NHANES Genetics Program Update

NCHS Board of Scientific Counselors Meeting
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Rosemarie Hirsch, MD, MPH
Deputy Director, NHANES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

Public Health Contributions

Benefits of NHANES DNA Analysis

- A unique genetic variant prevalence resource due to the representative nature of the sample
- Valuable genotype/phenotype resource due to the thousands of variables in NHANES

DNA specimens available for use from:

~7000 participants in 91-94

~8000 participants in 99-02

~13,800 participants in 07-12

Use of NHANES DNA Specimens

- Purified DNA specimens stored by CDC
- Proposals solicited through a Federal Register notice to conduct specific DNA tests
- Proposals reviewed by SME and ethics panels
- De-identified DNA samples sent for genotyping
- Test results are sent to NCHS, linked to requested NHANES data, then analyzed in RDC
- 61 genetic proposals since 1996
  (only non-clinically relevant projects accepted)
- Genetics Program has evolved
  - Anonymized testing → Candidate genes → GWAS

NHANES Genetics Protocol Issues – Past and Present

In the past, protection of confidentiality of the data had to be addressed – that has been sorted out by utilizing RDC

Genetic technology advances and analytic changes from candidate gene approaches to that of large scale assays

- **increased potential for incidental clinically relevant findings**

Now the main issue to address is report of findings

- **Linked to CONSENT and stored specimens**
- **ETHICAL considerations**
  - **What to report back**
  - **Who determines**
  - **How/When to report back**

NHANES Consent 2009-2010

- **The NHANES program will not contact you or your family with results from these future studies. We will describe the completed studies on our website. If you are interested in your results from any of these studies, you may call our toll-free number to request your specific results as they become available.**
- **Check a box:**
  - I agree that my blood may be kept for future studies using my genes to help understand genetic links to medical conditions, and that I will not be contacted with the results from these studies.
  - I disagree

Summary of NHANES Genetic Consent Parameters

NHANES consent for collection of DNA specimens varied slightly between surveys

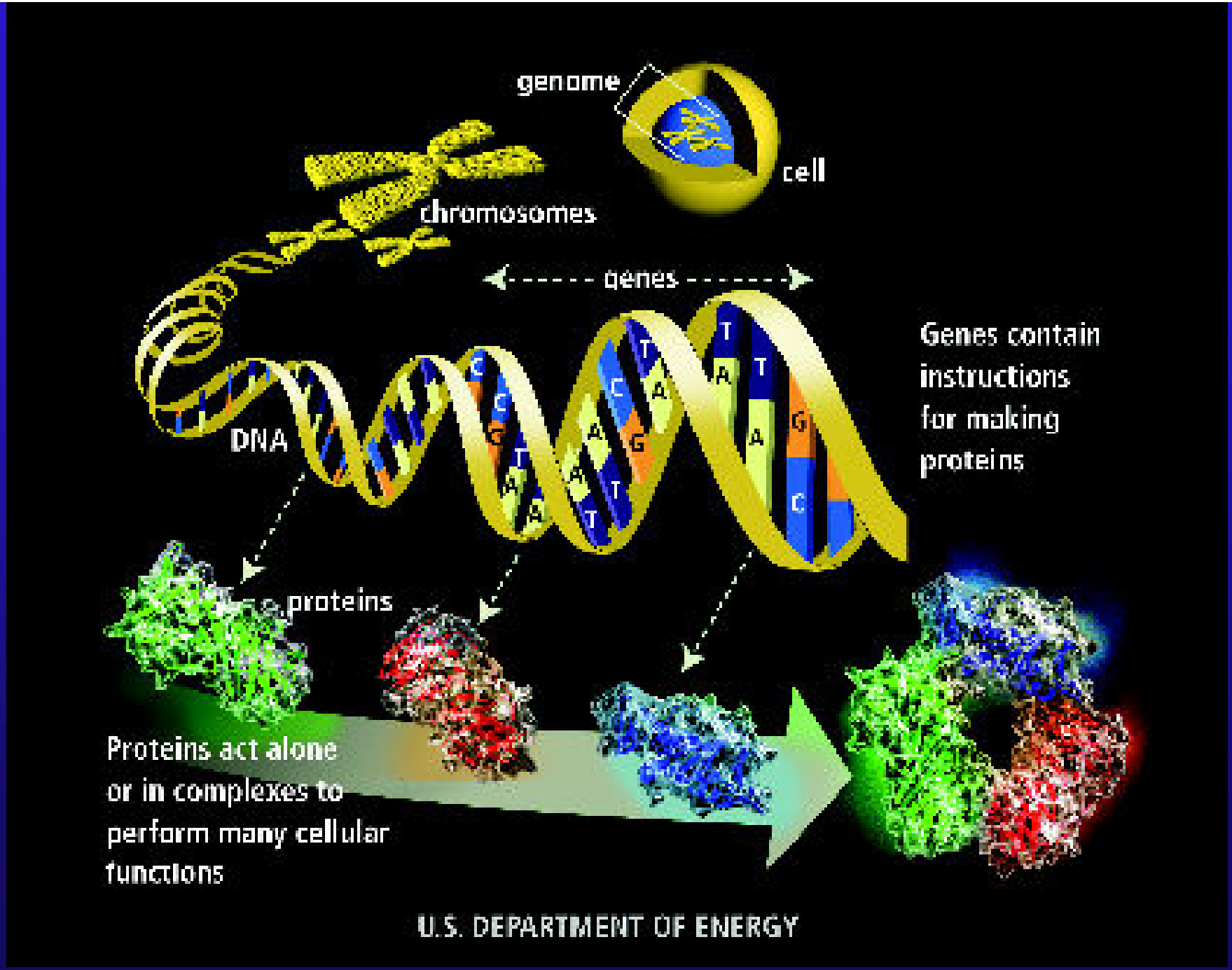
	Age	Separate DNA consent	Opt-out later	Notice of DNA studies	Plan to contact with results
NH III	**12+**	**no**	**no**	**none**	_
99-02	**20+**	**yes**	**yes**	**Newsletter phone**	**no**
07-08	**20+**	**yes**	**yes**	**website**	**no**
09-10	**20+**	**yes**	**yes**	**website**	**no**
11-12	**20+**	**yes**	**yes**	**website**	**no**

All consent forms state

All health data will be kept strictly private

No identifying information may be released

Under penalty of law [Section 308(d) of the Public Health Service Act (42USC242m) and the Privacy Act of 1974]



Human Genome Program, U.S. Department of Energy, Genomics and Its Impact on Medicine and Society: A 2001 Primer, 2001

Review

Trends in Genetics February 2011, Vol. 27, No. 2

Disclosure of individual genetic data to research participants: the debate reconsidered

Annelien L. Bredenoord[1], Hester Y. Kroes[2], Edwin Cuppen[2], Michael Parker[3] and Johannes J.M. van Delden[1]

Argument against:

- Promotes therapeutic misconception
- Rests on mistaken interpretation of autonomy
- Poses untenable burden on research infrastructure
- Not feasible
- Harmful consequences

Arguments for:

- Beneficence requires disclosure
- Autonomy requires disclosure
- Reciprocity requires disclosure
- Blurring research/ clinical care not bad
- Improves public understanding of genetics

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Human Genome Research Institute (NHGRI) National Cancer Institute (NCI) National Institute on Deafness and Other Communication Disorders (NIDCD)
Funding Opportunity Title	Development of a Preliminary Evidence Base to Inform Decision-making about Returning Research Results to Participants in Genomic Studies (R01)
Activity Code	R01 Research Project Grant
Announcement Type	New
Related Notices	• January 3, 2011 - See Notice NOT-CA-11-005 National Cancer Institute (NCI) will participate in Request for Application. • December 21, 2010 - See Notice NOT-HG-11-007 Information Teleconference and Webinar for Applications to NHGRI Sequencing and Ethical, Legal, and Social Implications (ELSI) FOAs.
Funding Opportunity Announcement (FOA) Number	RFA-HG-11-003
Companion FOA	RFA-HG-11-004, R21 RFA-HG-10-017, U01

Candidate Gene Proposal Process - 2003

- **Candidate genes**
  - Known chromosomal location associated with presumed biological function or disease phenotype
- **Solicited through a Federal Register notice and are reviewed by three panels**
  - Scientific technical panel (Genetic Technical Panel)
  - Internal CDC panel of senior scientists
  - Ethics Review Board
- **No clinical relevance of the proposed testing**
  - Limited to the testing of 1,000 or less genetic variations
  - Researchers receive de-identified DNA samples genotyping
  - Test results are sent to NCHS for processing (QC and linked to phenotypic data) and made available in RDC

Genetic Data – Report of Findings Issues

- **Historically, stored samples had not been used for studies that would produce results that were clinically relevant to participants because consent indicates we will not be giving back results**
  - Studies of stored specimens conducted long after sample collection would rarely be clinically relevant.
  - Genetics changed that, but in 2003, when candidate gene approaches were added to the program, no polymorphisms were clinically relevant.
  - In 2009 when GWAS was added to the program, the potential for incidental clinically relevant genetic findings was hypothetical.

2009 Ethics Review Resolution
(in collaboration with NIH Dept of Clinical Bioethics)

- **Clinically relevant results can be avoided when they are based on selected genetic variations, but may be unavoidable when doing whole-genome testing**
  - Genetics Technical Panel, when reviewing proposals based on specific hypotheses (<1000 genetic variations), only approves proposals that do not produce immediately clinically relevant information
  - Medical Genetics Panel, when reviewing GWAS proposals, determine:
    - **whether the genotyping might generate an incidental clinically relevant result**
    - **if so, whether reporting the results to participants would present a clear net benefit to them**

2009 Ethics Review Resolution

(in collaboration with NIH Dept of Clinical Bioethics)

- **Blanket nondisclosure of results is not ethically appropriate, but the costs of notification are high**
  - Avoid clinically relevant studies when possible
  - Set a high bar for disclosure of results based on incidental findings
  - Consider developing a policy for dealing with the issue of potential future notification
  - Accept that NHANES lacks an obligation to monitor whether existing data become clinically relevant at some future date

GWAS Proposal Process - 2009

- **Genome-wide/ large scale assay approach**
  - Hundreds of thousands of candidate genes tested simultaneously
- **Solicited through a Federal Register notice and are reviewed by three panels**
  - Scientific technical panel – (Medical Genetics Panel)
  - Internal CDC panel of senior scientists
  - Ethics Review Board
- **All GWAS proposals handled under secondary data analysis protocol**
  - GWAS proposals conducted thru NCHS contract to maintain proper stewardship re: confidentiality/protection
  - Contract lab receives de-identified DNA samples for genotyping
  - Test results are sent to NCHS for processing (QC and linked to phenotypic data) and made available in RDC

NHANES Genetics Program 2009
Identifying clinical relevance for GWAS

A panel of Medical Geneticists would be convened to determine if the results would provide a clear net benefit to the participant

- Genetic results would be reported to participant if the risk for the disease was significant
  i.e. relative risk >2.0
- The disease should have important health implications
- There are proven therapeutic or preventative interventions available

NHANES Genetics Program 2009
GWAS Testing Initiated

GWAS testing conducted under an NCHS contract using the Affymetrix Genome –Wide Human SNP Array 6.0 chip/ CHOP data

- **>1.8 million markers for genetic variation and > 900,000 SNPs**
- **Medical genetics panel assessment**
  - **No clinical relevance of the proposed testing**

Problems with Implementation - 2010

- **After first round of experience with a GWAS chip assessment, and continued advances in multiple SNP arrays**
  - Can the definition and criteria for clinical relevance still be meaningfully implemented?
  - Are there ways to ensure they are applied consistently and updated as appropriate?
- **As the potential for incidental clinically relevant findings increases, how will disclosure be implemented?**

Problems with Implementation - 2010

- **What to do with clinically relevant results within the context of the existing signed consent and other relevant constraints...**
  - "Set a high bar"
    - **ERB concurs that "dire duty to warn" cases should be the only ones that require individual subject re-contact, but how should "dire duty to warn" cases be identified?**
  - Should past participants be notified of any new NHANES disclosure policy, and if so, how?
  - How much effort should be made to disclosure results?

May 2011 NHANES Genetics Program Workshop Highlights

- **Panel of experts**
  - intra/extra mural experts
  - geneticists/bioethicists
- **What results should be reported back – are standards or guidelines available?**
- **How to determine and operationalize criteria for clinically relevant genetic findings with a dire duty to warn threshold?**
- **Who determines it?**
- **How/When to report back?**

NHANES Threshold for ROF

Support for NHANES' dire duty to warn target threshold for disclosure supported:

"Duty to rescue: A fundamental obligation"

Based on the premise that, when confronted with a clear and immediate need, an individual who is in a position to help must take action to try to prevent serious harm when the cost or risk to self is minimal

This condition is met when, in the course of research, an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available

Beskow & Burke. *Sci Transl Med* (2010)

Four Best Practices - Genetic Research Result Reporting

- **NCI** - informed consent document should state whether individual or aggregate research results will be released

- **eMerge** - subjects should not expect results. Results only should be reported if very important to health

- **NBAC** - if results are valid and confirmed, have significant implications, and treatment is available then disclosure can occur

- **NHLBI** - results should be returned if they are established, substantial, actionable and valid with an "opt" in clause in the consent

Not Just Clinical Relevance…

Clinical relevance = clinical validity but not necessarily actionable

Clinical utility = clinically valid (relevant) + actionable

Dire duty to warn = clinical utility + serious condition

Categorizing Potential Genetic Results
Binning by Loci

- **The significance of the vast majority of genomic studies will be utterly unknown**
  - Thus clinically inconsequential and do not mandate reporting
- **A few will be tangibly useful to subjects**
  - Report only those with established evidence of health benefit
- **Accomplish this by taking a locus-based approach to categorization of potential results**

Berg. *Genetics in Medicine* (2011)

Binning the Genome

Bin 3

Genes of unknown clinical implication

Bin 2

Variants within genes that are clinically valid but not directly actionable

Bin 1

Variants within genes that have direct clinical utility based on professional organization diagnosis and treatment guidelines

Only Bin 1 variants should be considered for reporting

Potential Examples
Bin 1

- **Clearly deleterious mutation in *BRCA1***
  - Pros:
    - Clear actionability
      - – Increased surveillance
      - – RR surgery
    - High penetrance
    - Professional organizations with recommendations
  - Cons
    - Potential for psychological harms
- **Other examples: *NF1, FBN1, MSH2***
  - *Professional guidelines and evidence exist to guide use*

Who Makes the Call on Binning the Genome?

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

Independent, nonfederal multidisciplinary expert panel charged with developing systematic, evidence-based processes for evaluating genetic tests and other applications of genomic technology

Iterative, centralized, consensus driven process
Anticipate ~1 year to bin the genome

www.egappreviews.org

Unclear whether all Bin 1 will be reportable in NHANES dire duty to warn context

Who Makes the Call on Dire Duty to Warn?

Medically actionable Bin1 variants that rise to the level of NHANES dire duty to warn

- ? Proposed Advisory Board Composition
  - Genetic clinicians
  - Research scientists
  - Bioethicists
  - Genetic epidemiologists

How/When to Disclose

One-time re-contact to inform of consent changes re: reporting back results

- anticipate low likelihood of need to report back

Opt-out option for future re-contact

Opt-in participants

- encouraged to keep NHANES informed of their current contact info

Implications of Revised Genetics Program Approach

Allows research on clinically relevant conditions

Revisit approach every few years as

- genetics science and ethics continues to evolve, and

- the number of clinically actionable genes expands

Thank You

Centers for Disease Control and Prevention
National Center for Health Statistics

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Panel Members

- James Evans MD, PhD, Chair
- Laura Beskow PhD, Co-Chair
- Benjamin Berkman JD, MPH
- Jeffrey Botkin MD, MPH
- Flavia Facio MS, CGC
- Sarah Hull PhD.
- Muin Khoury MD, PhD
- Alan Shuldiner MD
- Ben Solomon MD
- Elizabeth Thomson DNsc, RN, CGC, FAAN

NHANES and ERB

- Clifford Johnson MSPH
- Rosemarie Hirsch MD, MPH
- Kathryn Porter MD, MPH
- Geraldine McQuillan PhD
- Jody McLean, MS
- Stephen Blumberg PhD
- Helen Thackray MD, FAAP
- Anjani Chandra PhD
- Lara Akinbami MD

	Criteria:	*Loci with Clinical Utility*	*Loci with Clinical Validity*			*Loci with Unknown Clinical Implications*
Genes	Bins:	**Bin 1** Medically actionable incidental information	**Bin 2A** Low risk incidental information	**Bin 2B** Medium risk incidental information	**Bin 2C** High risk incidental information	**Bin 3 All other loci**
	Examples:	*BRCA1/2* *MLH1, MSH2* *FBN1* *NF1* PGx variants and common risk SNPs with proven clinical utility	PGx variants and common risk SNPs with no proven clinical utility	*APOE* Carrier status for recessive loci in bin 1	Huntington disease Prion diseases Frontotemporal dementia	
	Estimated number of genes/loci	10s	~10s (eventually 100s – 1000s)	1000s	~10s	>20,000
Alleles that would be reportable (YES) or not reportable (NO) in a clinical context						
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

N/A: not applicable
VUS: Variant of uncertain significance
[1] Reporting would be done in the setting of shared decision-making with an appropriate provider if elected by the individual sequenced.
[2] By definition, such variants have unknown implications at present and thus could not be considered deleterious.
[3] By definition, a common SNP or pharmacogenomic marker will either be present or absent.
[4] Since they occur in genes with unknown clinical implications, these variants will not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.