

Public Health Approach to Genomics SACGHS, June 2004

Muin J. Khoury, MD, Ph.D.

**Director,
CDC Office of Genomics and Disease Prevention**



Public Health:

Assuring Conditions for Population Health

- Continuum from genetic disease (medical genetics) to genetic information (genomic medicine)
- Honest broker/convener role: science based assessment of population health and assurance of delivery of health services
- Public health roadmap for filling the widening gap between human genome discoveries and population health benefits

Continuum From Genetic Disease to Genetic Information

- **Genetic Disease**
 - **5%-10% disease**
 - **Mutations/Few Genes**
 - **Inherited**
 - **High Disease Risk**
 - **Environment Role +/-**
 - **“Genetic Services”**
- **Genetic Information**
 - **90%-95% disease**
 - **Variation/MultGenes**
 - **Inherited/somatic**
 - **Low Disease Risk**
 - **Environment Role ++**
 - **General Practice**

Single Gene Disorders & Coronary Heart Disease

Apolipoprotein(a) excess

Apolipoprotein AI deficiency

Autosomal recessive
hypercholesterolemia

Cerebrotendinous
xanthomatosis

Fabry disease

Familial combined
hyperlipidemia

Familial defective apoB

**Familial
hypercholesterolemia**

Familial partial lipodystrophy

Familial pseudo hyper
kalemia due to RBCI leak

Heparin cofactor II deficiency

Homocystinuria/homocysteinemi
a

Niemann-Pick disease, type E

Progeria

Protein C deficiency

Pseudoxanthoma elasticum

Sitosterolemia

Spontaneous coronary
dissection

Tangier disease

Type III hyperlipoproteinemia

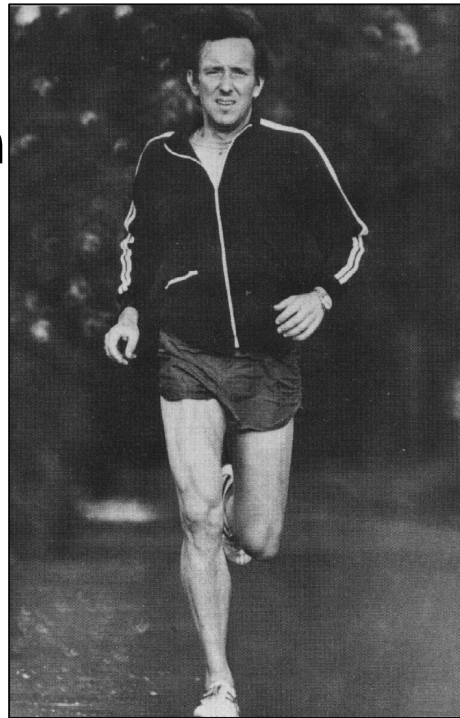
Werner syndrome

Williams syndrome



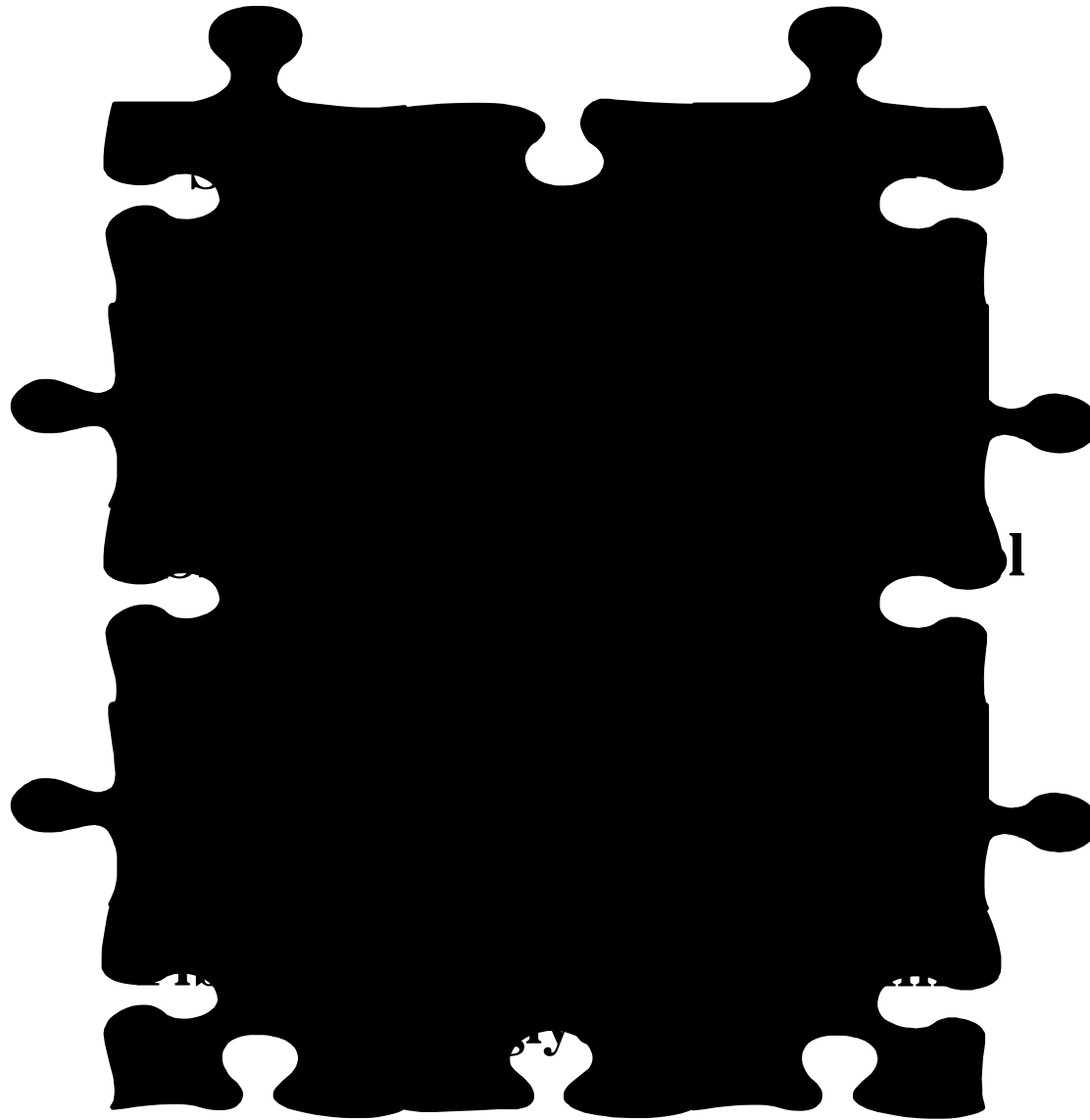
Gene-Environment Interaction in Cardiovascular Disease

- **“Some vegetarians with 'acceptable' cholesterol levels suffer myocardial infarction in the 30's. Other individuals...seem to live forever despite personal stress, smoking, obesity, and poor adherence to a Heart Association-approved diet”**



R.A. Hegele (1992)

Genetics and Cardiovascular Disease



Prediction of Risk of Myocardial Infarction from Polymorphisms in Candidate Genes

Yamada et al. NEJM 2002;347:1916-1923.

- Case-Control Study (5061 MI and 2242 Controls)
- Analysis of 71 candidate genes with 112 polymorphisms
- A few associations were found...small odds ratios...
- Accompanying editorial
 - “Findings should be used to initiate further research
 - Recommendations for primary prevention cannot be based on these findings.”



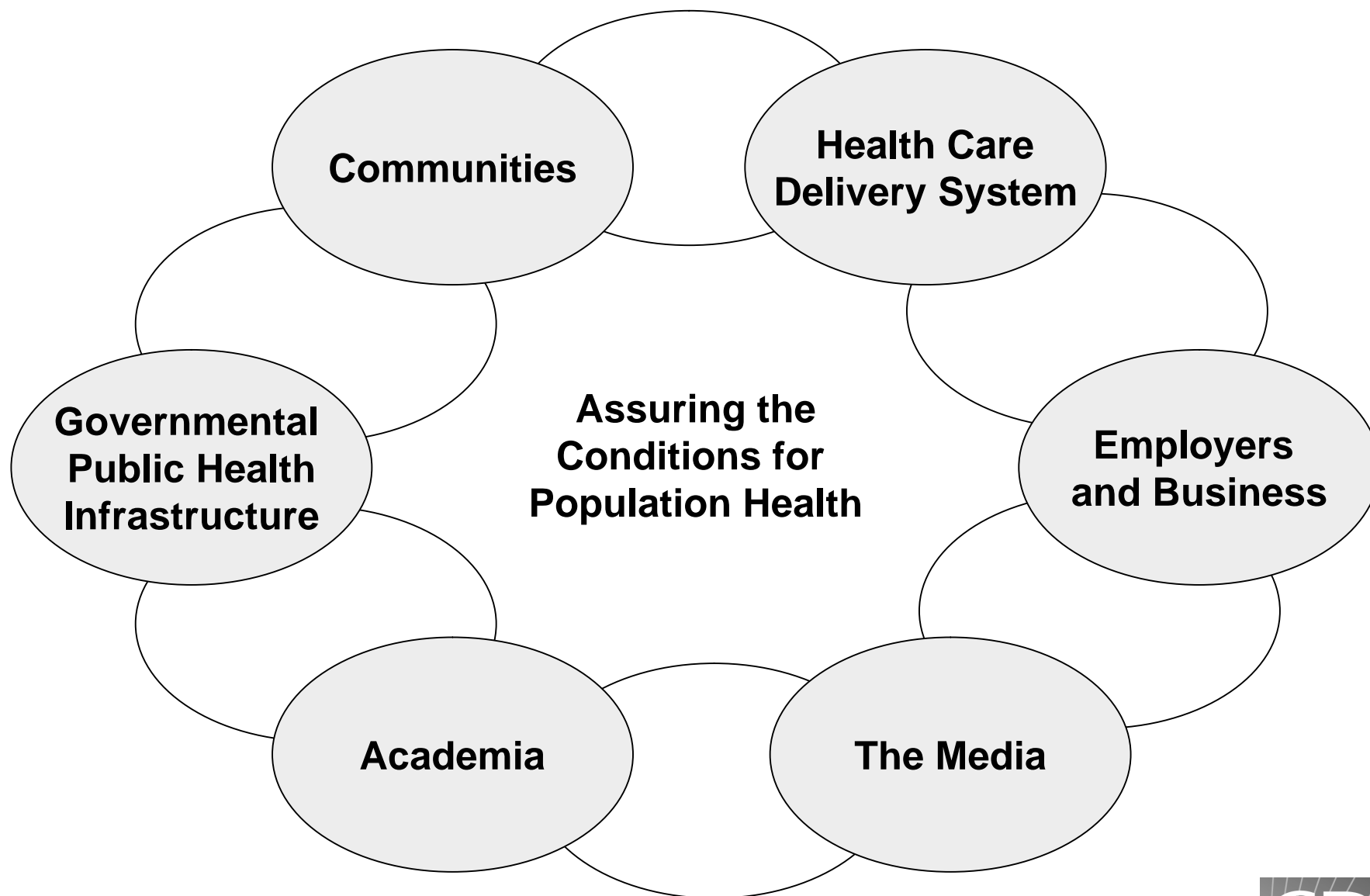
Why Do We Need Public Health?

- **FOCUS**
- **Population**
- **Prevention**
- **Science-based**

- **FUNCTIONS**
- **Assessment**
- **Policy**
- **Assurance & Evaluation**

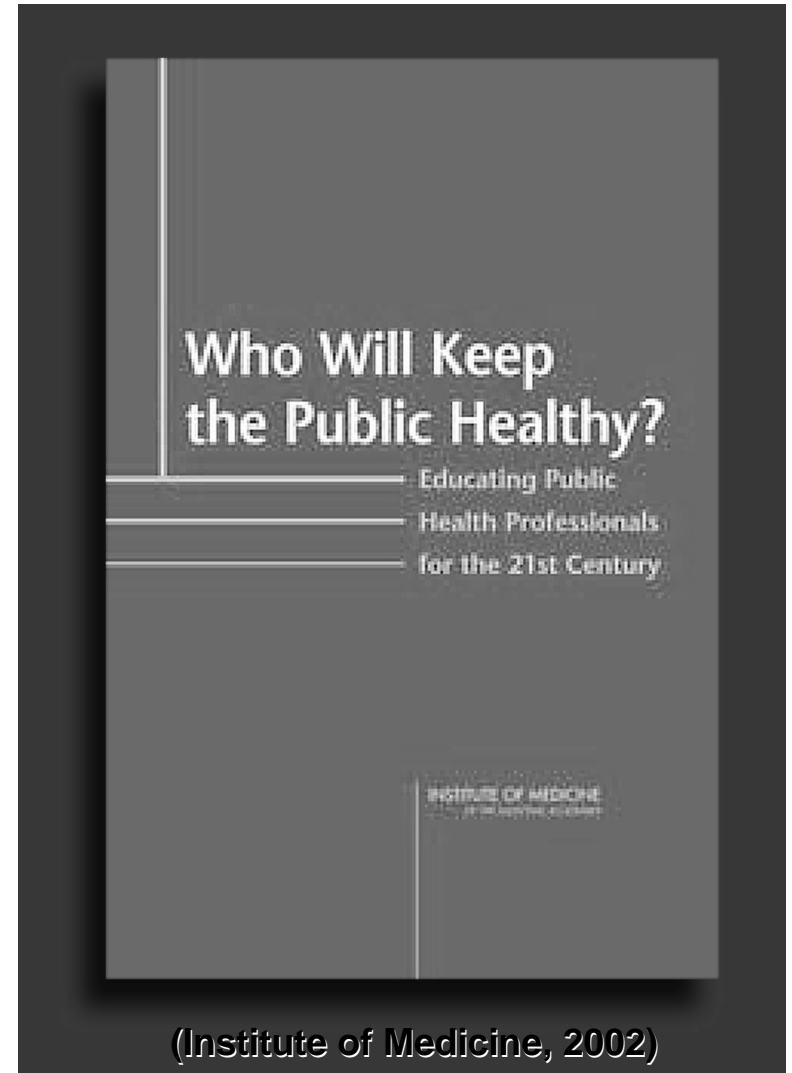


The “Public Health System” in the 21st Century (IOM, 2003)



Who Will Keep the Public Healthy? (IOM, 2002)

- ~ 500,000 professionals
- Critical areas
 - Informatics**
 - Genomics***
 - Communication**
 - Cultural competence**
 - Community-based research**
 - Global health**
 - Policy and law**
 - Public health ethics**



Public Health Approach for Translating Gene Discoveries into Population Health Benefits “Beyond the Bench to Bedside!”

**Role of genomic information in
population health?
(35,000 genes)**

**Value of genomic information
in treatment and prevention?
(1000+ tests)**

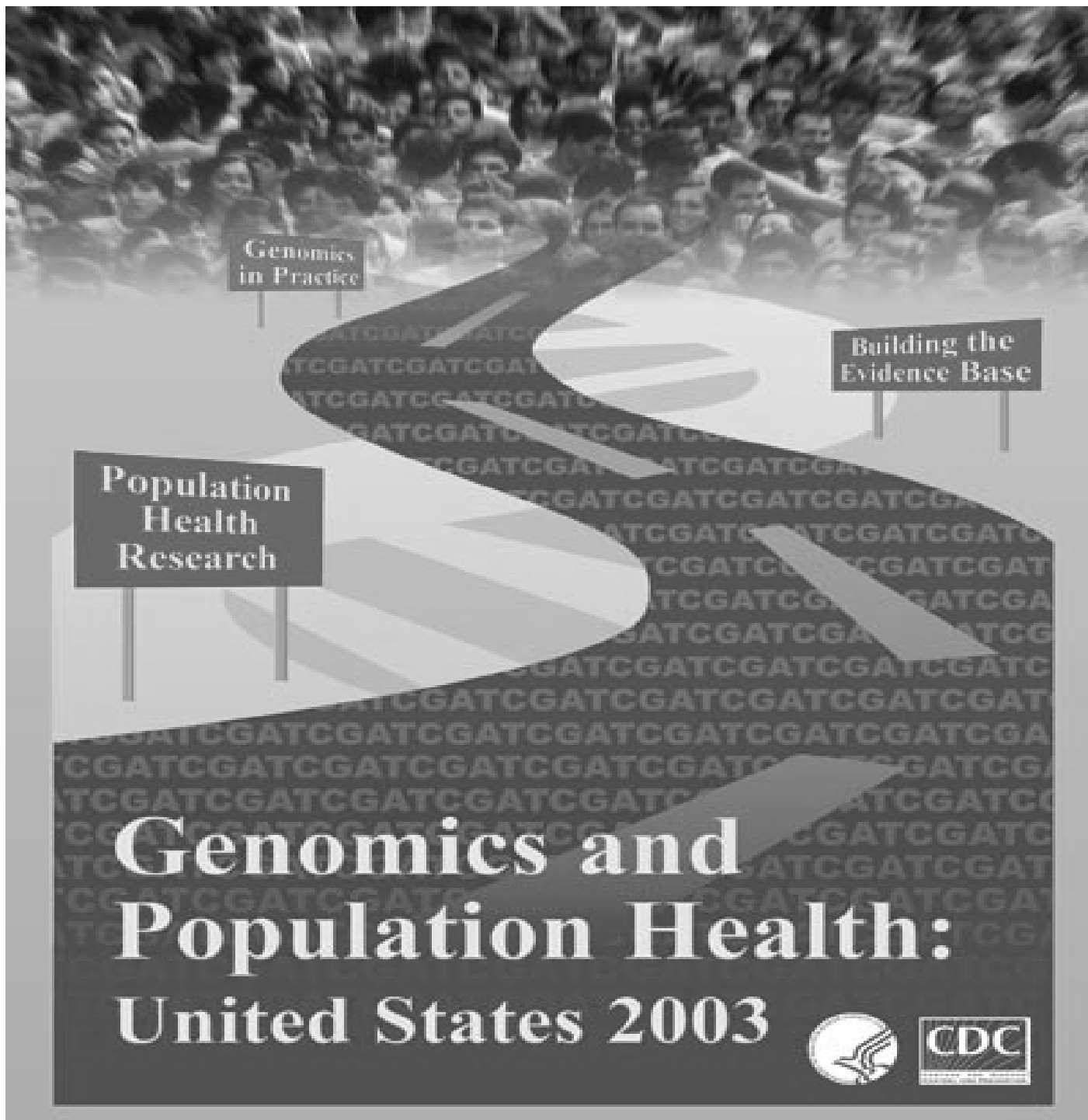
Implementation of
genomics in practice?

”Clinical Research to Clinical Practice — Lost in Translation?”

C. Lenfant NEJM 2003;349:868

- **< 33% of patients with coronary artery disease are prescribed aspirin**

”Let's be realistic: If we didn't do it with aspirin, how can we expect to do it with DNA?”



<http://www.cdc.gov/genomics/activities/oadb/2003.htm>



Selected Public Health Genomics Activities, 2004

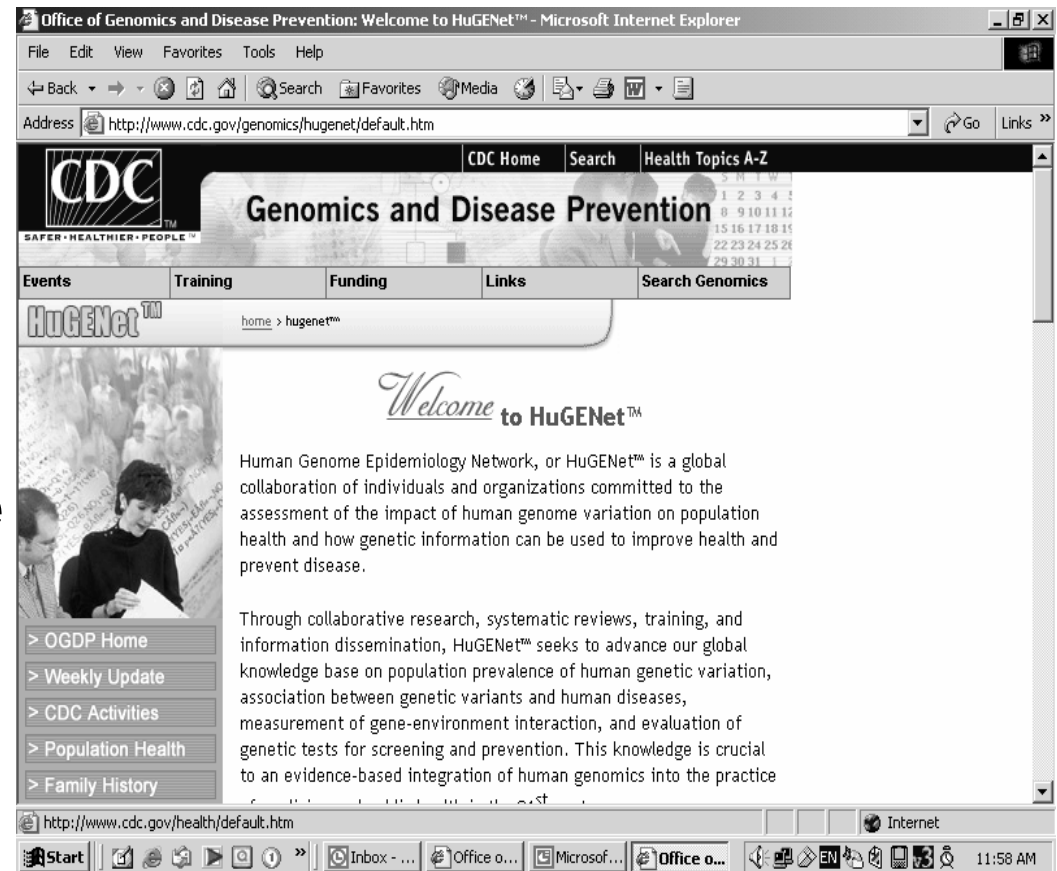
- Genomics and Population Health Research
 - Human Genome Epidemiology Network
 - NHANES Project
 - Genomics and Acute Public Health Investigations

“Real Communities in Real Time”



Human Genome Epidemiology Network (HuGE Net)

- **Epidemiology: the basic science of public health**
- **Global collaboration of individuals and organizations to assess how genomics can be used to improve population health**
- **700 individuals from 40 countries**
 - **Methods**
 - **Biobanks**
 - **Training**
 - **Knowledge Base**



HuGE Net Products (as of May 1, 2004)

• Reviews	25
• Fact sheets	13
• E-journal clubs	45
• Case studies	4
• Genotype Prevalence Database	8
• Methods workshop/guidelines	3
• Training workshops	6
• Book	1
• Published Literature Database	10,964
– 1387 genes	
– 1609 health outcomes	
– 460 nongenetic risk factors	





Genomics and Disease Prevention Information System (GDPInfo)

GDPInfo is a searchable database of documents available on the Office of Genomics and Disease Prevention's (OGDP) Web site as well as links to relevant documents on other sites.

Try it! Search by

Gene

Disease

Interactive Factor



What is in GDPInfo?

- fact sheets
- reviews
- case studies
- published literature
- online presentations
- books and book chapters
- materials from conferences and workshops

Why GDPInfo?

To provide access to information and resources for guiding public health research, policy, and practice on using genetic information to improve health and prevent disease.

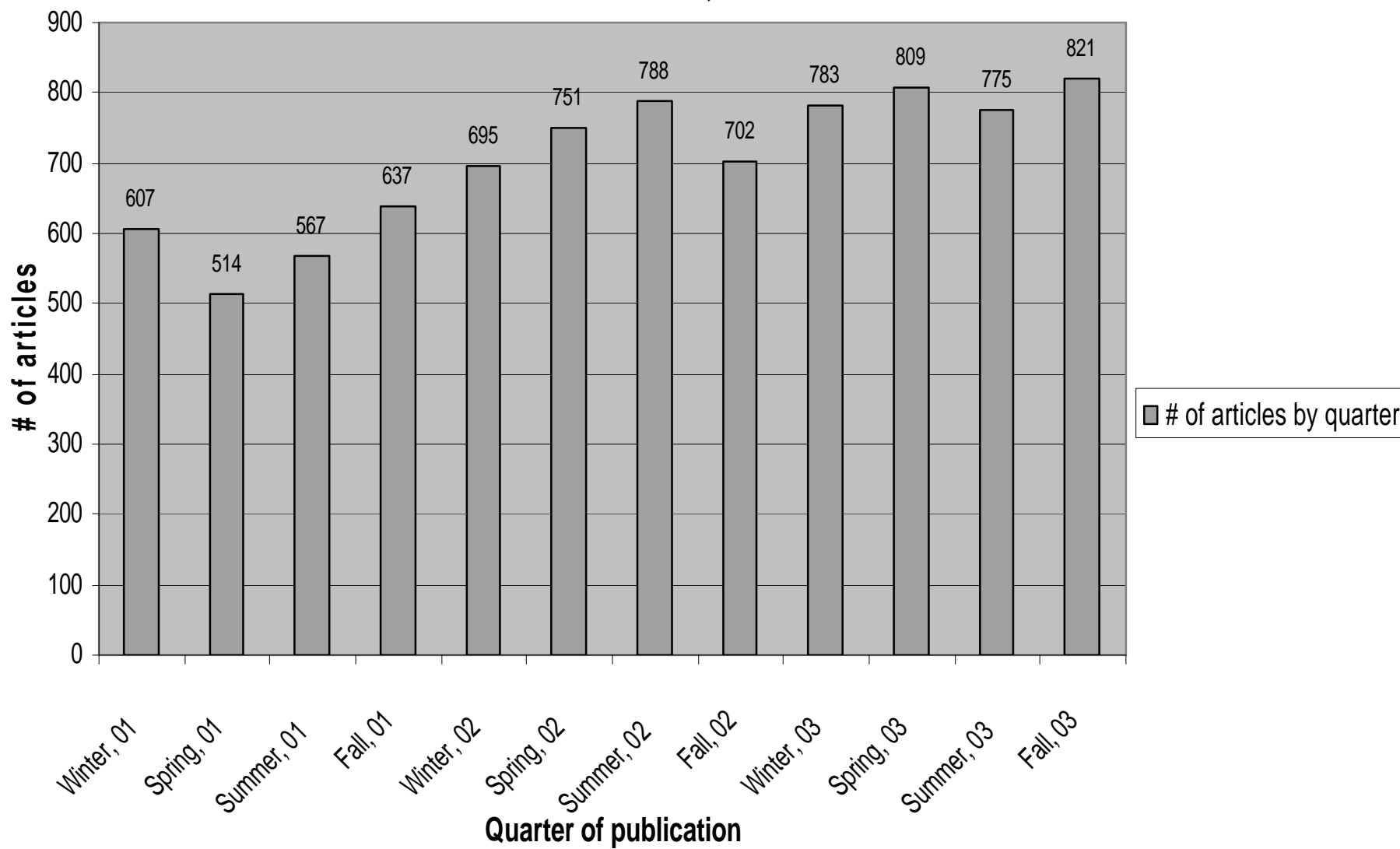
Who Uses GDPInfo?

Public health professionals are the target audience but there are data and information for researchers, health care providers, and the general public.

<http://www.cdc.gov/genomics>



No. of articles in Huge Published Literature db, 2001-2003



(Note: Missing month data during three year period: n= 540, 6% of all articles in db. Winter: Jan-Mar; Spring: Apr-Jun; Summer: Jul-Sept; Fall: Oct-Dec)



Rank	Gene Symbol	Gene name	# of Papers 01-03
1	APOE	apolipoprotein E	481
2	ACE	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	398
3	MTHFR	5,10-methylenetetrahydrofolate reductase (NADPH)	377
4	HLA-DRB1	major histocompatibility complex, class II, DR beta 1	376
5	TNF	tumor necrosis factor (TNF superfamily, member 2)	346
6	GSTM1	glutathione S-transferase M1	253
7	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	248
8	F5	coagulation factor V (proaccelerin, labile factor)	213
9	GSTT1	glutathione S-transferase theta 1	204
10	IL10	interleukin 10	177

NHANES III DNA BANK

Prevalence of Genes of Public Health Significance

Background

NHANES III DNA Bank

- > National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey
- > Detailed interviews, clinical, laboratory and radiologic examinations are conducted
- > Phenotypic data, such as serostatus for many infectious exposures, blood count, chemistries, etc. were collected
- > During second phase NHANES III (1991-1994), white blood cells were frozen and cell lines were immortalized with EBV
- > NHANES III DNA bank is located at NCEH, CDC, with specimens available from over 7000 participants
- > In 2002, NCHS announced a call for proposals to use these specimens in the Federal Register

Collaborative CDC-wide Proposal Objective

- > Determine the prevalence of genotypes of public health importance



Criteria for Genetic Variants

Public Health Importance

- > Known or hypothesized association with diseases of public health importance
- > Role in pathways affecting multiple diseases
- > Identified functional variants
- > Relatively common (i.e., >2.0%)
- > Previously described gene-environment or gene-gene interactions
- > Relevant phenotypic data available in NHANES dataset
- > No current use for clinical risk assessment or intervention

Challenges to Identifying Genes of Public Health Importance

- > Gaps in information in the literature
- > Methodological issues of many available studies
 - Selection bias, power, interaction
- > Non-replication of gene-disease association



Public Health Significance of Proposal

- > Prevalence of gene variants
 - Basis for estimating population attributable fraction in combination with measure of gene-disease association
 - Enable assessment of potential for screening population subgroups for susceptibility genes
 - Prevalence of combinations of variants in pathways and at different loci
- > Examine gene-disease association, gene-environment and gene-gene interactions

Selected Pathways of Gene Variants (87 variants of 57 genes)

- > Nutrient Metabolism (e.g., folate and homocysteine; lipids; glucose; alcohol; vitamin D)
- > Immune and inflammatory responses (e.g., cytokines, receptors)
- > Activation and detoxification pathways (e.g., drugs, carcinogens, environmental contaminants)
- > DNA repair pathways (e.g., ionizing radiation, environmental toxins)
- > Hemostasis pathway and renin/angiotensin (e.g. vasomotor) pathway
- > Developmental (e.g., hearing loss)

Laboratory Methods

- Genotyping
- Assessing Capability of External Laboratories to conduct high throughput, accurate, low-cost, genotyping for >600,000 SNPs (~7300 specimens X 87 variants*)

*Table of gene variants available upon request



Next Steps

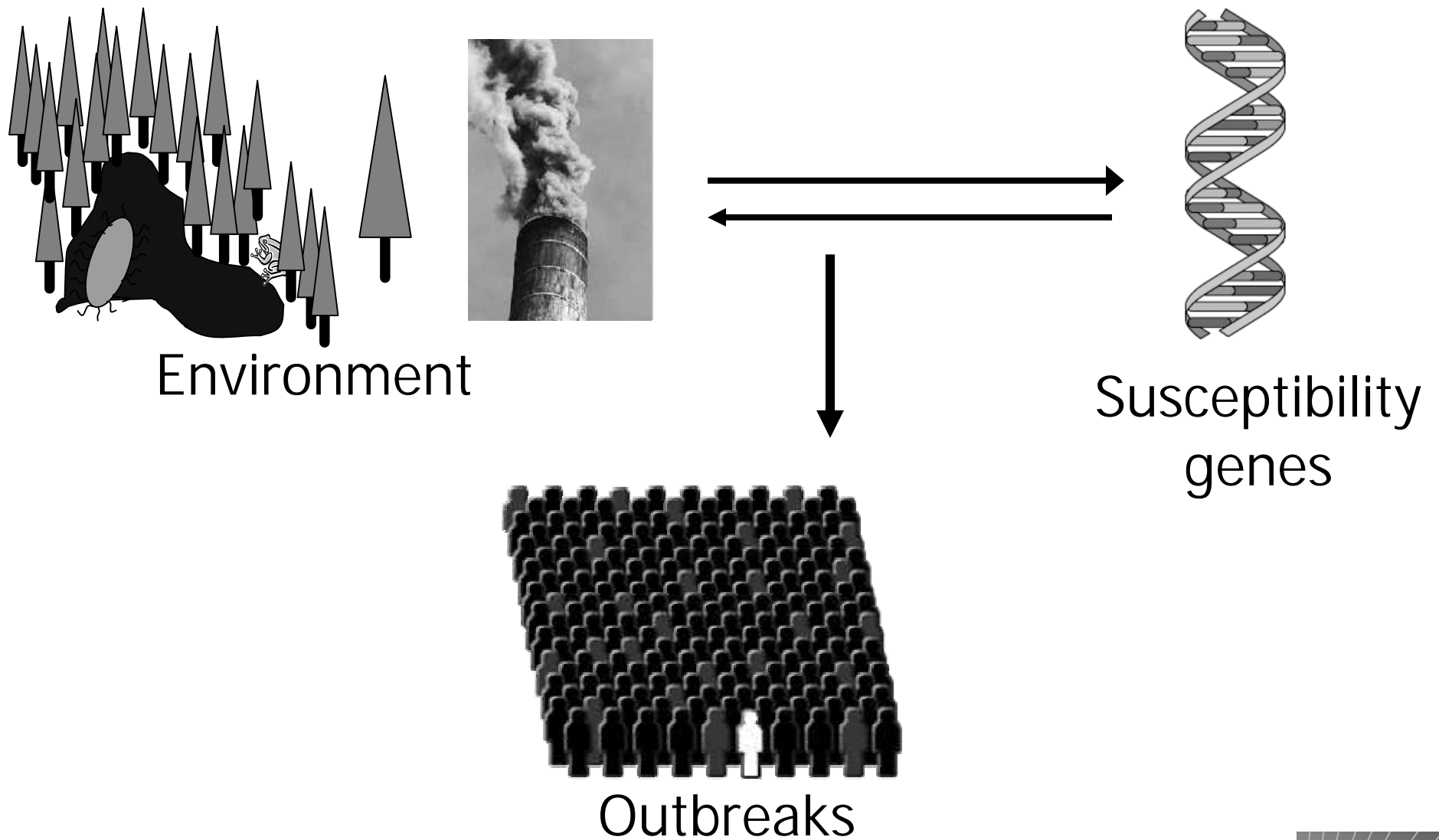
- > Pending approval from NCHS
- > Laboratory Selected
- > Genotype-Phenotype analyses

CDC Working Group

ATSDR Olivia Harris NCEH Karen Abe, Cynthia Moore, Lorenzo Botto, Qianhe Yang NCHSTP Mary Reichler NCID Tom Hodge, Craig Hooper, Jai Lingappa, Janet McNicoll, Arne Dilley
 NCEH Amanda Brown, Peg Gallagher, Marta Gaines, Omar Henderson, Bruce Lin, Mary Lou Lindgren, Julian Little, Karen Steinberg
 NCCDPHP Heidi Blanck, Wayne Giles, Ingrid Hall, Giuseppina Imperatore, Ann Malacher NIOSH MaryAnn Butler, Ainsley Weston PRRPO Bin Chen NIP Scott Campbell NCHS Gerry McQuillan



Integrating Human Genomics into Acute Public Health Investigations

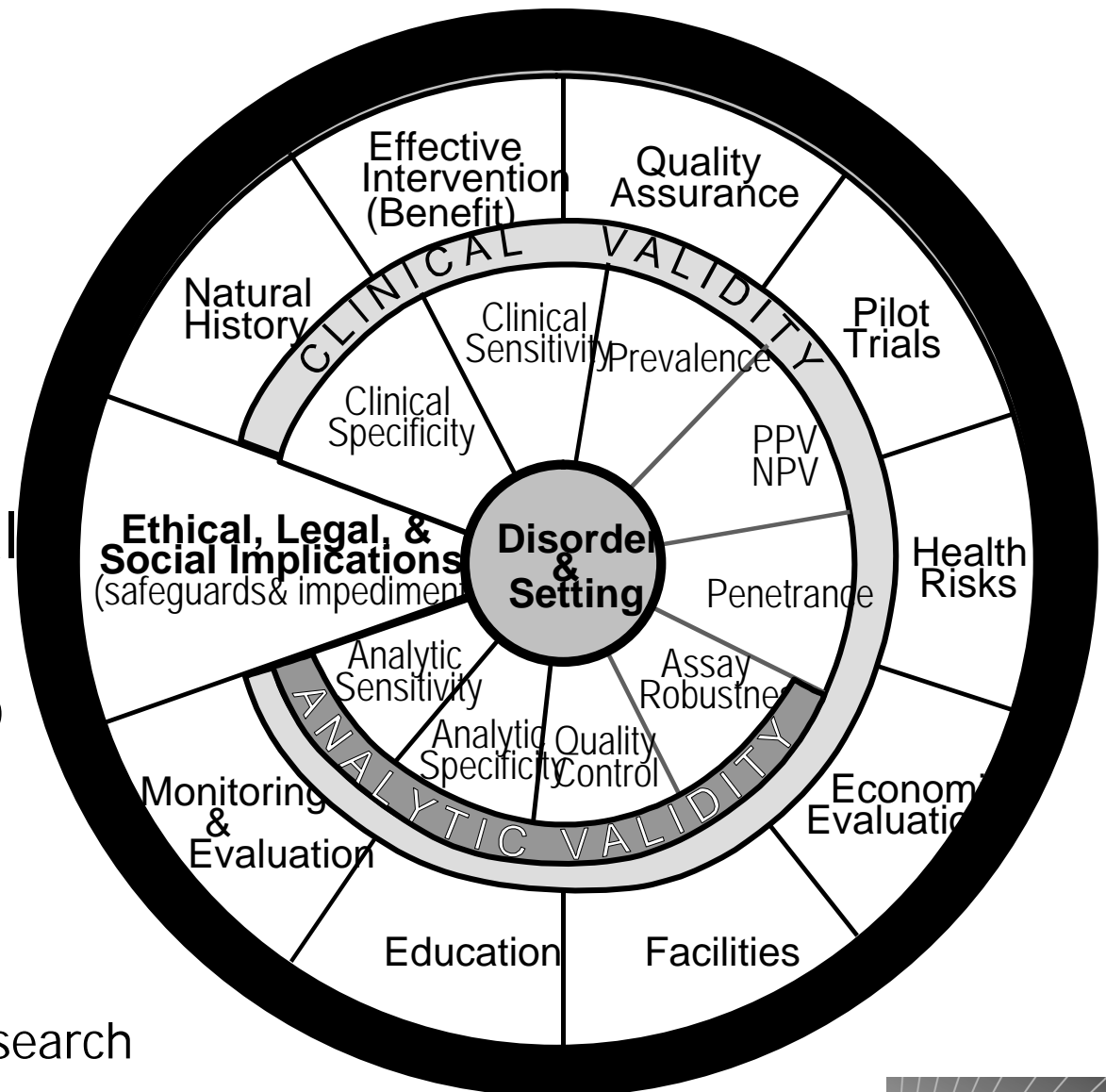


Selected Public Health Genomics Activities, 2004

- Building the Evidence Base
 - Evaluation of Genomic Applications in Practice and Prevention
 - Family History Public Health Initiative

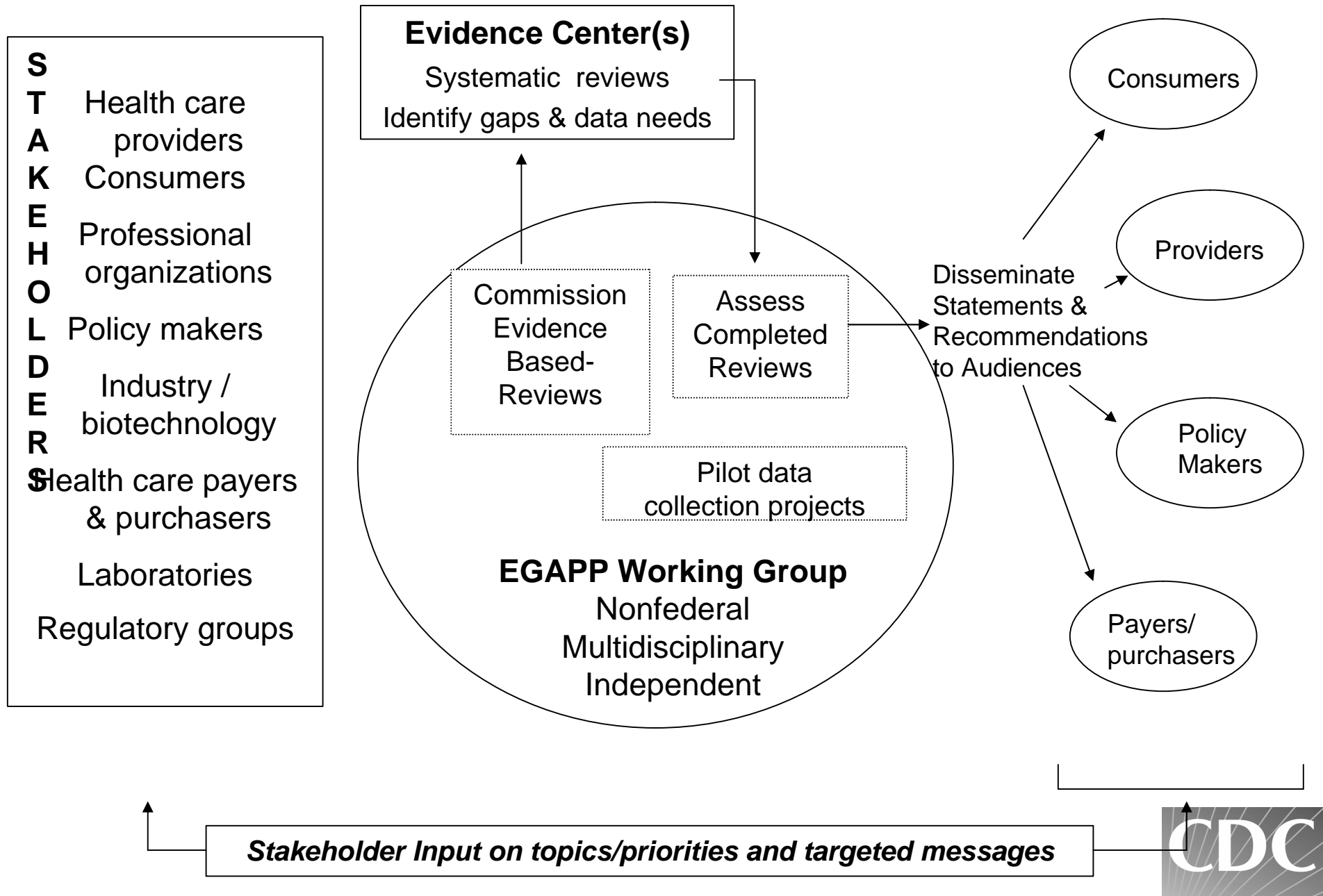
Systematic Reviews of Genetic Tests -ACCE

- Disorder & setting
- Analytic validity
- Clinical validity
- Clinical utility
- Ethical, legal & social implications
- Sections divided into > 40 targeted questions



Foundation for Blood Research
Model Project

EVALUATION OF GENOMIC APPLICATIONS in PRACTICE and PREVENTION (E-GAPP)



Family History Public Health Initiative



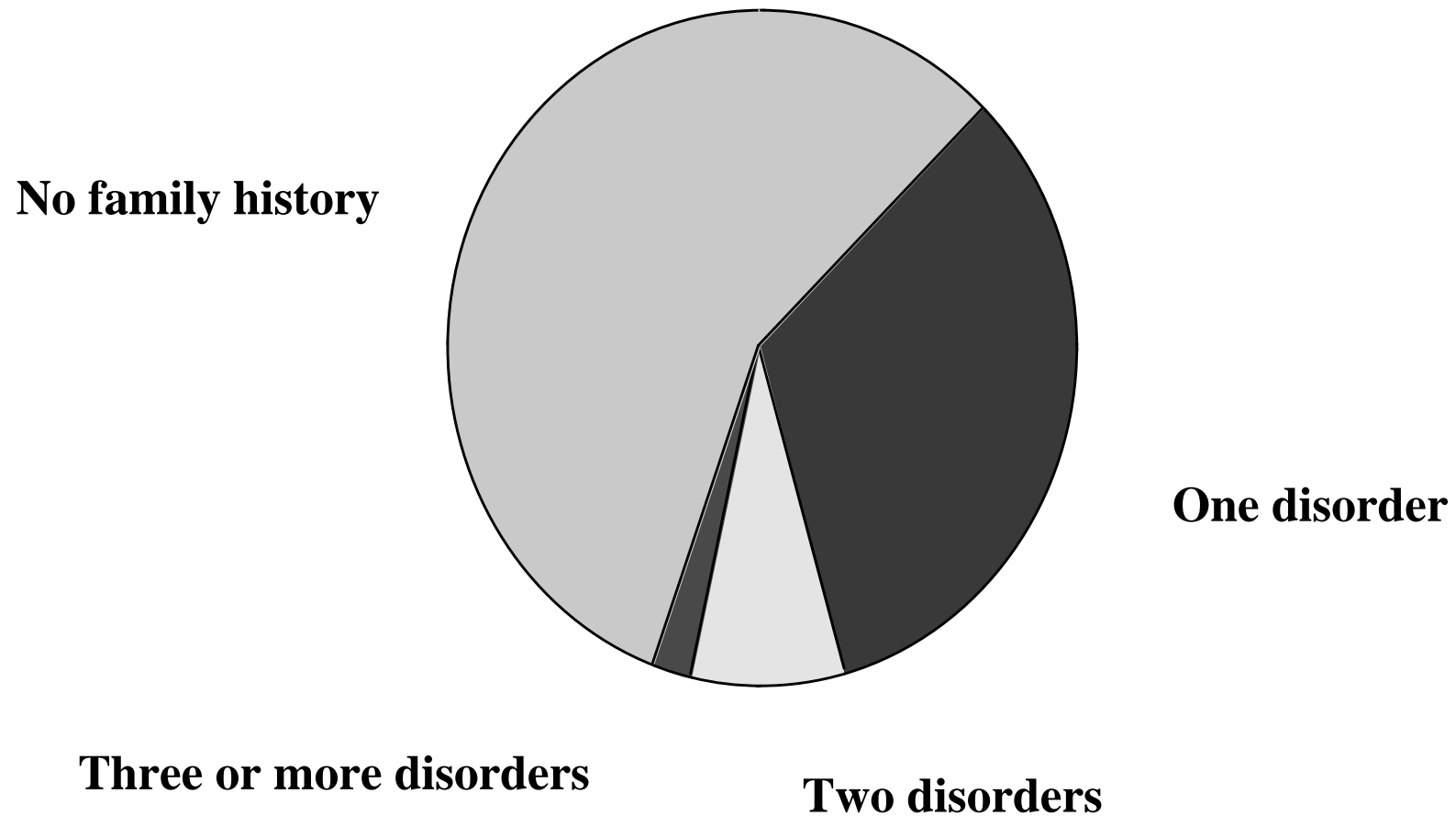
Why focus on family history?

- FHx is underutilized in preventive medicine
- Risk factor for most chronic diseases of PH significance

How can we use family history?

- assess risk for common diseases
- influence early screening for disease
- educate people about prevention measures

Family History of Common Diseases



Scheuner et al. Am J Med Genet 1997;71:315-324.



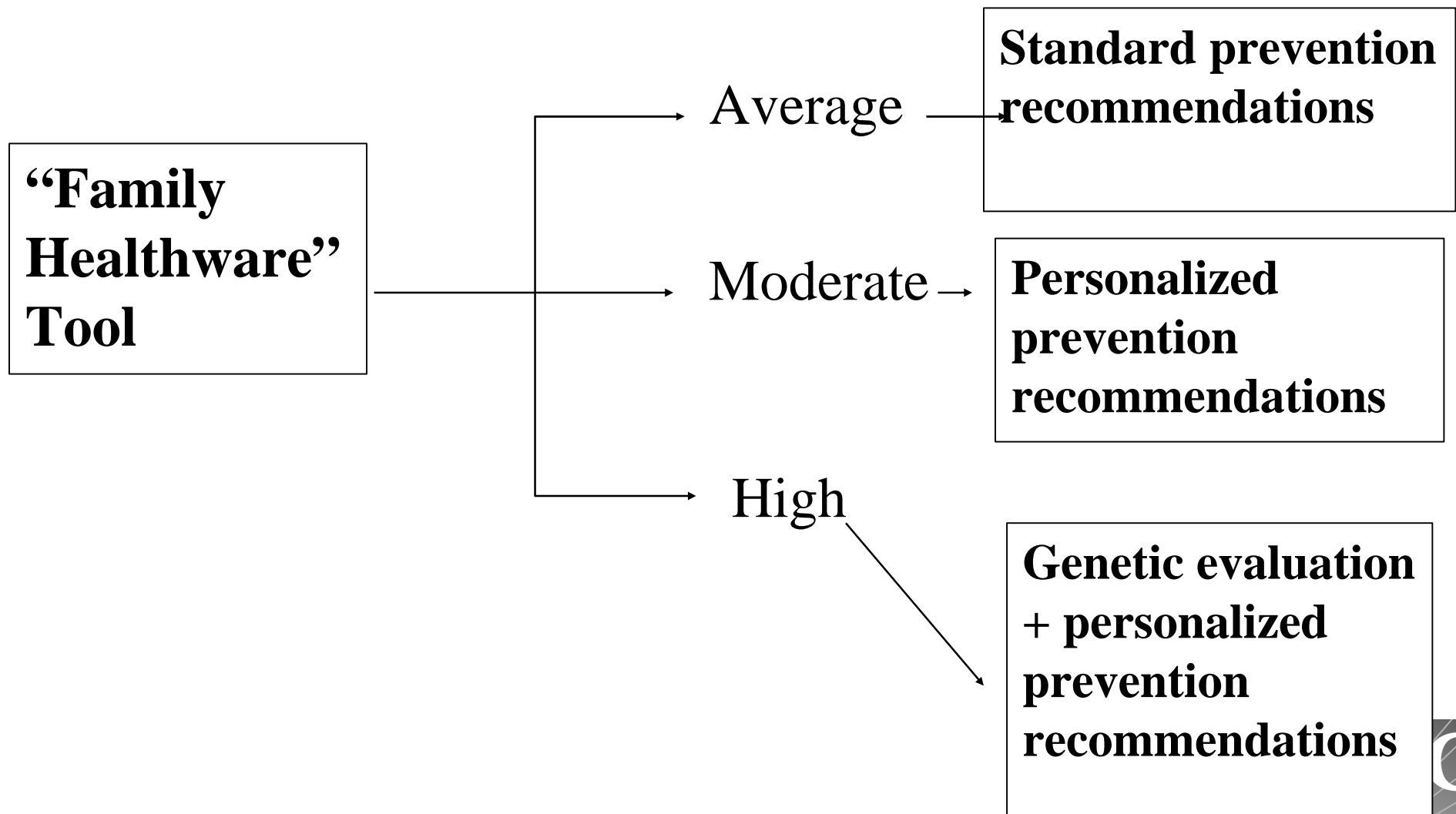
Family history as a risk factor for almost all common diseases

Relative Risk

Heart disease	2.0 – 5.4
Breast cancer	2.1 – 3.9
Colorectal cancer	1.7 – 4.9
Prostate cancer	3.2 – 11.0
Melanoma	2.7 – 4.3
Type II diabetes	2.4 – 4.0
Osteoporosis	2.0 – 2.4
Asthma	3.0 – 7.0

Family History Public Health Initiative: Building a bridge between

“one size fits all” and “one at a time” health practice



Selected Public Health Genomics Activities, 2004

- Integrating Genomics into Practice
 - Building Public Health Genomics Capacity
 - Population-based Monitoring and Outcomes Research
 - Ensuring the Laboratory Quality of Genetic Testing in Practice

Genomics and Public Health Capacity

- Genomics Competencies for Public Health
- Centers for Genomics and Public Health
 - University of Michigan
 - University of North Carolina
 - University of Washington
- Genomics and Chronic Disease State Programs
 - Michigan
 - Minnesota
 - Utah
 - Oregon



Press Release

Source: Myriad Genetics, Inc.

Myriad Genetics Launches Direct to Consumer Advertising Campaign For Breast Cancer Test

Thursday September 12, 6:30 am ET

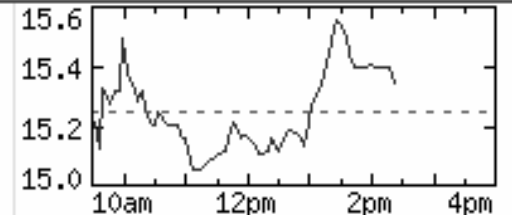
- First Ever Campaign for Cancer Predictive Test To Market BRACAnalysis in Denver and Atlanta -

SALT LAKE CITY, Sept. 12 /PRNewswire-FirstCall/ -- Myriad Genetics, Inc. (Nasdaq: [MYGN-News](#)), today initiated an intensive five-month advertising campaign to raise awareness of cancer prevention options among women with a family history of breast cancer or ovarian cancer. The first-of-its-kind campaign will focus on Atlanta and Denver, using television, radio and print media to carry its message of hope and help to those at high risk of cancer.

ADVERTISEMENT



Denver and Atlanta comprise 3.2% of the target population, consisting of women in the United States between the ages of 25 and 54, with a strong family history of breast or ovarian cancer. Market research among 300 high-risk women representing this population, conducted prior to the campaign, indicated that 85% would contact their doctor about having the test. An impressive 94% agreed with



MYGN 15.35 +0.10 News

[View Detailed Quote](#)

Delayed 20 mins

Quote data provided by Reuters

Related News Stories

- [Japan-Led Group Decodes Rice Genome](#) - Associated Press (Wed Dec 18)
- [MYRIAD GENETICS INC FILES \(8-K\) Disclosing Other Events and Financial Statements & Exhibits](#) - EDGAR Online (Tue Nov 26)
- [Myriad Genetics Raises \\$57.3 Million](#) - PR Newswire (Thu Nov 21)
- [Myriad Genetics Names Richard Marsh As General Counsel](#) - PR Newswire (Thu Nov 21)

[More...](#)

• By industry: [Advertising](#),

Public Health Assessment of Impact of DTC Campaign

- 4 Health Departments
- 2 “Exposed” Cities: Atlanta & Denver
- 2 “Unexposed” Cities: Raleigh & Seattle
- Survey of Women Ages 25-54 (N=1635)
- Survey of Health Care Providers (N=1070)
- Knowledge, Attitudes, Behaviors, Practices
- Association with Source of Information

Consumer Campaign Awareness and Interest in Test

	Denver n=401	Atlanta n=410	Raleigh n=403	Seattle n=421
Heard of test (%)	45	39	21	24
Interested in test (%) (n=473)	38	46	31	36
1 st DR (%)	46	47	54	46
Talk w anyone(%)	8	6	6	7
Provider	58	83	70	82
Friend/Family	61	61	43	61



Provider Practice Patterns by City

Comparing the last six months to one year ago

	Denver n=270	Atlanta n=292	Raleigh n=164	Seattle n=328
Testing requests Increased (%)	31	25	14	14
Number of tests ordered increased (%)	17	18	9	9



Public Health Approach for Translating Gene Discoveries into Population Health Benefits “Beyond the Bench to Bedside!”

**Role of genomic information in
population health?
(35,000 genes)**

**Value of genomic information
in treatment and prevention?
(1000+ tests)**

Implementation of
genomics in practice?

Public Health: Assuring Conditions for Population Health

- Continuum from genetic disease (medical genetics) to genetic information (genomic medicine)
- Honest broker/convener role: science based assessment of population health and assuring delivery of health service
- Public health roadmap for filling the widening gap between human genome discoveries and population health benefits