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U.S.  
Department of  
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Human  
Services

# Population Studies Beyond GWAS – Considering Genes and the Environment

U.S. Department of Health and Human Services  
National Institutes of Health  
National Human Genome Research Institute

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## Population Genomics: Mission

To promote multi-disciplinary research in epidemiology and genomics, by applying genomic technologies to existing population and clinical studies, and developing new population resources for investigation of genetic and environmental contributions to complex diseases.

# Population-Based Research Methods

- Findings can be generalized to broad population, not just to those coming to clinical care
- Phenotypes (diseases, traits, risk factors) and environmental exposures defined in valid, reproducible, and transportable manner
- Generally need to be large to reduce sampling variation and spurious findings, allow meaningful subgroup analyses representative of diversity of US population



**insight commentary**

# The case for a US prospective cohort study of genes and environment

Francis S. Collins

*National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, MSC 2152, 31 Center Drive, Bethesda, Maryland 20892, USA (e-mail: f23c@nih.gov)*

**The time is right for the United States to consider such a project.**

that contribute to health and disease. Well-designed case-control studies of people with and without a particular disease are essential for this, but rigorous and unbiased conclusions about the causes of diseases and their population-wide impact will require a representative population to be monitored over time (a prospective cohort study). The time is right for the United States to consider such a project.

Identification of the genetic and environmental factors that contribute to health, disease and response to treatment is essential for the reduction of illness. This, of course, is the primary goal of biomedical research. Several auspicious recent developments suggest that progress in this area could be quite rapid. The sequence of the human genome<sup>1,2</sup> and increasing information about the genome's function have provided a robust foundation for the investigation of human health and disease. Likewise, results from the exploration of human genetic

environmental exposure have improved. These techniques promise to extend the range of epidemiological investigation<sup>5</sup>. There is growing recognition that a change in the environment, in combination with genetic disposition, has produced most recent epidemics of chronic disease, and may hold the key for reversing the course of some diseases<sup>6</sup>. For example, consider the interaction of presumed famine-protective genetic predispositions with a modern environment in which there is a ready availability of excess calories. This has probably contributed to the current obesity epidemic



# NEW MODELS FOR LARGE PROSPECTIVE STUDIES SYMPOSIUM

January 22, 2010

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**ONE-MINUTE WORLD NEWS**



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## UK Biobank 'close to signing up 500,000 participants'

By Keith Doyle  
BBC News

Scientists behind one of the largest health projects in history say they are close to reaching their target of recruiting half a million participants.

UK Biobank hopes to find out how to prevent serious diseases, from cancer to

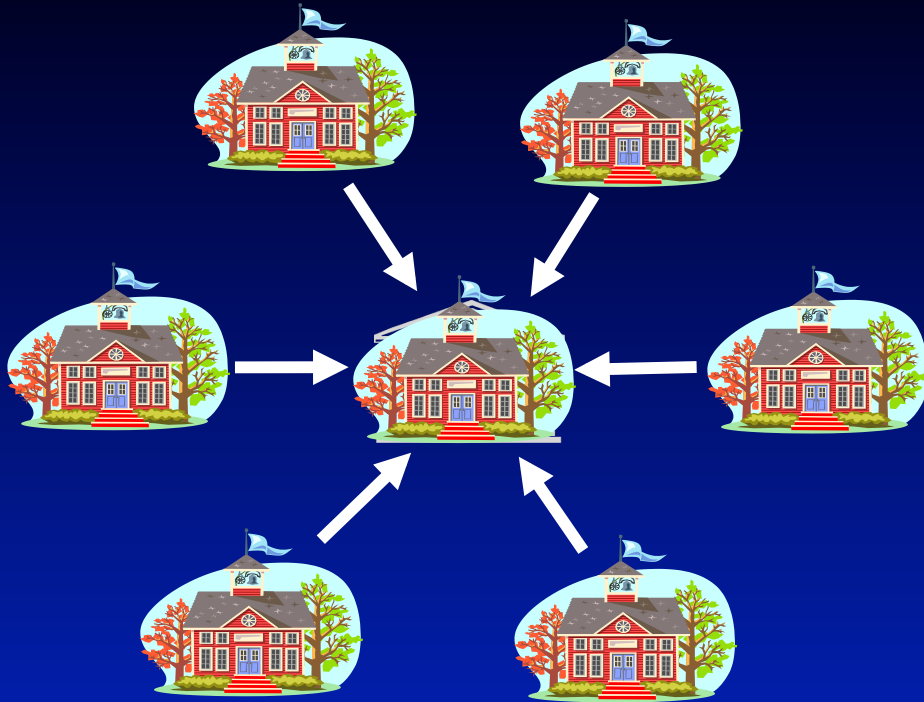


Blood samples make up a major part of the biobank

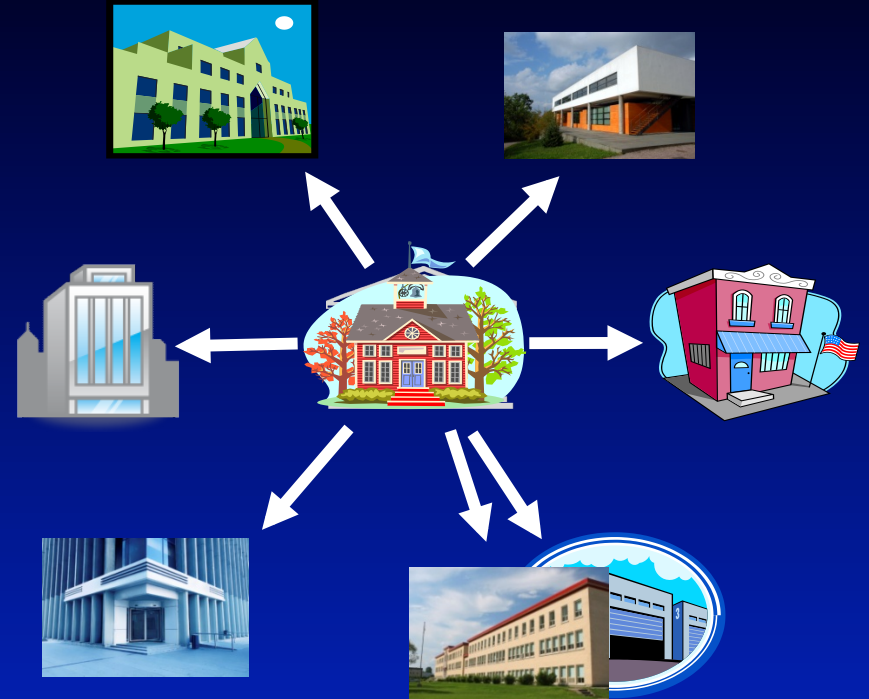
# Challenges in Conducting Cost-Effective, Population-Based Genomic Research

- Environmental exposure measures
- Defining phenotypes and exposures from EMR
- Representativeness vs inclusiveness
- Dynamic consent
- Widespread data sharing
- Existing cohorts

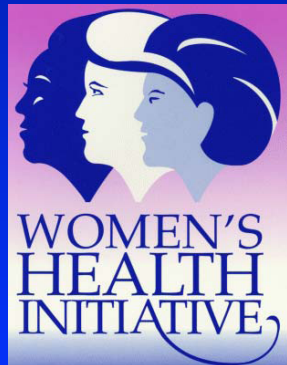
# Distributed and Centralized Models



Distributed Administration



Centralized Administration





# Key Points from New Models for Large Prospective Cohort Studies

## Recruitment

- Diversity >>> high recruitment yield
- Embed in population that permits follow-up
- Cost per ppt recruited is driving force in cost efficiency
- Centralized model provides greater control, nimbleness, cost efficiency

## Funding

- Leadership is critical
- Importance of clean, simple structure

# Why are Gene-Environment Interactions so Important to Geneticists?

- Genes and environment work together to produce almost all observable traits (“phenotypes”) of living beings
- Environment particularly important to geneticists because of pressure it exerts on genome through natural selection
- Environmental effects may provide clues to gene function or other mechanisms of disease

# Environment and Natural Selection: The Peppered Moth and Soot



Typical and melanic moths on oak tree near industrial Liverpool.



Typical and melanic moths on lichen-covered tree in rural Wales.

[http://www.arn.org/docs/wells/jw\\_pepmoth.htm](http://www.arn.org/docs/wells/jw_pepmoth.htm)

# Environment and Selection: The Peppered Moth and Soot AND *Parus major*



Typical and most common  
tree near industrial

Peppered moths on  
tree in rural Wales.

[http://en.wikipedia.org/wiki/Peppered\\_moth\\_evolution](http://en.wikipedia.org/wiki/Peppered_moth_evolution)

# Why are Gene-Environment Interactions so Important to Public Health?

- Environmental and behavioral changes interacting with genetic predisposition have likely produced most recent epidemics of chronic diseases
- GxE may be key in reversing their course, by suggesting approaches for modifying effects of deleterious genes
- Future public health measures may focus on avoiding deleterious environmental exposure, especially in genetically susceptible persons

# Why are Gene-Environment Interactions so Important to Research?

- Can mask detection of genetic (or environmental) effect if they are not identified and controlled for
- Can lead to inconsistencies in disease associations in different populations with:
  - Different environmental exposures that modify the effect of a genetic variant
  - Different prevalences of genetic variants that modify the effect of an environmental exposure

# Challenges in Studying Gene-Environment Interactions

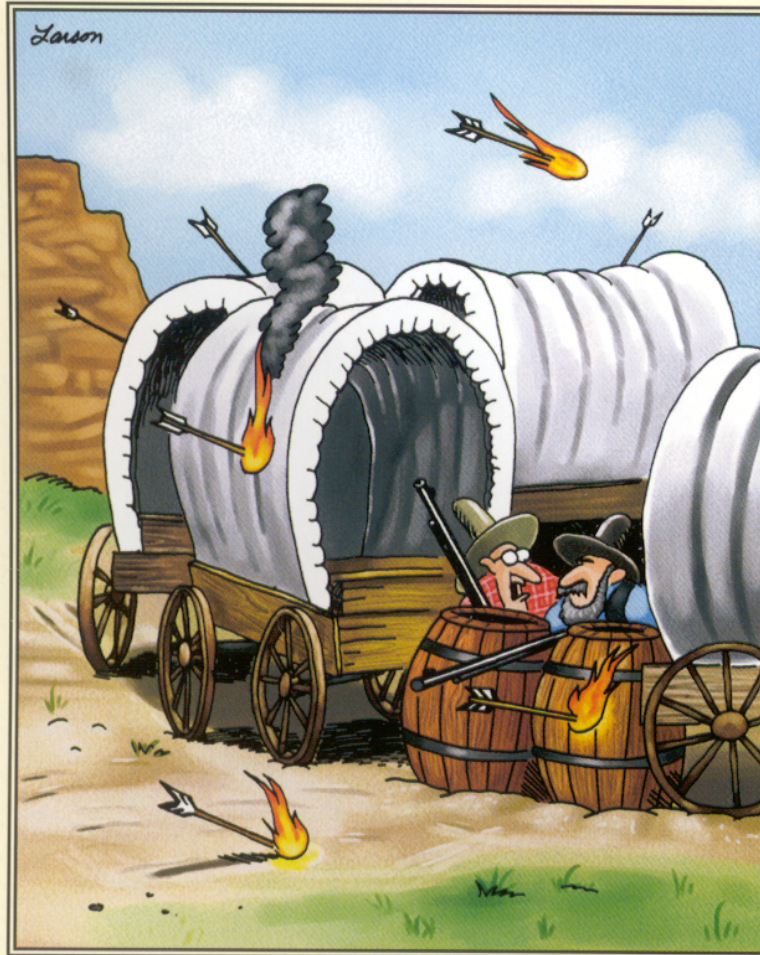
Challenge	Genes	Environment
Ease of measure	Pretty easy	Often hard
Variability over time	Low/none	High
Recall bias	None	Possible
Selection bias	Minimal	Possible
Temporal relation to disease	Easy	Hard

# Six Easy Steps to Implementing Large US Prospective Study of Genes and Environment

- Find inexpensive, simple, and reliable measures of key environmental exposures
- Find inexpensive, simple, reliable measures of broad range of phenotypes (outcomes)
- Cut recruitment/exam costs by 90% or more
- Use standardized, readily accessible, reliable electronic medical records for follow-up
- Mirror full richness and diversity of US population in recruited sample
- Vest responsibility in study leadership, backed by simple, clear lines of authority



10/11/82



“Hey! They’re lighting their arrows! ...  
Can they *do* that?”

Larson, G. *The Complete Far Side*. 2003.

