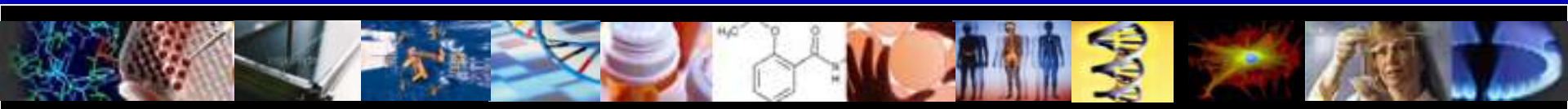


Cardiovascular Genomics in 2012: Starting a Career in Genomic Epidemiology



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No Disclosures

American Heart Association

November 3, 2012

An Unconventional Path to Sculpting a Cardiovascular Genomic Investigator



1987

Medical School

Residency
1st Clin Research

Contagious passion for epi
& outcomes research



CV Fellowship
Epi Fellow+MPH



“What am I good at→
move on→enjoy and succeed”

Faculty Job I
“50/50”



Focus on research, play
focussed clinical role



Faculty Job IIa
“80/20” NIH+Hospital
“Major” in Genetic
Epidemiology

Be rigorous, publish, focus
on genetics and imaging



Faculty Job IIb
“90/10” NIH+Hospital
Immerse in Gen Epi,
Genomics & Programs



Join a collaborative genomic
community

Lead novel genomic programs
at Framingham & NHLBI



1997

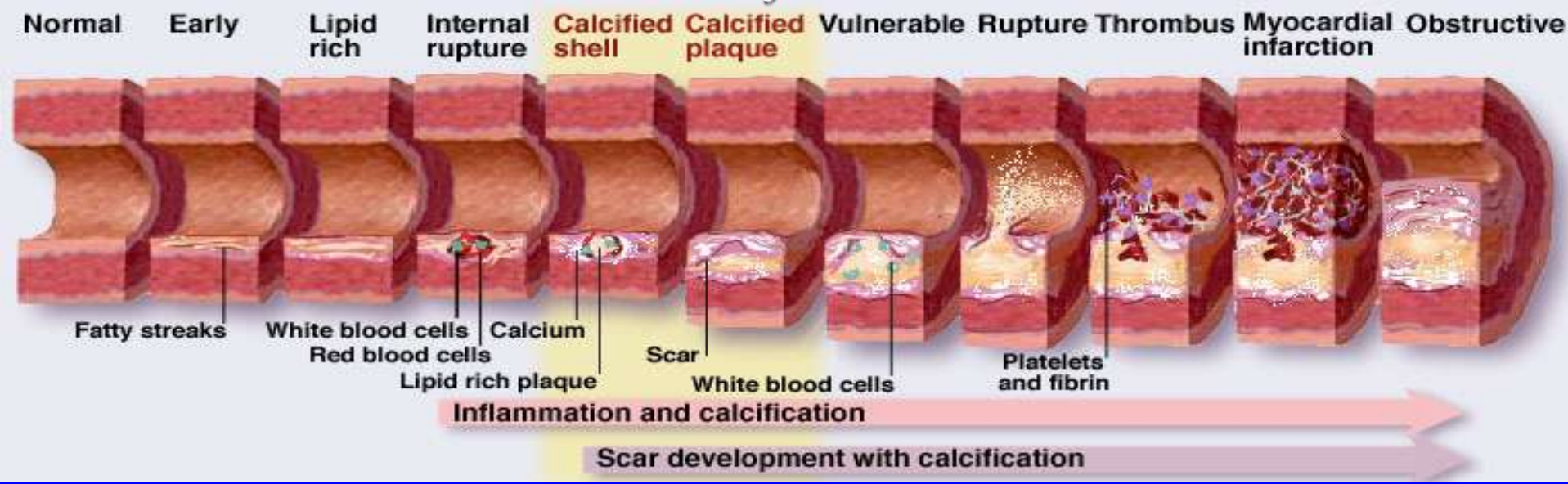
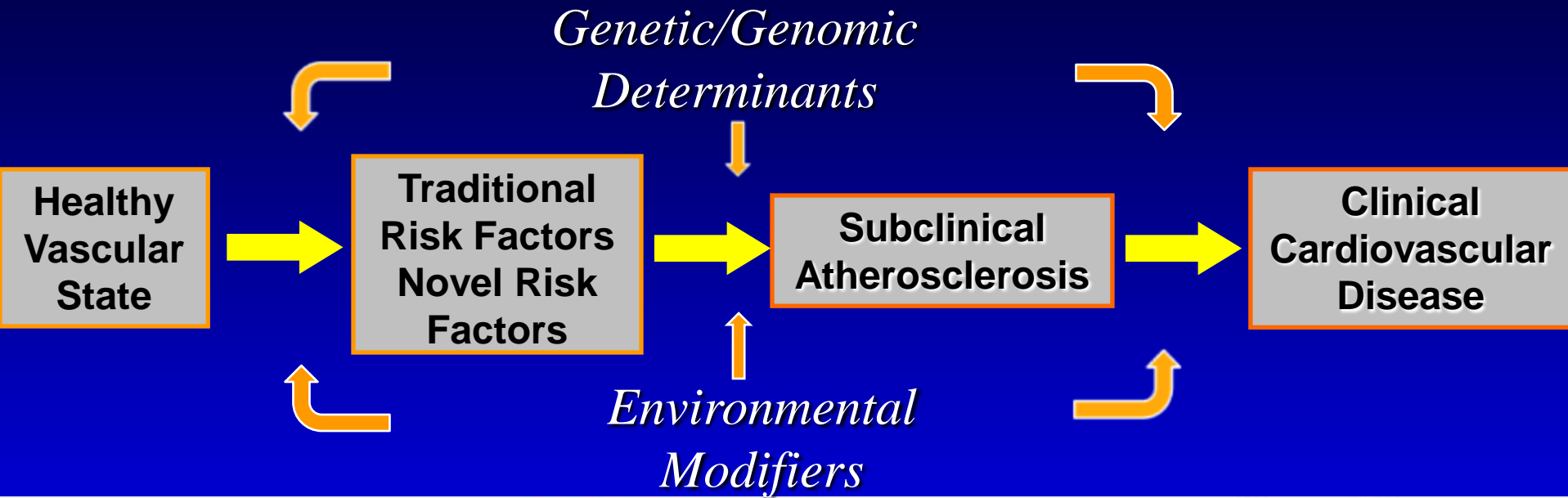
2007



Summary: Perfecting your Plan

- Passion
 - Predict, Prevent, Pre-Empt, Pharmacogenomics
- Population to Study
- Phenotype of Focus
- Program: Genomic Approach
- Plan for Provision of Funding
- Project Design
- Perspective on the Evolving Field
- Plan, Plan, Plan
- Publish!

Atherosclerotic Plaque Development: From Healthy Vessel to Clinical CVD



Framingham Heart Study

Downtown Framingham, MA (circa 1960)



Factors of Risk in the Development of Coronary Heart Disease—
Six-Year Follow-up Experience

The Framingham Study

WILLIAM B. KANNEL, M.D., THOMAS R. DAWBER, M.D., F.A.C.P.,
ABRAHAM KAGAN, M.D., F.A.C.P., NICHOLAS REVOTSKIE, M.D.,
AND JOSEPH STOKES, III, M.D.
Framingham, Massachusetts

INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary disease (CHD) have been obtained. Since it has been established that coronary atherosclerosis is present for many years prior to the development of symptomatic

- High Blood Pressure
- Increased Cholesterol
- Smoking
- Diabetes
- Male Gender
- Family History

Annals Internal Medicine 1961

1948 → 1958 → 1968 → 1978 → 1988 → 1998 → 2008

1948 → → → → → → 2008

Original cohort: N = 5209 men and women (ages 28-62)
1644 spouse pairs, 596 extended families

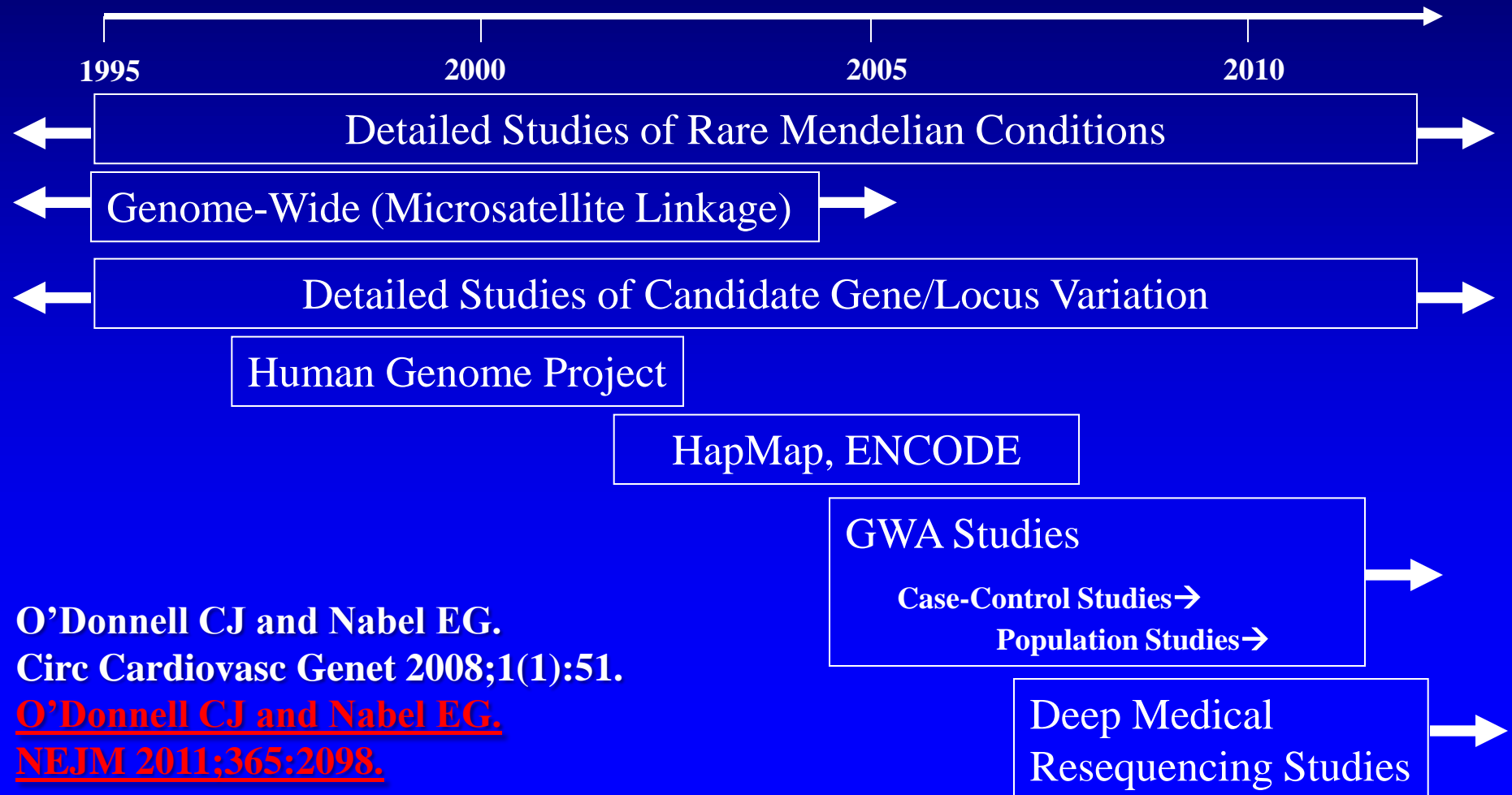
1972 → → → → 2008

Offspring study: N = 5124 men and women (ages 5-70)
1576 spouse pairs, 3514 biological offspring

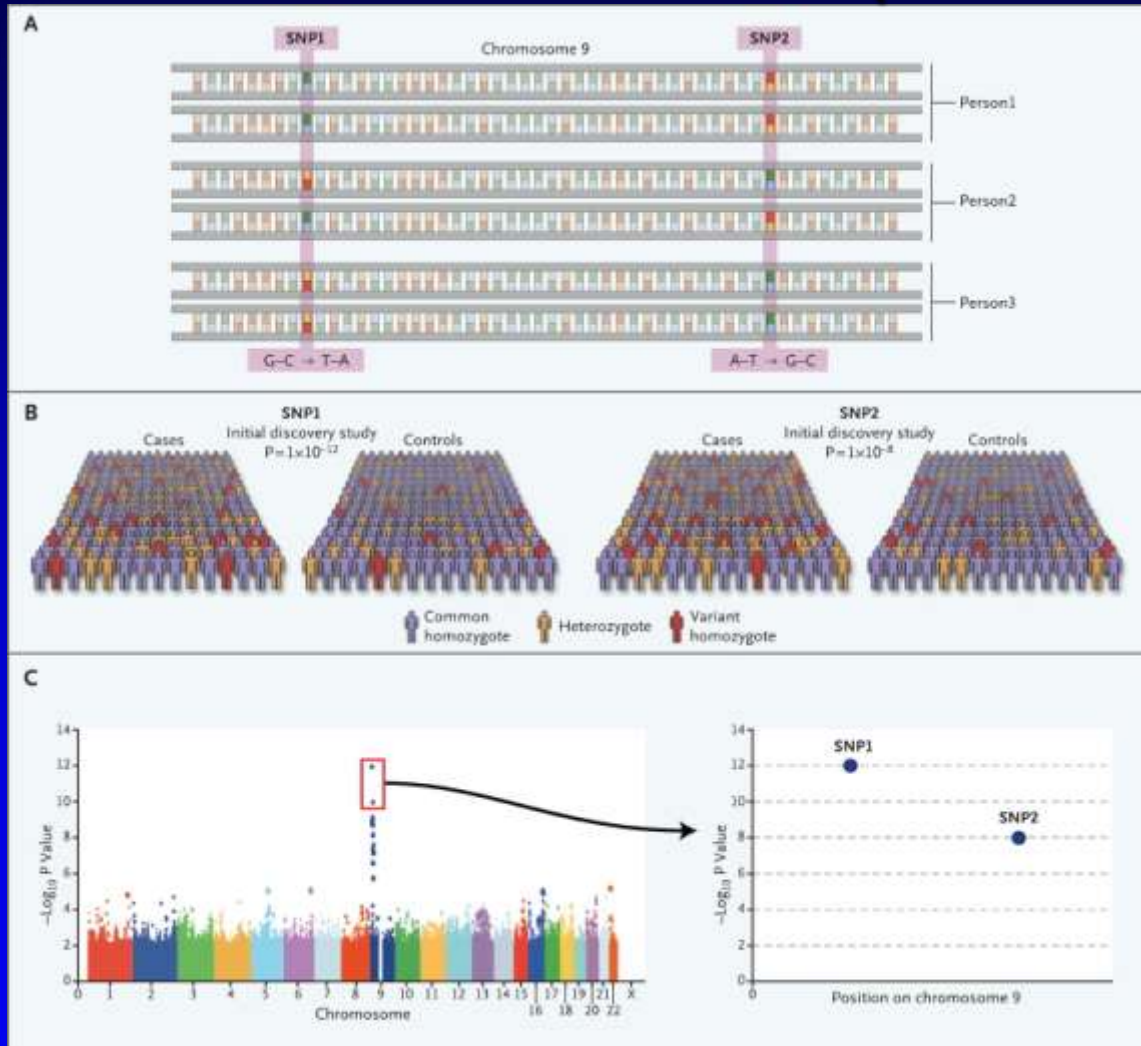
Third Generation study:
N~4000 men and women

2002 →

A Brief History of Genomic Studies of Common CVD in Populations



2005: Genome-Wide Association Studies (GWAS)



GWAS Fundamentals:

- 10s of millions of SNPs in genome
- Nearby SNPs are correlated
- SNP “chips” with 50K to 5M SNPs
- GWAS to ID SNP assoc. w/phenotype
- Strong association $p < 5 \times 10^{-8}$
- GWAS meta-analysis boost power

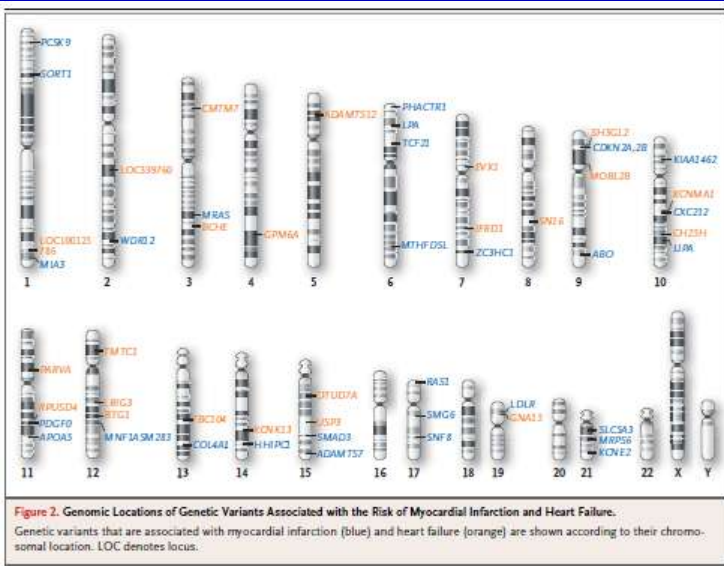
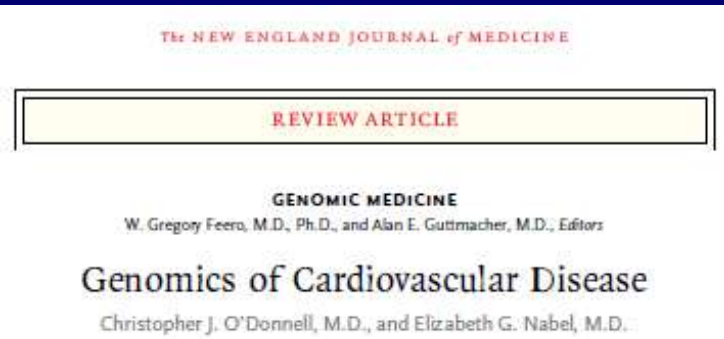
Manolio TA. *N Engl J Med* 2010;363:166-176.

GWAS Discoveries for CAD/MI and CAD/MI Risk Factors: Update 2012

Condition	N genes/loci	Consortium Name; Reference
CHD/MI	>30*	CardioGRAM + C4D; Nat Genetics 2011.
Lipids: LDL, HDL, Trigs	>95*	Global Lipids; Nature 2010.
Cigarette Use Behaviors	>12	TAG; Nature Genetics 2010
Obesity/BMI	>30*	GIANT; Nature Genetics 2010
Diabetes/ Glycemic Traits	>25*	International Diabetes Genetics; Nat. Genetics 2010
Hypertension	>25	Int. BP Genetics; Nature 2011.

O'Donnell CJ and Nabel EG. NEJM 2011;365:2098. *N increase ~30-50% with Metabochip.

GWAS for CVD and CVD Risk Factors: 2012



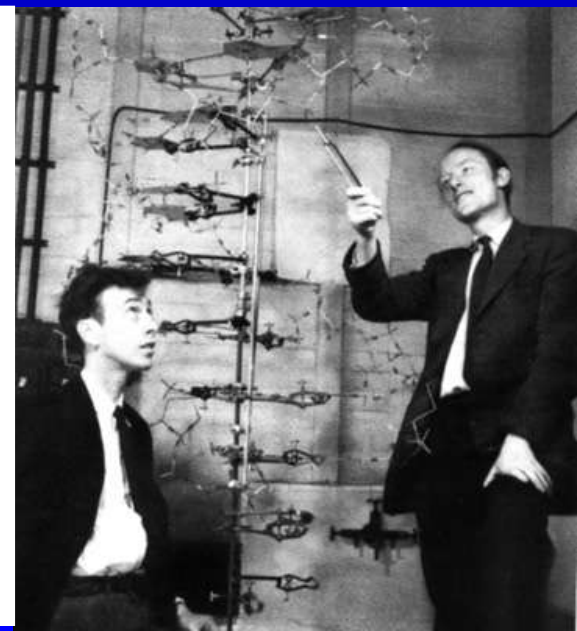
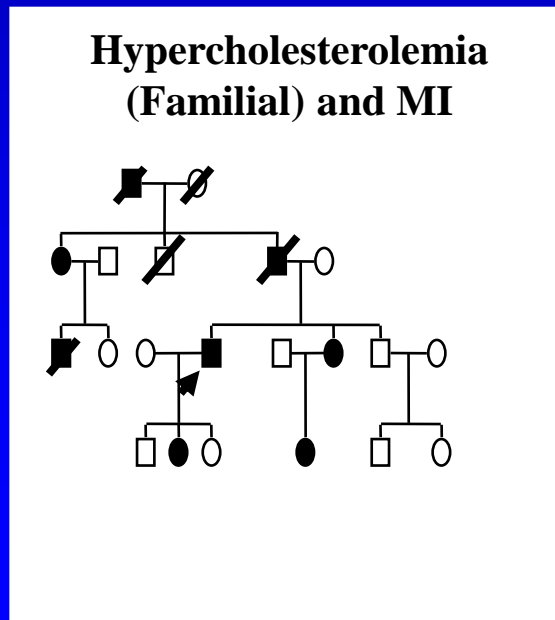
CVDAnatomical Area	GWAS Phenotype
Coronary Artery	MI, CAD
Left Ventricle	Heart Failure, HF Death, Sudden Death, Vent. Fibrillation
Left Atrium	Atrial Fibrillation
Cerebral Arteries	Ischemic Stroke Intracranial Aneurysm
Peripheral Arteries	PAD
Peripheral Veins	VTE

Risk Factor Domain	GWAS Phenotype
Lipids	LDL, HDL, Triglycerides
Blood Pressure	SBP, DBP, Hypertension
Glycemia	Type 2 Diabetes Mellitus, Fasting Glucose and Insulin
Adiposity	BMI, Obesity, Waist Circumf.
Smoking Behavior	Cigarette Use

O'Donnell CJ, Nabel EG. NEJM 2011;365:2098.

Pre-Genome Science Models

- Lone scientists in pursuit of basic knowledge
- Post-doc fellows toiling in a single lab/group
- Few collaborations, generally occur only when mutually beneficial (publish paper, patents, etc)
- Sharing of data discouraged
- RPG funded
- White male PIs
- Glory (Stockholm)



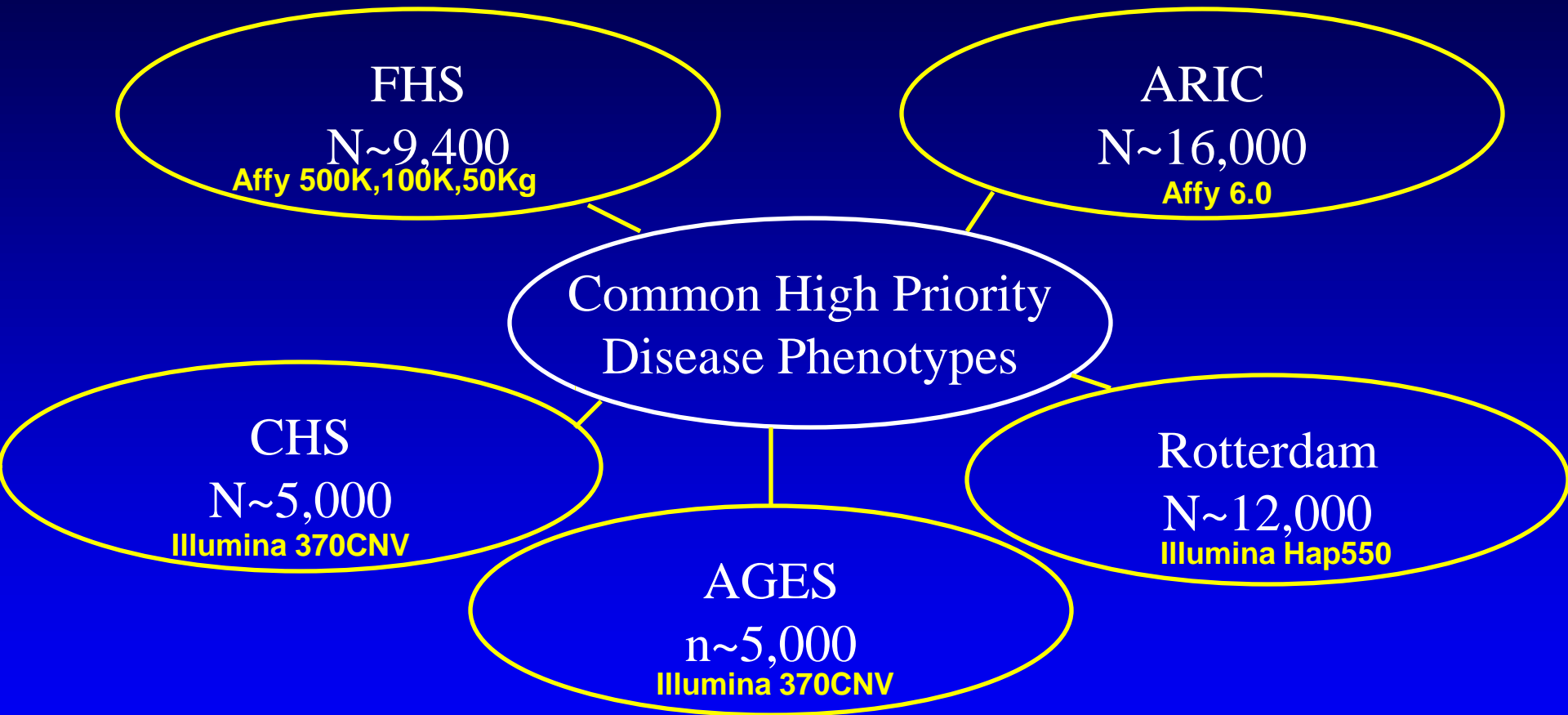
Post-Genome Epidemiology

- 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

facebook



CHARGE (Cohorts for Heart & Aging Research in Genome Epidemiology) Consortium, N~40,000

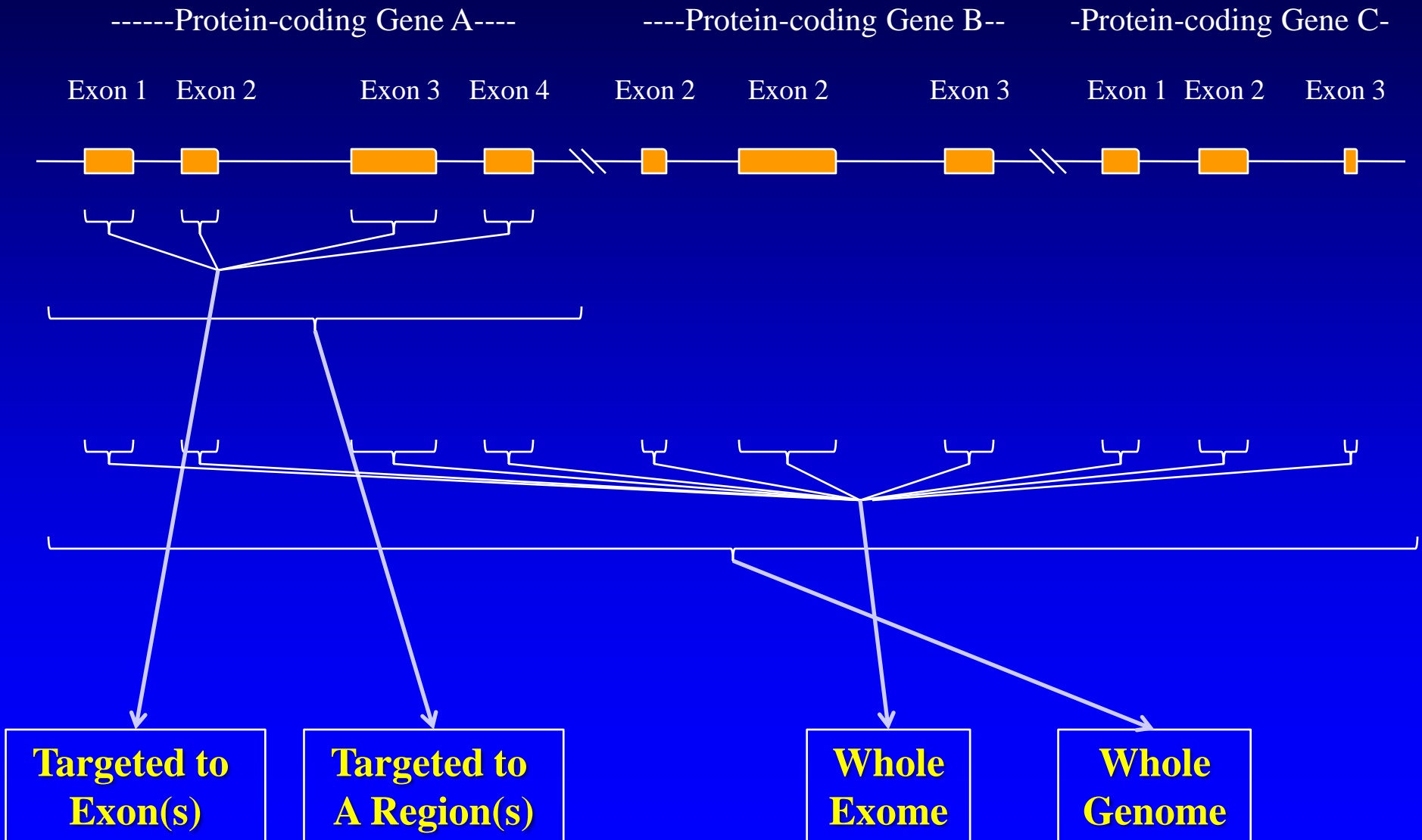


*Psaty BM, O'Donnell CJ, et al.
Circulation CV Genetics 2009.

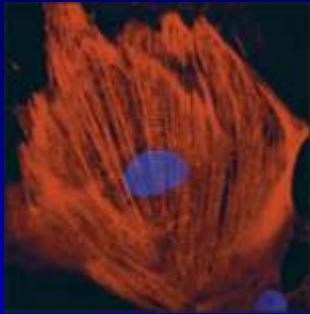
COHORTS FOR HEART AND AGING RESEARCH
IN GENOMIC EPIDEMIOLOGY

>600 Investigators, >80 Cohorts
>60 Phenotype Working Groups
Published Collaboration Principles
>140 Publications since 2008

Targeted & Genome-Wide Sequencing to Discover Causal DNA Variants



Tools, Resources & Applications for Advancing Genomic Medicine



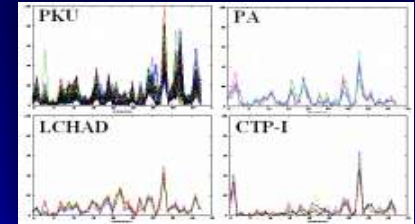
iPSCs



Patient Cohorts



Population Cohorts



Proteome/Metabolome

**Predict, Prevent,
Treat, and Pre-Empt
Cardiovascular
Disease**



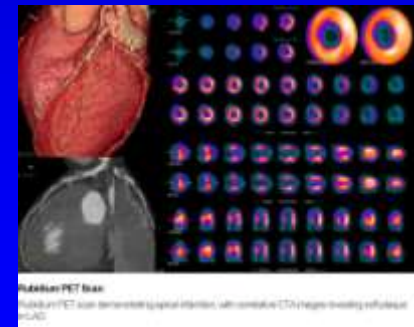
Genome/Transcriptome/
Epigenome



Big Data- Ontologies
Computational Models



Biorepositories



Imaging

Systems and Network Approaches to Translate Genomics to Disease Phenotypes

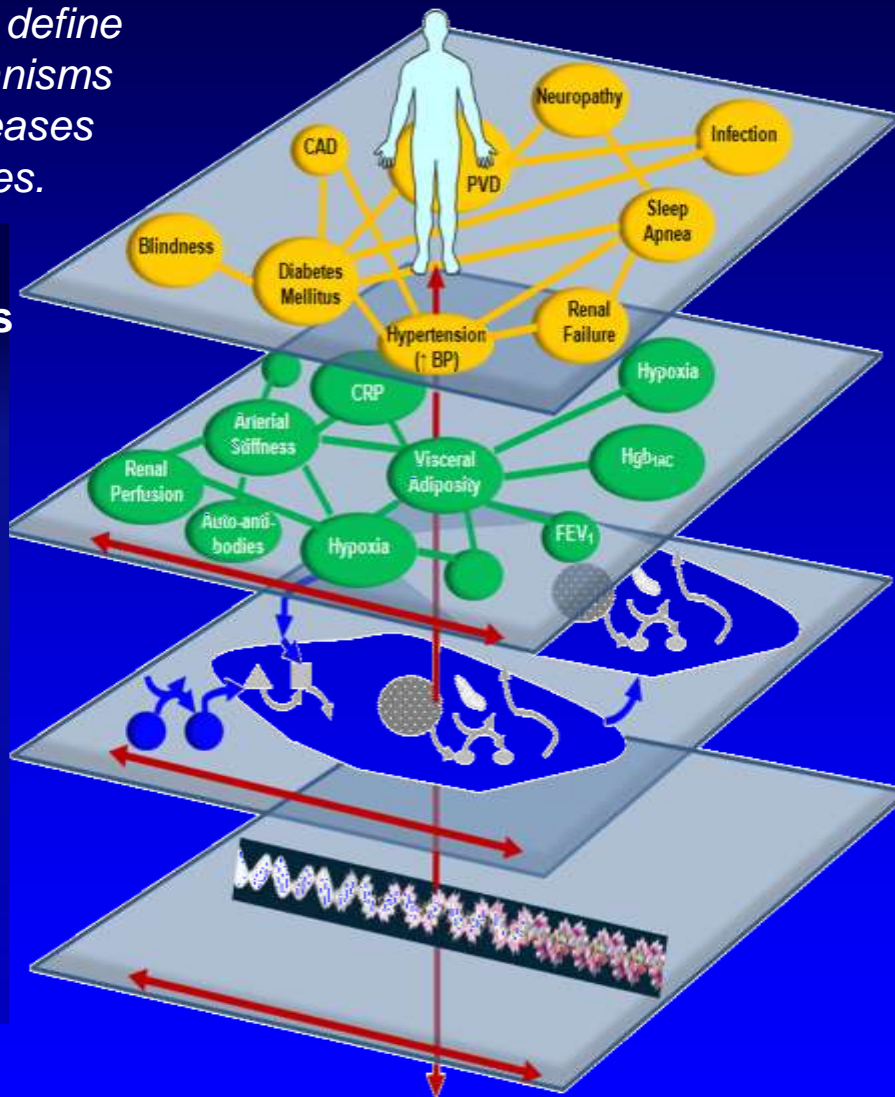
Use networks to define common mechanisms underlying diseases across tissues.

Patient Phenotypes

Traits

Molecular Networks

Genetics/Genomics



Tissue, organ, individual and population levels

Molecular and cellular levels

Figure adapted from Barabasi, *New Engl J Med* 357:404-7 (2007)

NHLBI GWA & Exome Cohort/Prgms: 2012

Program	GWAS Tot N	Exome Data*	Population(s): Sex; Ethnicity	Phenotypes Under Investigation
Framingham SHARe	9,500	Yes	Men, Women; EA	CVD, Risk Factors, Lung, Blood**
Asthma SHARe	5,000		Men, Women; EA	Asthma
MESA SHARe	8,500	Yes	Men, Women; EA, AA, HA, CA	CVD, Risk Factors, Lung, Blood**
Women's Health Initiative SHARe	12,000	Yes	Women; AA, HA	CVD, Risk Factors, Lung, Blood**
STAMPEED ARIC, CHS	~50,000	Yes, Yes	Men, Women; EA, AA, HA	CVD, Risk Factors, Lung, Blood**
CARe (CARe IBC)	~11,000 (~40,000)	Yes, var. cohorts	Men, Women; AA (EA, AA, HA, CA)	CVD, Risk Factors, Lung, Blood**
Women's Genome Health	28,000		Women Only; Largely EA	CVD, Risk Factors, Blood**
COPD Gene	~10,000		Men, Women; EA, AA	COPD, CVD, Risk Factors
Total Participants:	~140,000	~12,000		

Starting a Career in Genomic Epidemiology: Some Key Questions

- Major versus Minor?
- What is Your Pressing Question and Your Key Phenotype?
- Population vs Clinical vs Translational Research?
- What is the Genomic and Analytic Method?
 - Genome/epigenome, proteome/metabolome, RNAome
 - Bioinformatics/statistical genetics
- What is the Broad Area of Translation?
 - Discovery of Disease Mechanisms
 - Clinical Trials
 - Prediction/Prognosis
 - Pharmacogenetics
 - Clinical Genetics
 - Outcomes/Clinical Effectiveness/Cost-Effectiveness Research

Starting a Career in Genomic Epidemiology: Some Key Questions

- What is Your Program for Supplemental Learning?
 - Genomics, stat. genetics, bioinformatics, epi, clinical research
 - Masters Program? PhD?
 - Short Program? Eg, NHLBI programs, Keystone, Gordon Conf., CSH Symposium, Nature Genetics Conf.
- Right Mentor, Right Environment, Right Time?
 - Post-Doc Fellowship (AHA, NIH, Other Gov't Training)
 - Genetics Dept, Genomics Institute or School of Public Health
 - Cohorts and/or Consortia (eg, CHARGE Consortium)
- AHA Councils: Epi/NPAM, FG TB
- Fellowship and Career Opportunities at NIH?
- Pursue Training Grant and Map Fellow→Faculty Path
- Essential: your specific project should lead to specific, high quality first author manuscript(s)

Summary: Perfecting your Plan

- Passion
 - Predict, Prevent, Pre-Empt, Pharmacogenomics
- Population to Study
- Phenotype of Focus
- Program: Genomic Approach
- Plan for Provision of Funding
- Project Design
- Perspective on the Evolving Field
- Plan, Plan, Plan
- Publish!