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PEARLS OF LABORATORY MEDICINE

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TITLE: Biobanking

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Slide 1: Biobanking

Hello, my name is Christina Ellervik. I work in the Department of Laboratory Medicine at Boston Children's Hospital. Welcome to this Pearl of Laboratory Medicine on "Biobanking."

Slide 2: Definitions

The International Society for Biological and Environmental Repositories (ISBER) defines *biobank* or *biorepository* 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."

The National Cancer Institute (NCI) Dictionary of Cancer defines *biospecimen* as "the samples of material, such as urine, blood, tissue, cells, DNA, RNA, and protein from humans, animals, or plants."

Slide 3: Publication Trajectory

History: "Biobank" is the most widely-used term to describe what was in the past variously termed biorepository, biological resource center, or biospecimen resource.

As seen in this slide, the term "biobank" or "biorepository" appeared in PubMed for the first time in a peer-reviewed publication in 1994, and the number of publications have steadily increased since then. However, many human collections and cohorts were established long before "biobank" or "biorepository" became established terms. The word "specimen" appears in PubMed with the first publication dating from 1828. The term "biospecimen" appears in PubMed with the first publication in 1965.

Slide 4: Types of Biospecimens

Examples of biospecimens are listed here and divided into invasive, less invasive, and non-invasive categories. The risk associated with each type can also be categorized as high risk, moderate risk, and minimal risk.

Slide 5: Advantages and Disadvantages of Biospecimen Types

Examples of invasive specimens are blood (inclusive of whole blood, plasma, or serum), solid tissue, and cerebrospinal fluid.

The major advantage of invasive specimens is the majority of analyses possible. Disadvantages include requirements of trained staff, painful collection, many pre-analytical variables, and specimen processing, which makes it more time-consuming.

Dried blood spots and cord blood are examples of less invasive specimens. The advantages of less invasive specimens include less painful collection, no processing requirement, room temperature storage, small blood volume requirement, minimal risk, cost-effective, less storage space, and beneficial for pediatric or neonatal collections. The disadvantages are risk of a poor collection due to bad technique, a low or high hematocrit that may give rise to variability in results, or not enough blood volume collected.

Urine, saliva, hair, and stool are examples of non-invasive specimens. The advantages of non-invasive specimens include easier collections and patient-collections. With self-collection also comes risk of contamination. Non-invasive specimens must usually be kept on ice until long-term storage.

Slide 6: Pre-Analytical Variability

The term pre-analytical is defined as anything that comes before the analysis phase of a biospecimen sample. Thus, in biobanking, pre-analytical handling is basically all processes that precede the analysis of a biospecimen after it is collected from a donor or removed from storage. Pre-analytical variables are factors affecting the integrity of the biospecimens and eventually, the results of analyses. Assessing and controlling the pre-analytical handling of biospecimens is fundamental for the integrity and optimal future use of biospecimens. Thus, use of standard operating procedures are critical so that all specimens are treated the same.

Many factors influence the analytical results in clinical chemistry testing, i.e. pre-analytical biological or environmental variability, pre-analytical technical variability, analytical variability, and post-analytical variability. A majority of errors in a clinical chemistry lab are due to pre-analytical errors and may result in inaccurate test results or systematic biases. The most common pre-analytical errors occur in the ordering or collection phase. Pre-analytical variables can introduce *in vitro* modifications, either systematically or randomly, which can adversely affect laboratory results and/or interpretation of results.

Slide 7: Biological and Environmental Variability

This slide shows factors (due to biological and environmental variability) that may affect the level of downstream analyses. These are factors that should be standardized, documented, and taken into consideration when interpreting results or comparing or pooling the results of studies.

Here are a few examples that may affect biological variability:

- Smoking may affect levels of hematological indices
- 24-hour variation may be seen in many chemistry analytes, with peak and low values at different times of the day

- Marked metabolic and hormonal changes occur after food ingestion

Some biological factors can be controlled in studies by requiring certain conditions for participant inclusion, e.g. fasting/non-fasting, abstaining from smoking, and abstaining from strenuous exercise hours before collection. The timing of collection is especially important for the measurement of medication concentrations and hormones.

Examples of environmental factors affecting analytes are seasonal changes in Vitamin D levels, as well as direct sunlight affecting levels of bilirubin, porphyrins, and vitamin A.

In addition, collection of repeat samples from the same individual taken a few days apart may attenuate the effects of pre-analytical and analytical variation.

Slide 8: Impact of Long-Term Storage on Biospecimens

Biospecimens contain degradative molecules (e.g., proteases, lipases, nucleases). Long-term storage may result in aggregation, precipitation, or biochemical degradation of proteins (altering both structure and activity); ice damage; dehydration and increase in salt concentration resulting in osmotic damage); formation of water crystals; recrystallization after thawing; and toxicity from substances that are added to the specimens in the freezing state or in the drying state in order to protect the active ingredients.

There is considerable variation among biomarkers in stability and recovery; therefore, different storage conditions may apply depending on the downstream analyses. Freeze-thaw cycles are a major concern and may happen unintentionally during transport of frozen samples, from freezer failure, or intentionally because the biospecimens are thawed for analyses and then refrozen. It is advisable to perform pilot studies and to carefully search the literature before measuring biomarkers on stored biospecimens.

Slide 9: Long-Term Biospecimen Storage Facilities

Different types of long-term storage facilities are listed here and includes:

- Liquid nitrogen freezers
- Mechanical freezers
- Refrigerators
- Walk-in environmental storage systems
- Fully automated entry and retrieval systems
- Ambient temperature storage

The choice of facility and equipment depends on many factors such as sample size, accrual rate, complexity of collection and processing procedures, type and number of specimens to be stored, volume and number of aliquots, the anticipated length of storage, intended use of the specimens, the resources available for purchasing equipment, and storage density.

It is also worth mentioning that minus twenty freezers pull a vacuum and can cause dehydration of samples.

Slide 10: Potential Biobank Disasters

During the last few years, some unfortunate emergencies have provided insight into how to prepare for, respond to, and recover from emergencies and disasters. Disasters are not isolated events, and should be prepared for. Some natural disasters will tend to occur repeatedly in disaster-prone geographical areas. Here is a list of disasters which can occur with biobanks. Natural disasters include: Storms, hurricanes, heat/drought, cold/snow/frost, flooding as occurred in the Danish Cancer Biobank, earthquakes, and epidemics. Man-made disasters include theft, sabotage, accidental damage, chemical spill, and contamination. Technical disasters include: fire, freezer breakdown, water damage, air condition failure, power outage, explosion, vehicle accident during transport, and server breakdown of data storage.

Slide 11: Potential Consequences to Biospecimens Following a Disaster

The consequences of disaster to biospecimens are listed here and include:

- Concentration differences due to water or evaporation
- Oxidation
- Degradation
- Evaporation
- Desiccation
- Moisture
- Sunlight (strand breaks in DNA)
- Encapsulation in ice after re-freezing
- Microbiological contamination: yeast, mold, fungus, bacteria, and virus causing biological hazards
- Destroyed barcodes

Slide 12: Security Systems and Emergency Planning

Security systems are required to prepare for avoiding and/or responding to an emergency situation. Security systems may never be 100% safe no matter how many situations are prepared for. It is important to:

- Have redundant alert and monitoring systems remote and in near proximity
- Have duplicate and split collections
- Have redundant freezers in near and remote proximity
- Maintain service contracts and check equipment at fixed intervals
- Have uninterruptible power supply and emergency generators
- Have access control with
    - Locked doors
    - Controlled keys/codes
    - Surveillance with camera, door entry sensors, motion detectors, glass break sensors
- Prepare for fire with
    - Fire preventive plan
    - Detection systems
    - Fire extinguishing
    - Sprinkler Systems
    - Non-Water-Based Fire Retardants

- SOPs for emergency response

Slide 13: Biobank Administration and Oversight

Very few programs exist for accreditation or certification. The College of American Pathologists has developed a Biorepository Accreditation Program (BAP), which is the only US-based specific biobank accreditation program. The goal is to improve and standardize the biobanking process to ensure the highest possible quality of biospecimens. The Canadian Tumor Repository Network (CTRNet) certification program is applicable to the governance and quality aspects of all types of biobanks, and is based on self-evaluation and exposure to educational tools. Biobanks may also adopt ISO standards, but these do not address all key activities involved in biobanking such as governance. However, a new ISO standard specifically for biotechnology (including biobanking) is under development, covering aspects such as handling, processing, and data annotation.

According to health regulations and accreditation requirements, laboratory staff need to be educated in basic laboratory processes to assure safety and quality of biobanking-related processes. Furthermore, ISBER endorses certain biobank training courses.

For publication standards: the pre-analytical data should be documented simultaneously with the biobanking process by the investigators, and reported in the literature.

Biobank sustainability covers financial, operational (resources, technical and management aspects, environmental), and ethical, legal, and social issues sustainability. It implies providing the best methods and quality to remain productive with appropriate systems and processes to assure a long-lasting lifetime for the biobank.

For the other bullet points, listen to the next slides.

Slide 14: Laboratory Information Management System (LIMS) Features and Benefits Specific for Biobanks

The Laboratory Information Management System related to biobanking is a software or web-based system that integrates information about various aspects of biobanking informatics, such as pre-analytical, biological, and environmental aspects, analytical and post-analytical details, as well data management logs. The benefit of the LIMS is the automated high-throughput data management allowing efficient and accurate sample organization, traceability, and management, thereby improving productivity. Furthermore, it eliminates manual error-prone processes by simplifying and automating data administration, thereby improving data reliability. The LIMS makes it easier for quality management of the biobanking processes with the detailed logs and the ability to produce reports and statistics. Labeling and coding is essential for further tracking and retrieval of the samples.

Slide 15: Examples of Clinical Data Annotation

The need for data annotation to accompany the biospecimens depends on the research design, the coding of the biospecimens, data availability, consent from donors, institutional review board and ethical approvals, and the biobank’s economic situation. Examples of some types of data

annotation are listed here and include: disease endpoints, questionnaire data, laboratory measurements, and phenotypic characterization.

Slide 16: Biobankonomics

Establishing, operating, and maintaining a biobank is costly. With technological advancements in biospecimen science, downstream assays, and biorepository infrastructure needs, new investments are needed to keep the biobank processes, equipment, and infrastructure up-to-date. Furthermore, with an increasing number of researchers, complex datasets, analytical results, and national and international data-sharing, investments in IT security to protect privacy is a matter of concern.

When planning a biobank, it is important to determine the sources for financing. The approach to financing will depend on the aim of the biobank, the size, the number and type of projects etc. Funding biobanks is a challenge and may be a fragmented process as their scope is not always defined or too broadly defined. Funding for biobanks may include governmental, hospital, private, and public sources. Quality in the biobanking process is also important as this will reduce the number of repeat collections and measurements, increasing power, decreasing the need for over-collection of participants and samples, thereby reducing costs. A majority of academic biobanks belong to more than one organization, and thus financing is usually a patchwork from different sources. In a survey of US biobanks, the largest funding sources for biobanks are the federal government, the parent organization of the biobank, fees for services, and individuals or foundations.

Slide 17: ELSI (Ethical, Legal, and Social Implications)

The yearly distribution of published and cited articles related to ethics in biobanks has been steadily increasing during the last 20 years, covering topics such as consent, privacy, return of results to participants, public trust, commercialization, governance and the role of ethics boards, data sharing and exchange, and ownership. Ethical, legal, and social issues are continuously evolving and contribute to the persistent lack of international coordination and harmonization of biobanking practices. Several cases have been taken to court due to disputes on ELSI issues.

Slide 18: Examples of Content in Access Agreements between Biobanks and Researchers

A material transfer agreement is an agreement that governs the transfer of tangible research materials and data between two organizations, when the recipient intends to use it for his or her own research purposes. It defines the rights and obligations of the provider and the recipient with respect to the use of the materials. This slide lists some of the major content in a transfer agreement: biospecimens, data, costs, roles and responsibilities of the biobank and researchers, code of conduct, statistical review and pre-publication review by steering committee or advisory board, return of results created by the projects to the biobank for future research use, project description, and approvals.

Access to biospecimens and data in biobanks depends on the type, purpose, the sustainability plan, and the agreements among the stakeholders of the biobank. Some biobanks have

predefined projects and specimens are not available for most requests, whereas other biobanks maintain collections for future unspecified projects and are open to requests.

Slide 19: Reasons for Culling of Collections

The ISBER's definition of culling is "*Culling* is the process of reviewing and eliminating selected specimens or an entire collection either by destruction or by transfer to a new custodian." Different reasons for culling are listed in this slide. Closure of biobanks is associated with ethical issues such as informed consent, storage, and privacy. Biobanks should have long-term sustainability plans and policies for the collection's disposition, clearly described and transparent for all stakeholders and institutional review boards. Transfer of collections may require new institutional review board approval and material transfer agreements, as well as change of ownership, custodianship, and governance.

Slide 20: Summary Statistics of Biobanks

In 2012, representatives from 456 US biobanks participated in a national survey of biobanks which addressed questions regarding specimen collection, organizational structure, market contexts, and sustainability. This survey demonstrated that:

- More than 50% of biobanks were established after the year 2000, and 7% before 1980
- The majority of biobanks facilitate research on a particular disease or type of disease
- ~80% of biobanks store serum or plasma, ~70% store solid tissue biospecimens, and 30% store urine or stool
- ~50% of biobanks have more than 10,000 samples in storage
- ~50% of biobanks have more than 4 types of biospecimens in storage
- 75% of biobanks get biospecimens directly from individuals donating them
- ~60% of biobanks get biospecimens from residual specimens acquired from clinical care in hospitals, clinical laboratories, or pathology departments
- ~80% of biobanks are part of academic institution, ~30% are part of hospital or health care organization

Slide 21: Summary

In this Pearl on "Biobanking," the following issues were addressed:

- Collection, processing, storage, and retrieval of biospecimens
- Security measures and disaster planning
- Biobank administration
- Laboratory information management
- Annotation of data
- Cost and sustainability
- Ethical, legal, and social issues
- Governance and ownership
- Access criteria

Slide 22: References

Slide 23: Disclosures

Slide 24: Thank You from www.TraineeCouncil.org
Thank you for joining me, Christina Ellervik, on this Pearl of Laboratory Medicine on "Biobanking."