The ethical concerns of scientific discoveries utilizing population biobanks.

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Ethics of Synthetic Biology

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Identified five ethical principles

- **I. Public beneficence**
  - Maximize public benefits and minimize public harm
- **II. Responsible stewardship**
  - Demonstrate concern for those who are not in a position to represent themselves
  - Think and act collectively for the betterment of all
  - Demonstrate concern for the environment in which future generations will flourish or suffer
- **III. Intellectual freedom and responsibility**
- **IV. Democratic deliberation**
  - Collaborative decision making that embraces respectful debate of opposing views
  - Inclusive process of deliberation, informed by relevant facts and sensitive to ethical concerns
  - Encourages the adoption for a societal perspective over individual interests
- **V. Justice and fairness**
  - The distribution of benefits and burdens across society
  - Promote wide availability of information and fairly distribute the burdens and benefits of new technologies

Population biobanks

- Growing wealth of major scientific discoveries that have been made through the utilization of population biobanks

- Various ethical dilemmas
  - Individual validation
  - Consent
  - Risk of overstating the prospects of genetic discoveries for population screening, diseases diagnosis and therapy

New genetic discoveries

- Epilepsy gene LGI2
  - Insight s into the mechanisms underlying neurological development in the adolescent brain
- Amyotrophic lateral sclerosis (ALS) - Lou Gehrig's disease
  - Mutation on the SIGMAR1
- Nature 2012.
  - 29 new genes that underlie the development of MS
  - Resources from twenty-three research groups from 15 countries
  - Double the number of genes implicated in the onset and progression of MS
- March 2012
  - International team of scientists
  - Analyzed the genetic profiles of over 80,000 people, making it the largest screen for heart-disease related genes ever conducted (around ten times larger, to be exact).
  - The study confirmed 10 of 12 previously reported heart-disease-related genes, and identified 13 new ones

- The 1000 Genomes Project
  - International team of scientists led by researchers at The Sanger Institute
  - Massive genetic screen (eventually involving over 50,000 people) to identify a third genetic link: MCF2L.

- Cardiff University's
  - Recently led the world's largest-ever genetic investigation of Alzheimer's, screening around 20,000 people with the disease and 40,000 unaffected individuals
  - Identified five new Alzheimer's-linked genes, doubling the total number of genes known to increase the risk of developing Alzheimer's.

Clinical use of genetic testing

- Key components
  - DNA in establishing identity
  - DNA in unveiling the past
  - DNA in predicting the future
  - Manipulating DNA
  - Ownership and control of DNA
  - Deep cultural changes

- Genetic testing
  - ✓ Prenatal diagnosis
  - ✓ Newborn testing
  - ✓ Carrier testing
  - ✓ Forensic DNA testing
  - ✓ Direct-to-consumer tests.

Icelandic databases

- deCode genetics – Amgen
  - Genotypic and medical data from more than 140,000 volunteer participants
- Hjartavernd
- Krabbameins skrá
- Lífssýnasafn LSH

deCode

New genetic discoveries – 48 publications last 5 years

- **2012**
  - Kong A et al.
    Rate of de novo mutations and the importance of father's age to disease risk. Nature. 2012 Aug 23;488(7412):471-5. doi: 10.1038/nature11396.
  - Jonsson T et al.
    DA mutation in APP protects against Alzheimers disease and age-related cognitive decline. Nature. 2012 Jul 11. doi: 10.1038/nature11283. [Epub ahead of print]
  - Gudmundsson J et al.
    Discovery of common variants associated with low TSH levels and thyroid cancer risk [Epub ahead of print]
- **2011**
  - Sulem P et al.
    Identification of low-frequency variants associated with gout and serum uric acid levels. [Epub ahead of print]
  - Rafnar T et al.
    Mutations in BRIP1 confer high risk of ovarian cancer. [Epub ahead of print]
  - Stacy S et al.
    A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. [Epub ahead of print]
  - Holm H et al.
    A rare variant in MYH6 is associated with high risk of sick sinus syndrome. [Epub ahead of print]
- **2010**
  - Gudmundsson J et al. (PDF Version).
    Correction of PSA values with sequence variants associating with PSA levels. Science Translational Medicine 2010 Dec 15. [Epub ahead of print]
  - Kong A et al.
    Fine-scale recombination rate differences between sexes, populations and individuals. Nature 2010 Okt 28. [Epub ahead of print]
  - Thorleifsson G et al.
    Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. Nat Genet. 2010 Sep 12. [Epub ahead of print]
  - Gudbjartsson DF et al.
    Association of variants at UMOD with chronic kidney disease and kidney stones-role of age and comorbid diseases. PLoS Genet. 2010 Jul 29;6(7):e1001039.
  - Stacy SN et al.
    Ancestry-shift refinement mapping of the C6orf97-ESR1 breast cancer susceptibility locus. PLoS Genet. 2010 Jul 22;6(7):e1001029.
  - Gretarsdottir S et al.
    Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nat Genet. 2010 Aug;42(8):692-7. Epub 2010 Jul 11.
  - Thorgeirsson TE et al.
    Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. Nat Genet. 2010 Apr 25. [Epub ahead of print]
  - Kiemeney LA et al.
    A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. Nat Genet. 2010 Mar 28. [Epub ahead of print]
  - Holm H et al.
    Several common variants modulate heart rate, PR interval and QRS duration. Nat Genet. 2010 Jan 10. [Epub ahead of print]
- **2009**
  - Gudmundsson J et al.
    Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet. 2009 Sep 20. [Epub ahead of print]
  - Kong A et al.
    Parental origin of sequence variants associated with complex diseases. Nature. 2009 Dec 17;462(7275):868-74.
  - Gudbjartsson DF et al.
    A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. Nat Genet. 2009 Jul 13. [Epub ahead of print]
  - Stacey SN et al.
    New common variants affecting susceptibility to basal cell carcinoma. Nature. 2009 Jul 5. [Epub ahead of print]
  - Stefansson H et al.
    Common variants conferring risk of schizophrenia. Nature. 2009 Jul 1. [Epub ahead of print]
  - Thorleifsson G et al.
    Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. Nat Genet. 2009 June 28. [Epub ahead of print]
  - Sulem P et al.
    Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. Nat Genet. 2009 May 17. [Epub ahead of print]
  - Gudbjartsson DF et al.
    Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. Nat Genet. 2009 Feb 8. [Epub ahead of print]
  - Gudmundsson J et al.
    Common variants on 9q22.33 and 14q13.3 predispose to thyroid cancer in European populations. Nat Genet. 2009 Feb 6. [Epub ahead of print]
  - Stefansson H et al.
    Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet. 2009 Feb 1. [Epub ahead of print]
  - Rafnar T et al.
    Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009 Feb;41(2):221-7. Epub 2009 Jan 18.
  - Helgason A et al.
    Sequences from first settlers reveal rapid evolution in Icelandic mtDNA pool. PLoS Genet. 2009 Jan;5(1):e1000343. Epub 2009 Jan 16.
  - Styrkarsdottir U et al.
    New sequence variants associated with bone mineral density. Nat Genet. 2009 Jan;41(1):15-7. Epub 2008 Dec 14.

Icelandic Heart Association - Hjartavernd

- Founded 1964 to battle cardiovascular illness in Iceland.
- The purpose of IHA
  - conduct research into the causes of heart disease
  - educate the public about prevention of cardiovascular diseases and provide individual risk evaluations.
- Over the last 40 years, IHA has conducted large-scale studies of over 30,000 men and women born in Iceland between 1907 and 1935.
  - Focused on the multiple causes of disability in old age including heart disease, high blood pressure, and Alzheimer's.
- 143 scientific publications since 2006!

- AGES Reykjavik Study The Reykjavik Study of Healthy Aging for the New Millennium
  - Objective: The sequencing of the human genome and identification of candidate genes.
  - Phenotype the surviving 12,000 members of the Reykjavik Study cohort .
  - Recruitment to the study was finalized in January 2006. There were 5764 participants to the AGES-Reykjavik Study, almost 300 by home visits. The response rate was 72%
- The Monica Iceland Study
- Refine
  - The Icelandic Heart Association risk factor study, Risk Evaluation For INfarct Estimates (REFINE Reykjavik Study) was initiated in December 2005.
  - Objective: Increase the predictability of risk factors for the development of coronary artery disease on an individual basis.
  - 70% recruitment rate, resulting in the very thorough examination of 1,213 individuals , including genetic and personality testing.

Oversight of genetic testing

- USA
  - Several agencies are involved in oversight of genetic testing.
  - The Centers for Medicare and Medicaid Services (CMS) regulates clinical laboratory testing to ensure accuracy and reliability in conducting assays.
  - The Federal Trade Commission (FTC) oversees advertising of tests and products.
  - The Food and Drug Administration (FDA) regulates tests sold as "diagnostic devices," that is, tests manufactured by one company and then sold as a kit to a laboratory for genetic testing.
  - FDA does not regulate "home brew" tests, that is, tests that are both manufactured and performed by the same laboratory.

- Genetic Testing Registry
  - On February 29, 2012, the National Institutes of Health (NIH) **announced** the launch of the Genetic Testing Registry (GTR), a centralized online resource for information about genetic tests. The intended audience for the GTR is health care providers and researchers.
  - GTR: http://www.ncbi.nlm.nih.gov/gtr

Ethical dilemmas in human genetics

Specific ethical issues

- Genetic aspects
  - The individual level
  - The collective level
- Connectness of families
- Connectness of inter-related groups
  - Ethnicity
  - Nations
  - Tribes
  - Races
- Ethical concerns due to harmful potential

- Genetic testing
  - Outcome of inherited trait unknown
  - No treatment or intervention available
- BRCA
  - The estimated lifetime risk for breast cancer associated with the BRCA1 and BRCA2 mutations is in the range of 26% to 85%
  - Risk of ovarian and prostate cancer is also increased
  - Thus, genetic testing predicts increased risk, rather than certainty of disease
  - Making decisions about interventions, such as prophylactic mastectomy or oophorectomy, more difficult for individuals at risk

GWAS and Consent

- **Scope of Written Consent – NIH guidelines.**
  - **Is the informed consent consistent with the anticipated research activities**
  - **Does the consent form either allow or preclude:**
    - *genetic research or analysis?*
    - *future use and broad sharing of the participant's coded phenotype and genotype data for research?*
  - **Does the consent form have any restrictions, such as:**
    - *types of subsequent research using the participant's phenotype and genotype data?*
    - *location of such research?*
    - *types of medical conditions or diseases studied?*
    - *duration of storage and use of phenotype and genotype data?*
    - *limitations on who can use the participant's phenotype and genotype data (e.g. some consents may state that only non-commercial researchers can use the data)?*

GWAS and Consent II

- **Other Issues to Consider**
  - Does the study **involve children**? If so, has the IRB considered the appropriateness of the continued maintenance and sharing of the data when the child reaches the legal age of consent?
  - Does the study involve **proxy consent**? If so, are there any special ethical issues that should be considered?
  - Does the study involve **vulnerable populations**, and if so, have any special ethical concerns related to the study population been addressed?
  - Have any **special cultural considerations** or requirements been addressed with regard to the study population (e.g., the need for tribal consent from Native American populations)?
  - Are any issues of **group harm** relevant and have they been considered?

Critical concerns regarding genetic testing

- Lack of regulation
- Patenting of genetic testing
  - How does it affect scientific research
- Analytical validation (accuracy)
- Clincal validation (use of test as a diagnostic tool)
- Clinical utilization (treatment)
- Genetic Counseling
- Genetic discrimination