



Genetics-based Research and Human Subjects Protection: 'The Times They are A-Changing'

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Objectives – Human subjects protection and genetics research

- Upon completion of this program, participants should be able to:
 - Describe how genetic research regulations have changed with technological advancements
 - Explain the potential risks and unique challenges posed by genetic research relative to other types of clinical research
 - Discuss the CCHMC Biorepository, including it's role in providing access to genetic and non-genetic research material



Summary

- Real life experiences
 - Inside the walls of CCHMC
- The landscape of regulations regarding HSP and genetic research
 - Past, present, and future
- How can CCHMC help you?
 - The Cincinnati Biobank as a partner in your genetics-based research




Kickoff with a recent case study

- Large control cohort for disease of interest
 - >1,000 patients, general population (no direct relationship to hospital or patients)
 - Examination for genetic abnormalities for comparison with patients possessing known disorders
 - Samples obtained and banked over > five years
 - Studies performed in research lab
- Identification of a genetic abnormality in one subject that could influence fertility
- What now?



What should we do with this information?

- A. immediately call the subject and tell them that a genetic abnormality has been found
- B. Don't worry about it, since the condition is not likely to be life-threatening
- C. Slow down and take a look back at the protocol and informed consent document



Review of the ICF

- 'Option to receive information about results of identified treatable genetic disorders'
 - Yes
 - No
- Considerations:
 - Not a CLIA-certified lab
 - Results will require validation
 - Is this a 'treatable genetic condition'?
 - How is the information provided to the family?



Determining whether this is a treatable genetic disorder

- PI is not a clinician, and is focused on laboratory/genetic investigations
- **Options:**
 - A. Consult literature and wikipedia
 - B. Call some clinical colleagues and obtain input
 - C. Develop procedure for determining if genetic findings represent 'treatable genetic disorder'



PI discussed options with clinical geneticist and genetic counselor

- Developed procedure to evaluate whether newly identified genetic findings represent a 'treatable genetic disorder'
 - Face-to-face conversation among the three
 - Process to discuss findings with study subject
 - Process of rapid referral to genetics clinic
 - Discuss relevance of findings
 - Validate results in CLIA lab
 - Inform IRB for approval



Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

Objectives:

- Present an overall timeline covering the major milestones in human genomic research from the late 1980's to present from the NIH and Human Genome Project Perspective.
- Parallel the presentation of the science with major statutory, regulatory, policy changes related to human genomic research during the same time period to demonstrate how far the regulatory landscape has lagged.



Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

	<u>Science</u>	<u>Regulation/Policy</u>
1988	<ul style="list-style-type: none"> 1988: First NIH meeting to discuss the concept of the Human Genome Project 1988: NIH Center for Human Genome Research established. 1990: First genome research review committee to conduct peer review of human genome grant applications. 1990: Human Genome Project officially begins. 1994: Human genetic mapping goal achieved one year ahead of schedule 	<ul style="list-style-type: none"> 1993: NIH Working Group on the Ethical, Legal, and Social Implications (ELSI) of Human Genome Research issue first report.
1995	<ul style="list-style-type: none"> 1995: NIH Taskforce on Clinical Genetic Testing established. 	<ul style="list-style-type: none"> 1995: First version of GINA introduced in House and Senate.



NIH Working Group on the Ethical, Legal, and Social Implications (ELSI) of Human Genome Research

- ELSI Report: Genetic Information and Health Insurance (May 1993)
 - Makes Recommendation – NOT Regulation/Policy
 - Genetic Information should not be used to deny coverage or services
 - Genetic services should be treated comparably to non-genetic services and should include appropriate genetic counseling.
 - Cost of health coverage to individuals should not be affected by genetic information.
 - Access to basic health services should not be conditioned on disclosure of genetic information.
 - Until universal basic health services are in place alternative means for protecting against genetic discrimination should be developed.



Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

	<u>Science</u>	<u>Regulation/Policy</u>
1996	<ul style="list-style-type: none"> 1996: Human DNA sequencing begins as part of the Human Genome Project. 1996: NIH establishes Center for Inherited Disease Research (JHU) 1996: Map pinpointing the location of over 16,000 genes in human DNA. 1996: Location of first gene associated with Parkinson's disease 1996: Location of first gene that predisposes men to prostate cancer 	<ul style="list-style-type: none"> 1996: ELSI Report on the progress and impact of the Human Genome Project. 1996: H.R. and S. bills "Genetic Privacy and Nondiscrimination Act" H.R. and S. bills "Genetic Fairness Act" are both introduced but die in committee without formal hearings. 1996: HIPAA passed – No specific mention of genetic information.



Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

	Science	Regulation/Policy
1997	<ul style="list-style-type: none"> 1997: Specific alterations in BRCA1 and BRCA2 associated with increased risk of breast, ovarian and prostate cancer identified. 1998: HGP announces that a "finished" version of the DNA sequence will be ready by 2003 (2 years early) 1999: NHGRI holds first "Consumer Day" conference to educate the general public about the Human Genome Project. 	<ul style="list-style-type: none"> 1997: Public calls for federal policies prohibiting genetic discrimination. 1997: Series of 5 x House bills and 2 x Senate bills focused on genetic nondiscrimination in insurance are introduced but none make it out of committee. 1999: 2 more House bills and 1 Senate bill die in committee. 2000: President Clinton signs an Exec Order to prevent genetic discrimination in the federal workplace.
2000		



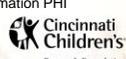

Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

	Science	Regulation/Policy
2001	<ul style="list-style-type: none"> 2001: Series of papers published in Nature presenting the first analysis of the human genome sequence. 2001: Microarray technology supports development of clinical useful genetic tests <ul style="list-style-type: none"> Differentiates hereditary from sporadic types of breast cancer. Accurately diagnose four complex, hard to distinguish childhood cancers 	<ul style="list-style-type: none"> 2001: NHGRI/ELSI hosts conference to review prior decade of genetic research and its impact on genetic health and policy. 2001: NHGRI co-sponsor conference looking at the impact of the HGP on minority communities. 2001: 3 x Senate bills and 1 x House bill all relate to genetic nondiscrimination in employment and insurance all die in committee.
2001		




Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

	Science	Regulation/Policy
2002	<ul style="list-style-type: none"> 2002: NHGRI begins to target funding towards research looking at genetic underpinnings of key diseases (e.g. cancer, diabetes, etc.) 2003: Human genome is published. 2004: DHHS and Office of Surgeon General release computer software that allows families to record family history of diseases. Research Community continues to identify new potential gene candidates for diseases. 	<ul style="list-style-type: none"> 2003: 3 x House and 2 x Senate Bills introduced still all related to genetic discrimination in insurance and employment. None make it out of committee. <ul style="list-style-type: none"> (Including a closer to final version of GINA) 2004: Version of GINA raised in House and Senate. 2007: Final version of GINA passed by both house and senate. 2013: Revisions to HIPAA making genetic information PHI

Genetic Information Nondiscrimination Act of 2008 (GINA)

- Initial version first introduced in 1995. Finally passed by House and Senate in May 2008.
- GINA Highlights
 - Federal law that generally prohibits the discrimination in health (only) insurance coverage and employment based on genetic information.
 - Does not apply to life, disability or long-term care insurance.
 - Does not apply to employers with fewer than 15 employees.
 - Genetic information includes, results of individual and family members (up to 4th degree relatives) genetic tests, family history, provision of care related to a genetic condition.
 - Genetic information includes genetic information resulting from research.
 - Protections from GINA are not retroactive.



Genomic Research and the Regulations Rolling for Research...but Rocky for Regulations

GINA Against a Patchwork of State Laws

# states	Topic	what's included in the state laws
2	Health Insurance Coverage	Requirements placed on insurers to provide coverage for genetic testing.
35	Employment Nondiscrimination	Restrictions on the use of genetic information by employers.
48	Health Insurance Nondiscrimination	Limits on the use of genetic information by insurers
37	Privacy	Protections to safeguard the privacy of genetic information and genetic test results.
25	Research	Protections pertaining broadly to research and genetic privacy and nondiscrimination measures that mention research.



The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples

Michelle M. Mello, J.D., Ph.D., and Leslie E. Wolf, J.D., M.P.H.

- Recent case that involved use of stored biospecimens for future research
- Arizona State University investigators collected blood specimens for research from 200 Havasupai Indians
- Collections occurred in 1990, and samples were stored for focused research questions



The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples

Michelle M. Mello, J.D., Ph.D., and Leslie E. Wolf, J.D., M.P.H.

- The original informed consent discussed use of samples for “the causes of behavioral/medical disorders”
- Conversations at the time of collection focused on research related to diabetes
- Samples ultimately used for a number of research projects. Tribal leaders objected to use for:
 - Genetic basis of schizophrenia
 - Inbreeding
 - Evolutionary-genetics studies

New Engl. J Med 363:3; Jul 15, 2010



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- Concerns voiced by tribal leaders
 - Genetic basis of schizophrenia (stigma)
 - Inbreeding (stigma)
 - Evolutionary-genetics studies (contrary to tribe's origin story, data indicated that ancestors migrated from Bering Sea)
- The tribe sued the university for \$50 million
 - Fraud, breach of fiduciary duty, negligence, trespass
 - Did the downstream uses of samples fall within the scope of the donor's informed consent?

New Engl. J Med 363:3; Jul 15, 2010



The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples

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- ASU ultimately settled for \$700,000 to 41 tribal members
- ASU formally apologized, agreed to work with the tribe on issues of health, education, economic development
 - Returned samples
- Did not set legal precedent, but could affect future litigation

New Engl. J Med 363:3; Jul 15, 2010



Questions raised

- Biospecimen donors do not retain property interests in samples collected/used in accordance with properly obtained informed consent
- What constitutes adequate informed consent?
- Little federal guidance on how to obtain consent for future, unspecific uses



Questions raised

- Research on previously collected samples is permitted without obtaining new consent when
 - samples cannot be traced back to individuals
 - when research presents only minimal risk
 - doesn't adversely affect their rights or welfare
 - could not be practically carried out if new consent required, and
 - pertinent information can be provided back to donors.



Questions raised

- Large amount of laterality in IRB interpretation
- Guidance from OHRP states informed consent for storing identifiable specimens should include a clear description of "the specific types of research conducted"
- What constitutes adequate informed consent?



Questions raised

- Does general permission (blanket or global consent) for future research constitute meaningful consent?
 - Can risks of unknown future research be quantified?
 - Is this negligible risk?
 - Risks include confidentiality, and detailed genetic data that could be traced to individuals
 - Mitigated by coded specimens?



Questions raised

- Does anonymizing specimens eliminate ethical dilemma?
 - Federal regulations stipulate that samples that are not individually identifiable do not trigger legal obligations to obtain informed consent
- Do people have the right to control how their specimens are used regardless of risk?



Possible informed consent options

- Specific consent
 - New consent for every new use
- Tiered consent
 - 'menu'
- General permission
 - Permit future use deemed ethical and scientifically valid (IRB approval)
- Presumed consent
 - Use for future research unless expressly deny permission



CCHMC IRB guidance

- All four of these general consent approaches are used at CCHMC (protocol-specific)
- Recommendations
 - Try to be thoughtful about potential future research on samples in the consent document
 - IRB can help 'broker' questions that come up about future research use
 - Regulations today are muddy, and what applies today may not apply in five years



Summary and questions?

- Genomic regulations have generally lagged behind genomic research
 - No specific laws govern genetic research at this time
- Decisions about sharing new genetic information identified during research are often based on clinical significance and impact on treatment/management
 - IRB can help with this decision
- Use of stored specimens in future research is best addressed during consent....
 - ...but it's very hard to predict the future
 - ...and the IRB can also help frame these questions/answers
- Cincinnati Biorepository is ramping up to provide specimens in a systematic fashion



The Cincinnati Biobank

Michael Barnes, PhD (michael.barnes@cchmc.org)
 Director Cincinnati Biobank Core Facility
 Assistant Professor, Rheumatology
 OCTR symposium



Disclosures

- No conflicts of interest to disclose.



Basic Definition of 'Biobank'

- Comprises personnel and infrastructure
- Supports sample
 - Collection
 - Processing
 - Storage
 - Distribution



The Cincinnati Biobank

- The Cincinnati Biobank Shared Facility will establish the prerequisite **knowledgebase and infrastructure** to expedite cutting edge translational research at Cincinnati Children's Hospital Medical Center and the University of Cincinnati by:
 - Providing centralized sample collection, processing, storage and distribution.
 - Developing innovative methods for banking using biospecimen research to develop evidence-based methodologies
 - Providing timely access to pre-existing sample collections
 - Promoting collaboration
- Our ultimate goal is to increase **competitiveness for grant funding** for researchers at the medical center and **improve child health**.



Research Building 5th floor (Room 5553)



UC's Reading Road Campus F-building



Pathology, R2



Solid Tissues



Biofluids



What Do We Offer?

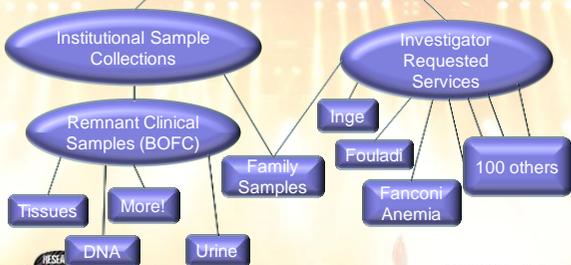
- Solid tissue collection
- Automated DNA and RNA extraction
 - 0.05 – 0.4 ml of blood (Promega Maxwell)
 - 0.5 - 5 ml of blood (AutoGenFlex STAR)
 - Blood, tissue, saliva, others
- DNA QC
 - OD260/280 (Trinean DropSense 96)
 - Molecular fingerprint (Fluidigm EP1; 96 SNPs on 96 samples)



Unique Identifier on Each Sample



Cincinnati BioBank Shared Facility

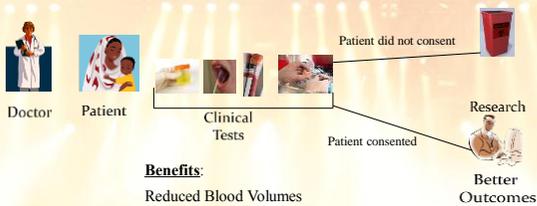


What is Better Outcomes for Children?

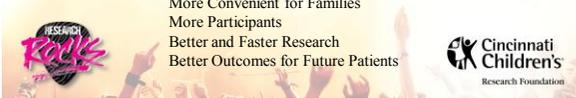
- Institutional project to **obtain consent** from patients to allow researchers to study **LEFTOVER** clinical samples



Improved Research Through Cooperation



- Benefits:**
- Reduced Blood Volumes
 - Fewer Needle Sticks
 - More Convenient for Families
 - More Participants
 - Better and Faster Research
 - Better Outcomes for Future Patients



Implementation of BOFC



Training

- **Biorepository WITH notification**
 - Patient and family agree to donate leftover specimens
 - They **DO** want to be notified of incidental research findings
- **Biorepository WITHOUT notification**
 - Patient and family agree to donate leftover specimens
 - They **DO NOT** want to be notified of incidental research findings

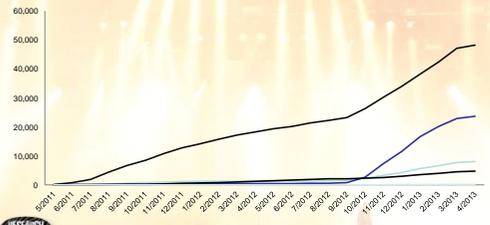


- **Biorepository UNDECIDED**
 - It is not an appropriate time to ask or the patient/family want to ask more questions before making a decision.
- **Biorepository REFUSED**
 - Family does not wish to donate their leftover clinical specimens
- **Assent**
 - We ask that the family discuss the donation with their child at the time of registration to make sure they have a voice



BoFC Consenting

Total Documents Collected by Month Cumulative



How Can We Help Researchers

- Biobanking services
- Compliance expertise
- Access to pre-existing sample collections
 - DNA
 - Approximately 10,000 patients
 - Tissues
 - Approximately 13,000 patients
 - Urines
 - Approximately 1,000 patients
- To request services or samples, contact me
[\(michael.barnes@cchmc.org\)](mailto:michael.barnes@cchmc.org)