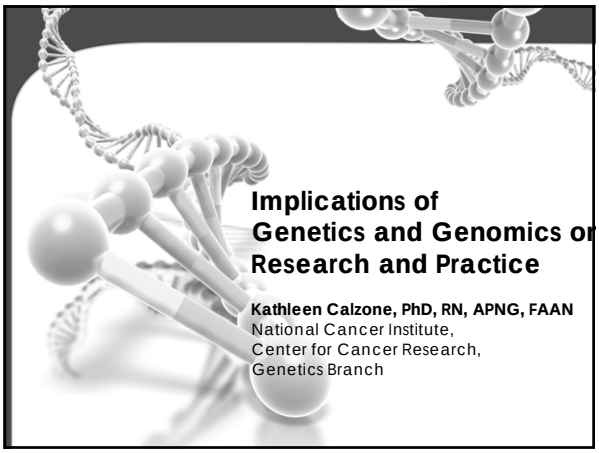

Implications of Genetics and Genomics on Research and Practice

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Center for Cancer Research,
Genetics Branch

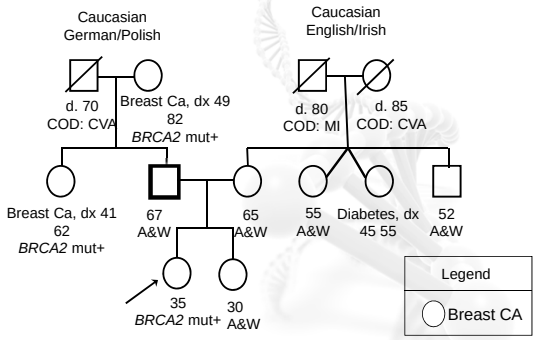
Definitions

- **Genetics** – study of individual genes and their impact on relatively rare single gene disorders
- **Genomics** – study of all the genes in the human genome together, including their interactions with each other, the environment, and other psychosocial and cultural factors

Genetic/Genomic Information

- Genetic and/or genomic tests
  - Stability of DNA
  - Testing can be performed on stored biospecimens
- Family history
- Manifestation of a disease or disorder
- Family germline genetic test results
  - Obligate carrier

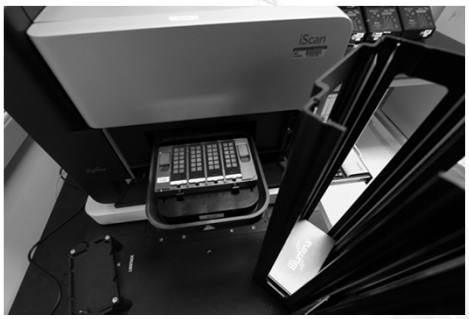
Obligate Carrier

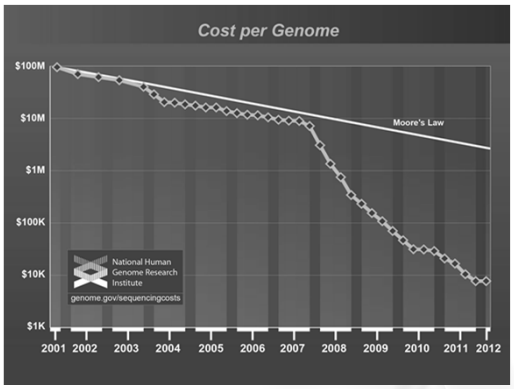


Genetic/Genomic Healthcare Applications

- Identification of at risk individuals before disease occurs
- Screening and/or diagnosis of disease
- Characterization of disease and its aggressiveness via gene expression
- Individualization of therapies over the disease course based on molecular profiles
- Development of genetically targeted therapies
- Monitoring for disease progression
- Individualized drug selection and/or dosing based on pharmacogenomics
  - Management of symptoms including pain control

Emerging Science/Technology

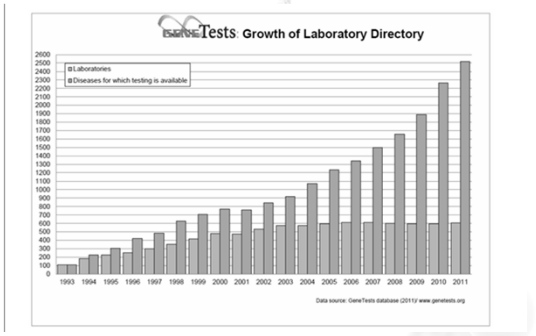




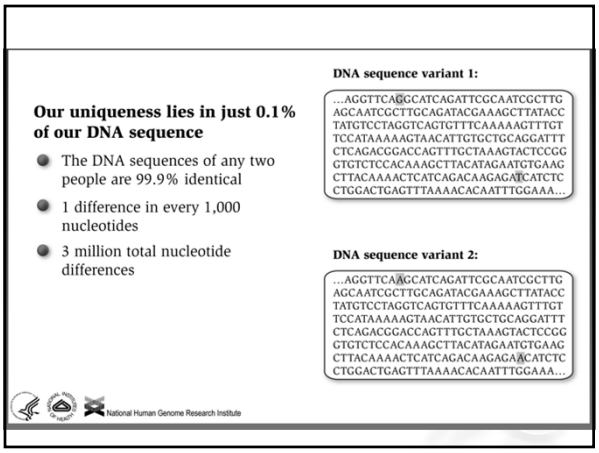
http://www.genome.gov/27541954

The Race for the $1000 Genome

Cumulative Pace of Disease Gene Discovery and Testing Capacity



http://www.ncbi.nlm.nih.gov/projects/GeneTests/static/whatsnew/labdirgrowth.shtml



The International HapMap Project

- Discovery of common human genetic variation
- 10 million single nucleotide polymorphisms (SNPs)
- World-wide population distribution

http://hapmap.ncbi.nlm.nih.gov/

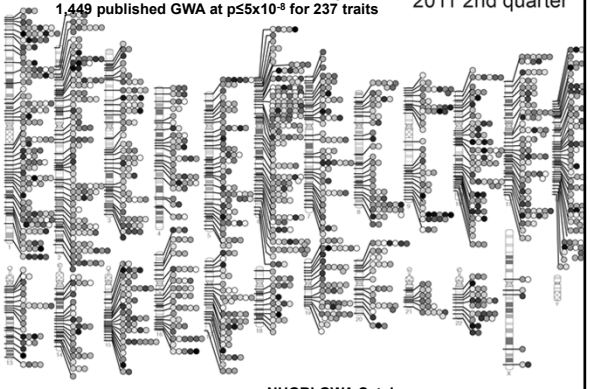
Implications of the HapMap

- HapMap is a catalog of common genetic variants
  - what these variants are
  - where they are located
  - how they are distributed within populations and among populations in different parts of the world.
- Almost 90% of SNPs have linkage disequilibrium
  - More than one SNP in a region are inherited together
- Enabled the development of Genome Wide Association Studies (GWAS) to correlate SNP variation using **representative** SNPs with diseases such as cancer

Hunter, D.J., et al. (2007). Scanning the horizon: What is the future of genome-wide association studies in accelerating discoveries in cancer etiology and prevention? Cancer Causes and Control, **18**, 479-484.

Published Genome-Wide Associations through 06/2011,
1,449 published GWA at p≤5x10^{-8} for 237 traits

2011 2nd quarter



NHGRI GWA Catalog
www.genome.gov/GWAStudies

Scope of Genome Analysis

- Has expanded to include any whole genome analysis such as
  - Whole genome sequencing
  - Whole exome sequencing
  - RNA and RNAi sequencing
  - Whole genome SNP analysis

Database of Genotypes and Phenotypes dbGap

http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap

Ethical, Legal and Social Implications for Research and Practice

Ethical Considerations

- Stability of DNA
  - Storage and future use
- Broad sharing of samples/data
- Limited control of downstream use
- Limited right to withdraw
- Identifiability
- Incidental findings
  - Duty to re-contact
- Implications for family/community

Lowrance, W., Collins, F. (2007). Identifiability in genomic research. Science 317, 600-602.
Caufield et al. (2008). Research ethics recommendations for whole-genome research: Consensus statement. PLoS 6, 430-435.
McGuire, A., Beskow, L. (2010). Informed consent in genomics and genetic research. ARGHG, 11, 361-381.

Genomic and Genetic Research

- Lightning rod for ethical issues in research
  - Sources of genomic information and DNA, stored tissues
- Regulatory guidance often insufficient and sometimes contradictory 45 CFR 46 Protection Of Human Subjects 46.102
  - "*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
    - (1) Data obtained through intervention or interaction with the individual,
    - (2) Identifiable private information"
- IRBs sometimes lack expertise in genomics

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102

Genetic/Genomic Research and Deceased Participants

- Can have consequences for living relatives
  - Relatives of the deceased may not be given the option of consent or the option to be exposed to information from the study
    - Should we be considering asking participant who would be offered information in the event of their death and how to reach them?
      - Standard procedure for clinical genetic tests
- Genetic education and counseling considerations may be overlooked

DeRenzo et al. (1997). Genetics and the dead: Implications for genetics research with samples from deceased persons. AJMG 69, 332-334.

Revisions to the Common Rule

- Advanced Notice of Proposed Rule Making
  - http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html
- The ANPRM comment period closed October 26, 2011
- Next revision not yet published

Privacy and Confidentiality

- Individuals who know the information may have difficulty keeping genetic information from family members, friends, insurers, and employers
- Genetic tests can be performed on stored samples (e.g. blood or tissue), including samples collected for other purposes
- Medical information is increasingly kept in electronic databases, tied to genomic information, and placed in widely accessible databases (e.g. dbGaP)

Public Access to GWAS Data

- Used high-density single nucleotide polymorphism (SNP) genotyping microarrays to demonstrate the ability to determine whether individuals are in a complex genomic DNA mixture
- Developed a theoretical framework for detecting an individual's presence within that mixture
- Showed through simulations the identification of the presence of genomic DNA of specific individuals within a series of highly complex genomic mixtures
- August 2008, NIH closes GWAS data from public view

Homer, N. (2008). Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. PLoS Genet. 4(8):e1000167

Certificates of Confidentiality

- Issued by DHHS agencies to protect identifiable research information from forced disclosure.
- Allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
  - Generally, any research project that collects personally identifiable, sensitive information

http://grants.nih.gov/grants/policy/coc/

Limitations of Certificates of Confidentiality

- Legal challenge that reached the North Carolina Court of Appeals
  - Duke longitudinal study of psychiatric disorders
  - Research participant's data, collected under a Certificate, were subpoenaed as part of a criminal case
  - 2004 criminal proceeding of defendant charged with indecent liberties with a minor and statutory rape
  - Attorney believed a prosecution witness was a study participant and requested a court order directing DUHS to supply all study records about the witness
  - Records were turned over in sealed envelope and ultimately the judge decided that the information was not material and returned it unopened

Beskow, N.L. et al. (2008). Research ethics. Certificates of confidentiality and compelled disclosure of data. Science. 322(5904):1054-5

Certificate Issues to Consider

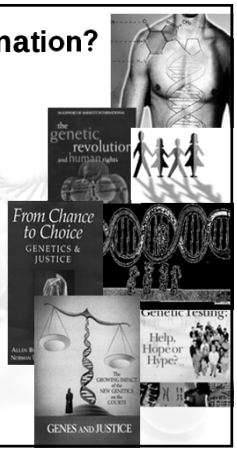
- Requests for research data may arise from legal proceedings unrelated to a the study
- A Certificate is granted to the research institution and NOT the PI
  - Their interests may not be identical
- Seeking to enforce a Certificate may result in some disclosure
  - Participation
- Institutions/investigators refusing to follow a court order may be found in contempt, resulting in fines or imprisonment
- Parties in both criminal and civil lawsuits have rights to obtain material relevant to their case.
  - A Certificate may be especially vulnerable if the records sought could affect a defendant's Constitutional rights to a fair trial or to confront and cross-examine witnesses.

Beskow, N.L. et al. (2008). Research ethics. Certificates of confidentiality and compelled disclosure of data. Science. 322(5904):1054-5

What Is Genetic Discrimination?

- Social or economic discrimination or stigmatization based on one's genetic information
  - denial of access to or increased cost of insurance
  - loss of employment, educational, or other opportunities
- Insurance considerations
  - Health, Life, Long Term Care, Disability

**Special consideration for the military



Other Uses of Genetic Information

- Federal Freedom of Information Act
  - "redaction of individual-level genotype and phenotype data from any disclosures made in response to FOIA requests and the denial of requests for unredacted datasets"
- Law enforcement
  - "law enforcement agencies could request access to the de-identified genotype and phenotype data within the NIH GWAS data repository and, for example, search for matches to DNA specimens collected for forensic purposes. While expected to be rare, **such requests may be fulfilled by the NIH**."
- Specific populations, groups, and communities

http://grants.nih.gov/grants/gwas/gwas_ptc.pdf

Genetic Information Nondiscrimination Act (GINA)

- Forbids genetic discrimination in the workplace and in health
- Genetic information broadly defined
  - "Genetic test" means a test that assess genotypes, mutations, or chromosomal changes.
  - "Genetic information" means information about:
    - a person's genetic tests
    - genetic tests of a person's family members (up to and including fourth-degree relatives)
    - any manifestation of a disease or disorder in a family member
    - participation of a person or family member in research that includes genetic testing, counseling, or education
- Specific to group and individual insurance plans
- Forbids use of genetic information in underwriting
- Forbids requiring genetic testing by employers and insurers

Genetics and Public Policy Center.: Information on the Genetic Information Nondiscrimination Act (GINA). http://www.dnapolicy.org/resources/WhatGINAdoesanddoesnotdochart.pdf

GINA Coverage Limitations/Exclusions

Limitations	Exclusions
Civil suit is restricted to those that have exhausted all administrative remedies Does not prohibit medical underwriting based on current health status Does not cover life, disability, and long-term care insurance Does not cover employers with <15 employees (those covered by the ADA)	Members of the United States military, veterans obtaining health care through the Veteran's Administration, and the Indian Health Service because the laws amended by GINA do not apply to these groups and programs

Withdrawal from Study

- Withdrawal of consent may be limited by
  - Analysis completed and reported
  - Data uploaded into public database
    - i.e. dbGaP [database of Genotypes and Phenotypes]
  - Specimens have been disbursed to other investigators
- Discussion of withdrawal can specify partial withdrawal
  - i.e. no further participation

Incidental Findings

- "A finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study."
- For analysis on identifiable specimens, establish a plan for handling incidental findings
  - Mechanism for assessing for incidental findings
  - Criteria for offering results
  - Confirmation
  - How long you will look for results

Wolf, S., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived datasets. Genetics in Medicine, 4, 361-384.
Caufield et al. (2008). Research ethics recommendations for whole-genome research: Consensus statement. PLoS 6, 430-435.

Considerations with Incidental Findings

- Family studies
  - Misattributed paternity
- Full genome analysis
  - Previously unknown information
    - Clinical and analytic validity of finding
    - Immediacy and seriousness of risk
    - Actionable finding
  - Timing
  - Confirmation in CLIA approved laboratory

Wolf, S., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived datasets. Genetics in Medicine, 4, 361-384.

Return of Research Results

- NHLBI criteria for return of research results
  - Risk should be significant, i.e. relative risk >2.0. Variants with greater penetrance or associated with younger age of onset should receive priority.
    AND
    The disease should have important health implications, i.e. fatal or substantial morbidity or should have significant reproductive implications.
    AND
    Proven therapeutic or preventive interventions should be available.

NHLBI Working Group on Reporting Genetic Results in Research Studies
http://www.nhlbi.nih.gov/meetings/workshops/gene-results.htm#guidelines

Establishing Clinical Utility and Validity of Incidental Findings

	Criteria:	Clinical Utility	Clinical Validity			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	*APOE* Carrier status for recessive Mendelian disorders	Huntington-Prion diseases ALS (SOD1)	
	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 through decision making with an appropriate provider if elected by the patient.
[2] By definition, variants in genes with unknown implications could not be considered deleterious.
[3] By definition, SNPs or PGx variants will either be present or absent.
[4] Variants in genes with unknown clinical implications would not be reported; however, they may serve as an important substrate for research, potentially uncovering new disease genes.

Fig. 1. Proposed system for "binning" of incidental WGS results

Berg, J. et al. (2011). Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. Genetics in Medicine, 13, 499-504.

Return of Research Results, continued

- Process of offering and delivering results
  - Inform subjects how they would be contacted
  - Involve healthcare professionals with the appropriate expertise (i.e., experts in the field, geneticist, genetic nurse, genetic counselor)
  - The research participants' right to not know certain test results
  - The process is in compliance with professional standards related to disclosure of genetic and genomic information for healthcare decision-making
    - Genetic education and counseling

US Regulation of Genetic Tests

Clinical Validity (genetic tests ability to detect or predict the associated disorder/phenotype).

- Centers for Medicare & Medicaid Services using the Clinical Laboratory Improvement Act (CLIA) regulates all clinical human laboratory testing that generate diagnostic or other health information
  - address personnel qualifications, laboratory quality assurance standards, as well as documentation and validation of tests and procedures
  - CLIA categorizes tests based on the level of complexity
  - Genetic tests are considered high complexity which indicates that a high degree of knowledge and skill is required to perform or interpret the test. Laboratories conducting high complexity tests must undergo proficiency testing at specified intervals
    - consists of an external review of the laboratories' ability to accurately perform and interpret the test
    - specialty area specific for molecular and biologic genetic tests has yet to be established

Hudson, KL, et al. (2006). Oversight of US genetic testing laboratories. Nat Biotechnol 24 (9): 1083-90.
Javitt GH, Hudson K (2006). Federal neglect: regulation of genetic testing. Issues Sci Technol 22: 58-66.

US Regulation of Genetic Tests

Analytic Validity (Defines the ability of a genetic test to accurately and reliably measure the genotype of interest)

Genetic tests fall into two primary categories; test kits and laboratory developed tests (previously called home brews)

Test Kits

- The U.S. Food and Drug Administration (FDA) regulates test kits as medical devices
  - Despite more than 1,000 clinically available genetic tests, there are fewer than 10 FDA-approved test kits

Laboratory Developed Tests

- Laboratory-developed tests are performed in a laboratory that assembles its own testing materials in house
  - Neither CLIA nor the FDA evaluate the laboratories' proficiency in performing the test or clinical validity relative to the accuracy of the test to predict a clinical outcome
- FDA does regulate manufactured analyte-specific reagents (ASRs) as medical devices
  - ASRs made in the laboratory are NOT subject to FDA oversight

Hudson, KL, et al. (2006). Oversight of US genetic testing laboratories. Nat Biotechnol 24 (9): 1083-90.
Javitt GH, Hudson K (2006). Federal neglect: regulation of genetic testing. Issues Sci Technol 22: 58-66.

Regulatory Action

- April 2006 the Department of Health and Human Services (HHS) placed the issuance of a genetic testing specialty on its regulatory agenda, with a target date of November 2006.
- July 2006, CMS reversed course, decided not to issue a regulation for a genetic testing specialty.
- Despite the fact that genetic testing appears to be among the most rapidly expanding areas of laboratory medicine, CMS officials now assert that creating a specialty lacks sufficient "criticality" to warrant rulemaking and that existing regulations are adequate.

http://www.dnapolicy.org

FDA Recent Actions

- May 2010 FDA acted to say that it interprets home brew tests to meet the definition of a medical device according to Section 201(h) of the Federal Food Drug and Cosmetic Act
- Thus far six companies have been approached to provide analytic and clinical validity data of their tests for FDA approval
  - The companies approached to date sell tests directly to consumers without healthcare provider involvement
  - 629 laboratories registered with genetests that offer genetic tests for 2888 diseases

http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm
http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests

Informed Consent Elements

- Purpose of genome analysis
- Scope of genome analysis
  - Germline vs. somatic
- Data Sharing
- Risks, Benefits and Alternatives
  - Whether to include GINA
- Incidental Findings
  - Will investigators look for incidental findings
  - How long will you look?
- Disclosure of Research Results
  - Disclosure
    - Infrastructure for re-contact and disclosure
  - Non-disclosure

Informed Consent Elements, cont

- Confidentiality
  - Certificates of Confidentiality
- Withdrawal from Study
- How samples and health information will be coded and stored.
- Whether there will be access to a research participant's medical records
  - If so, the process for accessing them (*e.g.*, one-time vs. ongoing collection of information from medical records).
- The duration of storage
- Storage for future use

Resources

- NCI, CCR Model Informed Consent for Whole Genome Analysis https://ccrod.cancer.gov/confluence/display/CCRCRO/Templates
- NHGRI Informed Consent Web Resource http://www.genome.gov/27531909
- Wolf, S., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived datasets. Genetics in Medicine, 4, 361-384.
- Berg, J. et al. (2011). Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. Genetics in Medicine, 13, 499-504.
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- Cho, M. (2008). Understanding incidental findings in the context of genetics and genomics. Journal of Law, Medicine and Ethics, 36, 280-285.
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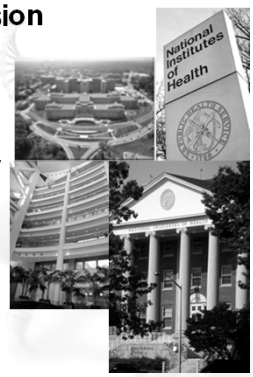
Questions/Discussion

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