Testing new models of research funding: One Brave Idea

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Disclosures

- Revenue from gene testing in cardiomyopathies
- Patents for cardiotoxicity testing in zebrafish
- Patents for drug discovery in zebrafish

- Novartis
- AtlasVentures
- ArrayBioPharma
- The Medicines Company
- Synthon
- Biogen Idec
- Sanofi
- Merck
- Pfizer
- Vertex
- AHA/Verily/Astra Zeneca

- Academic self-interest

One Brave Idea : **AHA/Verily/Astra Zeneca**

- $75M for a single investigator
- 3 month/3 stage timeline
  - 250 words
  - 10 pages
  - Shark tank
- No constraints on use of funding
- Distinctive reporting structure

Executive Board
(Funders)

AHA

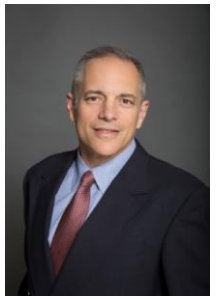
One Brave Idea™

Central Organization/CEO/CSO/CIO

Overall scientific strategy and direction

- Core data science
- Day to day operations/Project management
- Scientific, reporting, financial and legal accountability
- Incubator and other partnership development and maintenance
- Cross-functional collaborative teams to maximize project velocity/efficiency
- Lean and nimble

Scientific thought leaders - ad hoc advisors



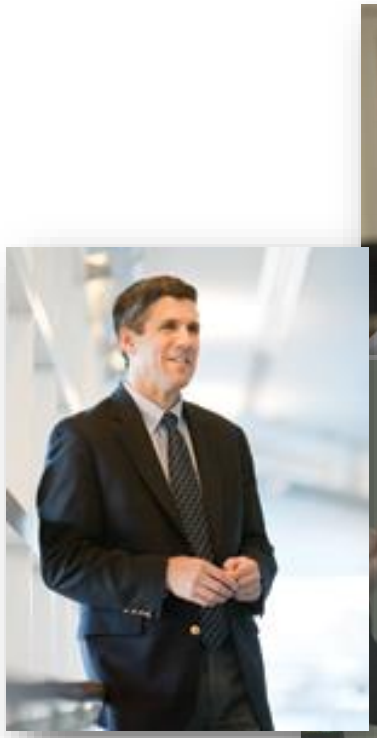
Idea(s)

- Redefining coronary heart disease: at the edge of wellness
  - Redefinition of CHD in dynamic and quantitative biological terms
  - Identify new and much earlier true endophenotypes
  - Establish empiric approaches to moving from **deep to broad**

  - **New disease genes, new environmental contributors**
  - **New therapeutic approaches or new therapies**
  - **New preventative strategies**

- Testing new approaches to research execution and funding
- Contributing to a new ecosystem for discovery and care

Personnel: Initial core team



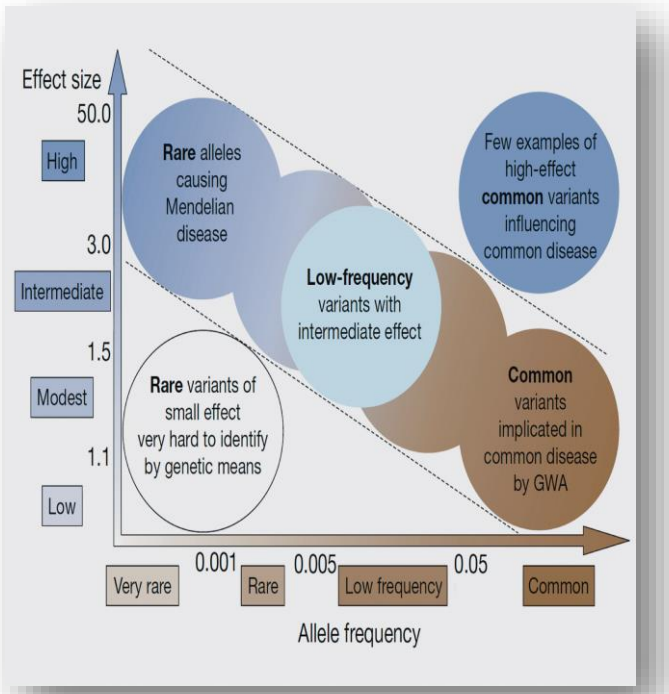
AHA/AZ/Google

Euan Ashley
Lazlo Barabasi
Elazer Edelman
Mike Gaziano
David Grayzel
Calum MacRae
Chris O'Donnell
Fritz Roth
Ramachandran Vasan

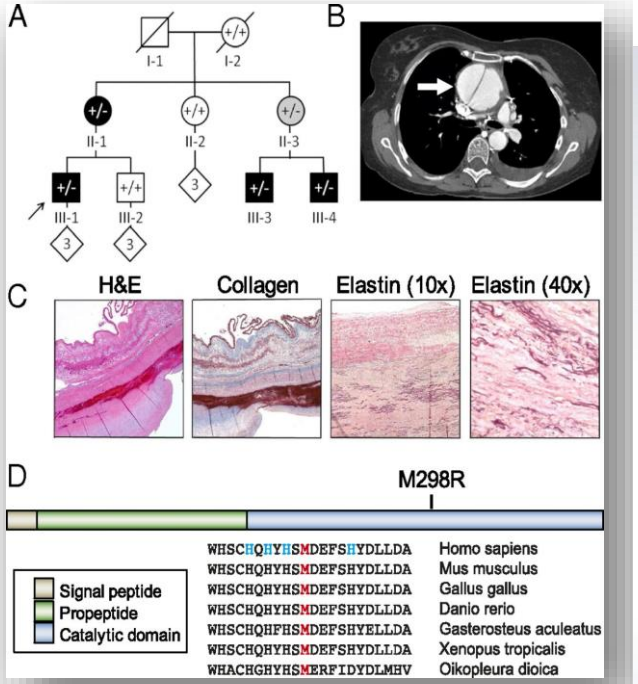
American Heart Association®

AstraZeneca

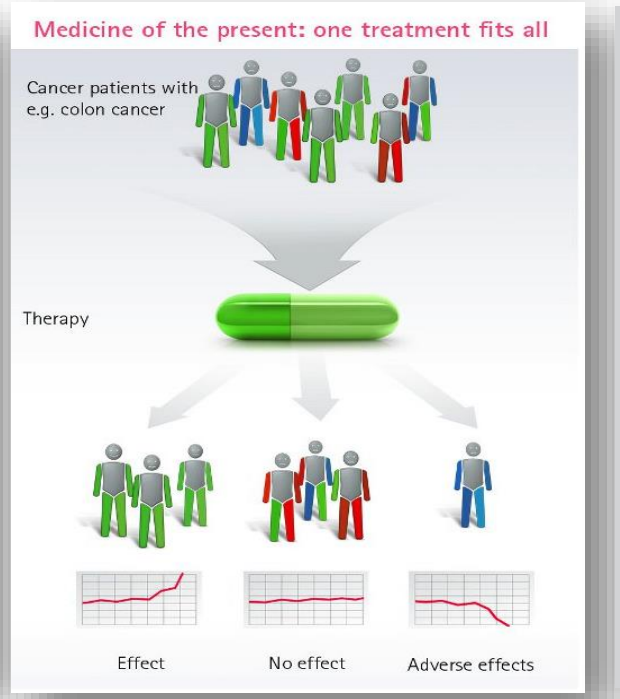
Project: Where is all the information?



Genetics



Clinical genomics



Clinical trials

Care redesign

- **Phenotype is limiting in multiple areas of biomedical science**
  - Static or limited dynamic range
  - Almost all aggregates
  - Unidimensional with no organizing metadata
- **Few if any conditioning variables ever measured**
- **Most medical data**

The phenotype gap

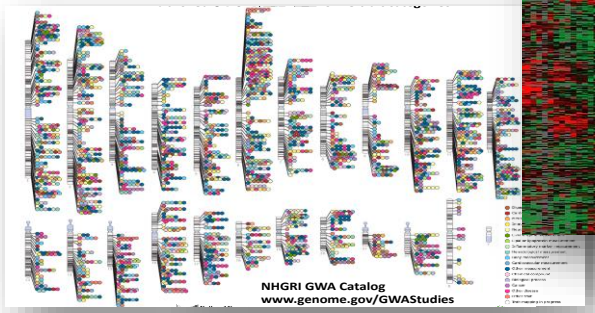
Connectome

Physiome

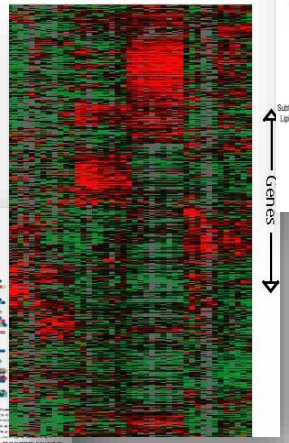
Proteome

Transcriptome

Genome



10^9



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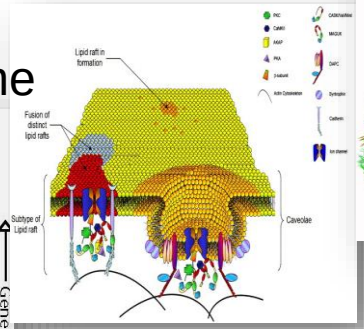

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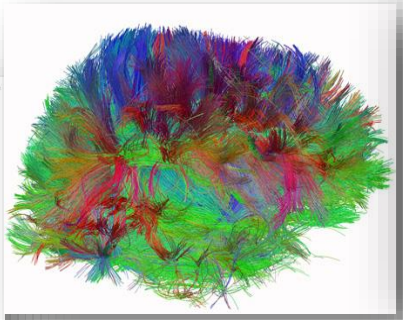

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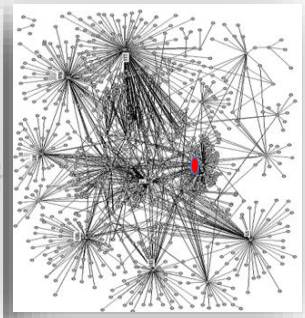
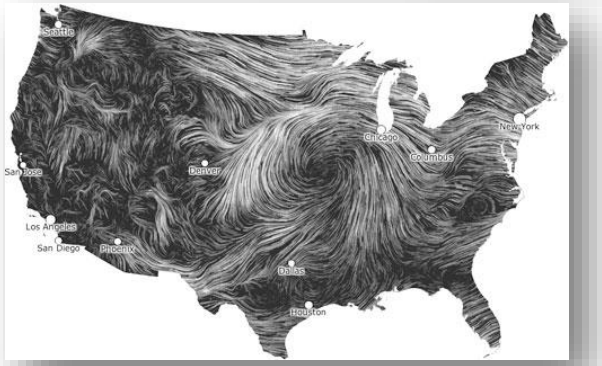
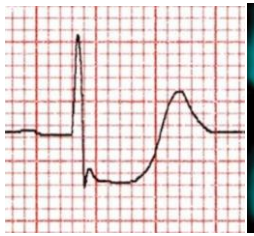


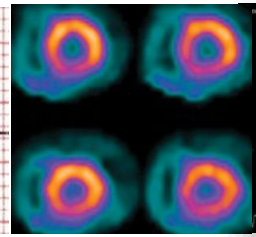
Timescale Dependent

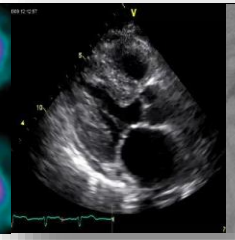


Exposome

All clinical phenotypes 10^4





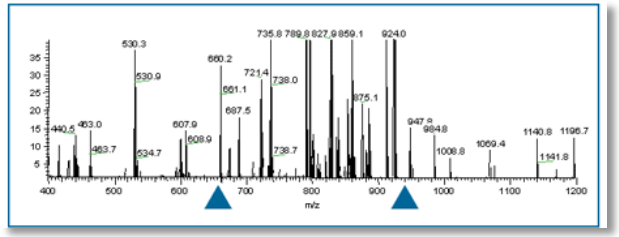


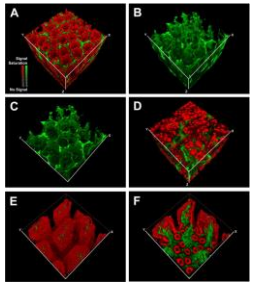
Moving beyond legacy phenotypes

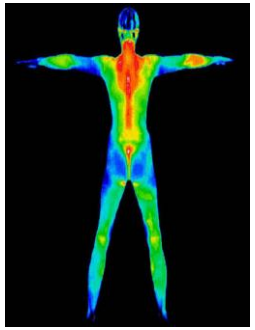
Unstructured
18th century
Semi-subjective and duplicative
Lack of standardization
Cross sectional and static
No metadata

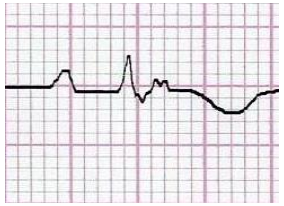
High threshold for innovation
Tied directly to implementation evidence base

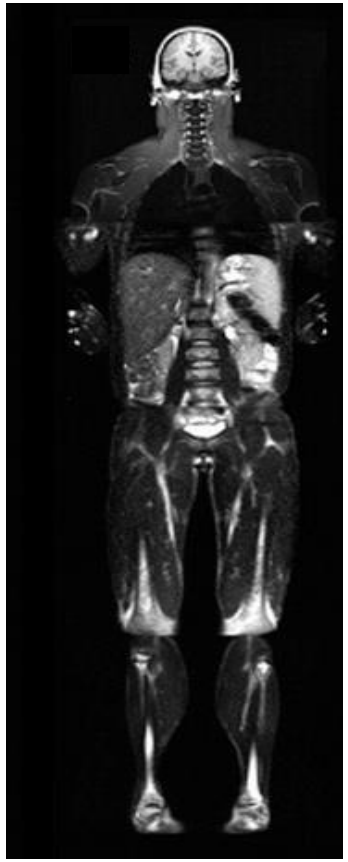
Glycosuria











EKG

Specific metabolites

Microbiome

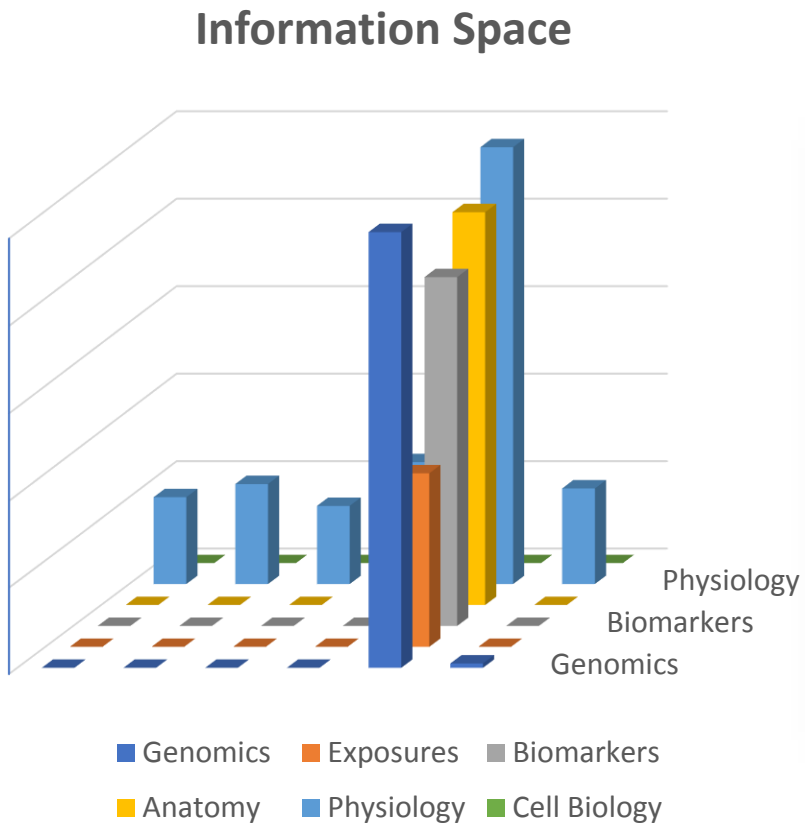
Microcirculation confocal imaging

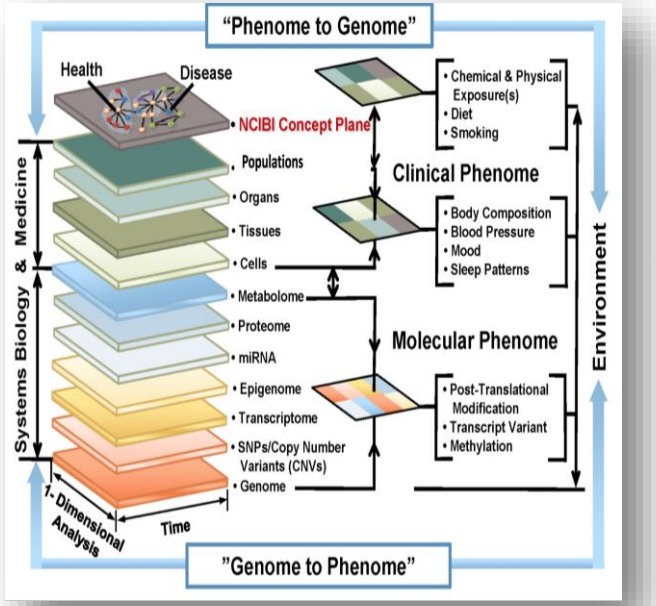
Adipose tissue mapping

Thermography

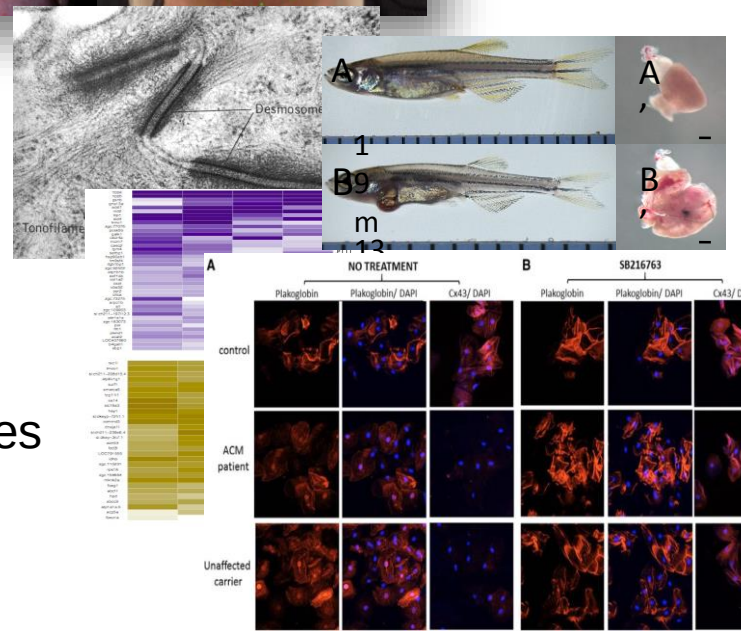
Everything else

Broad vs deep





Kohane et al.



- Comprehensiveness
- Organizing metadata across datasets and models: perturbations and timescales
- New datasets-shared across biological models
- **A computable molecular/cellular/physiologic 'physical exam'**

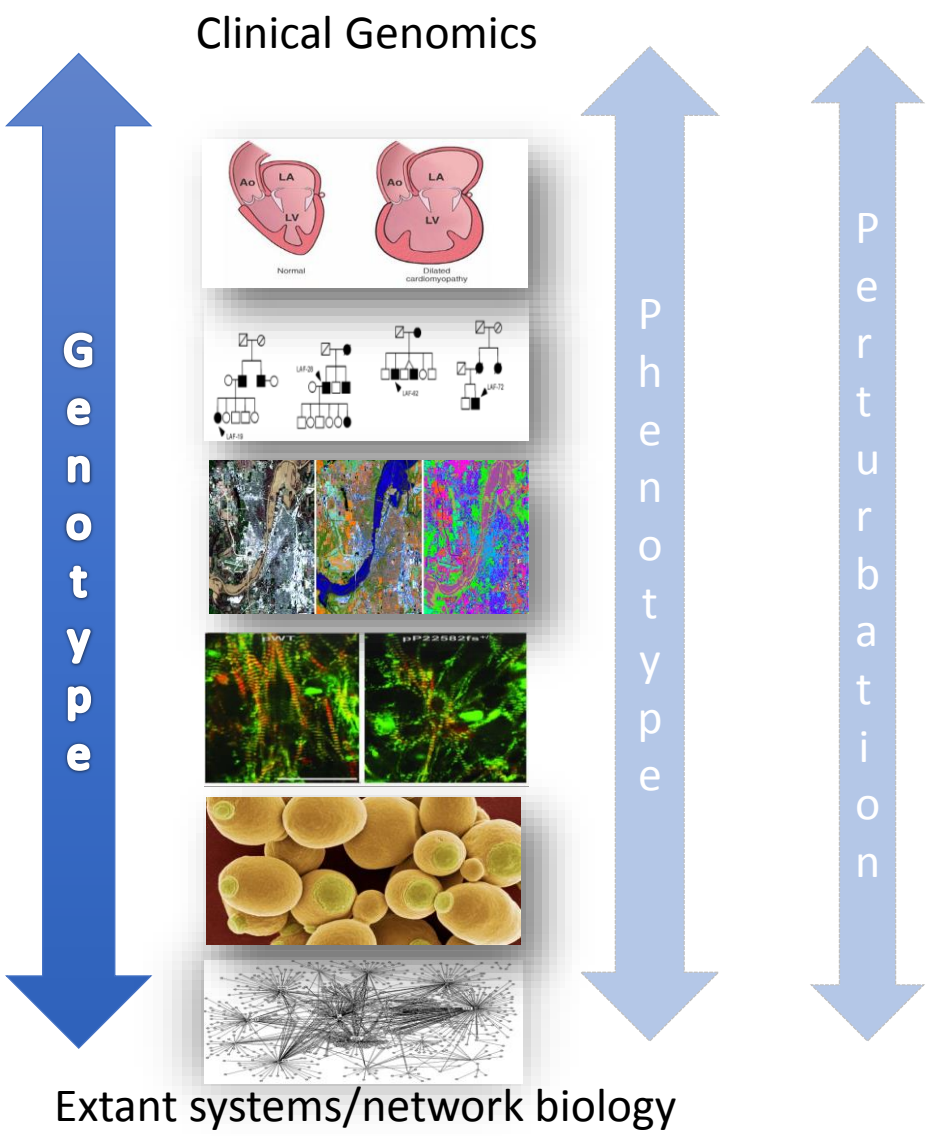
Linking clinical and basic science

- Mapping relationships across species
  - Genome
  - Phenome
  - Perturbations

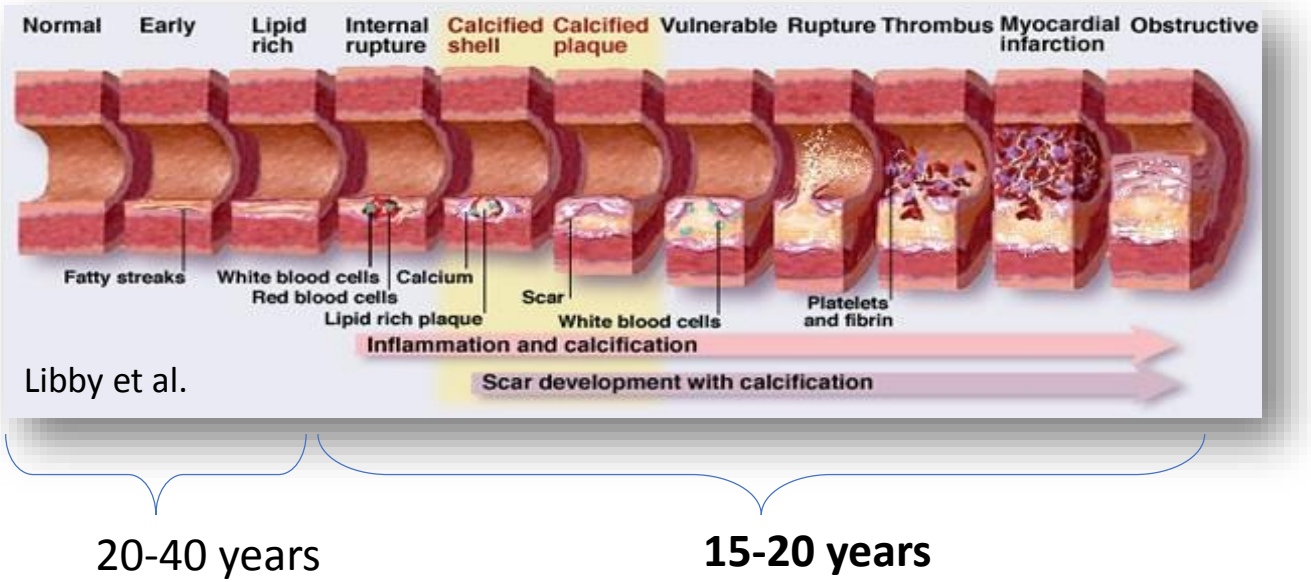
- Multiple ‘omics
- Cell biology, physiology
- Environmental and drug responses

- Multiple dimensions improve specificity

- Shared phenotypic lexicon
- ‘Mechanistic’ phenotypes in all species
- ‘Co-clinical’ modeling: real time application



OBI: Detecting the earliest phases of disease



20-40 years

15-20 years

Generic pre-CHD

Different underlying forms of CHD

New ways to detect different forms of CHD

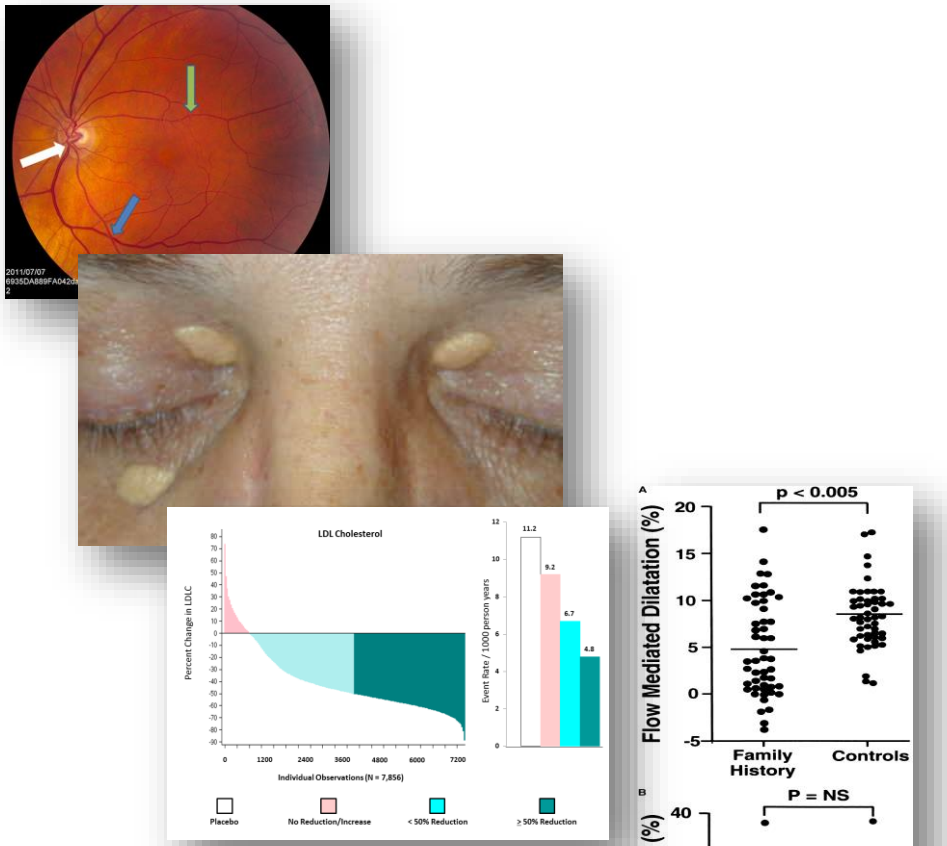
Scaling to general population for screening and disease Rx

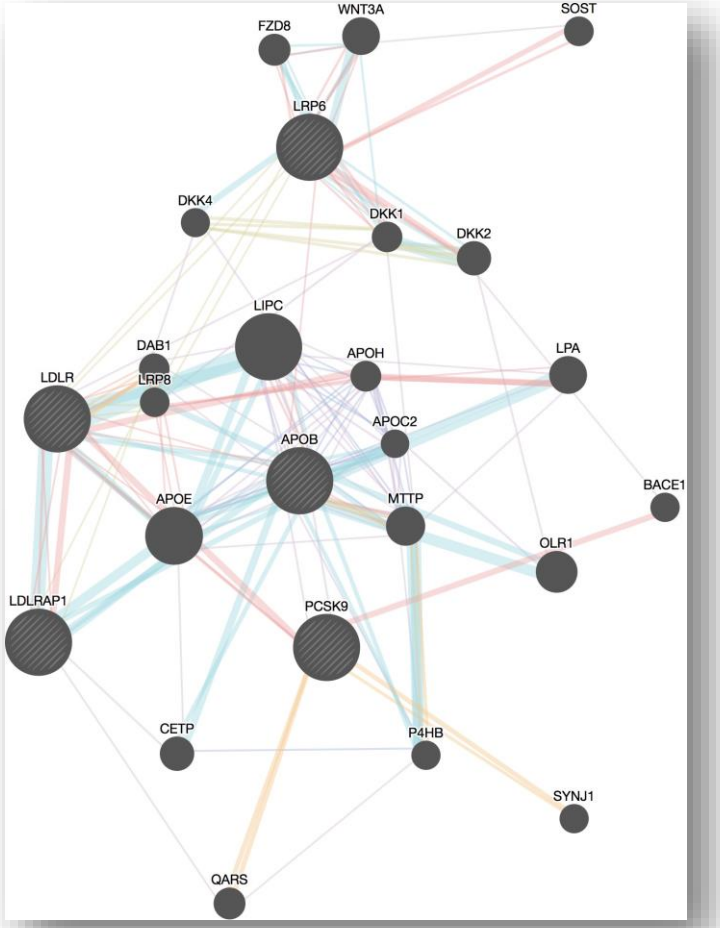
- Most of what we know about CHD has emerged from a focus on the **latter 15-20 years** of the disease
- CHD represents many different disorders which resemble each other most in their later stages
  - Identifying new translatable markers of the very earliest stages of CHD
  - Define new underlying causal factors for CHD,
  - Develop technologies for population detection,
  - Move towards new therapies and preventative strategies

New pathways in atherosclerosis?

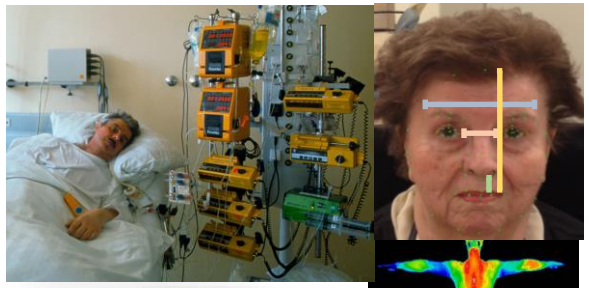
- Preclinical phenotypes
  - Discrete genetics
- Core genes
  - LDLR, ApoB, PCSK9
- Extant biology predictions
  - HTN
  - T2DM
  - Cognitive decline

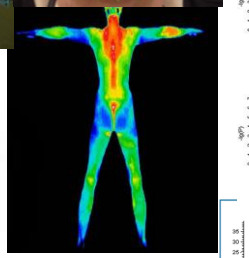
Preclinical phenotypes



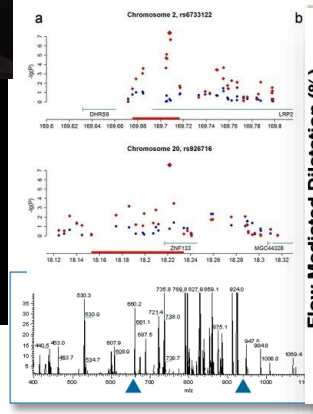


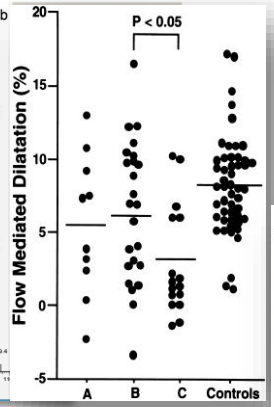
A generalizable approach for phenotype discovery



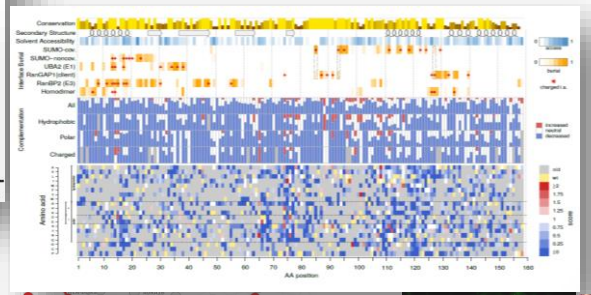


Phenotype and perturbation discovery
Cells to organisms

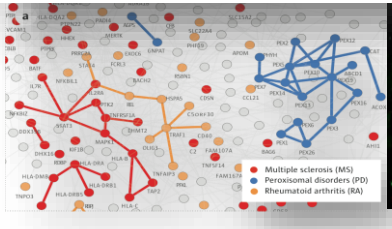


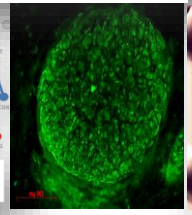


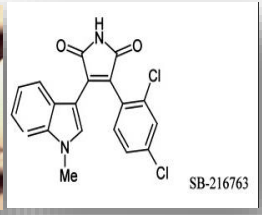
Validation in kindreds and genotyped cohorts



New causal pathways
Perturbation/phenotype discovery



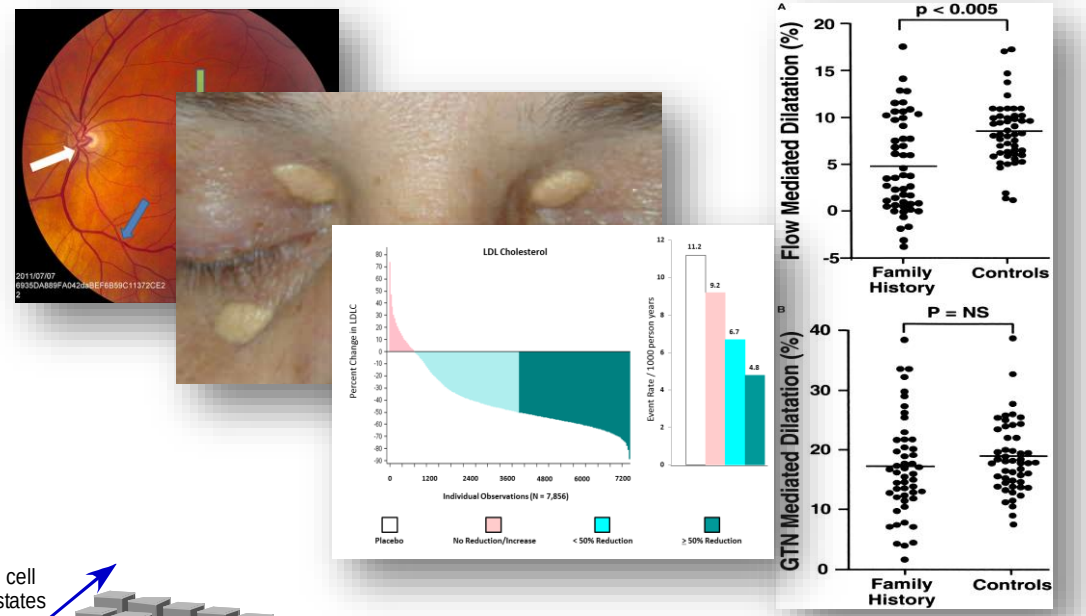


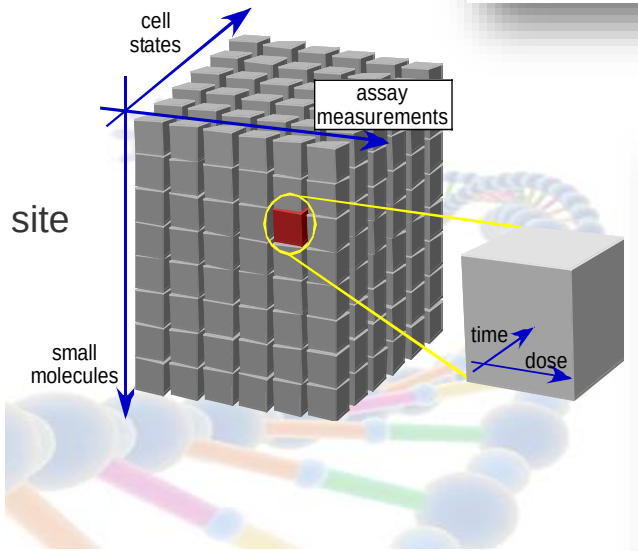


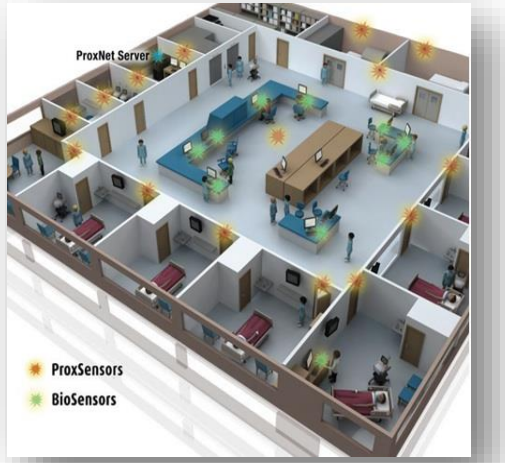
Democratization of phenotyping
Large simple trials

Orthogonal phenotypes: scalability by design

- Rapid cycle development
  - Plug and play
  - Flexible bioengineering and computational infrastructure
  - Benchmarking technologies
  - Developing our own technologies
  - Rigorous biologic insight for positioning
  - Stimulus identification
- Disease-enriched populations
  - Large numbers of subjects
  - Large proportion already genetically defined
  - Active Precision Medicine efforts
- Based in outpatient clinic
  - Physician encounter occupies <20% time spent on site
  - Integrating genomics and care reinvention
  - Mapping onto existing disease framework
  - Controlled environment: stimulus-response pairs
- Efficient scaling to population cohorts
  - FHS
  - Million Veterans Program
  - Verily, Microsoft, AHA My Research Legacy







Funding mechanism considerations

- PPG format
- Venture fund: ‘for profit’ vs ‘not for profit’
- Discrete commercial entity
- Closed end vs sustainable

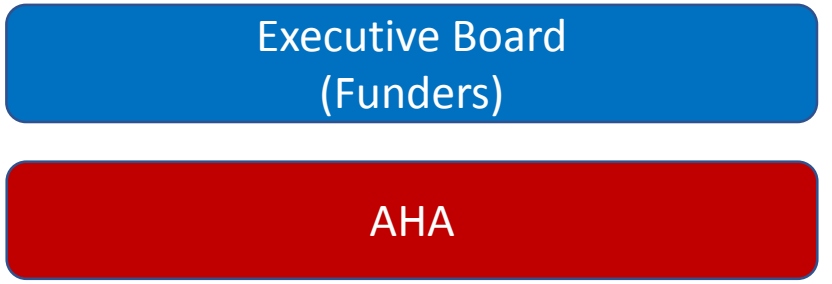
- Additional partners and fundraising
  - Industrial/Foundations/Philanthropy
  - Focused on alignment: Pharma/Tech/Biotech/Device/Retail/other
  - In-kind resources
  - Governance
- Partnerships with traditional funders
  - Joint investments: shared returns
  - Federal and international cohorts-fee for service
  - Training mechanisms
  - Infrastructure development

Structural features of program

- Administrative
  - Central core with fiduciary, legal and reporting responsibility
  - Renewable engagement of scientific team members and SAB
  - Flexibility to continue to engage/disengage based on science
  - Executive board with oversight

- Highly goal directed
- Objective go/no go metrics for each funding component
  - Scientific rigor
  - Alignment with goals of program
- Efficient funding cycles-<6 weeks

- Indirect costs
- Intellectual property



One Brave Idea™

Central Organization

CEO

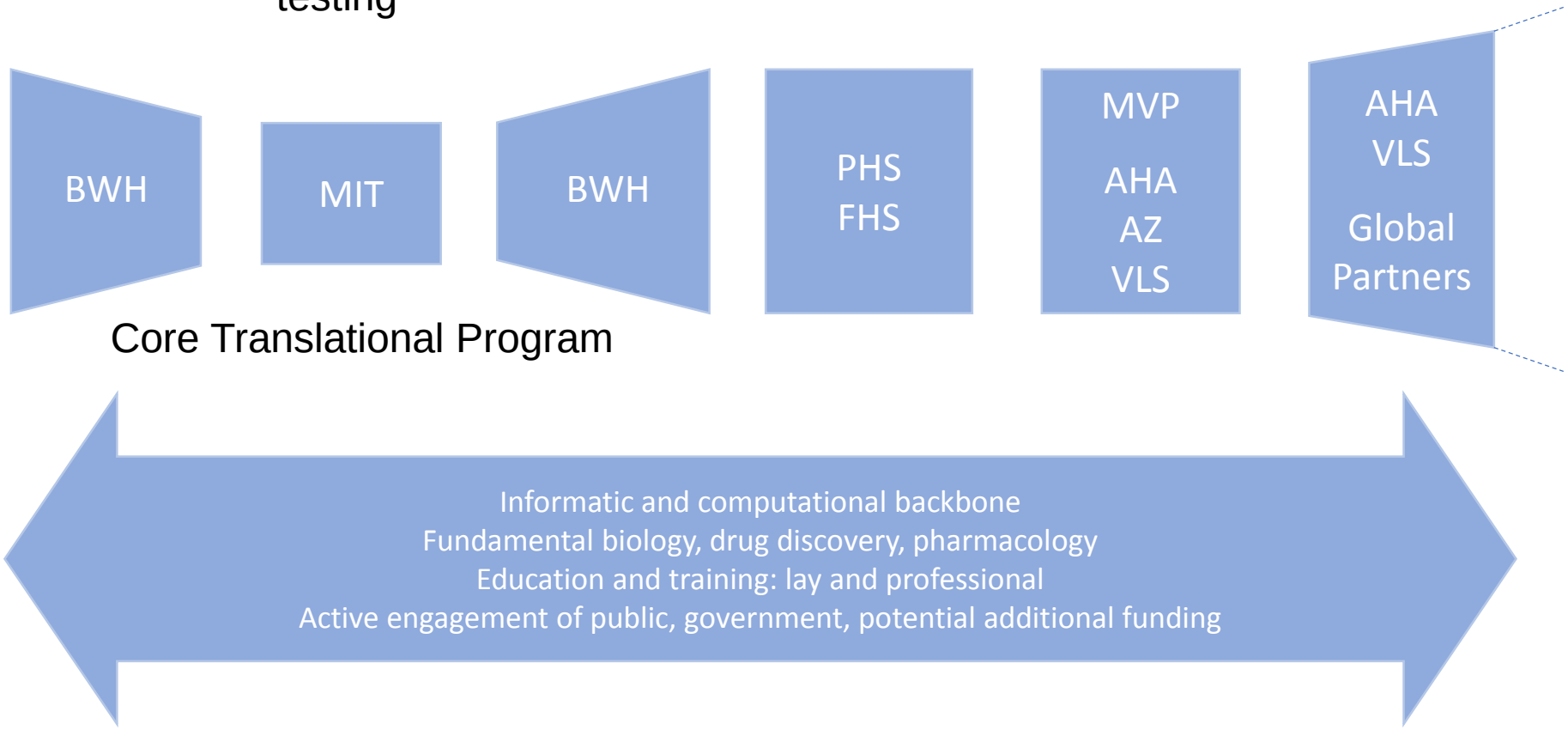
CSO/CDO

Active projects
Participating scientists

Core infrastructure

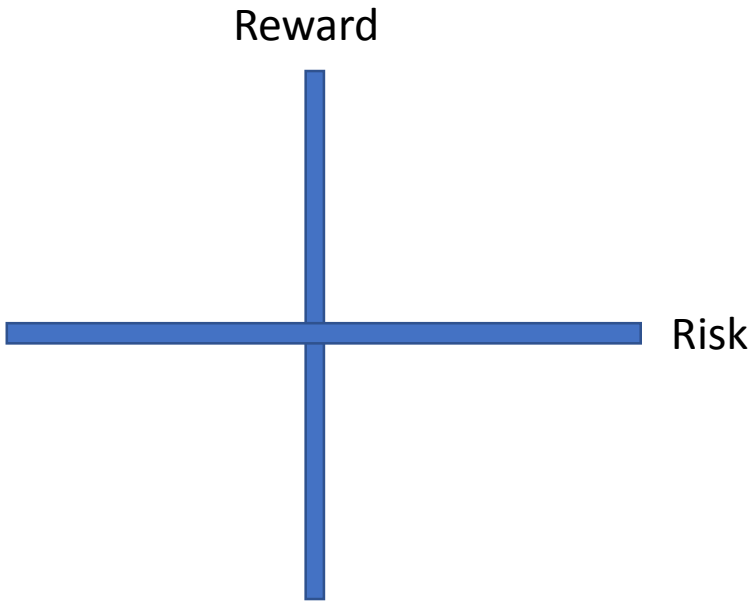
Ideation & initial development | Selection | Fabrication Prototyping Initial human testing | Initial clinical testing & validation | Population studies

- Traditional science
- AHA/AZ/Verily
- Commercial entities
- Patients
- General public
- Crowdsourcing



Initial science strategy

- Core data science
- Balanced portfolio
  - Early initiation of low risk/high yield
    - Exposure quantitation
    - Extant atherosclerosis cell biology
    - Population science with existing data
  - Prioritization of high risk/high return projects
    - Early basic science
    - Foundation for later implementation
  - Developing criteria for moving to scale
- Internal and external RFAs
    - ‘Quality, price and performance’
    - Testing the structure of the program
- Optimization of teams for projects
    - Members
    - Locations
- Exploring partnership mechanisms



Agnostic vs Directed
Funding vs Engagement

Culture

- **Emphasis on alignment and engagment**
- **Diversity-personnel, ideas etc**
- **Building community engagement for the long haul**
- **Balancing comprehensiveness and utility-the academic conundrum**

- Rigorous metrics including effect size
- Active cross-fertilization between projects **within OBI**
  - 20% rule or equivalent: rewarding multi-disciplinarity/engagement
- Teaming across groups to advance goals
- Team member development
  - Maintenance of long term fundability for investigators
  - Development of orthogonal skills for all team members

Reappraisal in new funding context

- Creating and testing approaches to:
  - Team science
  - Data accessibility
  - Science process-planning, budgeting, execution
  - Academic-private partnerships
  - Public-private partnerships
- Communication
  - Engagement across entire program: channels
    - Scientists/Funders
  - Project management
  - Regular videoconferencing: I2 based solutions
  - Shared dashboards-metrics
- Publication

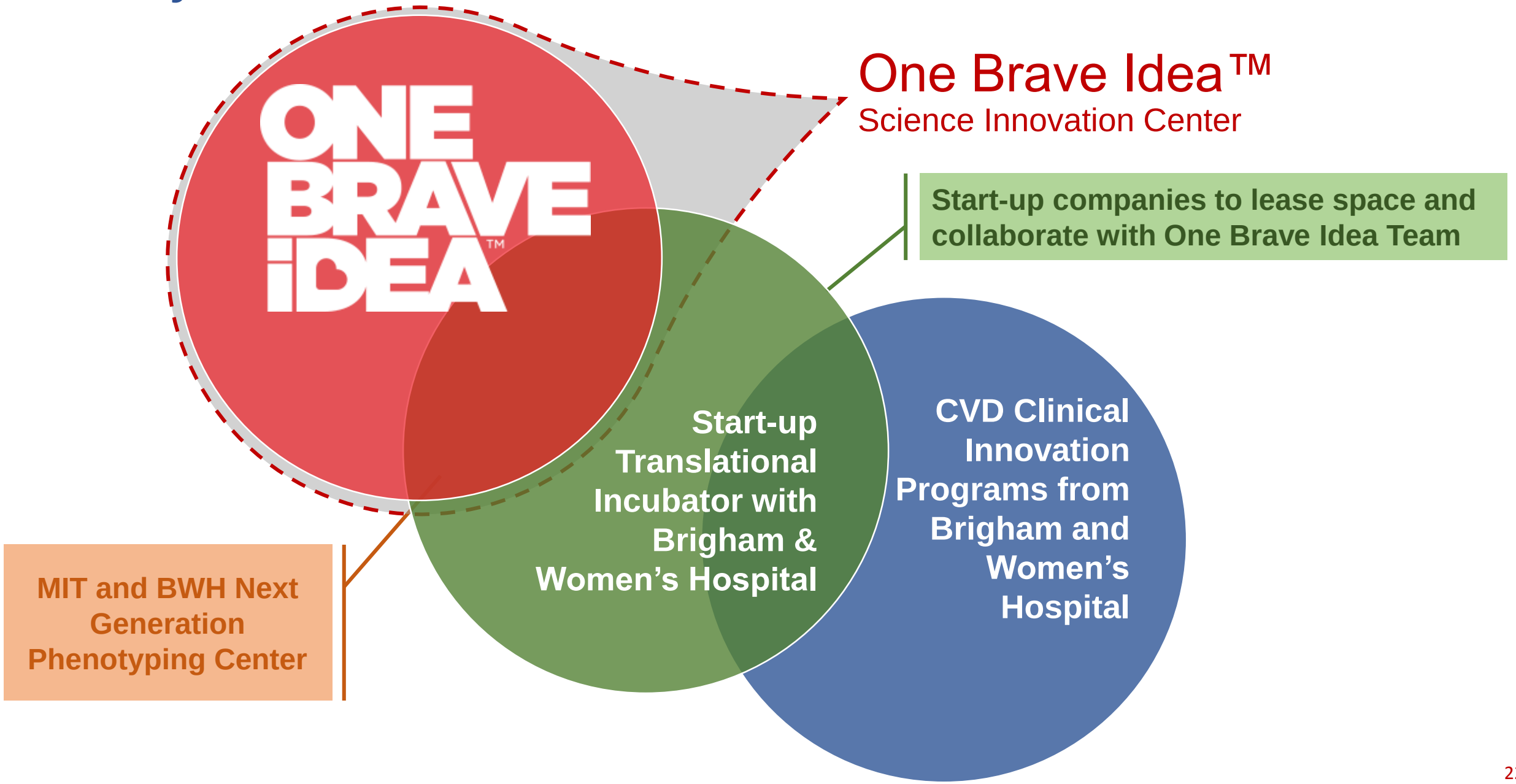
- Sociology
- Economics
- Process
- Sustainability or otherwise-by design

Partnership models

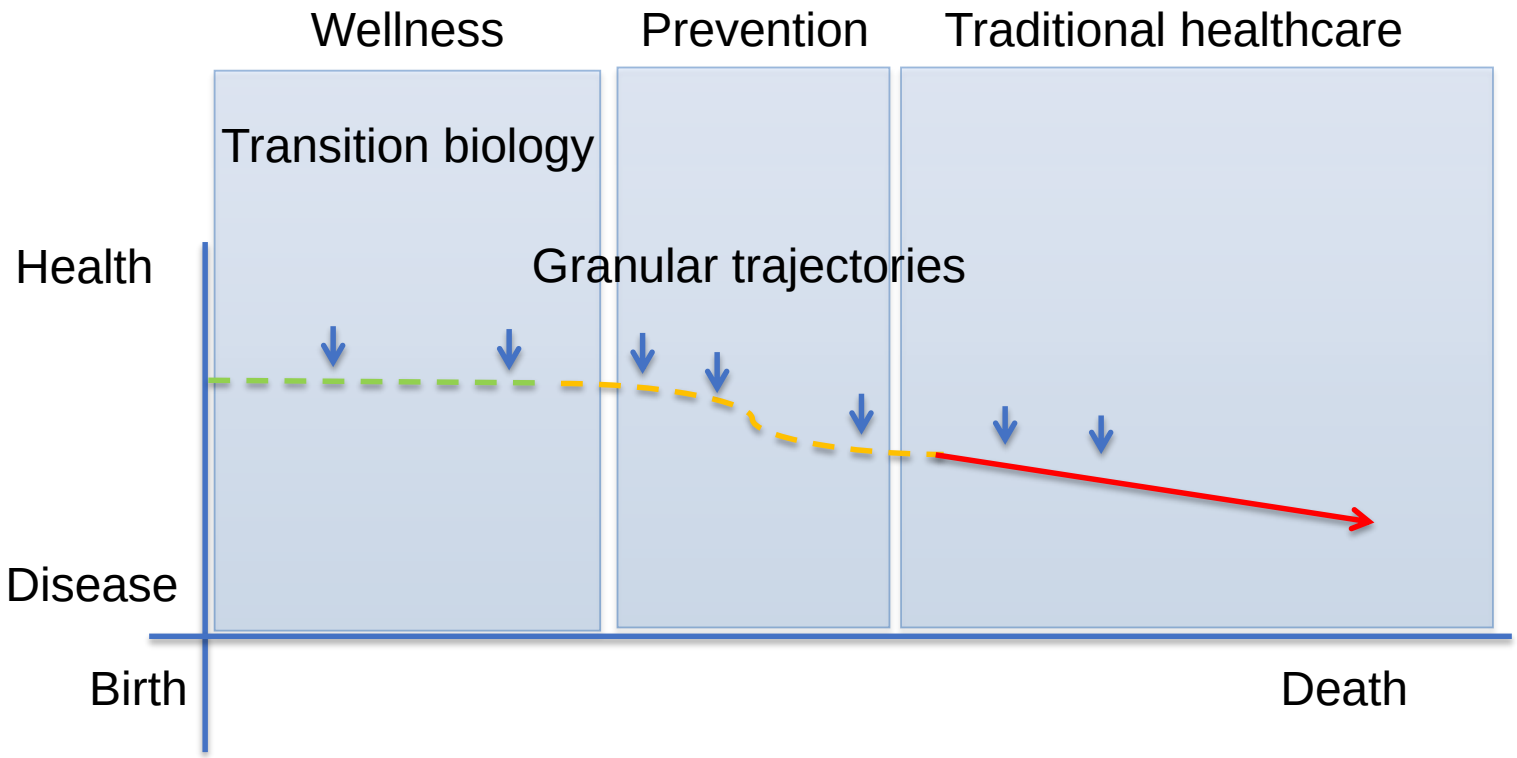
- Direct investment in the original project
- In-kind collaborations

- Joint investment in specific projects with shared risk/reward
  - e.g. a real world clinical trial
- Joint investment in communal projects
  - Data escrow or other strategies to overcome the long-term issues with ‘de-identification’
- Joint investment in external RFAs
  - e.g. In specific population cohorts to test/validate new phenotypes
- Training and education

Physical location



Information content drives integration and ‘learning’



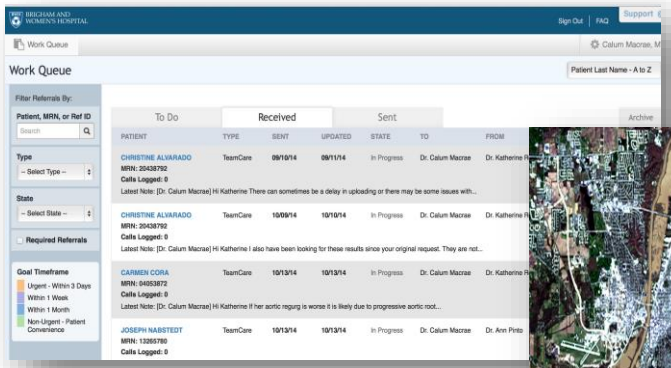
Orthogonal data streams
Devices
Response dynamics
Real-time stratification
Continuous audit
Adaptive optimization
- Cost/Risk
- Virtual/Physical

Care networks

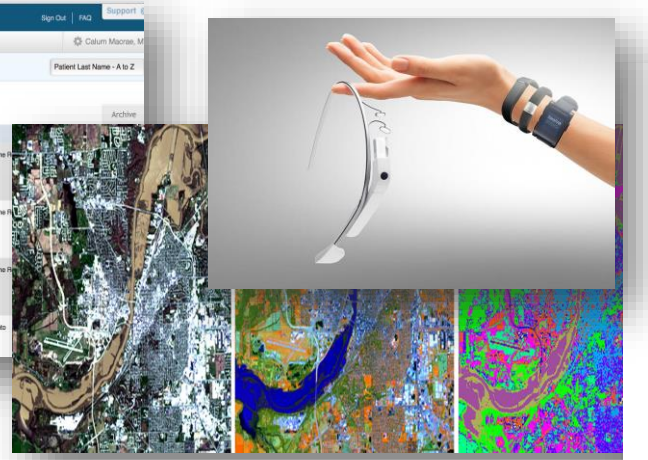
Areas of potential transformation

- Timing and resolution of care delivery, research and education
- True scalability
- Value as well as its measurement and attribution
- New partnerships across multiple areas: devices, delivery channels, etc,
- Biomedicine as learning platform: knowledge generation/ implementation
- Basic or Translational science/Hybrid trials/Real world randomization

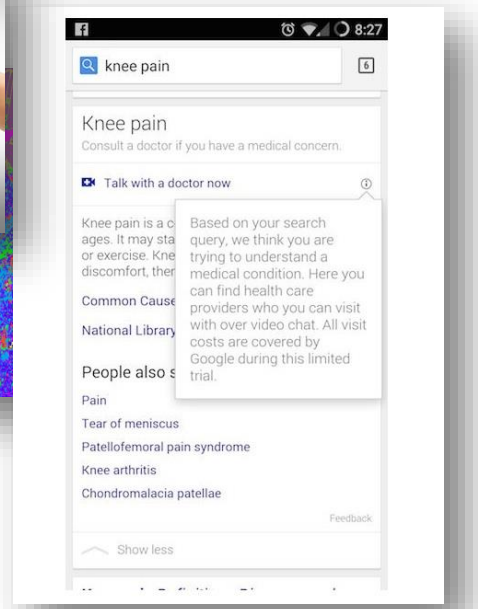
The real driver for new models of funding



New workflow



New data streams



New delivery systems

- Disruptive partners/competitors with deep pocket: PBMs, eHR companies, Global IT Players, VCs, Pharma, Banks, Real Estate, Supermarkets etc
- New revenue models
  - ACO, pay per click, subscription, added services
  - Renewed focus on knowledge generation, knowledge management and knowledge transmission
  - Different transaction types: direct to patient, educational, research premium
  - Lower cost larger markets
- Failure of many AMCs
- Emergence of small number of ‘global’ networks

Summary

- Information content is a core problem in biomedicine
  - Overcoming entrenched legacy phenotypes
  - Overcoming lack of comprehensiveness
  - Actively balancing broad (fewer metadata) vs deep (lower scale) phenotyping
- New models of funding are required that align all of the potential partners
  - Complement traditional biomedical science funding models
  - Directly associated with data sources
- Convergence of care and discovery
  - Data management, data science and decision support
  - Trajectories - across health and disease
  - **Funding**

- We need systematic approaches to acquiring the right information content
  - New earlier, orthogonal and more granular data and new data gathering tools
  - Eliminating non-biological silos
  - Structured perturbations-translatable by design to models-to allow integration
- Quantitative learning health systems-generalizable rules

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