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TITLE: Ethical Issue in Biobanking

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Slide 1:
Hello, my name is **Ann Gronowski**. I am a Professor of Pathology & Immunology and Obstetrics & Gynecology at Washington University School of Medicine. Welcome to this Pearl of Laboratory Medicine on "**Ethical Issues in Biobanking**." This Pearl was developed with Gwen Clrake and in collaboration with the IFCC Task Force on Ethics.

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In order to discuss ethics in biobanking, let's start first with some basics on biobanking. Biobanks have also been referred to as: biolibraries, biorepository, tissue repositories, biological resource center, genetic databases, or DNA banks.
A biobank can be defined as: An entity that receives, stores, processes and/or distributes specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. There are many definitions for biobanks and this one was chosen because it is consistent with a 2016 Pearl on biobanking by Dr. Christina Ellervik. Certainly in medicine there are other banks for instance image banks. These also would need to apply similar sets of principals as outlined here.

There are many types of biobanks.
There are some that are established for general medical & academic research for instance by a University and the specimens may be available to many researchers. Some may be for specific clinical studies and not generally available to other researchers. Clinical laboratories often have a collection of specimens sent to the laboratory for physician ordered pathology or laboratory testing. These specimens may be retained for long periods. Some banks may be in the biotechnology domain and contain collections of well characterized cell lines. Some are in the Judiciary domain and contain huge collections of biological material, and DNA fingerprints. These have very restricted use. There are also commercial biobanks which sell human biological material for use in research.
The existence of biobanks has proven to be very important. For example, the large genetic heterogeneity of acute leukemias was discovered by retrospective analyses of ~~retrospective~~ biobank samples. Biobanks of samples from large families obtained over several decades were

essential for the identification of breast-cancer genes. And, the relationship between infection with *Helicobacter pylori* and risk of gastric carcinoma, the causal relation between human papillomavirus and cervical cancer, and the link between Epstein-Barr virus and multiple sclerosis were demonstrated through the use of biobanks.

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In order to discuss ethics in biobanking, we also need some basics on biomedical ethics.
In 1978, in the United States, the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research" created the "Belmont Report" which outlines ethical principles and guidelines for the protection of human subjects. The Belmont Report is one of the leading works concerning ethics and healthcare research. It identifies three core principles (shown on this slide):

Respect for persons: In other words, protecting the autonomy of all people & treating them with courtesy & respect & allowing for informed consent. Researchers must be truthful and ~~conduct no deception &~~ tolerate no deception.

Beneficence: Doing good. Maximizing benefits for the research project & minimizing risks to the research subjects. Beneficence goes hand-in-hand with Non-maleficence which means "do no harm"

and

Justice: Ensuring that reasonable, non-exploitative, & well-considered procedures are administered fairly~~— the fair distribution of costs & benefits to *potential* research participants —~~ & equally. In other words, the fair distribution of costs & benefits to *potential* research participants.

Application of these principles for research subject includes informed consent, assessment of risks and benefits and selection of subjects. These fundamental concepts are also outlined in the Common Rule, a set of Federally-enforced regulations under the Department of Health and Human Services. The Common Rule is written into the US Code of Federal Regulations, Title 45, Volume 46.

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Why do Biobanks cause ethical challenges? Biobanks are unique compared to other research projects that may require human subjects. For one thing, specimens may be stored for a very long time before they are used; A single specimen~~s~~ may be used for multiple studies; Therefore, at the time of consent, it may be unclear how many studies a specimen may be used for. Together these things make it difficult for a subject to give truly informed consent. Because you can't tell a subject exactly what their specimen may be used for. In addition, a multitude of private health information may be collected making protecting the privacy of the subject very important. And finally, depending on the biobank, specimens may be sold, maybe even for a profit. This makes many people feel uncomfortable and needs to be made clear to subjects.

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In this pearl, we will cover some of the most frequently discussed ethical issue in biobanking, including: Consent, Privacy, Return of Results, Public trust, Governance, Data sharing & exchange, and Ownership & commercialization.

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Let's start with consent. Fundamental to the Belmont report and the Common Rule, any subjects involved in research must be fully informed about the research and its risks and benefits and freely give consent. There are exceptions of course for persons who are unable to give consent such as children, mentally impaired and deceased. In these cases family members or guardians may be able to provide consent.
Typically, subjects give consent to participate in one specific research project and knowledge of the study is very specific with a clear presentation of the risks and benefits and an option to withdraw at any time.

As stated previously, a biobank may store specimens for a very long time before they are used and a single specimen~~s~~ may be used for multiple studies. At the time of consent, the nature of all future research is unknown and it would be impossible to consent for each and every future project. Therefore biobanks have two options: 1) Re-contact subjects as each new research study presents itself and get a new consent for each project. This is logistically difficult, time consuming and expensive. Or,~~2)~~ t~~T~~he other option is to allow patients to give a broad consent that allows for future use of the specimens. However, the more general the consent is, the less "informed" it is. In effect, subjects have decreased autonomy.

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This figure illustrates a scale between broad blanket consent to very specific consent for a specific research study. The less a subject knows about the type of research that is being performed on their specimens the less autonomy they have. Biobank policy requires tradeoffs among personal goods (such as consent and autonomy) to be balanced against creation of public good. No matter what form of consent is given (broad or specific) ~~that~~ the specimens ~~are~~ must only used for research for which the patient has consented. For instance, Often times a general consent will define the "area of research" that will be done; for instance "diabetes" or "cancer" etc. Those in charge of the biobank must be good stewards of the specimens and make certain that the specimens are used for the purpose for which they were consented.

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There have been some very high profile legal cases in which specimens were used for research other than what subjects consented to. For instance, members of the Havasupai Native American Indian tribe sued Arizona State University. They alleged that they had consented to use of their blood samples for diabetes research. However, they learned that their DNA was also being used for studies on schizophrenia, metabolic disorders, alcoholism, inbreeding, and

population migration. *The case was settled out of court and t*he Arizona State University Board of Regents agreed to pay $700,000 to the tribe members, provide other forms of assistance to the impoverished tribe, and return their blood samples.

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In the case *Baleno v. Texas Department of State Health Services*, a lawsuit was filed claiming *that* more than 5 million residual dried blood-spot samples, collected for newborn infant screening, had been retained for use in research. The plaintiffs claimed that consent was not obtained for indefinite storage and undisclosed research. They also claimed that the blood spots contained deeply private medical and genetic information and use of the samples violated plaintiffs' rights to privacy and liberty under the United States' 14th Amendment. The case was settled out of court, and the state agreed to destroy nearly 5 million residual specimens. So, it is very important for biobanks to make certain that specimens are only used for research for which the subjects have consented.

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Subjects should always be allowed to withdraw their samples from a biobank, but of course withdrawal does not mean the samples can be withdrawn from researchers who have already received the samples.
Finally, it is important that the consent document disclose whether genetic information will be obtained from the specimens. This is important because Genetic information can affect not only the patient but also other people including relatives, spouses, future children, etc.

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That brings us to the topic of privacy. Among the fundamentals of bioethics are: beneficence, non-maleficence, and justice. In other words, doing no harm and protecting the subjects from any potential discrimination. In the context of biobanks, subjects' data should not be disclosed to any third parties (including insurance agencies, employers, or family members). As in any research project, subject privacy is of the utmost importance. This slide shows some of the many terms used for ways in which we protect specimens.
Identified- samples are linked to subject in a way that is immediately identifiable. This is obviously at high risk if data fell into the wrong hands.
Coded (traceable)- which means that direct link to the subject usually through random set of numbers
Double code-to link sample & data to individual requires 2 codes
Encrypted-further level of protection, code is transformed & requires a third party to link
Anonymized-link to subject has been irreversibly cut
Anonymous- there was never a link between subject and sample/data
Obviously, the more anonymized specimens are, the safer they are from being able to have a third party obtain personal information about a subject.

It is important to note that in certain regions, including the United States, biological samples that are anonymous may not even be considered human materials and hence do not require researchers to obtain subject consent. It is important that researchers always seek approval

from a human research protection committee before using any samples for research. Even in cases where samples are de-identified. The human research protection committee will determine if consent is required and if committee approval can be waived.

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However, many people argue that the problem with genetic information is that it is always possible to identify donor & relatives. In 2008, geneticists showed that they could ~~easily~~ identify individuals within pooled, anonymized data sets if they had a small amount of identified genetic information for reference. See the online version of this transcript for a link to te reference (N. Homer *et al*. PLoS Genet 4, e1000167; 2008). And it may become possible to identify a person in a public database from other information collected during a study, such as data on ethnic background, location and medical factors unique to the study participants, or to predict a person's appearance from his or her DNA. They argue that confidentiality cannot be fully guaranteed despite all efforts and hence full confidentiality should never be promised.

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Another controversial topic in the area of ethics and biobanking is return of Incidental findings or individual research results. Let's define each of these terms. These are results that have potential health or reproductive importance & are discovered during research. If the finding is one of the variables under study and in the stated aims of the research then it is termed "Individual research result (IRR)"; If the finding is unrelated to the research it is called an "Incidental finding (IF)"

Participants in research have expressed interest in receiving research results when it may be important to their health or reproduction. The issue of returning results to participants is not unique to biobanks. However there are a number of issues that make biobanks particularly complex: 1) the number of results are large and 2) they are generated over a long period of time through multiple studies; 3) the clinical applications of genomic information are in early stages of development and not yet well-incorporated into routine practice; 4) research laboratories are not likely to meet the standards required for clinical laboratories (for example CLIA certification); 5) research subjects may view genetic findings as having personal significance; 6) and genetic findings may have implications for the subject's family as well as the subject. Many informed consent documents have explicitly stated that no results will be returned. However, if results with important clinical utility are discovered, researchers should consult with their human research protection board to discuss whether that provision should be overridden. Some have argued not only that highly actionable research results should be returned, but that there is a legal obligation to do so. Needless to say, this is currently a hot topic that continues to garner attention especially as more genomic studies are conducted.

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Biobank governance is about the regulation of the relationship between: subjects, society and the biobank and it goes hand in hand with public trust.

Who owns and operates the biobank affects the public's opinion. The public places a good deal of trust in the university-based scientific community. However, studies have shown that public trust is much lower if the bank is operated by the government or industry.

There is evidence that people fear that their donated biological specimens will be used in ways they find morally problematic and they fear losing control over how their samples & data are used and with whom it is shared when the government or industry are involved. A lack of public trust is the biggest threat to biobanks, so this relationship is very important. Many people argue that the relationship between banks and contributors need to be a mutual partnership—and they encourage sharing of data with subjects for this reason.

How the biobank operates and the rules they have to follow varies by country, the type of bank and how the specimens were obtained. Governance really encompasses much of what has been discussed here: consent, privacy, ownership, access and benefit sharing. With the growth of biobanks and growth of genetic research on banked specimens, biobank governance has become under increased scrutiny.

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Biobanks provide an important contribution to biomedical research and~~. However,~~ the effective~~ness~~ use of biobanks depends on their accessibility. However, the sharing of data are complicated by a number of ethical, legal and social issues. First of course is the need to abide by all **national laws and regulations**. The United States & Europe both have strict rules about the protection of personal identifiable data. Hence to protect privacy, samples are coded or **anonymized**. This has already been discussed, but several things to note are that it is important to understand the different terms and degrees of protection. With biological samples it is unclear to what extent samples can really be anonymized and if they are anonymized, whether some of their value for research is lost. Also, full anonymization both deprives the donor the possibility to use their right to withdraw consent (which is essential for autonomy) and it makes the return of results or incidental findings impossible (which is essential for beneficence). We have also discussed **informed consent** but it is important to note that subjects must be informed that their samples will be shared with other researchers and the risks that may be associated with this sharing. Another question is to **whom biobanks will share their specimens and data**. Few biobanks will offer free and unconditioned access to their samples. Most require specific conditions to be satisfied in order to give permission to access their samples and most time there is some type of fee to cover the costs of retrieving and storing the sample. Biobanks should ensure that the specimens will be used for the type of research covered in the consent document. Finally, it should be noted that there are on line tools that can be used to help biobanks navigate all these issues.

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The ownership of samples, data and databases is a complex matter and source of tension.

There is a conflict between the need for open exchange and intellectual property rights. In a number of cases, courts have considered the question of whether an individual retains an

ownership interest in his/her excised tissue that would authorize that person to share in the profits of any commercialization of research results.

This raises questions, such as: Who can make money off specimens? Who has to pay for specimens? Should subjects be paid if researcher makes money? There is a ~~G~~general principle that subjects have no property in their samples (termed *res nullis*, 'no one's thing'). In a few cases this principle has been challenged.

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In *Greenberg v. Miami Children's*, the father of 2 children with Canavan disease worked with a researcher to set up a registry of affected families to collect tissue to begin studying the molecular basis of the disease. With the families' support, the Canavan gene was found and a genetic Test was developed. Miami Children's Hospital subsequently, obtained a patent on the gene and began licensing the test.

Four families and 3 nonprofit organizations filed suit, alleging that the children's tissue was used without consent to license a patent and develop a commercial test. They claimed that they had an owner-ship interest in the excised tissue.

However, the court found that the tissue was given voluntarily for research without any expectation of return, and therefore the plaintiffs had no ownership interest in the tissues, or the research performed using the tissue. This ruling and many others suggest that patients and other human research participants do not retain ownership interests in their excised tissue. This should be clearly stated in the consent form.

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Unfortunately, there is a not an ethics guideline or standard operating procedure for biobanks to follow. Biobank directors must be good stewards for the biospecimens that subjects have entrusted them with.

To summarize, in order to up hold the fundamental principles of ethics (autonomy, beneficence & justice), biobanks must: Abide by all national and local laws and they should also abide by association guidelines & relevant standards; Obtain broad informed consent from all subjects; Handle personal information safely & confidentially; Allow subjects to withdraw at any time; and, require recipients of samples/data to undergo review by an ethics or human research protection committee.

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References

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Disclosures

Slide 21: Thank You from www.TraineeCouncil.org
Thank you for joining me on this Pearl of Laboratory Medicine on "**Ethical Issues in Biobanking".**