidence of success, beyond statistical
- Listed in ICH requirements for surrogate endpoints
- Psychologically rewarding

- Biological plausibility does not predict success
- No guarantee of clinical utility
- Assumes homogeneous populations
- Excludes biomarkers where prior knowledge is absent
- Limits discoveries to what humans can understand

Utility first strategy

- Performance is unconstrained by prior biological hypotheses or knowledge
- Clear and early go/no-go decisions
- Unique products for complex people

- Demands big data and measurement capacity
- No guarantee of biological plausibility
- Psychologically uncomfortable

THE FIRST “APP”: PREDICTING AND MONITORING MAJOR ADVERSE CARDIOVASCULAR EVENTS

Precision Risk Profiling in Cardiovascular

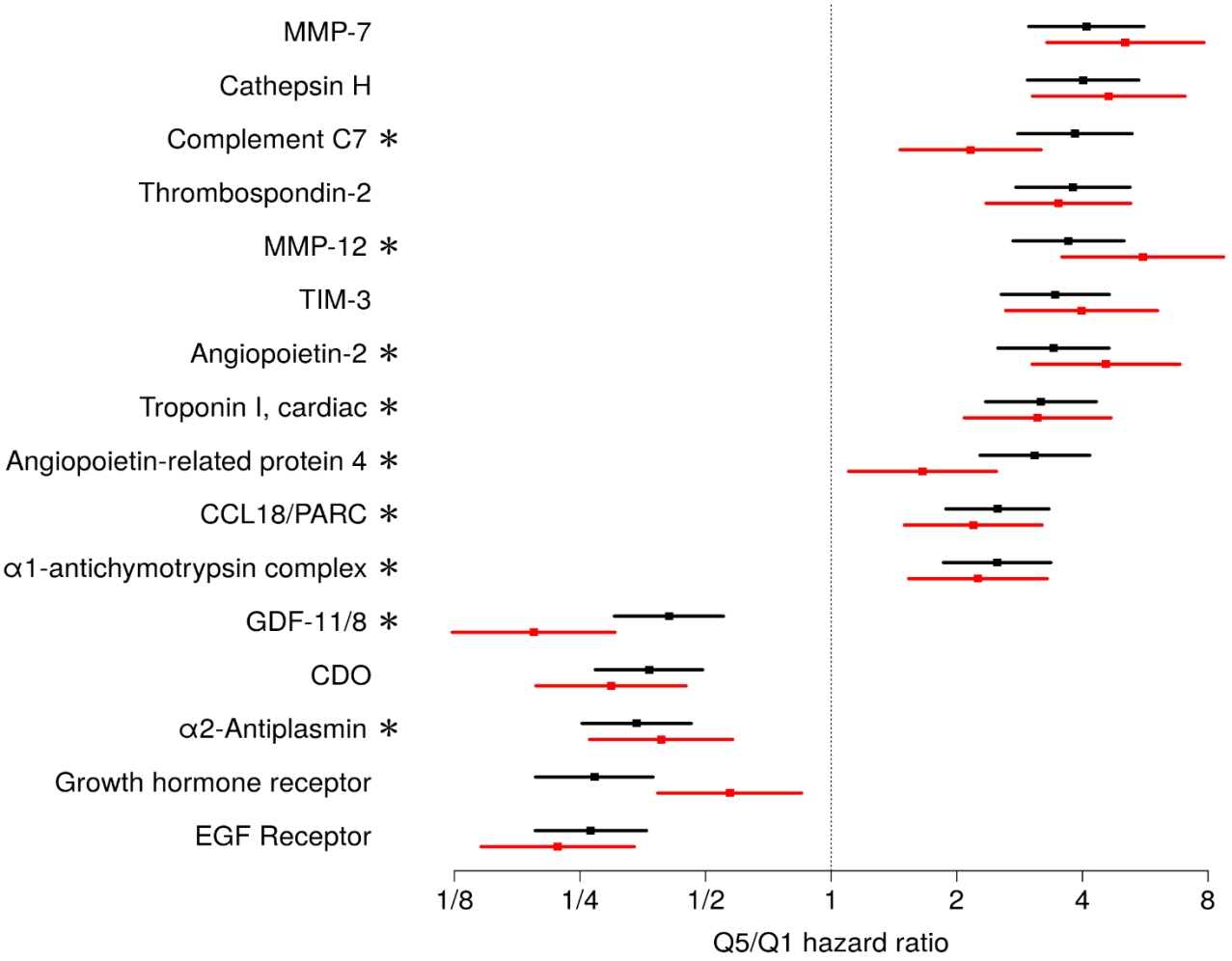
- **Discovery study: Heart & Soul (UCSF)**
  - 938 plasma samples from patients with stable CHD
  - 10 year follow-up
  - Biomarker discovery with SOMAscan 1.1K Assay
    - 1,130 proteins measured simultaneously
  - Outcomes: Bioinformatics analysis to identify proteins prognostic of death, MI, stroke/TIA or hospitalization heart failure
  - Created a multivariate 9-protein model for 4-year composite endpoint
- **Independent validation study: HUNT 3 (Norwegian cohort)**
  - 971 samples matching entry criteria for Heart & Soul
  - All subjects had at least 5 years follow-up
  - Blood collection and transport was more representative of real world conditions: a biomarker stress test

A Coherent Combination Of Proteins Selected By Multidimensional Mathematics

Discovery study (black)

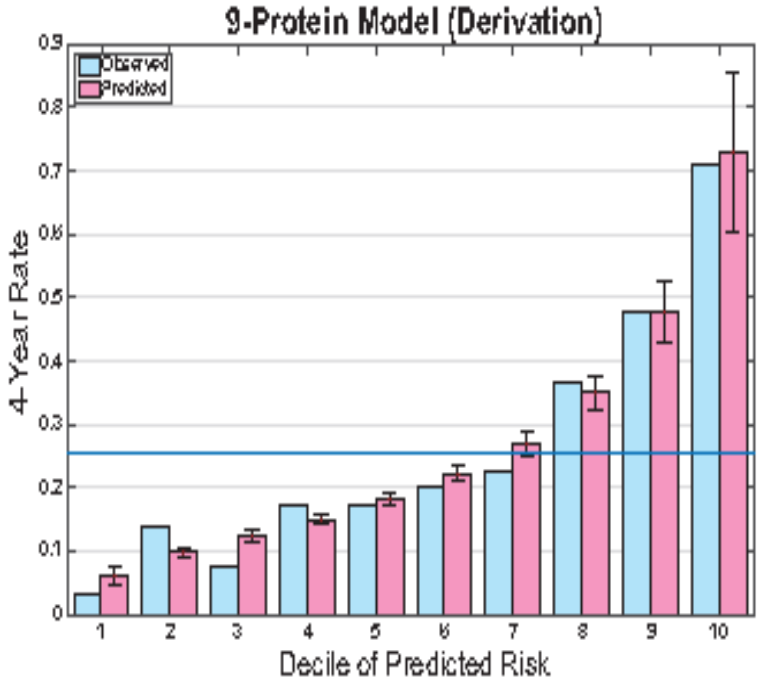
Independent validation study (red)

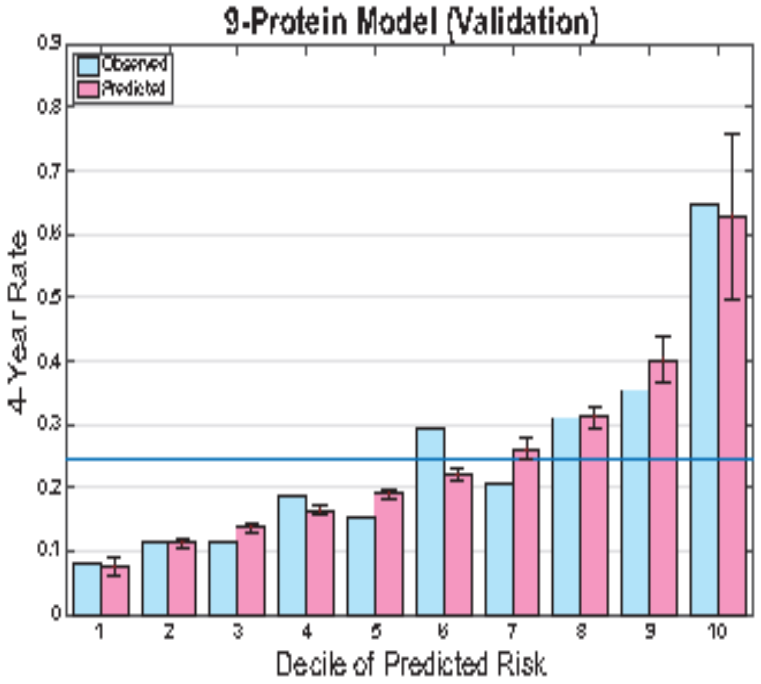
* = subset of proteins used in the final risk score



Calibration of 9 protein model

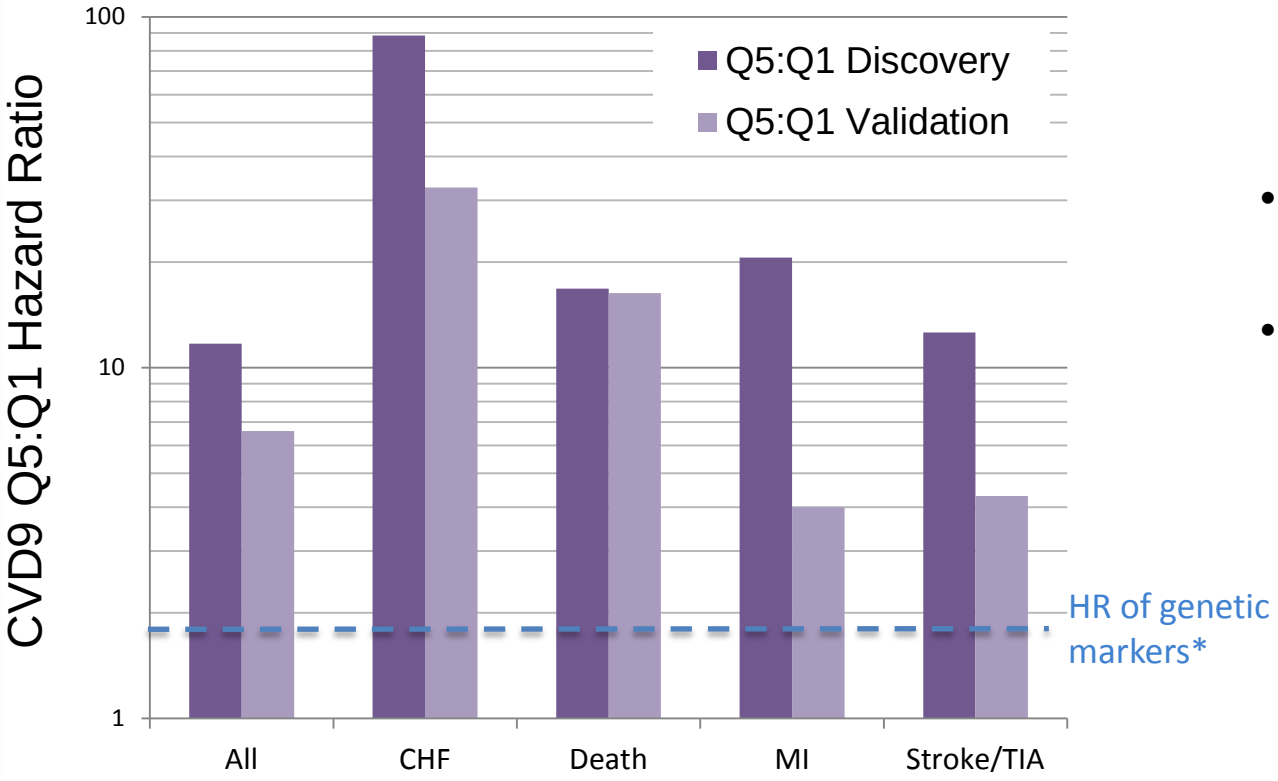
- Predicted (pink) vs. observed (blue) event rates by decile





Hazard Ratios For All Event Types

N=1854 Subjects



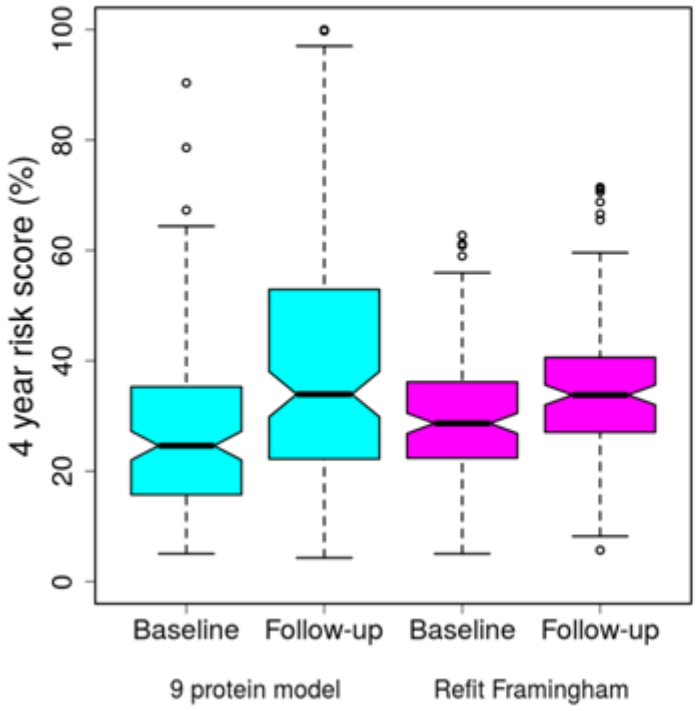
- Consistent performance across event types
- Strongest in predicting congestive heart failure

**Mega JL, Stitziel NO, Smith JG, et al. Lancet 2015.*

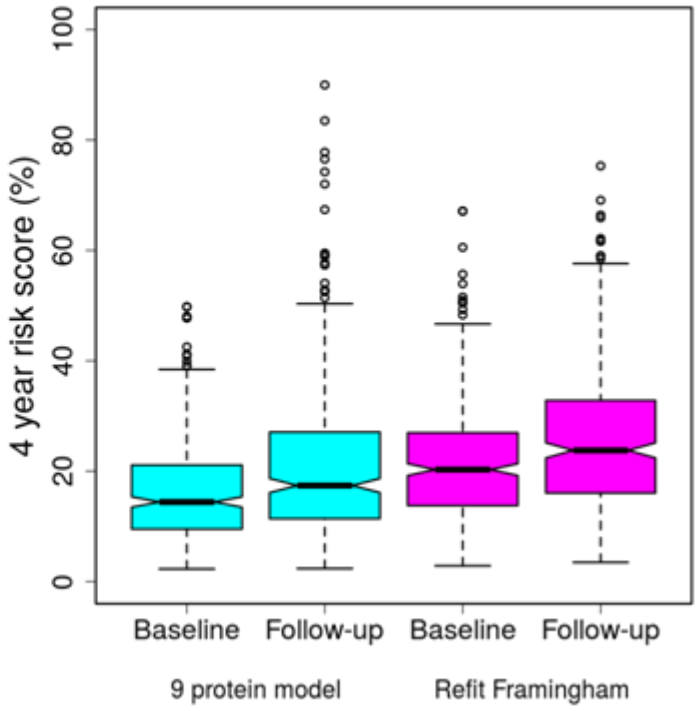
Sensitivity to approaching events

1148 paired plasma samples from 574 subjects with apparently stable CHD
Baseline sample; no events for first 5 years; second sample; 5 years subsequent follow up

139 participants with subsequent events

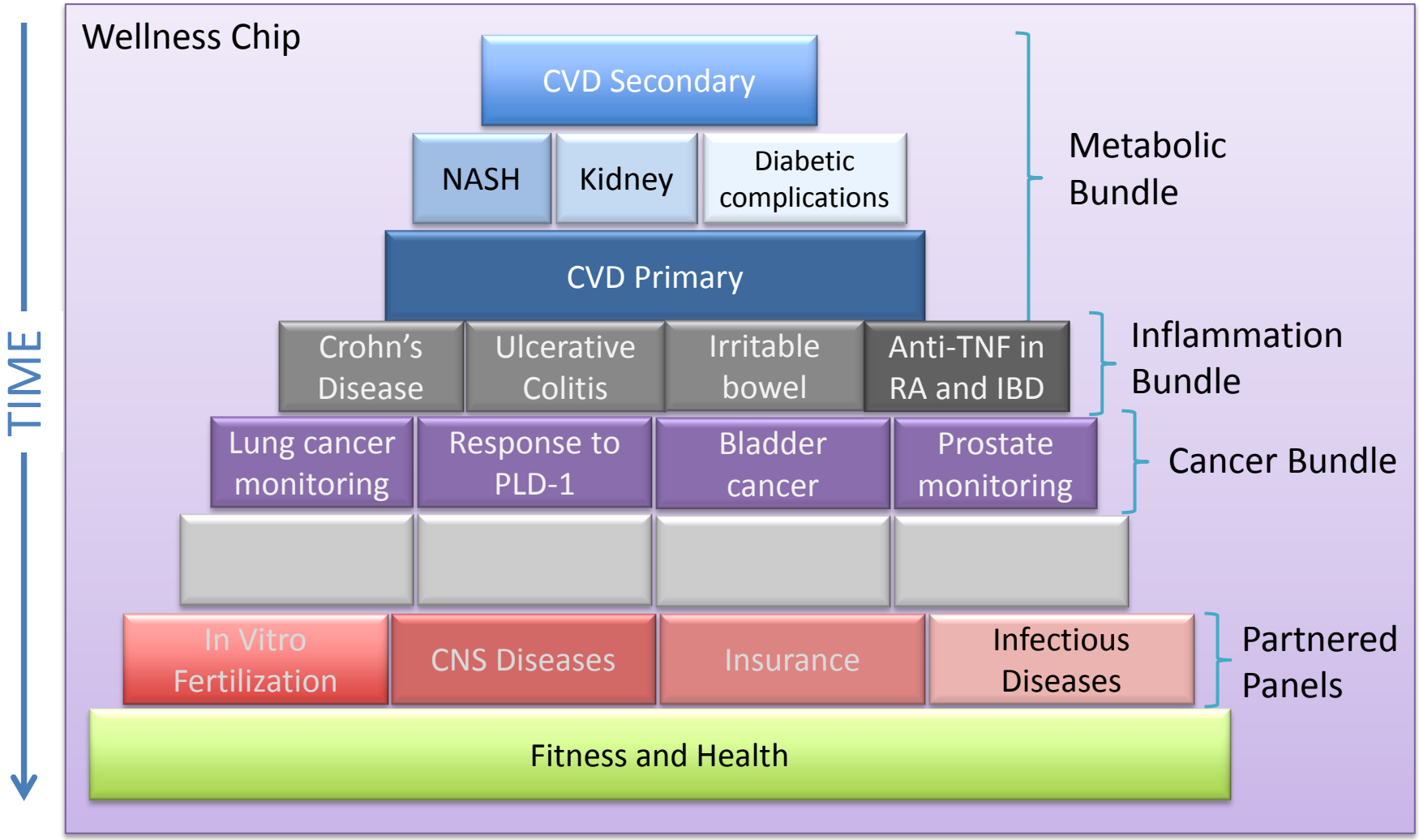


375 participants without subsequent events



Δ in 5 years:	+9.4%	+3.5%	+3.0%	+3.1%

Path to the Wellness Chip: Apps



How do we implement learning at scale?

- We are intending to open a SOMAscan laboratory on the Oxford life sciences campus
- Local projects under discussion/planning:
  - Can we add SOMAscan to “Live Well Stay Well” program commissioned in Bucks?
  - Can we start prospective SOMAscan projects with Oxford AHSN, academics and NHS?
    - Metabolic health in diabetics
    - Prediction of health deterioration in frail elderly
    - Metabolic health in the mentally ill

Better outcomes, lower costs