Genetics of Atherosclerotic Cardiovascular Disease: Translating Genome-wide Discoveries to Biology, Prevention & Treatment in Patients and Populations

Christopher O’Donnell, M.D., M.P.H.
Chief, Cardiovascular Epidemiology and Human Genomics Branch, NHLBI’s Division of Intramural Research
Associate Director, NHLBI Framingham Heart Study
Associate Clinical Professor, Harvard Medical School
Cardiology, Massachusetts General Hospital
February 7, 2014

NO DISCLOSURES

Translating CVD Genomics to the Clinic

• Pathophysiology of CVD & Risk Factor Paradigm
• Rationale for Genomic Approach to CVD
• High Frequency Variants: GWA Studies
• Low Frequency Variants: Population Sequencing
• Dissecting the Function of Genomic Discoveries
• Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization
Translating CVD Genomics to the Clinic

- Pathophysiology of CVD & Risk Factor Paradigm
- Rationale for Genomic Approach to CVD
- High Frequency Variants: GWA Studies
- Low Frequency Variants: Population Sequencing
- Dissecting the Function of Genomic Discoveries
- Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization

Atherosclerotic Plaque Development: From Healthy Vessel to Clinical CVD

Framingham Heart Study

Downtown Framingham, MA (circa 1960)
Major Risk Factors and ASCVD Risk

- Framingham 10-Year ASCVD Risk Profile
- Total Chol 180 240 240 240 240
- HDL Chol 50 50 35 35 35
- Smoking No No No Yes Yes
- Diabetes No No No No Yes


CT & Ultrasound Imaging for Coronary, Carotid, & Aortic-Peripheral Atherosclerosis

- Coronary, Aorta by MICT
- Peripheral Arteries by ABI

Current (Evidence-Based) Approaches to Predict, Prevent, and Pre-empt ASCVD

<table>
<thead>
<tr>
<th>Clinical Risk Factor</th>
<th>Evidence-Based Testing and Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>Lipid Panel, ASCVD Risk Profile</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>HbA1C, FG, HgA1C, ASCVD Risk Profile</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting BS, HgA1C, ASCVD Risk Profile</td>
</tr>
<tr>
<td>Coagulation, Inflammation, Biomarkers</td>
<td>Measure CRP, other biomarkers?</td>
</tr>
<tr>
<td>Subclinical Atherosclerosis</td>
<td>CACCT, CIMT, ABI</td>
</tr>
</tbody>
</table>
Translating CVD Genomics to the Clinic

- Pathophysiology of CVD & Risk Factor Paradigm
- Rationale for Genomic Approach to CVD
- High Frequency Variants: GWA Studies
- Low Frequency Variants: Population Sequencing
- Dissecting the Function of Genomic Discoveries
- Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization

“Mendelian” versus “Complex” Transmission in Monogenic Forms of CHD

<table>
<thead>
<tr>
<th>Familial Hypercholesterolemia:</th>
<th>Premature Onset MI Without Extreme Hyperlipidemia:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal Dominant Transmission</td>
<td>Complex Transmission</td>
</tr>
</tbody>
</table>

Prevalence of CHD in Families with a Positive ‘Family Risk Score’ in 122,155 Families

<table>
<thead>
<tr>
<th>Family Risk Score</th>
<th>Strength of family history</th>
<th>% of all families in population</th>
<th>Relatives with CHD, early onset (%)</th>
<th>Relatives with CHD, any age (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2.0</td>
<td>+++</td>
<td>1</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 0.5 - 1.9</td>
<td>+/-</td>
<td>13</td>
<td>55</td>
<td>42</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>Average</td>
<td>86</td>
<td>28</td>
<td>52</td>
</tr>
</tbody>
</table>

Williams RR Am J Cardiol 2001;87:129.
Clinical & Subclinical CVD Heritability

Premature Parental CVD Increases Risk of CVD

<table>
<thead>
<tr>
<th>Adjusted for All Major CVD RFs</th>
<th>Parental Hx Premature CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Men*</td>
<td>1.0</td>
</tr>
<tr>
<td>Women*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Heritability of Quantitative CVD Phenotypes

<table>
<thead>
<tr>
<th>Domain</th>
<th>Variable</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Risk Factors</td>
<td>Systolic Blood Pressure**</td>
<td>24-40%</td>
</tr>
<tr>
<td></td>
<td>Total Cholesterol**</td>
<td>47%</td>
</tr>
<tr>
<td>Blood</td>
<td>C-Reactive Protein***</td>
<td>26%</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>tPA, vWF, Fibrinogen†</td>
<td>24-40%</td>
</tr>
<tr>
<td>Subclinical Atherosclerosis</td>
<td>Carotid Artery IMT††</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Coronary Artery Calcium††</td>
<td>38%</td>
</tr>
</tbody>
</table>


A Brief History of Genomic Studies of Common CVD in Populations


- Detailed Studies of Rare Mendelian Conditions
- Detailed Studies of Candidate Gene/Locus Variation
- Human Genome Project
- HapMap, ENCODE
- GWA Studies
- Case-Control Studies
- Population Studies
- Deep Medical Resequencing Studies
- Next Gen ‘Omic Studies


“Mendelian” versus “Complex” Transmission in Monogenic Forms of CHD

Familial Hypercholesterolemia: Autosomal Dominant Transmission

Premature Onset MI Without Extreme Hyperlipidemia: Complex Transmission
Genetic Lipoprotein Disorders Underlying CAD: LDL and Remnant Lipoproteins

- **LDL Particles**
  - Familial hypercholesterolemia (FH) LDL-R
  - Familial defective apo B-100 Apo B
  - Auto. Dom. hypercholesterolemia PCSK9
  - Auto. Rec. hypercholesterolemia ARH
  - Abetalipoproteinemia MTP
  - Hypobetalipoproteinemia Apo B
  - Familial sitosterolemia ABCG5/ABCG8
  - Familial lipoprotein(a) hyperlipoproteinemia Apo(a)
- **Remnant Lipoproteins**
  - Dysbetalipoproteinemia type III ApoE
  - Hepatic lipase deficiency HL

Adapted from: "Genetic lipoprotein disorders". Braunwald's Heart Disease 2008.

Genetic Testing for Mendelian Forms of Coronary Artery Disease

- Virtually all diagnoses by FHx + blood test (eg, LDL)
- Genotype tests are available for some conditions, but a negative test does not preclude a genetic Dx and in most cases the treatment is unaffected by Rx
- For lipids, benefits outweigh risks of Rx (eg, statins)
- Current research follows the cancer paradigm to examine targeted genetic testing for directing treatment choices
- For familial hypercholesterolemia, genetic testing as part of a “cascade screening” may be cost-effective in Scandinavian countries to identify persons at risk

Estimated impact of screening children without and with DNA diagnosis

Child-parent screening for FH using blood tests alone or with DNA tests
**“Mendelian” versus “Complex” Transmission in Monogenic Forms of CHD**

<table>
<thead>
<tr>
<th>Familial Hypercholesterolemia: Autosomal Dominant Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Premature Onset MI Without Extreme Hyperlipidemia: Complex Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

**Human Genome Sequence: SNP=Single Nucleotide Polymorphism each 1000 Bases**

- **Human Genome Project:** ~3 billion bp, ~25K genes
- A more limited N of SNPs can be used to describe human diversity due to high correlation of nearby (~50,000 bp) SNPs
- Genome-wide screening CHIPs 250K-5M SNPs: good coverage of common (>5%) variation
- More SNPs now known for non-Europeans via 1000G Project
- Next generation CHIPs are now testing rare/low frequency functional variants (MAF<1-5%)

**Basic Genomics 101**

- **Dogma:** DNA\(\rightarrow\)RNA\(\rightarrow\)protein
- **Exon:** coding DNA sequence
- **Intron:** noncoding DNA sequence
- **Transcription:** Creation of mRNA complementary to DNA (ATCG)
- **Splicing:** ‘Introns’ +/- exons are spliced out of final mRNA
- **Translation:** production of protein polypeptide from mRNA
- **“Nonsynonymous” or “Functional” DNA variant:** alters polypeptide
- **Exome:** all protein coding regions (exons) in ~24,000 human genes
Post-Genome Science: a New Pathway

• Common mission: scientific discovery for preventing and treating (complex) disease
• Multidisciplinary: epidemiologists, clinicians, statisticians, genome scientists, bioethicists
• Multinational PIs, multiethnic populations
• Data sharing required (by NIH) mostly embraced
• A village of scientists
• Communicate via WIKI
• Shared credit, resources

Translating CVD Genomics to the Clinic

• Pathophysiology of CVD & Risk Factor Paradigm
• Rationale for Genomic Approach to CVD
• High Frequency Variants: GWA Studies
• Low Frequency Variants: Population Sequencing
• Dissecting the Function of Genomic Discoveries
• Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization

GWAS Discoveries for CAD/MI and CAD/MI Risk Factors: Update 2014

<table>
<thead>
<tr>
<th>Condition</th>
<th>H genes/loci</th>
<th>Consortium Name</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette Use</td>
<td>&gt;12</td>
<td>TAG</td>
<td>Nature Genetics 2010.</td>
</tr>
<tr>
<td>Diabetes/ Glycemic Traits</td>
<td>&gt;53*</td>
<td>Int1 Diabetes</td>
<td>Genetics 2010; 2012.</td>
</tr>
</tbody>
</table>

**Genome Studies of MI/CAD 2007-2013**

- N=25,000
- Nature & Science 2007

- N=25,525
- Nature Genetics 2009

- N=142,677
- Nature Genetics 2011

- N=194,427
- Nature Genetics 2013

**47 GWAS Loci ~11% of MI/CAD Heritability**

<table>
<thead>
<tr>
<th>Genome Study</th>
<th>SNP Associated with a Major CVD Risk Factor?</th>
<th>Yes (Lipids or BP)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial MI GWAS</td>
<td>sp21, LDLR, SREBP</td>
<td>LDLR, SREBP</td>
<td></td>
</tr>
<tr>
<td>MiGen Consortium GWAS</td>
<td>PCSK9, LDLR, SREBP</td>
<td>LDLR, SREBP</td>
<td></td>
</tr>
<tr>
<td>CARDIoGRAM Consortium + Other GWAS</td>
<td>ABCC9, AKT1, AMPK, AOCE-C1, CHRM2, ZC3H10</td>
<td>AOCE-C1, CHRM2, ZC3H10</td>
<td></td>
</tr>
<tr>
<td>CARDIoGRAM Plus-C4D (Meta)</td>
<td>PON1, PLIN, SULT1A2</td>
<td>PON1, PLIN, SULT1A2</td>
<td></td>
</tr>
</tbody>
</table>

Coronary Artery Calcium: GWAS Meta-Analysis for log(CAC+1)

- CAC by MDCT or EBCT; Agatston Score
- 5 discovery cohorts: FH, RSI, RSII, GENOA, AGES; N=996
- GWAS meta-analysis
- 2.5M HapMap SNPs
- 3 replication cohorts: Family Heart, MESA, Amish; N=6061

Concordance with CAD SNPs in CARDioGRAM

Concordance of GWAS for MI/CAD with GWAS for Coronary/Carotid Atherosclerosis

<table>
<thead>
<tr>
<th>Genome Study</th>
<th>SNP Associated with a Major CVD Risk Factor?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (Lipids or BP)</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Initial MR GWAS</td>
<td></td>
</tr>
<tr>
<td>MiGen Consortium GWAS</td>
<td>PCSK9 LDLR* SNQ29 PHACTR1 CDC7 SERPINI1 COL4A2 (IRS2) HAL</td>
</tr>
<tr>
<td>CARDioGRAM Consortium + Other GWAS</td>
<td>APOE-A1-2 APOC1-2 LPL LDLR* ZFCH1 PDGF2 PRNP* LIPA COL4A1-4Z</td>
</tr>
<tr>
<td>CARDioGRAM-Plus-CAD (Metabochip)</td>
<td>APOB LPL FLRN SLCO1B1-8 GCYF1A3 IL6R</td>
</tr>
</tbody>
</table>

*=GWAS loci (p<0.05) for carotid IMT/plaque. Gene =GWAS loci (p<0.05) for CAC.

Mendelian Randomization: Harnessing Genomics to Assess MI/CAD Causality

DNA Sequence Variant

Mendelian Randomization:
LDL (LDLR) CAD YES Evidence
IL6 (IL6R) CAD YES Evidence
FBNG (FGF8) CAD NO Evidence
CRP (CRP) CAD NO Evidence
HDL (LPL) CAD NO Evidence

Blood Biomarker, Expression Marker

Subclinical or Clinical CVD Outcome

Lessons from MI/CAD GWAS 2014

- Mechanism of most GWAS variants unknown but MR studies may help define
- Most hits NOT in exons (protein-coding) imply regulatory/transcriptional mechanism
- Common variants: <10% MI/CAD heritability
- Data mostly from European populations:
  - Studies underway in other major ethnic groups
  - Male/female differences need to be defined
- SNPs for prevalent MI may differ from those for incident MI

Translating CVD Genomics to the Clinic

- Pathophysiology of CVD & Risk Factor Paradigm
- Rationale for Genomic Approach to CVD
- High Frequency Variants: GWA Studies
- Low Frequency Variants: Population Sequencing
- Dissecting the Function of Genomic Discoveries
- Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization

Allelic Architecture for the Genetic Determinants of ASCVD

- Very rare personal alleles MAF<.10%
- Low frequency disease alleles MAF ~10-5%
- Common disease alleles MAF ~5-50%
- Rare variant association study (RVAS)-aggregating variants across a functional unit
- Common variant genome-wide association study (GWAS) -uses each variant individually
Targeted & Genome-Wide Sequencing to Discover Causal DNA Variants

- Protein-coding Gene A
- Protein-coding Gene B
- Protein-coding Gene C


Targeted to Exon(s) Targeted to Region(s) Whole Exome Whole Genome

Excess Rare Variants in Genes from GWAS of Hypertriglyceridemia

<table>
<thead>
<tr>
<th></th>
<th>APOA5</th>
<th>APOB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Heterozygous</td>
<td>Homozygous</td>
</tr>
<tr>
<td></td>
<td>APOA5</td>
<td>APOB</td>
</tr>
<tr>
<td></td>
<td>Genes</td>
<td>Genes</td>
</tr>
<tr>
<td></td>
<td>APOA5</td>
<td>APOB</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>5.0 × 10^(-8)</td>
<td>4.0 × 10^(-6)</td>
</tr>
</tbody>
</table>


NHLBI Exome Sequencing Project: Early Onset MI Project Design

Study design summary

Follow-up strategies

Observations from Targeted and Whole Exome Sequencing

- Many positive controls and “suggestive” findings representing the “tip of the iceberg”
- A modest yield of strong findings
- Most findings involve functional (protein-coding) variants
- Quantitative CVD traits improve power, and larger sample sizes will be needed to make discoveries especially for CVD events
- Confirmation of biological mechanism needed

What About Whole Genome Sequencing?

- The “$1000 Genome” requires high up front cost for sequencing machines and “Big Data” costs ($100,000 Analysis”), for storage, distribution, QC, annotation, analysis, test notification
- Nevertheless, the field of Cardiovascular Genomics is well-positioned to examine WGS genotype-phenotype analysis
- Whole genome sequence available on most or all patient is soon possible

Whole Genome Sequence Association Analysis for HDL-C and other Complex CVD Traits in ~1000 Persons

A couple of observations

1. Feasible: Whole genome sequencing and analysis is feasible in human populations to relate genotype to clinical phenotype.
2. Heritability: Common variants (MAF>1%) explain 62% (±14%) and rare variants (MAF<1%) an additional 8% (±9.8%) of the variance in HDL-C levels

Translating CVD Genomics to the Clinic

- Pathophysiology of CVD & Risk Factor Paradigm
- Rationale for Genomic Approach to CVD
- High Frequency Variants: GWA Studies
- Low Frequency Variants: Population Sequencing
- Dissecting the Function of Genomic Discoveries
- Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization

Proof of Concept for GWAS Translation to Drug: Reduced CHD Incidence in Persons With Lifelong Low LDL-C Levels from PCSK9 Mutations

PCS19 Timeline From Discovery to RCTs.

2003 AbuRikel et al NEJM Q71 mut
2006 Cohen & Hobbs LDL muC
2008 Abifadel et al Preclinical Studies
2010-11 Phase I RCT
2011-13 Phase II RCT McKenney et al JACC, DAAS Trial AHA/JAMA

Next Generation Tools for Genomic Medicine Research: “Framingham 3.0”

- Patient Cohorts
- Population Cohorts
- Proteomics
- Metabolomics
- Genomics
- Imaging
- Biorepositories
- Big Data: Ontologies, Computational Models

Beyond DNA Variation: From Genome to Transcriptome to Metabolome to CVD

OMIC Technologies
- Genome: Whole Exome & Whole Genome DNA Seq
- Transcriptome: RNA Seq
- Epigenome (Methylation)
- Metabolome
- Proteome
- Microbiome (Meta-Genome)
- Cellular/Tissue: iPSC
- Phenome:

Systems and Network Approaches for Translating Genomics to Disease Phenotypes

Use networks to define common mechanisms underlying disease across tissues.

Translating CVD Genomics to the Clinic
- Pathophysiology of CVD & Risk Factor Paradigm
- Rationale for Genomic Approach to CVD
- High Frequency Variants: GWA Studies
- Dissecting the Function of Genomic Discoveries
- Low Frequency Variants: Population Sequencing
- Future Directions for Translating Common Disease Genomics into Prediction, Prevention and Personalization
Prospective Prediction of CVD Beyond Risk Factors Using MI/CAD Genetic Risk Scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Dataset</th>
<th>Gen. Risk Score</th>
<th>Predict?</th>
<th>Reclassify?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paynter et al., JAMA 2010</td>
<td>WHS</td>
<td>13 MI/CAD SNPs</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ripatti et al., Lancet 2011</td>
<td>Finnish/Swedish</td>
<td>13 MI/CAD SNPs</td>
<td>Yes</td>
<td>Modest, no increase C-stat</td>
</tr>
<tr>
<td>Thannasoulis et al., Circ CV Genetics 2012</td>
<td>Finnish/Offspring</td>
<td>29 MI/CAD SNPs**</td>
<td>Yes</td>
<td>Modest, no increase C-stat</td>
</tr>
<tr>
<td>Ganna et al., ATVB 2013</td>
<td>Swedish</td>
<td>46 MI/CAD SNPs</td>
<td>Yes</td>
<td>Modest, small increase C-stat</td>
</tr>
<tr>
<td>Tikkanen et al., ATVB 2013</td>
<td>Finnish</td>
<td>28 MI/CAD SNPs</td>
<td>Yes</td>
<td>Good, small increase C-stat</td>
</tr>
</tbody>
</table>

29 SNP Genetic Risk Score for High CAC in the FHS Offspring. Model with age, sex, risk factors and MI/CAD GRS:
- Increased C statistic of 0.64 to 0.67
- Continuous NRI 29% (p = 2.7 x 10^-7)

Caution on SNPs and Risk Prediction

...More research needed to define full spectrum of common and rare genetic risk variants and integrate with transcriptome & other ‘omic measures...but...

Personalized Genomics & DTC Testing
Pre-Emptive Pharmacogenomics

- Pre-emptive testing identifies 91% with >1 actionable variant
- Prescription-triggered single-gene tests lead to >50% more tests than a pre-emptive multiplex test
- The evidence base is still accruing regarding the efficacy of specific tests (e.g., warfarin, clopidogrel)

Need for Evidence Based Research

Putting science over supposition in the arena of personalized genomics

Collaborative efforts are required to translate findings into actionable insights.

Integrative Deep Genomic Characterization and Risk for T2DM

- Personal Omics Profiling reveals dynamic molecular and medical phenotypes
- Comprehensive analysis of genetic variation
- Integrative genomics approaches

References:
### Current (Evidence-Based) Approaches to Predict, Prevent, and Pre-empt ASCVD

<table>
<thead>
<tr>
<th>Clinical Risk</th>
<th>Evidence-Based Testing and Treatment</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Predict CVD</td>
<td>Prevent CVD*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Office BP, ASCVD Risk Profile</td>
<td>Diuretics, Beta-blockers, ACE-inhibitors, ARBs</td>
</tr>
<tr>
<td>Lipid Panel</td>
<td>ASCVD Risk Profile</td>
<td>Statins, Resins, Fibrates</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting BS, HtgT, ASCVD Risk Profile</td>
<td>Treat Diabetes?</td>
</tr>
<tr>
<td>Coagulation, Inflammation, Biomarkers</td>
<td>Measure CRP? Other Biomarkers?</td>
<td>Aspirin or Plavix</td>
</tr>
<tr>
<td>Subclinical Atherosclerosis</td>
<td>CAC? CIMT? ABI?</td>
<td>Treat Modifiable RFs</td>
</tr>
</tbody>
</table>

*Lifestyle modification is essential: cigarette cessation, diet, exercise, weight loss*

### Current (Evidence-Based) Approaches to Predict, Prevent, and Pre-empt ASCVD

<table>
<thead>
<tr>
<th>Clinical Risk</th>
<th>Evidence-Based Testing and Treatment</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Predict CVD</td>
<td>Prevent CVD*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Office BP, ASCVD Risk Profile, Genomics, Omics</td>
<td>Diuretics, Beta-blockers, ACE-inhibitors, ARBs, Pharmacogenomics</td>
</tr>
<tr>
<td>Lipid Panel</td>
<td>ASCVD Risk Profile, Genomics, Omics</td>
<td>Statins, Resins, Fibrates, Pharmacogenomics</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting BS, HtgT, ASCVD Risk Profile</td>
<td>Treat Diabetes?</td>
</tr>
<tr>
<td>Coagulation, Inflammation, Biomarkers</td>
<td>Measure CRP? Other Biomarkers?</td>
<td>Aspirin or Plavix</td>
</tr>
<tr>
<td>Subclinical Atherosclerosis</td>
<td>CAC? CIMT? ABI?</td>
<td>Treat Modifiable RFs</td>
</tr>
</tbody>
</table>

*Lifestyle modification is essential: cigarette cessation, diet, exercise, weight loss*

### Acknowledgements

- **NHLBI’s Framingham Heart Study**
  - FHS SHARE Collaborators
  - CARDIoGRAM Consortium
  - CHARGE Consortium
  - NHLBI CHS and ARIC
  - Iceland and NIA AGES
  - Netherlands Rotterdam Study
  - Other European and US Cohort/All Study

- **NHLBI Framingham Fellows**
  - C. Thammanon, C. Tuom, M. Chiang, X. Zhuang, J. Huang
  - Mass Gen Hospital Collaborators
    - N. Kathiresan, Ben Do, Nate Sztizik, C. Newton-Chub, L. Hofmann, Y. Wang, E. Gershon
  - UMass Collaborators
    - J. Freedman, K. Tanriverdi
  - NHLBI Exome Sequencing Program
    - HeartGO Consortium
    - Women’s Health Initiative
    - ReSeqGO, SmithGO
    - Washington University GO
  - Framingham Heart Study Participants