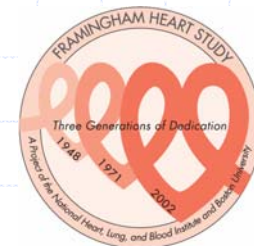
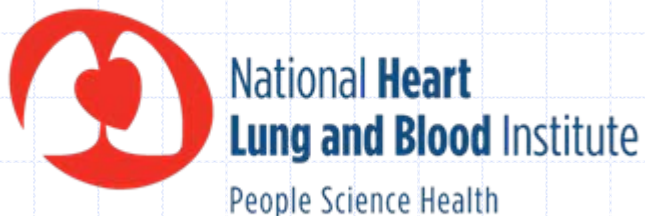


NHLBI's SABRe CVD Biomarker Initiative

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Current Biomarker-Based Strategies for CVD Prevention

- Current biomarker strategies for CVD prevention are hypothesis based and center on understanding the biology of CVD (e.g. cholesterol, blood pressure)
 - Basic science
 - Observational studies
 - Large-scale clinical trials of interventions
- These approaches work but have been slow and are poorly integrated

New Biomarker-Based Strategies for CVD Prevention

- New strategies for CVD prevention will be technology-driven
 - Genetics and genomics
 - Proteomics
 - Metabolomics/lipomics
 - Bioinformatics
 - Systems biology (data mining)
- Will be integrated to rapidly identify causal risk factors for CVD

Biomarker Science in the NHLBI Strategic Plan

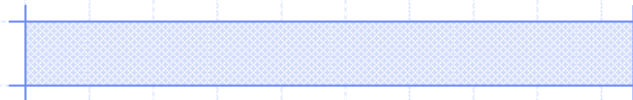
- We need to discover new biomarkers to:
 - Provide clues to causes of disease
 - Diagnose diseases at an early stage when prevention is most effective
 - Predict disease progression or regression
 - Anticipate desirable or adverse response to therapy
 - Serve as effective drug targets
 - Monitor the response to specific therapies

Biomarker Science in the NHLBI Strategic Plan

- “Omic” technologies will uncover many new biomarkers that may become useful tools for evaluating risk, individual responsiveness to interventions, and for identifying new therapeutic targets
- The identification of new biomarkers forms an essential foundation for the development of *personalized medicine*

Recent Developments in Biomarker Science

- Major advances in immunoassays, proteomics, metabolomics, and lipomics permit measurement of thousands of biomarkers
- Are we ready to apply these markers in clinical practice?



SABRe CVD Initiative

- **Systems Approach to Biomarker Research in NHLBI's Framingham Heart Study**

Why is Framingham Ideal for Biomarker Research?

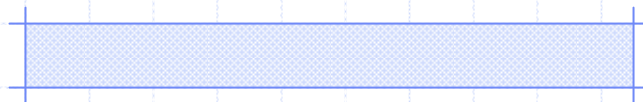
- **Breadth of Data**
 - Traditional risk factors (lipids, BP, BMI, diabetes, smoking)
 - Novel risk factors (inflammation, hemostasis, ox-stress, insulin)
 - Extensive non-invasive imaging (CT, MRI, U/S, echo, PWV, FMD)
 - Many cardiovascular disease endpoints
- **Available DNA Resources**
 - Large repository of DNA and immortalized cell lines
 - SHARe study is complete
 - 550k SNPs in 9,300 participants
 - 5 billion genotypes available October 2007

SABRe CVD Initiative: Specific Aims

- Characterize the molecular signatures of clinically important diseases:
 - Atherosclerosis
 - Metabolic risk factors

SABRe CVD Initiative: Design

- Use high-throughput technology to measure large numbers of circulating biomarkers
 - Targeted immunoassays (e.g. ELISA)
 - Discovery proteomics
 - Discovery metabolomics/lipomics
 - Gene expression profiling
 - MicroRNA profiling



SABRe CVD Initiative: Design

Laboratories

Immunoassays
(ELISA or Luminex)

Proteomic
Discovery/validation

Metabolomic
Discovery/validation

Lipomic
Discovery/validation

Gene Expression
Profiling

MicroRNA
Characterization

Biomarker data

Feedback

Data Management

Quality Control

Association Analysis

SABRe CVD Initiative: Study Sample

1971 → → → → → → → 2008

Offspring Study: 8 Exams

N = 5124 men & women (ages 5-70)

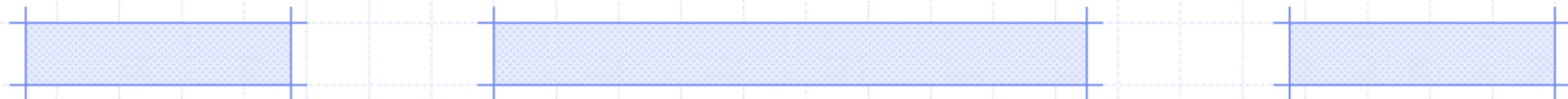
1576 spouse pairs, 3514 biological offspring

2002 → 2005

Third Generation Study

N = 4095 men and women

SABRe CVD
available
sample size:
~7000



SABRe CVD Initiative: Primary Traits

Atherosclerosis

Coronary calcium by CT

Aortic calcium by CT

Carotid IMT by ultrasound

CVD by medical history

Bone mineral density by DXA

Aortic plaque mass by MR

Ankle brachial index

Metabolic Risk Factors

Body mass index/waist girth

Visceral adiposity by CT

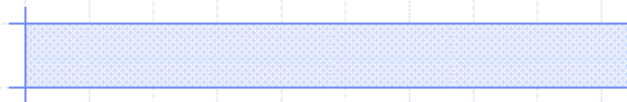
Epicardial adiposity by CT

Diabetes

Insulin resistance by HOMA

HDL/ triglycerides

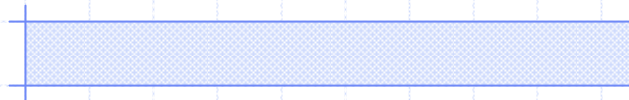
Blood pressure



SABRe CVD Initiative:

"Omics" Discovery

- Discovery proteomics, metabolomics, and lipomics
 - Case-control design
 - Atherosclerosis cases vs. matched controls
 - Metabolic risk factor cases vs. matched controls
- Follow up with validation of promising biomarkers in entire study sample
- Replication in other observational study cohorts

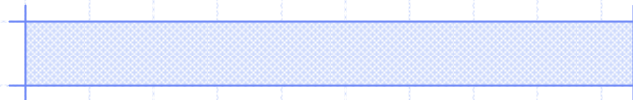


SABRe CVD Initiative: Biomarker Selection for Immunoassays

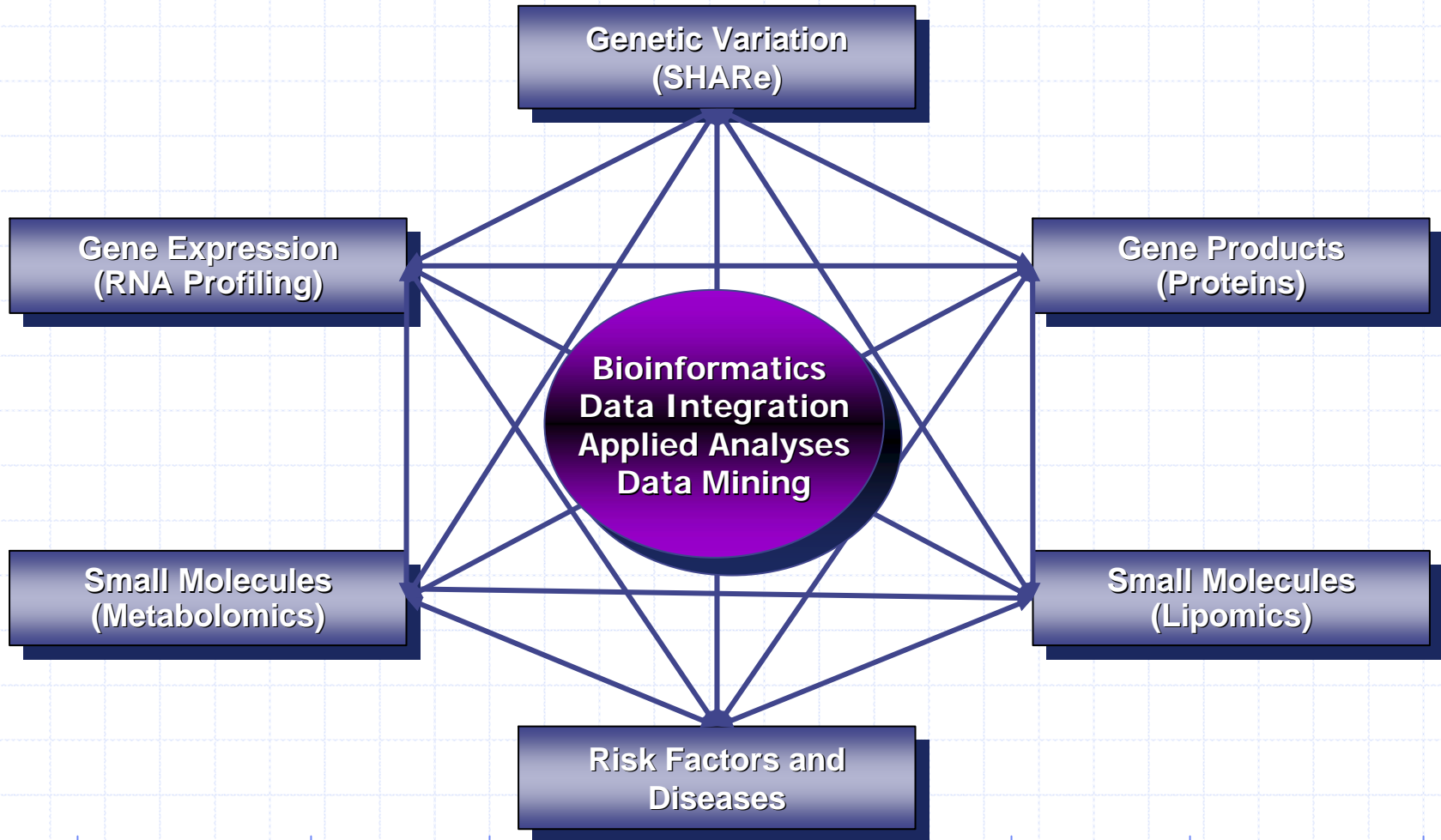
- Literature review
 - Human and animal studies
- Discovery proteomics
 - Target promising proteins from discovery phase
- Analysis of GWAS
 - Target proteins of genes showing association
- Interim analyses
 - Expand and extend pathways showing association
 - Include markers suggested by expression profiling

SABRe CVD Initiative: Data Sharing

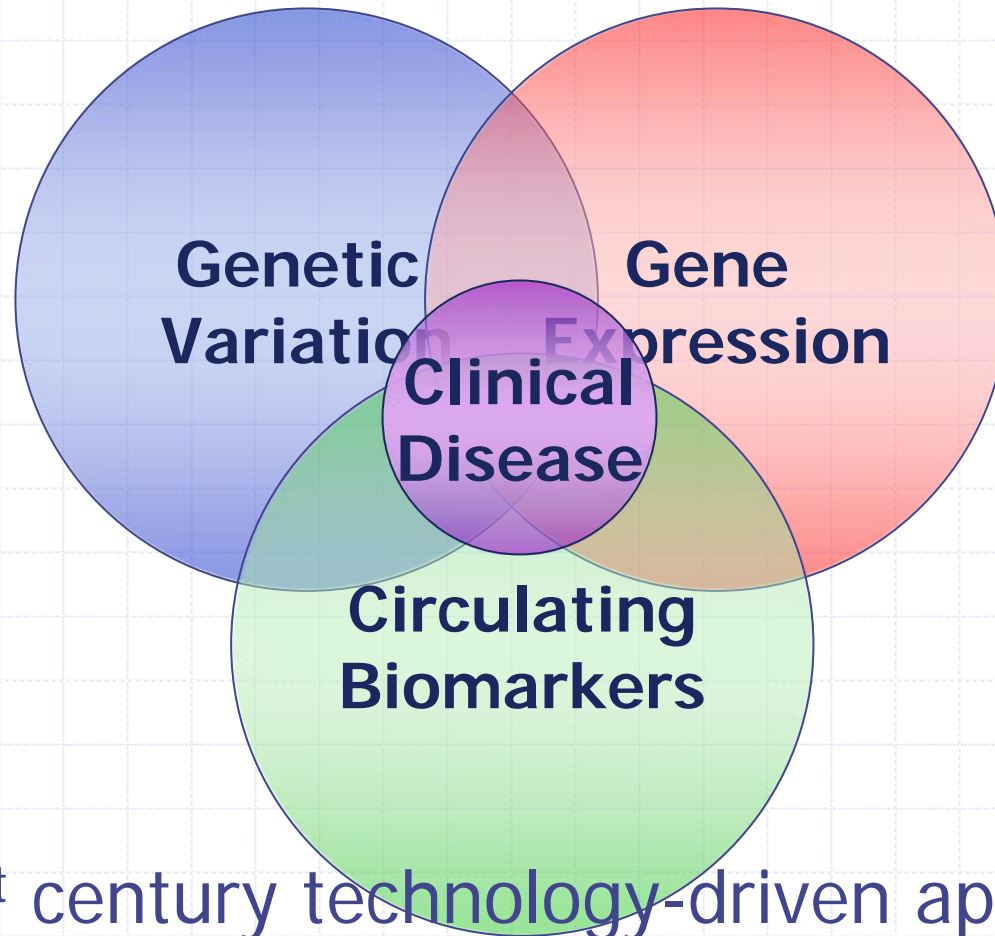
- Rapid sharing of biomarker data with the scientific community via National Library of Medicine to make this a national resource



SABRe CVD Initiative: A Complex Mosaic



SABRe CVD Initiative: Genomic Convergence



A 21st century technology-driven approach
to unravel mechanisms of disease

SABRe CVD Initiative: Unmet Needs

- The success of this proposed initiative will require:
 - Improved methods for high throughput biomarker measurement
 - Novel strategies for data integration
 - New algorithms for data analysis and mining
 - systems biology and network approaches
 - Applied analysis of huge data sets
 - Sharing the resource with the scientific community

SABRe CVD Initiative: Future Implications

- In-depth study of biomarkers of atherosclerosis and metabolic risk factors will provide additional insights into the pathogenesis of CVD
 - Promote development of new diagnostic tests
 - Personalized medicine
 - Advance understanding of the biology of health and disease
 - Identify new therapeutic targets
 - Create a pipeline for new drugs to treat and prevent disease