Genetic Research in Human Populations

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Introduction

Human genetic and genomic research is one of the most dynamic areas of current biomedical and social-behavioral research.

- **Genomics** tends to be used as a blanket term, describing the many relationships between the DNA sequence in a cell and the resulting biological function.
- **Genetics** tends to refer to the relationship between inherited differences in DNA sequence between individuals, and the effect (if any) that those gene sequence differences have on biological function.

The ethics of genetic and genomic research have received a great deal of attention due to several factors. Genetic testing can reveal a strong predisposition to future disease, making the information psychologically powerful and raising concerns about stigma or discrimination. Related individuals share many of the same gene sequences in their DNA, meaning that genetic information about one individual provides information about other individuals who may or may not have consented to genetic testing. Genetic testing can reveal characteristics of recent and distant ancestry that may conflict with peoples' family history, with their social history, or with their religious beliefs. Historically, genetic concepts and information have sometimes been misused to affect social and political ends. Whether scientifically founded or not, our inherited gene sequences are often considered central to our health and behavior. This suggests that a control of genes confers great power that can be used or misused. This concept is termed "genetic determinism."

Most contemporary genetic research seeks to understand the relationship between genes and diseases, genes and behaviors, and genes and health-related traits like responses to drugs or environmental exposures. As such, most genetic research tends to pose informational risks, that is, risks that flow from potential breaches in privacy or confidentiality of genetic information. Genetic research involving gene transfers or gene therapy remains in early stages of development. The risks associated with gene transfer studies are more than informational and the uncertain nature of these risks has slowed the development of this field. Issues in gene transfer studies are not addressed in this module.

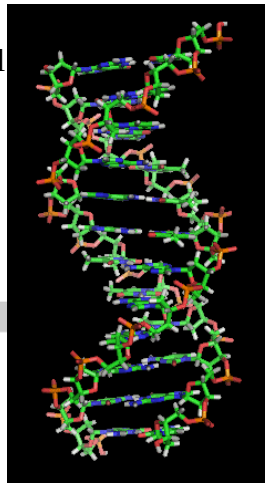
Learning Objectives

By the end this module, you should be able to:

- Discuss the risks associated with genetic and genomic research.
- Describe the difference between privacy and confidentiality with genetic and genomic research.
- List the information that should be disclosed to subjects during the consent process with genetic and genomic research.
- Identify the risks and regulatory issues relevant to research using biospecimens.

Common Examples of Genetic Research

Genotyping and Genome-Wide Association Studies



The human genome consists of approximately three billion nucleotide bases, and the completion of the Human Genome Project in 2003 reached the initial goal of deciphering representative sequences. Genotyping is determining the genome DNA sequence of an individual at one or more selected locations in their genome. While we all have the same genes, several "versions" of the DNA sequence exist in the population for many genes. Many variations will have no functional consequence, meaning that different versions of the gene will function in a normal way; however, sometimes these variations influence the function of those genes and are associated with differences in biological function. These types of variations may influence disease risk or an individual's response to drugs or environmental factors. A mutation is a variation that causes either a loss or significant reduction in gene function or a significant gain in function.

Another term commonly used in the field of genetics is phenotype. Someone's phenotype is the sum collection of the person's observable traits and characteristics. In biomedical research, the phenotype often refers to whether or not they have a particular disease or condition under study. In research addressing diabetes, for example, the presence or absence of diabetes would be the relevant phenotype in the individuals under study, although the phenotype could be more refined to include other variables (such as, the severity of their diabetes and/or responsiveness to dietary elements or treatments). Much genetic research is focused on identifying genotype-phenotype correlations, that is, how specific genetic variations are correlated with certain observable traits in individuals.

The analysis of DNA sequences and of variations between individuals with and without a trait or disease enables researchers to consider whether specific variations are causally associated with certain traits or diseases. Understanding whether a particular genetic variation in the human population is associated with a characteristic of interest (for example, blood pressure, drug response, drug toxicity, disease risk, longevity, or hair color) can advance science in ways that may or may not have immediate benefit to people. Such findings may provide a clue to scientists

about which biological pathways are important in the development of a disease. They may offer predictive tests, to provide advance warning to patients regarding risk of important health consequences in the future (some, but not all, of those risks may be "actionable" or subject to risk modification if the person takes certain actions).

In genome-wide association studies (GWAS), genetic variation across the entire genome can be identified and associated with various subject characteristics (Manolio 2010, 166-76). Increasingly, genetics research is moving beyond GWAS and is employing whole genome sequencing (WGS) or whole exome sequencing (WES). WGS involves determining almost the entire DNA sequence of an individual. The "exome" is that part of the genome that codes for proteins. WES involves sequencing only those coding parts of the genome and represents only about 1 percent of the entire DNA sequence. The cost of WGS and WES has dropped dramatically in recent years, making these approaches potentially affordable and useful in a broad range of clinical genetic and genomic research (Presidential Commission 2012).

Large scale genomic studies funded by the National Institutes of Health (NIH 2014) must now de-identify and upload all data to central databases; these studies are complex, difficult, and expensive. Therefore, data sharing allows researchers to make maximum use of the information generated.

Genotyping studies pose interesting and difficult challenges for the protection of confidentiality and privacy and for the consent process. These challenges are particularly important for Institutional Review Boards (IRBs) to address.

Pharmacogenomics and Pharmacogenetics

Pharmacogenomics is the study of how the genetic makeup of individuals may affect their response to a particular drug or class of drugs. Pharmacogenetics is a science that examines the inherited variations in genes that influence drug response and explores the ways to use these variations to predict how a patient will respond to a drug.

Pharmacogenomics is the key to "personalized medicine;" the use of knowledge about an individual patient's genetic make-up to guide the treatment selection, drug(s), and doses physicians choose for that patient. While personalized medicine is still in an early stage of development, the anticipated benefit of pharmacogenomics includes the ability to tailor drug choices to the biology of the individual patient, more effective and faster therapeutic effects, and a reduction in adverse effects of drugs. This is the basis of personalized medicine: providing "the right patient with the right drug at the right dose at the right time" (Wei et al. 2012, R58-65). Increasingly, pharmaceutical companies conducting clinical research will include a pharmacogenomics component to determine whether genetic factors influence safety or efficacy outcomes.

This type of research requires special attention to privacy and confidentiality, the role and scope of the valid consent process, and the appropriate approach to and process for the secondary use of data and stored biological samples.

Biorepositories

Biorepositories have come to play an increasingly important role in genetic research. Nearly all research organizations maintain collections of biological material. The growth of pharmacogenetics and the goals of personalized medicine have accelerated the utility of these collections. Analysis of these materials, usually blood or biopsy specimens, poses important challenges for organizations, researchers, and IRBs, including:

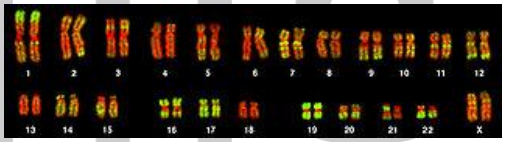
- How specific must consent be to permit research on stored samples?
- Do researchers have a duty to contact people who are the sources of samples to inform them of health risks identified through the analysis of their sample?

Despite rapid growth and utility, governance of biorepositories remains one of the most challenging problems for researchers and organizations. Biospecimens are largely useless without associated data about the source individuals and the nature of their health. However, the more detailed the dataset associated with specimens, the higher the risk to the privacy of the source individuals. Therefore, research with biospecimens requires a balancing between scientific utility and the adequate protection of research subjects. To date, the measures taken to protect the privacy and welfare of biospecimen donors has been highly effective.

Ethical Issues

Privacy and Confidentiality of Individuals and Communities

The terms privacy and confidentiality are not synonymous.



- Confidentiality relates to information shared within a professional relationship. Confidential information should be accessible only to professionals with a need to know the information. A breach of confidentiality occurs if the information shared with a clinician becomes available to others who are not authorized to access it. Therefore, for example, if a clinician conducts a genetic test on a patient with informed consent, but communicates the results to the patient's family members without the patient's permission, a breach of confidentiality has occurred.
- Privacy refers to personal control over information, to one's body, or to decision-making processes. A breach of privacy occurs when, without the permission of the individual, someone accesses personal information, sees or touches the individual's body, or intrudes upon a personal decision without the legal or ethical right to do so. For example, if a clinician conducts a genetic test on a patient without their knowledge or informed consent, a breach of privacy has occurred.

Many people consider genetic privacy and confidentiality more important than the privacy and confidentiality for other types of health information. This could be because of concerns over increased risk of genetic discrimination and stigmatization. For these reasons, genetic

information is sometimes compared to information obtained from other research involving sensitive information (such as, research addressing sexually transmitted diseases or psychiatric illnesses). This level of caution is controversial, and there are strong arguments against the concept called "genetic exceptionalism."

The results of some genetic tests can be highly predictive of future disease. Research involving this type of testing warrants a high level of concern over privacy and confidentiality. The results of other genetic tests can be weakly associated with, or not relevant to, the future health of the subject. A genetic study that seeks to test a relatively weak and seemingly innocuous association between genetic variation in the APOE gene and response to cholesterol-lowering drugs, may potentially identify a group of subjects that has a high risk of developing late-onset Alzheimer's disease, a characteristic also predicted by the APOE gene. While the protection of privacy and confidentiality are always important, understanding the purpose and context of a specific genetic study is critical to determining the degree of subject risk involved. It is important to understand that genetic research is not inherently risky and many genetic studies confer no more than minimal risk to subjects. Accordingly, IRBs should not reflexively consider all genetic research to be greater than minimal risk.

Researchers preparing to conduct genetic research must tell potential subjects which entities and persons will have access to the data. This might include researchers at other organizations, corporate sponsors, and government agencies. Many organizations do not segregate clinical and research information in electronic medical records. If information obtained during research will be recorded in a subject's medical record, this must be disclosed. Subjects should also be told of the risks of others having access to his or her genetic information. De-identifying biospecimens and/or personal health information in the conduct of research reduces the risk to the source individual. There is currently an active debate over whether DNA sequence information can be "anonymized" due to the fact that each of us has a unique sequence, just like a fingerprint. However, in order to re-identify DNA sequence information, those attempting the re-identification must have a reference sequence that includes individual identifiers. That is, the DNA sequence is not intrinsically identifiable. While the risk of re-identification currently is low, it may increase with time due to technological developments. Therefore, research subjects should be told that there is a small risk of future re-identification of de-identified information or biospecimens. As with all research involving informational risks, complete confidentiality cannot be guaranteed.

Unlike most other kinds of health information, genetic information applies to or is about more than one person. Analyzing genomes allows researchers to learn presumptively about a person's parents, siblings, children, and others. This is because an individual shares 50 percent of his/her genetic information with each parent, sibling, and child. If, for example, a research subject carries a BRCA1 mutation, we know that one of his or her biological parents is also a carrier of the BRCA1 mutation and that each of his or her children and siblings is at a 50 percent risk of being a mutation carrier. Therefore, knowledge about the genetic makeup of "blood relatives" is usually probabilistic in nature

unless, of course, a blood relative is showing clinical signs of the disease in question. This means that the privacy and confidentiality of these individuals are at risk even if they are not the source of the specimen or of the information or the research topic.

More broadly, some genetic research can produce discoveries about entire subpopulations, some of which correspond to racial or ethnic groups. Although not addressed in federal regulations, researchers and organizations must take seriously the concept of group privacy. That is, researchers and IRBs should take steps to address risks of stigma to groups with a shared genetic background even when risks to individuals are minimized through, say, anonymization of data or specimens. Data or specimens that have been de-identified often retain demographic information (such as, race and ethnicity) on population groups. Measures to address group concerns may include involving community members from potentially vulnerable groups in the planning and management of genetic research and in developing plans for the disclosure of research results.

Some genetic research plans will involve longitudinal follow-up of subjects in order to see who develops the disease in question and how the disease is manifest. Research that includes follow-up studies and attempts to identify clinical correlations requires that a subjects' unique information be linked to their genetic information. These links, in conjunction with particular aspects of research plans, might be used to seek out or re-contact subjects in the future. Researchers must disclose to subjects who has research access to clinical information and the anticipated use of this information at the start of the study.

When clinical follow-up is not necessary, many researchers will unlink or decouple personal identifiers from genetic information or biological specimens. Successful unlinking reduces or eliminates some threats to privacy and confidentiality. However, it is increasingly possible to take even "unlinked" information or samples and use "surrogate identifier ensembles" (for example a combination of demographic information, birth date, postal code, and diagnostic code) to identify an individual. As noted, some scholars question whether genetic samples can ever be completely anonymized. However, there is little incentive for researchers to re-identify data or specimens other than to demonstrate that they can do so. Accordingly, to date, there are no instances of re-identification of data or specimens for illicit motives. Further, researchers obtaining access to some de-identified datasets, like the National Institutes of Health's (NIH) dbGAP resource, are required to guarantee that they will not attempt to re-identify data. Any attempt to re-identify data or specimens would be a serious breach of research ethics unless explicitly authorized by an IRB for a critical purpose (for example, notifying a subject of a clinically relevant genetic finding).

It is important for organizations to consider policies surrounding the use of genetic information. These processes should address data collection and management, encryption, destruction of specimens and/or genetic information, and loss of data. Some organizations have adopted "trusted broker" (or "honest broker") systems to oversee the flow of data from subject to researcher. (See section on Stored Biological Samples.)

Informed or Valid Consent

Ethical research on humans generally requires meeting three conditions. Subjects must be:

- Adequately informed.
- Free from coercion or undue influence.
- Able, generally, to understand and appreciate the risks, potential benefits, and alternatives of participating. This is sometimes called "competence" or "capacity," where the former usually refers to a legal standard.

Note that the term valid consent is increasingly preferred to informed consent because it captures the fact that other criteria, in addition to adequate information, ensure the legitimacy of the process. There are many challenges in genetics research in fulfilling these conditions. For instance:

- In the case of traditional medical and behavioral research, it is difficult to determine how much information and what level of complexity or detail are appropriate for potential subjects. Genetics research magnifies this problem.
- The informed consent process should describe the limitations of genetic testing. Testing alone may not be able to verify:

  (i) Whether the individual will have symptoms of the disease or condition;
  (ii) The severity of symptoms; or
  (iii) The rate of disease progression.

- It is often unclear how to describe risks of harm to potential subjects. In genetics research, the risks are generally not physical but psychological, social, economic, and these are sometimes more difficult to evaluate and present.
- In pedigree (studies involving family ancestry) and other studies, information collected might affect entire families, including members who do not wish to know or participate. If relevant, researchers and IRBs need to ensure that these concerns are discussed in the consent process. IRBs may require special precautions to protect against or to manage pressure or coercion and to communicate risk. Consideration of including genetic counseling in the consent process is appropriate for some genetic studies.
- Community engagement may be required for studies involving community groups with a shared genetic background. This process should balance individual autonomy and community consensus.

The consent process must take into account whether and when researchers will re-contact subjects. Options include:

- The samples will be unlinked from subjects' identifying information and researchers will not inform subjects of any results. If subjects are interested in obtaining genetic information about themselves, researchers can advise them to be tested independent of the research. Note that if a sample is successfully unlinked

or anonymized, it might be impossible for the source of the sample to withdraw from research (the unlinked sample cannot be found to remove it). This constitutes one of the few exceptions to the rule that research subjects can withdraw from studies. However, once data or biospecimens are no longer individually identifiable, the source is no longer a human subject under the federal regulations.

- If re-contact is possible but not planned, researchers must inform subjects for the same reason.
- If researchers plan to re-contact subjects (perhaps to measure subsequent clinical correlations) disclosure is crucial for those who might not want to know their genetic status.

The return of results to subjects is under active debate by the research ethics community. Research results can mean several types of information.

- There are general results of the research, that is, whether the research project was successful or unsuccessful in achieving its aims.
- There are individual research results relevant to the information targeted by the study. For example, if the study is targeting genetic correlations with, say, diabetes, there may be individual results relevant to the risk of diabetes.
- If the research involves genetic analyses, such as whole genome or exome sequencing, the research may lead to incidental or secondary findings (for example, genetic variants associated with other conditions). The example provided earlier, a study that tested the APOE gene for the purpose of assessing a potential predictive test for patient response to cholesterol-lowering drugs, but in doing so also generated a prediction of risk of Alzheimer's disease, illustrates the concept of an incidental finding. The incidental finding (a finding that is not the primary purpose of the genetic test) in this case, risk of Alzheimer's disease, is far from incidental in its affect to the subject.

There is little consensus about how the return of research results should be managed. The federal regulations do not address this issue so it is a matter of organizational policy and procedure. There is an emerging consensus that, at a minimum, researchers should address the return of results in their study plans and IRBs should review and approve the plan. If researchers believe the return of results is not appropriate because, for example, the results will have no clinical utility, the study plan should justify this approach. Similarly, if the genetic analysis is likely to yield incidental findings, the study should describe plans for management of such findings. Management plans should include a description of the responsible individual that makes the determination of what results to return and who will inform the research subjects. These functions may require involving clinical experts who are not otherwise involved in the research.

In general, the researcher discusses the following information with prospective subjects during the consent process (Presidential Commission 2013):

- The purpose of the research, in lay language.

- How the specimens and the data will be stored and who will have access to them or the information they contain.
- If subjects will be re-contacted later with information about the study findings or their individual results.
- If the samples or genetic information have a code that can be linked to the identity of individual subjects. When a link to identifiers is retained, the sample/information is not anonymous.
- If the researchers will use specimens to develop commercial products or assays, and whether the subject will be able to share any financial gain from these products.
- Whether the researchers plan to conduct future testing of samples.
- If samples may be used for other research studies, including those that may have a different focus.
- If research results, including general results, personal results, and incidental findings, will be returned to subjects.

Legal and Regulatory Issues

In the U.S., the passage of the Genetic Information Nondiscrimination Act (GINA) in 2008, provided, at least in principle, sweeping protections for patients and subjects. GINA prohibits discrimination in healthcare insurance and employment based on genetic information. However, the law admits a number of exceptions, and there is extensive debate about whether the law enforcement mechanisms are adequate to its anti-discrimination intent (Prince and Roche 2014, 891-902).

Many states also have their own genetic discrimination legislation. These laws vary in their scope and intent. Some state laws explicitly require consent for genetic testing of any sort. Some do not explicitly address research. Researchers and their organizations should be familiar with state laws, governing procedures, and disclosures for research and other purposes. Research should follow the more restrictive regulation, be it at the state, provincial, or national level.

The NIH regulations were revised in 2014. These federal regulations pertain to all NIH-funded research that generates large-scale human or non-human genomic data and the use of the data for subsequent research. The data in NIH repositories are accessible on two levels. Genomic data without associated phenotypic characteristics are available in an unrestricted fashion to the general public. Controlled access to data with phenotypic information is available to researchers with IRB and NIH approval.

Beginning on 25 January 2015, studies proposing to use genomic data from cell lines or clinical specimens that were created or collected after this date, the NIH (2014) expects that informed consent for future research use and broad data sharing will be obtained even for cell lines or specimens that are de-identified. If there are compelling scientific reasons to use data or specimens collected after this date that do not have such consent, exceptions can be made.

NIH Policy: Institutional Certification When Submitting Data (NIH 2014)

The Institutional Certification should state whether the data will be submitted to an unrestricted- or controlled-access database. For submissions to controlled access and, as appropriate for unrestricted access, the Institutional Certification should assure that:

- The data submission is consistent, as appropriate, with applicable national, tribal, and state laws and regulations as well as relevant institutional policies;
- Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated;
- The identities of research participants will not be disclosed to NIH-designated data repositories; and
- An IRB, Privacy Board, and/or equivalent body, as applicable, has reviewed the investigator's proposal for data submission and assures that:
    - The protocol for the collection of genomic and phenotypic data is consistent with 45 CFR 46;
    - Data submission and subsequent data sharing for research purposes are consistent with the informed consent of the study participants from whom the data were obtained;
    - Consideration was given to risks to individual participants and their families associated with the data submitted to NIH-designated data repositories and subsequent sharing;
    - To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing; and
    - The investigator's plan for de-identifying datasets is consistent with the standards outlined in this Policy (see section IV.C.1.).

Stored Biological Samples

Research on stored biological samples allows researchers to conduct studies long after subjects have completed all research procedures. The primary ethical challenges posed by the research use of biospecimens arise from the separation in time and place between the acquisition of the sample and its use in research. In many cases, the future research uses of biospecimens are unknown at the time of acquisition. It is helpful to think of research on stored samples as two kinds:

- **Prospective**, in which researchers obtain samples to create new collections

- **Retrospective**, in which researchers use blood or tissue for example, from pre-existing collections or biorepositories

Federal regulations stipulate that research using records or specimens that are not readily identifiable to the researcher is not human subjects research (Protection of Human Subjects 2009). If the researcher using the resources cannot determine the identities of the data/tissue sources, then the research does not involve human subjects and the research is not under IRB oversight. Generally, IRBs or someone not associated with the research study should make the determination whether a particular study is human subjects research or whether it meets criteria for exemption. This remains true even if the data/tissues are coded and linked to a database with individual identities as long as the researcher conducting the research does not hold the key to the code.

Alternatively, if the data/tissues are identifiable, then the research will be considered human subjects research, but an IRB can approve a waiver of consent (or re-consent) if the project meets the criteria under 45 CFR 46.116(d) (Protection of Human Subjects 2009). It should be noted that on 24 July 2017 that the FDA indicated that it would not object if an IRB approves an alteration or waiver to informed consent provided the criteria stipulated in the guidance were met (FDA 2017). All four criteria in general requirements for informed consent must be met for a waiver, but the two most relevant criteria are that the research must be no more than minimal risk, and, consent must be impracticable to obtain. Most research on data/tissues is considered minimal risk unless sensitive information is being generated, and often consent is not considered practicable when the sources of the tissue/data are large in number and/or remote in time or place.

Even if federal regulations may permit some research on existing samples without consent, an IRB may determine that consent is necessary if the cohort is small, the health condition or trait is stigmatizing, and there are concerns about maintaining confidentiality. If it is possible to re-contact individuals who were the sources of specimens, the issue highlighted below needs to be considered.

Suppose you have received IRB approval to study banked tissue without obtaining the consent of subjects. Your protocol meets the federal criteria for waiver of consent. Now imagine that you discover a medically important DNA variation in the sample belonging to subject XYZ. You do not know who subject XYZ is, or even if the subject is alive. However, you can find out subject XYZ's identity because the sample is linked to patient records with a code number.

- Should you use the link to find and warn subject XYZ? What if subject XYZ does not want to know of this condition and you tell the subject anyway?
- What if the subject would want to know but you do not tell the subject?

- What about subject XYZ's children? Is there a duty to warn or inform them?

Laws and regulations do not provide clear answers to these difficult ethical issues.

IRBs face difficult challenges when researchers seek permission to bank or archive biological specimens for future, unspecified research. If researchers want to bank tissue but are unable to say what it will be used for, it is controversial whether the consent is valid, as subjects arguably should know the purpose of the research in order to decide whether to consent to it. Until recently, the official interpretation of the Health Insurance Portability and Accountability Act (HIPAA) regulations was that consent for future, unspecified research was not appropriate. More recently, the interpretation of HIPAA authorization has become more flexible, permitting consent for future, unspecified research as long as subjects have a reasonable idea what the future uses will be. The specific implications of this change have not been determined. At the present time, it may be reasonable for a consent form to include consent for, say, future cancer research on stored specimens, but IRBs and researchers should be cautious about using consent language that is completely unspecified regarding future research use.

The secondary use of tissues or the information they contain is emerging as one of the greatest challenges of genetic and genomic research. Researchers should consider all potentially relevant analyses of genetic information, so that subjects are as fully informed as possible.

The growth of bioinformatics or computational genomics makes it clear that, in the near future, the concern will not be so much with stored biological samples but with digitalized samples-electronic data that can be stored, transmitted, and analyzed with new ease and power. The use of this technology may also provide a process for contacting research subjects. Therefore, IRBs might wish to consider the role of staged consent and/or re-consent as part of the consent process.

Genetic Research

Dr. Jackson plans to conduct genotyping research on stored blood samples from a small New England community. The purpose of this research is to determine the prevalence of genetic variants associated with heart disease within this population. Public health records suggest an increased

prevalence of heart disease in this community. The blood samples were originally collected several decades ago as part of research on the possible link between the cancer cases and water contaminated from a closed cannery. Many of the original research subjects have passed away and the construction of a new highway has forever changed the community's demographics and landscape. The original consent form stated that the research subject agreed to "have a portion of their blood stored for future research."

- Given the statement in the original consent form, what is Dr. Jackson's obligation to re-contact the subjects for their valid consent?

  Dr. Jackson may not have any obligation to re-contact subjects if the IRB reviews his proposed research and grants a waiver of the requirement to obtain consent. However, the waiver criteria in the federal regulations do not address whether an original consent form should be "consistent with" or "not inconsistent with" secondary uses of biospecimens. Many IRBs will not require re-consent in this context (assuming it meets waiver criteria) as long as the proposed new research project is "not inconsistent with" the language of the original consent form. For example, if the original consent form stated that the biospecimens would only be used for cancer research, many IRBs would be reluctant to permit other types of research to be conducted without reconsent. In this case, it could be concluded that the proposed research regarding heart disease is not inconsistent with the original consent statement regarding unspecified future research.

  Alternatively, the IRB may require Dr. Jackson to re-contact subjects if possible. In making this decision, the IRB would consider how the blood samples are identified (directly or through a coded link) and whether the information from the research might have health implications to those still living and their family members. Additionally, the IRB would consider whether the timing and confidentiality implications of re-contacting subjects are more harmful, particularly if individuals were not aware of the family's research participation or do not wish to have this type of information. These considerations are relevant to whether the proposed research is considered minimal risk, a requirement under the waiver criteria.

Summary

The genomic sciences have changed biomedical research. Concepts as fundamental as privacy and informed (valid) consent are now seen through lenses that have reshaped the ethical and legal duties of researchers and organizations to research subjects. Indeed, it has been suggested that a regulatory environment crafted in the wake of the "Tuskegee Study of Untreated Syphilis in the Negro Male" is probably inadequate to the subtleties of genotyping and genome-wide association studies.

For those who believe the job of IRBs is to parse federal law and give thumbs up or down to individual projects, the genomic science revolution is likely a source of great consternation - the law barely contemplates that revolution. For those who regard IRBs as a grand exercise in applied ethics, then whole genome sequencing offers exciting obligations to explore the protection of subjects in highly probabilistic sciences posing novel and complex new risks.

Put differently, the genetic and genomic sciences of the 21st century present opportunities both to fledge potentially exciting new treatments - and to underscore the unwavering importance of ethics in the service of shared values.

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