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CriticalValues

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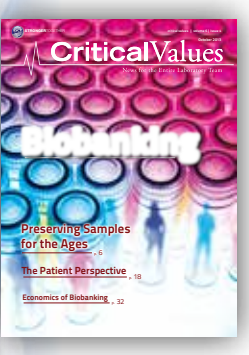

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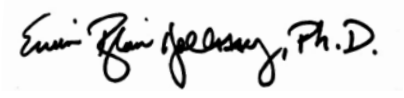
Cultivating Innovation in Biorepositories



E. Blair Holladay, PhD, SCT(ASCP)CM

Young scientists such as Jack Andraka show what is possible by keeping an open mind to find unusual solutions. In Jack's case, it paved the way to developing an inexpensive screening test for the early detection of pancreatic cancer. His tenacity and resourcefulness will vastly improve patient outcomes for those with the deadly disease.

Likewise, many of the best minds in pathology and laboratory medicine are grappling with the best practices and methods for the development of an infinite variety of research biorepositories. Pathologists and laboratory professionals have to be open to possibilities, be willing to tap many resources, and be persistent despite obstacles to construct exceptional biorepositories.

Why are biorepositories so important to patient outcomes? Because well-constructed and maintained biorepositories are central to broadening the world of biomarker discovery and research.

Why are biorepositories so important to patient outcomes? Because well-constructed and maintained biorepositories are central to broadening the world of biomarker discovery and research. Pathologists and laboratory professionals need access to well-organized collections of human specimens to conduct basic and translational research for treating human diseases. Preserving and studying these tissues is a treasure trove for vast improvements in patient care.

Profound Discoveries

Steven H. Kroft, MD, FASCP, discusses how much has changed in saving tissues since he was a resident and how pathologists can set up an effective biorespository in their institutions, avoiding major hurdles. Jack A. Hager, MT(ASCP) SBB, considers how cervical cancer cells taken in the 1950s from Henrietta Lacks were used by George Gey to establish the first human cell line and have made a profound impact on medical research and advanced patient care.

Breast cancer survivor Peggy Devine, MT(ASCP), formed the Cancer Information & Support Network to help other women better cope with their cancer diagnosis and treatment. In this issue, Ms. Devine writes that "personalized medicine where individuals receive the right drug at the right time is a real possibility in the near future." Scientists are investigating biomarkers for early detection, prevention, and after-treatment monitoring.

In the article "The Other Side of the Story: Ethical, Legal, and Social Issues in Biobanking," one new model of biorepositories being considered seeks to make data more visible by boosting people's community engagement in the research process. For example, ClinSeq® is a large-scale pilot study that uses whole genome sequencing as a clinical research tool.

As in all health care, the economy is affecting biorepositories. The traditional method of freezing large numbers of tissue samples is costly. Alternative approaches are being explored, such as dry storage, where sample cards store infant blood spots and then are used to track genetic disease in babies. The cards can be stored at room temperature, so that humidity is the only factor to control, according to Jim Vaught, PhD, at the National Cancer Institute.

In the age of genomics, ASCP encourages you to consider innovative solutions to different types of biorepositories and to use these resources to develop breakthrough ideas to improve patient care. As always, thank you for your support of ASCP. Please send me your comments and suggestions at Blair.Holladay@ascp.org. My best regards to you.

Dr. Holladay is Executive Vice President of ASCP.

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Message from the President

Dr. Kroft

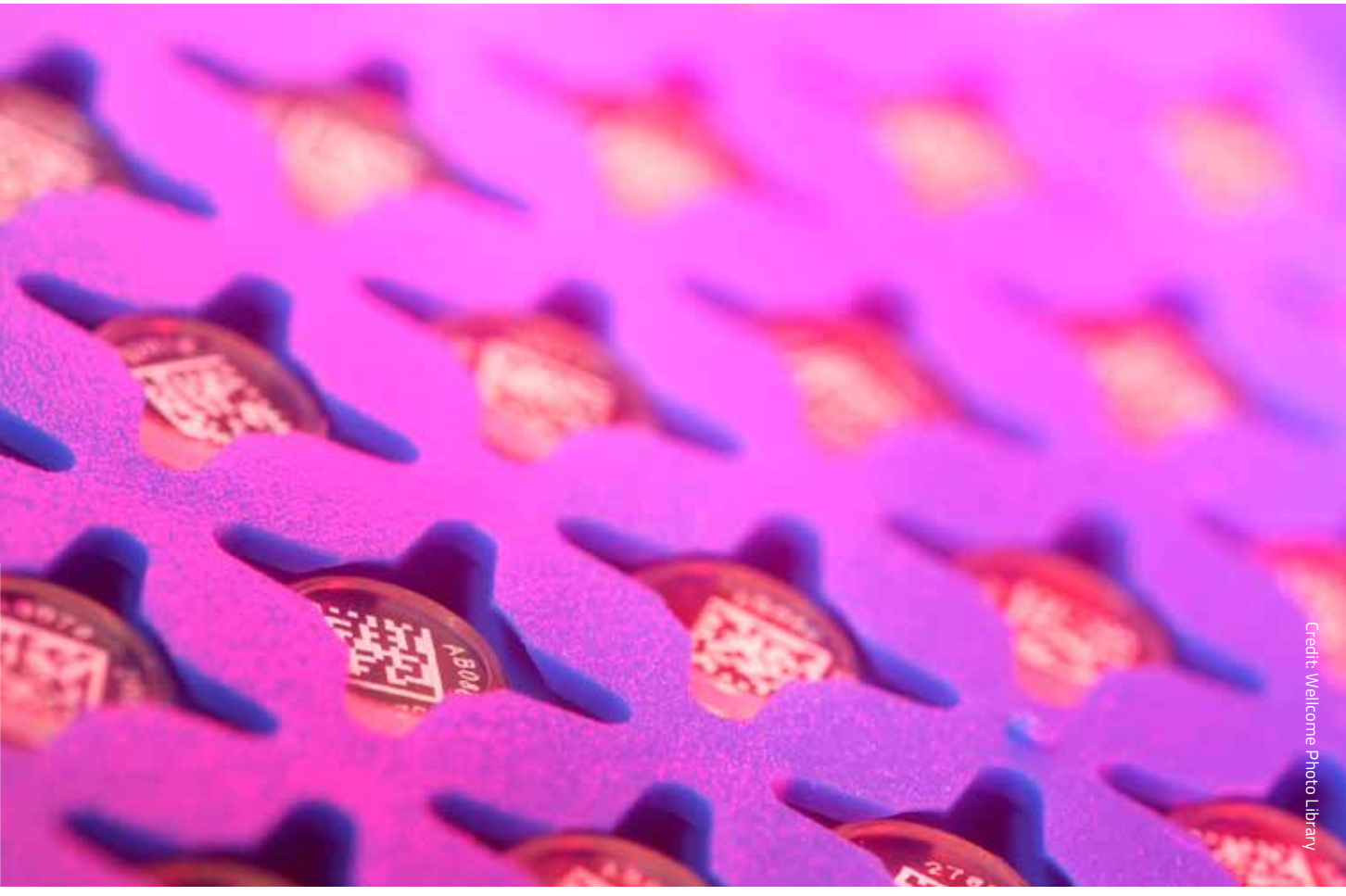
By Steven H. Kroft, MD, FASCP

Preserving Tissue Samples for the Ages

When I was a pathology resident, my concept of a biorepository was hacking off a piece of tumor tissue, wrapping it in aluminum foil, and throwing it into the -70°C freezer. Quality control involved making sure that the piece of tumor wasn't too necrotic, and ensuring that my scribbles on the card in the specimen bag were legible. Needless to say, as a review of the articles in this issue of *Critical Values* will readily demonstrate, it's a little more complicated than that.

Biorepositories may be designed for therapeutics, research, or both. A cord blood bank, as described in the Q&A with Joanne Kurtzberg, MD, later in this issue, is a good example of a therapeutic biorepository, although a traditional blood bank also qualifies. Research biorepositories may be large or small, general or specific, public or private, single- or multi-institution.

Despite their infinite variety, what is clear is that well-designed and maintained biorepositories are the key to the ever-expanding universe of biomarker discovery and investigation. Without the ability to access organized



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and annotated collections of human tissues, large areas of basic and translational research into human disease would grind to a halt. It is thus incredibly important that our country's biorepositories, of all shapes and sizes, be nurtured; they are an invaluable national resource.

A Daunting Endeavor

Having said that, however, it must be noted that the development of a research biorepository is not for the faint of heart; it is a formidable and daunting endeavor. Consider what is required to create a general cancer biorepository in a single institution, as we recently did in the department of pathology at my medical center. Before the first specimen is safely tucked away in the freezer, a huge amount of planning and implementation must occur. Extensive groundwork must be laid, and many questions must be answered, the following among them:

How do we obtain buy-in across clinical departments?

While one might expect that the opportunity to help create an institutional resource designed to aid all human tissues researchers in their work would be an easy sell, this is not necessarily the case. Groups of specialists may jealously guard what they see as "their" tissues, considering tumor tissue from their patients to be for their exclusive use. It may also be difficult to convince clinicians who do not engage in research to devote their time and energy to the development of a resource that will not benefit them personally. Overcoming these cultural barriers requires the enlistment of champions, careful development of arguments explaining the general benefits of such a resource, and development of protocols that help reassure the specialists that they will not be deprived of the use of "their" tissues if they contribute to a general bank.

What is going to be banked?

For a general cancer tissue bank, considering tumor tissue from their patients to be for their exclusive use. However, a central challenge in tissue banking is trying to anticipate what questions future researchers might be interested in asking, and planning accordingly. Thus, perhaps it might be useful to collect adjacent normal tissue for comparison to the cancerous tissue. Maybe tissue should be sampled from various areas of a tumor to assess for intra-tumoral heterogeneity or sampled from both primary and metastatic foci. Perhaps an investigator would like to be able to assess cancer-

Message from the President

related biomarkers in concurrent samples of blood or urine. Or a future researcher will be interested in testing for toxins in hair.

In what form will tissues be stored?

How a sample is processed and what forms the final banked specimens take are critical issues in the creation of a maximally usable biobank. What components of tissues will researchers need preserved for analysis? DNA? RNA? Enzymes and other proteins? Carbohydrates? Viable cells? All of the above?

Different analytes are differentially sensitive to various processing and pre-processing variables, and thus rigorous control and validation of these elements is critical, as emphasized by Katheryn Shea, in her article in this issue. If the integrity of analytes in future "withdrawals" from the bank can't be guaranteed, the repository has little value. As the old saying goes: Garbage in, garbage out.

How will the consenting process be managed?

Nothing gets in the door of a biorepository without proper consent being obtained. Creating a general consenting process for tumor banking that is effective, efficient, and manageable can be extraordinarily difficult. Building the tissue banking consent into a general consent at admission might seem like an obvious solution, but this approach may not be acceptable to the local institutional review board, as we have discovered.

Relying on individual practitioners to consent their own patients is a time-tested recipe for failure. Thus, it might be necessary to create dedicated consenting personnel to be deployed around the medical center, doggedly tracking down patients to ask them to participate in the biobanking process.

What about informatics?

A biorepository is only as good as its informatics systems allow it to be. This is an enormous and complex topic, but databases need to be robust, flexible, secure, and interoperable. Biospecimens must be anonymized, uniquely identifiable, and trackable, and must be annotated with sufficient information to allow retrieval based on a variety of clinical and pathologic variables.

How are samples distributed to researchers?

This is a sensitive area, given the cultural issues involved in building a robust biorepository. Decisions regarding allocation must be made by an interdisciplinary group of stakeholders, based on clearly established policies and procedures. Clearly, these precious human materials cannot be distributed to whoever wants them. So a set of rules to allow for priority ranking of proposals must be developed, and these must be entirely transparent. A procedure for resolving disputes over distribution of tissues must also be devised.

Moving into the Future

The considerations discussed briefly above merely scratch the surface of the logistical challenges involved in biobank development and maintenance. Because of the complexity of this area, both the National Cancer Institute and the International Society for Biological and Environmental Repositories (ISBER) have created detailed best practices guidelines to address all aspects of biorepository management.[1,2]

Finally, if maintaining a biorepository isn't for the faint of heart, it also is not for amateurs. To do it right, medical centers must deploy expertise in the transport, handling, processing, and storage of biospecimens; in the management of large amounts of confidential patient information; in the standardization of processes and procedures; in the rigorous application of quality control and quality management; and in the ability to work effectively in multidisciplinary teams.

If this all sounds familiar, it should, because it is what laboratory professionals do every day, and they do it better than anyone else. And to make sure we are making best use of these precious resources, it is incumbent on the biomedical sciences community to ensure that the highest standards are adhered to in the construction of teams to manage them.

To this end, the ASCP Board of Certification is partnering with ISBER to explore the development of a Biorepository Technician Certification Program. Our collective ability to develop the best possible modalities for treating human disease depends on biorepositories, so why shouldn't we apply the same gold standards of quality we apply to clinical laboratory diagnosis every day?

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Dr. Kroft is Professor of Pathology, Vice Chair for Clinical Pathology, and Director of Hematopathology at the Medical College of Wisconsin in Milwaukee.

Around ASCP Journals

The American Society for Clinical Pathology offers information and education that can aid your practice as pathologists or laboratory professionals. Whether you read the printed journals or get your information online, the *American Journal of Clinical Pathology* (*AJCP*) and *Lab Medicine* provide the latest research, reports, and studies. Highlights from recent issues include:

AJCP An article in the August issue by Dr. Kenneth Blick describes how providing critical laboratory results in a timely manner for patients under emergency department care reduces the length of time they spend in the emergency department. A September article by Dr. Somak Roy et al studies the communication of frozen section diagnosis between pathologists and surgeons and how potentially harmful miscommunication can be avoided. The October issue offers an article by Drs. Songlin Zhang and Yun Gong on the cytology of lymphoproliferative disorders and soft tissue tumors. These articles and others can be accessed at www.ajcp.com as part of your ASCP membership.

Lab Medicine The Summer 2013 issue of *Lab Medicine* features an article evaluating automated versus manual immature granulocyte counts by Dr. Gulati et al, and Dr. Agarwal et al report on the changes in high-performance liquid chromatography pattern in hemoglobin after treatment with hydroxyurea. Visit the journal's website at www.labmedicine.com for extra content relevant to today's laboratory professional, including:

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Questions? Contact the Web editor at editor.labmed@ascp.org.

Message from the Chair of the Council of Laboratory Professionals

Mr. Hager

By Jack A. Hager, MT(ASCP)SBB

Spurring the Imagination to Infinite Possibilities

We read these types of headlines on almost a daily basis: "Scientists create a functional human liver from stem cells derived from skin and blood" and "Two patients HIV-free after stem cell treatment."

What we see in the headlines is the culmination of years of research and countless hours of work, and the treatments are remarkable if not miraculous. At first glance, the possibilities seem endless, and it spurs the imagination to think of what may lie ahead.

Placental cord blood can be collected and pluripotent cells harvested, cryopreserved, and stored frozen for years. Perhaps these can be reused for the treatment of a future illness. Induced pluripotent cells can be collected from the bone marrow or apheresed from the peripheral blood and coaxed by cytokines to differentiate into numerous cell lines for use in various treatments.

Medical Miracles

Our medical technologies allow stem cell therapies to be used to treat blood disorders from leukemia to sickle cell anemia, as well as a variety of other diseases, including HIV and atherosclerosis. Scientists today are working with 3-D printers and other technologies to grow tissues and even organs such as hearts, livers, lungs, and kidneys for transplantation.

These lab-grown tissues and organs could ease the shortage of donor tissues and organs and reduce the need for patients to take immunosuppressant drugs to prevent rejection. Surgeons have already transplanted lab-grown windpipes, bladders, veins, and urethras based on patients' own cells.

There is great medical and business potential behind this growing industry. Contemplate the processes used to collect, test, and store the various cells in the body. Next consider the bioengineering behind developing technologies to regenerate and manipulate cell lines and for manufacturing treatments, tissues, and organs from individual cells.

Then think about the regulatory requirements that will be needed to standardize processes as they evolve from a theoretical or research basis to becoming licensed and approved for routine use. Envision the new industries with associated sales and marketing, finance and commerce, trade, production, and engineering based on these wonderful technologies.

Diversity of Biorepositories

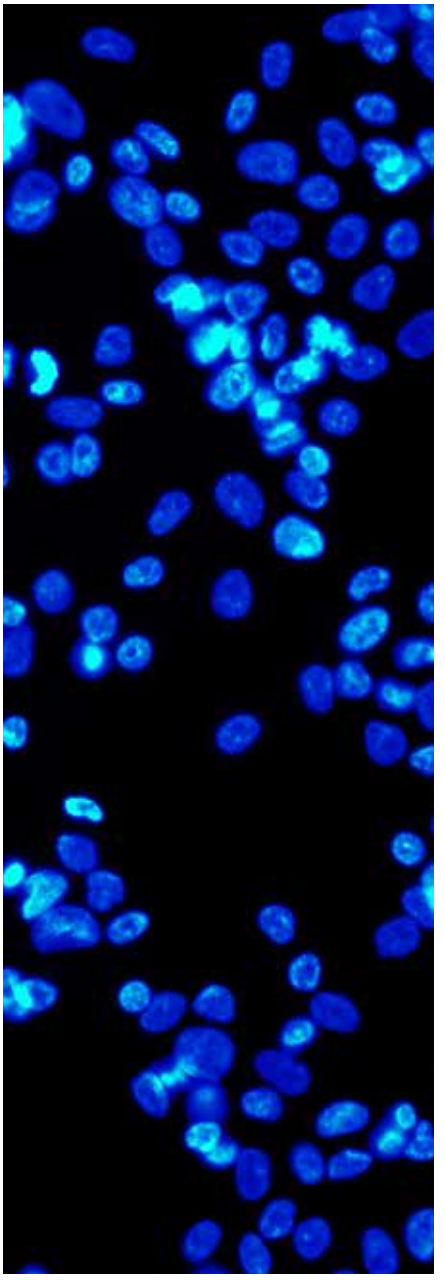
This October 2013 issue of *Critical Values* focuses on biorepositories, which are collections of a wide range of biospecimens, such as tissue, blood, plasma, serum,

urine, DNA, RNA, and live cells. A clear distinction can be made between biorepositories that store biospecimens (serum, plasma, urine) for testing and research, and those that store cells and tissues that are intended for transplant purposes or could be used for development and commercialization of individualized medicines and targeted therapeutics.

My first exposure to biorepositories came during the summer of 1981, when the Centers for Disease Control and Prevention reported five cases of Pneumocystis carnii pneumonia among five young homosexual men. At that time, I was a young medical laboratory scientist who had just begun working at a hospital in Colorado.

Through the years, as more sophisticated testing was developed for HIV detection, samples stored away in freezers were tested and found positive. The oldest was a blood sample tested in 1998 that had been taken in 1959 from a man living in the Belgian Congo, today's Democratic Republic of Congo.

The virus was also found in tissue samples from an African-American teenager who died in St. Louis in 1969 and from a Norwegian sailor who died around 1976. These are examples of biospecimens used for research. These specimens build on our scientific knowledge base and can be precious, perhaps invaluable.



Harnessing Cell Lines

Cells and tissues that are intended for transplantation and development of medicines and therapeutics are not a 21st century phenomenon. The oldest and most commonly used human cell line was derived from cervical cancer cells taken in February 1951 from Henrietta Lacks, a Maryland woman who died from the cancer later that year.

Scientist George Gey, having started the Tissue Culture Laboratory at Johns Hopkins University in Baltimore, utilized these "HeLa" cells' unique ability to divide indefinitely in culture to establish the first human cell line to be successfully grown in vitro. This primitive biorepository has become the world's most commonly used human cell line.

HeLa cells were used by Jonas E. Salk, MD, to test the first polio vaccine, and they have since made a profound contribution to medical research by helping in the growth of a host of viruses and development of many of our most important vaccines and cancer medications.

Complexity in Collection, Storage, and Use

Collecting the samples or specimens is just the beginning. Good manufacturing practices apply, and specimens must be linked with donor records and patient data and comprehensively tracked through processes, compatibility testing, and treatment records that require a sophisticated Laboratory Information Management System.

Preparation and storage require state-of-the-art facilities, equipment, supplies, materials, and monitoring systems. These must be secure, and continually maintained and monitored. Utilities must be continuous and managed to avoid interruption from human-generated incidents and those caused by natural disasters.

The historical records of the technical, legal, monetary, ownership, ethical, and managerial events associated with the cells harvested from Henrietta Lacks more than a half century ago point out that the issues relevant to repositories of biological specimens are as mindboggling as the possibilities for their use. Though many standards and best practices have been established for custodianship, informed consent, privacy protection, access to biorepositories, intellectual property, and resource sharing, a number of unresolved questions remain. Business practices, determining the costs and value of specimens, payment for storage and release, and ownership of the biorepository and its materials are contentious and create ethical and legal issues that will continue to be challenged.

Advancements in both public and personalized medicine and research support the need for scientific and medical communities to continue to compile and keep biorepositories. Now we have embarked on a time when we will realize more of their potential.

Mr. Hager is Chief Executive Officer at the American Red Cross National Testing Laboratory in Portland, Ore.

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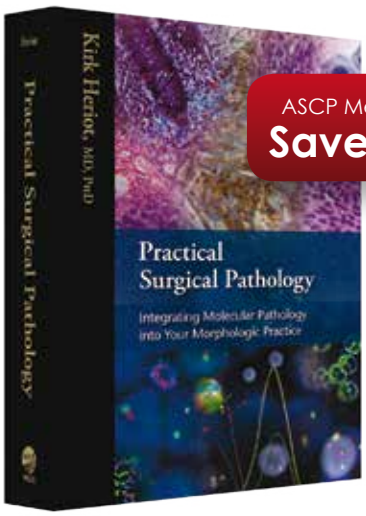

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Message from the Chair of the Resident Council

Dr. Stall

Biorepositories: Accelerating Improvements in Patient Care

By Jennifer N. Stall, MD

As pathology residents, our exposure to biorepositories varies significantly during training. Most commonly, residents are involved with the procurement of tissue specimens. The process itself, however, is much more complex than simply selecting a region of tissue, and it requires the coordinated efforts of several team members across multiple locations.

While the process of tissue procurement is often just one small part of residents' daily tasks, the importance of biorepositories and the tissues and information they obtain and maintain cannot be understated. Numerous disease discoveries stem from research performed on specimens collected by biorepositories and they often lead to revolutionary changes in disease detection and treatment modalities.

With the advent of sequencing technology, these advances will continue to unfold at an even more rapid pace than the field of medicine has previously witnessed. However, these potential advancements rely heavily on the availability of both normal and abnormal tumor research specimens, which must be procured and processed prior to any research being performed. The presence of biorepositories increases the availability of tissue samples that make many of these research endeavors possible.

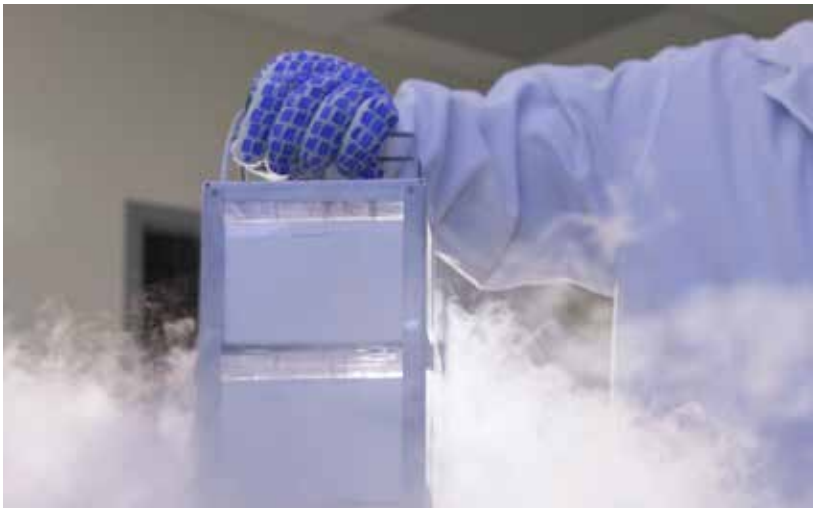
Focusing on Teamwork

Although there are a few major types of biorepositories, those most commonly encountered by a pathologist are disease-oriented and hospital-based biorepositories, which typically handle tissue that is intended for diagnostic and therapeutic purposes. The process of obtaining tissue from the patient and delivering it in proper condition to the researcher requires the concerted efforts of numerous skilled team members, including but not limited to surgeons, pathologists, and tissue-bank technologists.

Once proper informed consent and tissue are obtained, it is often necessary for a specific area of tissue to be selected for research while the remainder is evaluated for a final diagnosis. Within this acquisition stage of tissue procurement, it is essential to have a trained, specialized individual (i.e., a pathologist, resident, and/or pathologists' assistant) involved in tissue selection.

Placing Patients First

While research studies often desire a certain amount of tissue, it is also extremely important to retain the necessary portion of tissue to make a complete and accurate diagnosis for the current patient. At times, for small-sized tumors, this may result in not having enough fresh tissue for procurement. While there may be pressures from the biorepository to obtain tissue, it is essential that residents maintain what is needed for the patient currently receiving care.



The patient is the first priority; biobanking is the second. More often than not, there is enough tissue for at least a small sample for the biorepository. In these cases, selecting from areas that will not compromise the current assessment is important. That explains why involving properly trained individuals with knowledge of pathologic tissue assessment is essential.

Biorepositories may face an added struggle for the immediate availability of trained individuals. At many institutions, pathologists, residents, and pathologists' assistants are often engrossed in their everyday clinical care tasks, and tissue procurement tasks may at times seem like an added burden.

It's important for all of us to keep in mind the importance of the research stemming from biorepositories—and how it may help future patients and populations—and take the few extra minutes to assist with tissue acquisition.

Emphasizing Quality

A further added complexity to this tissue acquisition phase is the timeliness of collection. The quality of tissue obtained is often affected by the cold-ischemia time, or the time from tissue removal to fixation and freezing. Increased ischemia times may lead to tissue degradation and alteration of gene expression profiles, which, depending on the specific research being performed, may render specimens inadequate or may drastically affect results.

Therefore, it is not only important to select the appropriate areas for procurement, but also to work closely with clinical staff to obtain specimens as quickly as possible. Collection, however, does not end at the level of the tissue. Proper data collection is imperative for meaningful research studies to be conducted.

Demographic, clinical, and environmental factors all play important roles in interpreting and utilizing the information provided from each tissue sample. Establishing robust data sets and having the infrastructure to support large data sets are essential. Collaboration among IT departments, research facilities, and biorepositories is necessary to establish parameters to organize and protect this information as well as to facilitate transfer of information. Institutional collaborations continue to become increasingly important to maintain robust, diverse data sets for research.

Clearly, the process that occurs within a biorepository is anything but simple, and only a few aspects are even mentioned above. Ultimately, the success of biorepositories in obtaining and providing meaningful specimens for research requires the harmonization of numerous dynamic aspects all working within a complex framework of ethical, legal, and social constructs.

While numerous challenges still exist and continue to evolve, pathologists and residents cannot forget the crucial importance that biorepositories play in the care of future patients. It is imperative that the pathology and laboratory medicine community continue to support and establish repositories with the proper infrastructure and internal standards needed to provide diverse samples and data. The potential gain for future populations is without question large, and what starts as one small sample from a single individual may help elucidate the key to new approaches and treatments for entire populations.

Dr. Stall is a fourth-year pathology resident at the University of Michigan, Ann Arbor, Mich.

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Biobanking

By Peggy Devine, MT(ASCP)

Biorepositories and Biospecimen Research: The Patient Perspective

Ms. Devine

In 1994, I was diagnosed with breast cancer. I retired from my career as a medical technologist, where I'd worked in both clinical and research laboratories for more than 25 years, and went to work at the University of California, San Francisco as an assistant administrator in its breast oncology program. There I had the chance to learn the world of breast cancer research from the inside. Six years later, I merged all of those experiences and formed the Cancer Information & Support Network (CISN).

CISN conducts in-person trainings for patients and advocates, and provides information on clinical trials, personalized medicine, and Cancer 101. Helping people understand the many aspects of cancer research, and helping them understand that in order to receive a "bench to bedside" approach to care they must enter clinical trials and donate tissues, is a challenge. So we also train clinical research associates and primary investigators on how to communicate clinical trials to their patients, and how to help patients better understand standard of care vs. clinical trials. This technical side of donating tissues can be easy to teach and grasp, but the emotional side of it isn't always as simple. As both a patient and an advocate, I realize that the emotional side of treatment plays a large role in patient care.

Cancer Care in the New Era

When I was initially diagnosed, I was shocked to hear cancer advocates refer to surgery, radiation, and non-targeted systemic chemotherapy as "slash," "burn," and "poison," given the harshness of these treatments. And almost 20 years later, the same basic approach is still the norm. Although patients do not hear this kind of language during treatment, their personal experiences validate these terms, and if they become advocates or talk to others, they use these terms to describe their care.

During my career as a medical technologist, I worked in a clinical lab for an oncology group. I would complete basic blood work before each round of a patient's chemotherapy treatment, and the pharmacist next door

would make up the bag of chemo based on the patient's height and weight. The pharmacist would be in full protective gear—rubber gown, mask, gloves, and under a ventilation hood—while she worked. If she dropped or spilled any of the chemo on her way across the hall to the patient infusion room, the area would be cordoned off until a Hazmat team could do a full cleanup. If she made it across the hall, the chemotherapy would be injected into the patient's vein or port.

Since then, surgery has been refined and is usually less aggressive, and the same goes for radiation, but chemotherapy for most cancers is non-targeted and toxic in both the long and short term. And while the idea of a "magic bullet" to cure cancer has been around for years, advances in medical research have shown that due to the extensive heterogeneity of individual tumors, there isn't just one "magic bullet," there are several. With the advent of genomic sequencing of individual tumors, there are many more to come.

Subgroups of patients are being identified and the pharmaceutical pipeline is filling up with targeted treatments. This is a great advancement. Personalizedmedicine where individuals receive the right drug at the right time is a real possibility in the near future. Biomarkers for early detection, prevention, and after-treatment monitoring are also being explored.

But to deliver better care, gaining a patient's trust is foremost. For laboratory professionals, that means presenting test results that are accurate. Patients need to trust that their test results are correct, and that the biomarkers found in tumor tissue are reliable. This should start with the standardization of all steps involved in collection, processing, storing, and analyzing tissue. Before we can even get to standardization, we need to know what the pre-acquisition and post-acquisition variables are. That means we need research to find out what these variables are and which ones will affect the accuracy of the result if not followed. Do we know for sure if the drugs or antibiotics the patient is taking affect the biomarkers? What type of anesthesia or duration of anesthesia should the patient have while tissue is being removed? Does arterial clamp time affect biomarker accuracy? Are these the same for all biomarkers, or does each have its own collection profile?

How can we move forward if we don't know these answers? As a medical laboratory scientist, I would never run a chemistry or hematology panel on hemalized blood, as the number value would not represent that patient's actual value. The same holds true for reporting out biomarker values.

Moving to the post-acquisition variables, do we know if time at room temperature affects the accuracy of the result, and what about the type or time the tissue is in fixative, or the rate of freezing or the size of the stored aliquot? Again, how can we move forward without research into these areas so these questions are answered and biomarker results can be safely given to doctors to treat their patients?

The National Cancer Institute has recognized the importance of biospecimen research to find answers to the questions above. The established Office of Biorepositories and Biospecimen Research (OBBR) is doing research into these variables and has published best practices for biospecimens.

It is an important first step, but it is up to each organization and person working in this field to incorporate these best practices into their daily structure, which takes time, money, trained personnel, and proper equipment and storage facilities. A patient deserves to know they can have their tissue biomarker tests run anywhere in the country and have that value be accurate.

During a presentation at an OBBR meeting several years ago, one of my slides mentioned "garbage in/garbage out" as a concern of mine as a patient. I did not mean that professionals in this field are not technically qualified, or are ethically lax. For me, that statement means we do not have all the needed research knowledge to know how to best collect, process, store, and analyze tissue. We also do not have the ways and means to monitor that best practices are being observed by all in the field.

The era of personalized medicine is a freight train speeding down the track. Human specimens that serve as analytes for new and developing technology platforms have emerged as a critical resource for basic and translational research in cancer, as they are a direct source of molecular data from which targets for therapy, detection, and prevention are identified and molecular signatures of cancer are derived.

The reliability of those molecular data is dependent on the quality and consistency of the biospecimens being analyzed. The patient community counts on the professionals in the field collecting, processing, and storing these specimens to report out accurate results.

Ms. Devine is President of the Cancer Information & Support Network in Auburn, Calif., and a breast cancer survivor and patient advocate.

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By Molly Strzelecki

The Other Side of the Story:

Ethical, Legal, and Social Issues in Biobanking

Every story has two sides, and the tale of biorepositories is no different. One side is technical: Storing and collecting samples, the cost of running a facility, complying with best practices.

On the other side are the ethical, legal, and social issues that can make for complex situations where one size does not fit all. After all, the samples collected and used for research aren't just pieces of tissue, or vials of cells, they are—or used to be—pieces of a living, breathing human being. Informed consent, therefore, is necessary protection for patients. However, in the context of biobanking and genomic testing, the traditional models of informed consent may need to be re-evaluated.

Privacy, Please

Protecting a biospecimen donor's privacy is at the heart of the issues surrounding informed consent. Under the terms of the Health Insurance Portability and Accountability Act (HIPAA) and the federal policy

for protection of human subjects, donated specimens are often stripped of identifying characteristics like name, birthday, or medical record numbers. De-identifying tissues not only protects a patient's privacy, but according to the federal policy, tissues without these identifiers are no longer considered materials from human subjects.

"But these rules were written decades ago, and modern genomics techniques and data sharing are raising new questions about privacy," says Marianna Bledsoe, an independent research consultant with more than 15 years' experience addressing the legal and ethical issues related to specimen research, and the 2007-2008 president of the International Society for Biological and Environmental Repositories.

Researchers have deposited vast amounts of genomics-based data in aggregated databases and are sharing them with the research community, based on the common assumption that the data are de-identified and therefore the donors' privacy is protected. Recent studies, however, have raised questions about these assumptions.

There are an accumulating number of cases, explains Carol Weil, JD, program director for ethical and regulatory affairs in the National Cancer Institute's Cancer Diagnosis Program, in which enterprising researchers took de-identified data from these pooled databases, and using matched genetic samples and/or publicly available data correctly identified multiple individual donors.

These studies, Ms. Weil notes, were isolated cases, conducted more or less to demonstrate the feasibility of identifying a sample donor. But the results raise new questions about privacy and traditional models of consent.

"It's becoming increasingly clear that de-identification is a moving target in today's big data environment, and that the ability to guarantee privacy protection is narrowing," Ms. Weil says. "We have tended to minimize the risk of re-identification in consent forms, giving people a strong sense that coding mechanisms and other standard protections employed by researchers meant that biospecimen donors didn't need to worry about their privacy. But in the context of all the genomic research that's going on, we're beginning to question whether that's really accurate to say."

In turn, changes to the federal policy protecting human subjects are currently under consideration. And the big question, Ms. Weil explains, "Is whether or not the revisions will move away from the concept of identifiability as the touchstone of how we decide what requires protection."

These changes, however, are not likely to be based on input by government officials alone. Says Ms. Bledsoe: "The community can provide input as regulations and policies are developed. In particular, there is a public rule-making process that generally involves publishing

What was Mine is Now Yours

In June of 2013, the American Civil Liberties Union and the Public Patent Foundation made headlines when they won a Supreme Court ruling against Myriad Genetics, Inc. The case focused on whether the company, based in Salt Lake City, could rightfully patent the BRCA1 and BRCA2 genes. Following months of arguments, the high court decided that Myriad could not. The majority opinion, written by Justice Clarence Thomas, stated that genes are a product of nature, and thus are ineligible for patents.

The landmark case put a bright spotlight on an often-debated topic in health care: Ownership of the human body. And specifically for biorepositories, the question centers on ownership of tissues and other biospecimens.

"It's pretty clear that before anything has been cut out of you, it's yours," says Carol Weil, JD, program director for ethical and regulatory affairs at the National Cancer Institute (NCI). "No one can remove your tissues for use in medical research without your consent. No one can intentionally take your tissue for use in medical research without asking your permission to do so. That's an issue that gained recent public attention from Henrietta Lacks," she continues, citing the 2010 book by Rebecca Skloot that delved into the life of the woman behind HeLa cells. The cells were taken from Ms. Lacks and used extensively in research, unbeknownst to her or her family. "Admittedly, that was done back in the 1950s. But in this day and age, we have regulations that protect against that."

Still, the past few decades have seen multiple lawsuits over the potential commercial use of biospecimen samples, and because of this, the language that goes into informed consent documents now specifically stipulates that patients will not personally benefit from the research project in which their samples are used nor will they benefit from any downstream commercial use of their tissues. The cases are under limited jurisdiction and specific to the states in which they were filed, but the end result is the same.

"Some courts have ruled that tissue donation for research should be considered as a gift," explains Jim Vaught, PhD, chief of the Biorepositories and Biospecimens Research Branch at NCI. "You made a gift to laboratory research when you donated your blood or tissue for a research project."

But making a gift of tissue as a research participant doesn't mean you can ultimately decide who gets the tissue. Ms. Weil describes an example of tissue donation in which a researcher wanted to take a cache of specimens collected from his former patients to a new job at a different university. He therefore asked his former patients to inform the university that they were authorizing the researcher to take the specimens.

"The court ruled against the researcher, stating that he couldn't take the specimens with him," Ms. Weil explains. "It ruled that the university, not the researcher, owned the specimens and controlled their use."

While the gift theory has been used by some state courts to decide ownership issues, it's not perfect. "Not by a long shot," Ms. Weil notes. "For example, research participants who donate their specimens retain the right to discontinue participation in research, and can therefore have stored specimens withdrawn from storage or destroyed, even if they can't direct that someone else be allowed to take them."

"Once a tissue is cut out of you, and it's been de-identified, it's not considered human subject research under the current regulatory scheme," she says. "It gets really complicated figuring out what's appropriate in terms of using excised tissue in future research studies because lots of players can get involved and seek control over stored research tissue."

A recently updated document from NCI on best practices dedicates an entire section to the ethical, legal, and social issues surrounding biospecimens, and Ms. Weil explains that understanding—by patients and researchers alike— about what will happen to specimens once they are removed for research purposes is the most important issue in the ownership debate.

"The section talks about appropriate stewardship and custodianship of tissue, and that's the relationship we perceive between biospecimen donors and biorepositories. Biorepositories have responsibilities and ethical duties to protect the integrity of donated tissue, and most importantly, to respect the autonomous preferences of biospecimen donors," Ms. Weil says. "It's a relationship of trust. Donors provide their tissue to a biorepository, and the biorepository has an ethical obligation to preserve whatever consent arrangements are in place.

"There's a higher ethical duty to respect the understandings that were in place through the consent form when the tissue was donated," she says.

Editor's Note:

As this issue was going to press, an agreement was reached between the National Institutes of Health and Henrietta Lacks' family over the use of Ms. Lacks' cells. Access to the complete genome sequence of her cancer cells will be restricted to scientific research funded by U.S.-government grants, an August 8, 2013 article on Forbes.com reported. Requests for the cells will be reviewed by a six-person panel that includes two Lacks family representatives, and publications that result from any research with the cells must include an acknowledgment of Henrietta Lacks as the source of the cells.
For more information on the agreement, visit www.nih.gov/news.

proposed regulations in the Federal Register, and a public comment period where people can weigh in." Comments can be submitted during the public comment periods online at http://www.regulations.gov.

More New Ways than One

As modifications in the federal informed consent policies are being considered to reflect changes in the research environment, experts and patient advocates are pushing for different paradigms to protect human subjects. Rather than struggling to keep identifying data hidden, one new model under consideration strives to make data more visible by increasing people's community engagement in the research process.

"Instead of posing it as an 'us vs. them' mentality, or researchers vs. participants, some experts are encouraging more of an engaged process, where individuals are empowered to select consent options, data sharing models, or the degree of information returned," Ms. Weil explains.

One study taking the empowerment approach is ClinSeq®, a large-scale pilot study sponsored by the National Human Genome Research Institute in Bethesda, Md., that is looking at whole genome sequencing as a clinical research tool. Researchers are combing through genomic data from participants with certain risk factors for cardiovascular disease to look for other genetic determinants of disease.

"They're using the research as a way to generate hypotheses for more research on the relationship between particular genotypes and phenotypes," Ms. Weil explains. What's more, the researchers are providing an added benefit for participants: Those with certain variants that are determined to be clinically actionable and medically significant would be notified of their risk, even if that's not the information they sought when they originally enrolled in the study.

"Let's say you enroll in ClinSeq® because you have high blood pressure, and you're concerned about your risk of heart disease," Ms. Weil says. "And in the course of the research study they find you have a high-risk BRCA variant." That information could be provided to the participant. "Because next-generation sequencing is more widely employed in medical research today, researchers are coming up with all sorts of genetic findings that may be completely unrelated to the original study," she says, adding that while not all incidental findings are significant now, they could be in the future as research advances.

Community advisory boards comprising lay people—former patients and their families, or simply people who have a real interest in and experience with the research at hand—are also weighing in on how biospecimens should be used and their donors protected, particularly when the specimens are collected for future research. These boards comment on aspects of study design, the language used in the consent forms, or even policies on result reporting or data sharing. They weigh in on the appropriateness of controlled versus public access to study data and check in with participants to gauge their feelings about how their tissue might be used in future studies.

All of these models must strike a balance between the need to share data to promote important research with broad public benefit versus the need to protect individual-level data.

Reporting individual research results to tissue donors presents a complex situation: Participants may want their individual research results, but there are risks regarding the return of incorrect data, particularly in the biorepository context, where specimens and data may change hands many times, says Ms. Bledsoe. In addition, there are practical implementation issues and costs, and the challenge of how to return results in an ethically appropriate way.

"From an ethical perspective, the issue of return of research results has been debated for years," Ms. Bledsoe says. A number of groups have made recommendations regarding when to return research results to participants. Arguments in favor of returning results to patients are that returning results shows respect for the donor, as well as beneficence, reciprocity, justice, and duty to rescue. Arguments opposing the practice are that returning research results to patients would promote a therapeutic misconception. Furthermore, returning incorrect or unvalidated findings could pose real harm to study participants.

"There is an emerging view that in at least some circumstances, some results should be returned," Ms. Bledsoe says. "But that varies widely by context, and again there are risks and practical implementation challenges associated with that, so great caution is needed." Additional empirical data is needed, she adds, regarding the actual benefit and risks of returning individual research results to participants and the practical implementation challenges and costs.

Additionally, adds Ms. Weil, "We need to do more empirical work to figure out which research participants are more inclined to share data openly. For example, sharing may be more acceptable within rare disease registries involving an intimate population of patients and their families. In order to develop policy in this area we need to learn the circumstances under which people are more interested in sharing or protecting their data, and where they fall on the spectrum of the privacy/utility trade-off."

Striking the right balance on these complex policy matters will be critical to respect the interests of participants and facilitate important research that will benefit patients and the public.

Ms. Strzelecki is Senior Editor of *Critical Values*.

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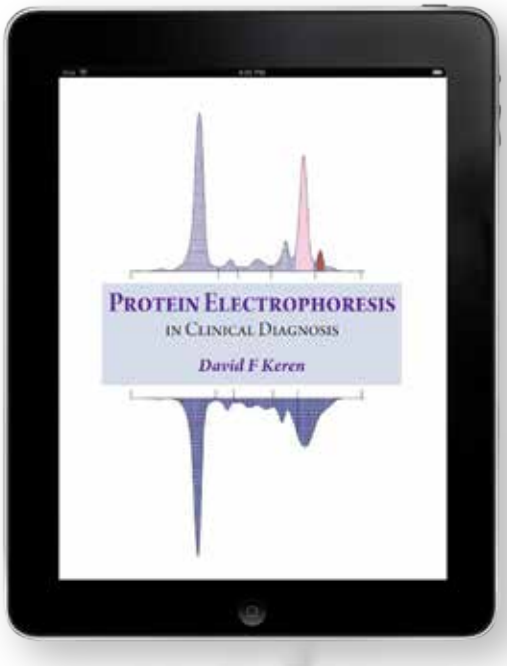

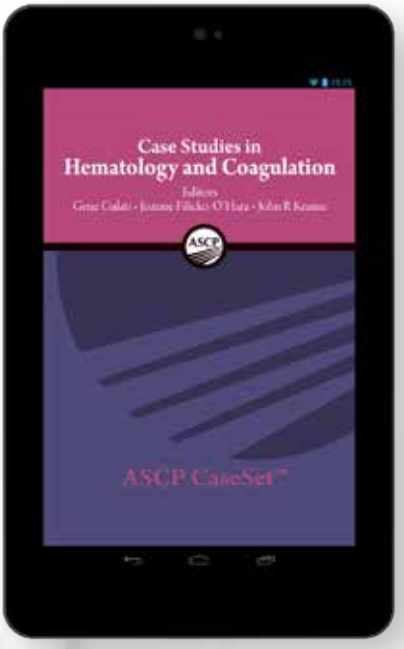

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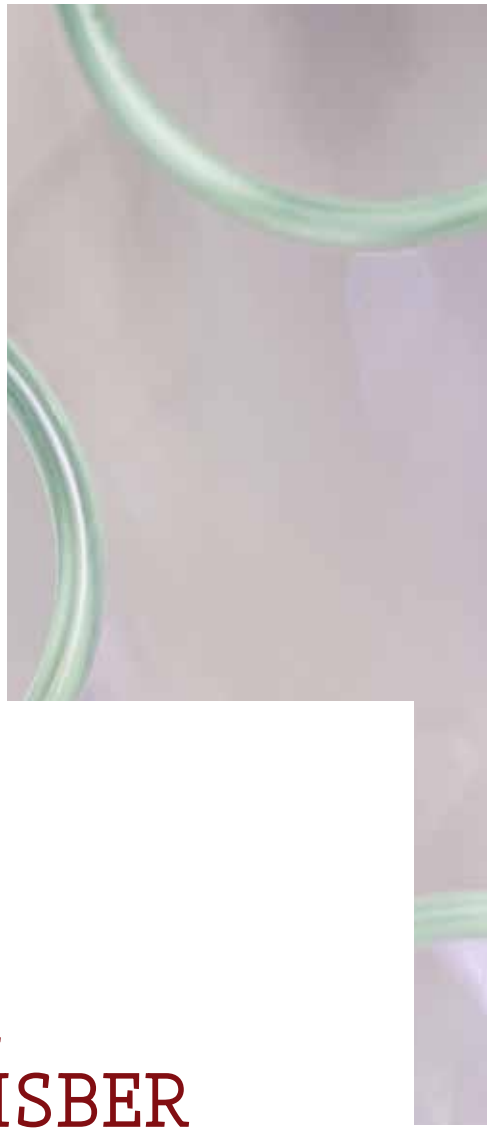

By Katheryn Shea

The Need for Global Biorepositories in Medical Research and the Role of ISBER

Biorepositories and biobanking are critical to the medical research community, and awareness of their functional role in precision medicine is growing rapidly.[1] Well-annotated specimens collected in a consistent manner are indispensable to research results; inconsistent collection practices can cause conflicting results to be obtained from specimens, leading to hard-to-reproduce results and delays in research advancement.

In the new era of precision medicine, global biological collections have been deemed an essential resource for identifying novel biomarkers for specific therapies and allowing a broader assessment of the clinical importance of genetic variation across a range of conditions.[2,3] Having access to a wide collection of biological samples with epidemiological, clinical, biological, and molecular data from a large number of patients and healthy persons will be required to understand the etiology of disease[4] and to identify the genomic and proteomic biomarkers associated with disease so better diagnostics and individualized therapies can be developed. For this to be achieved, it is important to have established best practices and standards for the ethical collection and proper preservation of the samples used to make these discoveries.

Taking Ideas Around the World

The biorepository field is expanding at a rapid rate and the promise of these global collections for personalized medicine and disease treatment is tremendous. The International Society for Biological and Environmental Repositories (ISBER) is the leading international forum focused on creating opportunities for sharing ideas internationally and harmonizing approaches to evolving challenges in biobanking and biological and environmental repository operation. ISBER is a professional society

of individuals and organizations from across the globe who share an interest in promoting consistent, high-quality standards, ethical principles, and innovation in biospecimen banking by uniting the global biorepository community. ISBER also addresses the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens.

The goals of ISBER include:

- Dissemination of information on repository management issues;
- Education and sharing of information within the Society;
- Providing a voice for repositories to influence regulations on shipping, human subjects, etc.;
- Development of best practice guidelines;
- Provision of centralized information resources for existing repositories; and
- Bringing members together to work on "hot button" topics.

ISBER educational resources and meetings focus on technical issues such as quality assurance and control, regulation, human subject privacy, and confidentiality, and providing information about sources of equipment and expertise.[5] One such resource is the ISBER 2012 Best Practices for Repositories Third Edition ("Best Practices"), which focuses on the collection, storage, retrieval, and distribution of biological materials for research.[6] These Best Practices are based on the cumulative expertise of the ISBER community, which comprises almost 1,000 biobanking professionals representing individual and organizational members of the Society. The first edition of the ISBER Best Practices was published in 2005 and new editions were issued in 2008 and 2012 to reflect the evolution of standards and best practices as the field of biorepository and biobanking has evolved. The practical implementation of these best practice guidelines

Photo courtesy of Precision Bioservices

requires careful planning by the collection designers.

Developing a Global Biorepository

Biorepositories can have a variety of collection types, from individual study collections to archives built solely for future research purposes, but the main goal of each is to provide well-annotated specimens that were collected in a consistent manner to ensure they fit their intended purpose. This can only be achieved by providing information on the pre-analytical variables to which the specimens were exposed. The pre-analytical variables commonly considered the most critical include the method and type of collection, the method used for preservation, and the time and temperature of the specimen and its derivatives during each step of the preservation and storage process.

When planning a new collection, the potential impact of these pre-analytical variables on the expected research needs to be carefully evaluated and, where uncertainty exists, pilot studies should be conducted to determine the potential impact. Careful documentation of each event during the sample acquisition and storage process is also important so that variation in these parameters can be taken into account when results derived from the specimens in the collection are analyzed. For example, differences in the temperature of blood between draw and processing for plasma affects the levels of TGF-ß1[7], and differences in tissue fixation time affect proteomic data. [8]

Standardized nomenclature for describing the pre-analytical procedures has been developed by the ISBER Biospecimen Science Working Group. The Standard PREanalytical Code (SPREC) was developed to provide repositories with a short, simple, and standard method of describing sample processing. SPREC allows repositories and researchers to rapidly communicate the essential elements of sample processing without the need for sharing massive operating procedures. [9]

The logistical feasibility of the collection parameters

must also be taken into consideration. Common variables to consider include the resources available in each participating geographical region, the proximity of sample collection location to the site that will be processing the samples, and the technical capabilities of the staff. Sample input requirements for the planned and envisioned testing must also be considered.

The legal and ethical issues surrounding biobanking are evolving rapidly throughout the world. Some of the major areas of debate include the use of a broad consent that would allow for undefined future research versus a dynamic consent process in which each specific use must be separately consented, and when individual research results should be returned to participants and/or healthcare providers. Consent variables including the purposes for which a specimen may be used (for example, specific disease-focused studies, or genetic analysis), and under what conditions participants should be contacted for re-consent must be catalogued in the datasets associated with the collection.

Ensuring Quality, Ensuring the Future

Foundational to any biorepository is that it be designed in a manner that provides a safe and secure environment for the specimens it will store. Each collection from a donor is unique and, as such, the individual specimens are irreplaceable. Redundant systems including backup freezers and utility power are essential, particularly if the biorepository is in an area that has unreliable power sources. While assisting with the set-up of a biorepository in Costa Rica, for example, all material was stored in LN2 freezers capable of holding temperature for up to two weeks without power, as there was not a reliable utility power source. Furthermore, multiple vendors for critical supplies such as fuel, liquid nitrogen, and dry ice coolants, and laboratory supplies and emergency systems for fire and security breaches must be considered to ensure a safe and secure environment.

A clearly documented Quality Management system that describes the controls used to guarantee that all specimens are prepared and stored in a uniform manner is also needed to ensure future specimen utility. Documented training and competency assessment programs, clear policies, and detailed standard operating procedures minimize the variability that can be introduced in specimen handling activities.

Sample logistics for both incoming and outgoing samples are critical to the effective functioning of a biobank. Specimens must be able to arrive at the repository in a timely manner to minimize changes in critical markers. In addition, the repository must be able to ship samples to researchers so they arrive in useful condition. This is best served by location near a major transportation hub, although that may not be near the sample collection sites; this is an example of the compromises and risk considerations involved in the development of a biorepository.

Future use and sustainability considerations must also be taken into account. The finest collection of specimens is useless if researchers do not know it exists and/or cannot obtain samples from it, or if the repository cannot be sustained due to lack of resources. Repositories must have plans and policies in place for how the collection will be utilized, who will be able to access it, and how the requests for access will be reviewed and approved. Sustainability of the repository is dependent on the availability of funds to cover the cost of maintaining the repository and performing the necessary sample handling and administrative tasks. In addition, repository designers must consider the short- and long-term funding mechanisms that will be available.

ISBER continues to lead the way on developing standards for the ethical collection, preservation, and use of specimens to help advance medical research. Access to specimens with fully documented processing information and donor data has the potential to allow researchers to accelerate the discovery of relevant biomarkers for existing and emerging diseases, improving health worldwide.

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By Molly Strzelecki

The Economics of Biobanking

Launching a business—any business—starts with a good idea, followed by a lot of time, dedication, and, most important, money. But once a business is up and running, the next step often proves the trickiest: Making it financially sustainable.

In today's uncertain economy, keeping a business running and in the black can be tough. Biorepositories—institutions that collect human biospecimens like blood, tissue, or DNA— are not immune to the economic forces buffeting all businesses, and so must navigate both a fickle economy and the uncertain consequences of healthcare reform. In addition, the government contracts and grants on which biorepositories rely, and which also help facilitate large-scale studies using biospecimens, are dwindling. Adding to that, most biorepositories are set up for specific research or clinical trials, and often collect specimens with limited downstream utility.

These challenges have prompted the biobanking industry to take a cold, hard look at their facilities and practices, and delineate new ways to ensure financial stability.

Storage, Redefined

To understand the dilemma faced by biorepositories, one must understand something about the costs. Biospecimen research often requires large sample collections. And those sample collections are often stored in large ultracold freezers, which are expensive to maintain.

Jim Vaught, PhD, chief of the Biorepositories and Biospecimens Research Branch at the National Cancer Institute (NCI), which is part of the National Institutes of Health (NIH), addresses this issue. "From our perspective, and I think it's true at other academic and clinical institutions, maintaining large specimen collections, especially in freezers that are very expensive to operate, is becoming a huge economic problem," he says. He notes that while freezer compressor technologies have improved, and freezers have become more cost-efficient on the whole, storing large sample collections still constitutes a major portion of the budget.

To reduce these costs, many institutions are looking at alternative storage methods. One such alternative, Dr. Vaught explains, is dry storage, which is used at The Centers for Disease Control and Prevention (CDC) in Atlanta. The CDC uses sample cards to store the infant blood spots it collects, which are then used to track genetic diseases in newborns.

"For years there have been ways to determine some genetic abnormalities from blood spots," Dr. Vaught says. "It's an inexpensive way of collecting and storing samples, because generally the cards don't have to be stored in freezers. They can be stored at room temperature, and controlling the humidity is the only thing you have to worry about."

Other dry storage technologies are being developed, and some are already in the field. Dr. Vaught notes one company that stores samples in cellulose matrices. Blood and other samples embedded in these matrices remain stable at ambient temperatures long enough for researchers to extract DNA, RNA, and proteins for proteomic and genomic studies.

And it's not only advances in storage technologies that are having a positive effect on biobanking economics—advances in research technologies are, too. "The sample size you need is orders of magnitude less than you needed five to 10 years ago for various genomic and proteomic analyses. So storing smaller volumes of samples and smaller numbers of samples is possible these days, and that is of course an economic consideration," says Dr. Vaught.

Costs, Reclaimed

Economic viability means that biorepositories have to recover their costs somehow. That's easier said than done in some cases, particularly for non-profit institutions. At NIH, Dr. Vaught says, the biorepository is under fairly severe restrictions as to which costs can actually be recovered.

"As a public institution, we're providing money to grantees and contractors to collect samples for studies," he says. "So we can't turn around and charge those same grantees and contractors to access the samples here." The NCI biorepository recovers some minimal costs by charging research institutions outside of the NIH nominal fees for research tissue.

Dr. Vaught notes that some institutions, like the University of Pennsylvania, set up a cost-recovery system that charges their investigators for handling and storage within the institution's biobank. That pushes the cost of the central biobank back down to the investigators, and costs are worked into departmental budgets.

"It makes investigators more aware and careful about what they collect, and it's a good incentive to be more economical about how many samples you're collecting and how long you keep them without using them," Dr. Vaught says.

For-profit and private non-profit biorepositories, on the other hand, are more adept at completely recovering their costs and making a profit from biospecimens.

Frank Simione, vice president of external affairs at ATCC in Manassas, Va., a non-profit biobank, notes that institutions like his have two routes to long-term financial sustainability. One is to charge for the use and delivery of high-demand products. The second is to leverage core competencies and add value, by, say, genetically sequencing the materials provided.

Other competencies for ATCC include low-temperature preservation and a robust distribution network. By leveraging these, ATCC secured multiple government contracts over the years, including one for the influenza virus. When the H1N1 virus hit pandemic levels in 2009, ATCC was able to get reagents and diagnostic kits to more than 130 countries within four weeks.

Other commercial biorepositories recover costs by connecting with foreign clinical institutions, where medical systems may not be as advanced as those in the United States, NIH's Dr. Vaught adds. It's a complicated process, but a profitable one. "At each point of the transaction, the cost increases," he explains. Biobanks can sometimes sell samples and accompanying clinical documentation for thousands of dollars.

"The original cost from the institution may have been $50 or $100 per sample," he says, "but by the time it changes hands and ends up with the researcher requesting it from the company, they're paying more than $1,000 per sample."

Repositories, Centralized

Biorepositories are spread across the country, which introduces inefficiencies and drives up cost. So about 10 years ago, NCI started work on a blueprint to centralize operations, taking a cue from the centralized networks established in other countries, including Korea, China, Australia, Canada, and across Europe. The idea was simple: Create a network that would allow multiple institutions to share samples, enabling research that might otherwise be impossible.

"If an institution wanted to research a rare tumor, but just didn't have the resources to create one large sample collection, they could turn to this central network and combine forces with another institution to collect the sample number needed," Dr. Vaught explains.

"A national biobanking resource would make things broadly visible," Mr. Simione adds. He notes that the National Institute of Allergy and Infectious Diseases launched a similar initiative for malaria research at the request of the international community. ATCC holds the contract to manage that resource and continues to add to it.

"According to the data we've looked at, what that has done is increase the number of people using the resource four times since it started in 1998," says Mr. Simione. "Which means you've got a lot more people doing malaria research. If you make resources visible, and you make sure scientists know about them, the resource will get used, and it will increase research in an area."

The economic advantages of a national central biorepository are abundant: Better standardization of the collection and informed consent processes; coordinating informatics systems; and large coordinated sample collections. But, says Dr. Vaught, those advantages are at present outweighed by the disadvantages.

"There has to be a large, upfront effort to have all of the quality and standard operating procedures coordinated," he explains. "The informatics systems need to be developed, and money has to be put into the infrastructure." In these rocky economic times, however, that kind of money just isn't available.

The other concern, notes Mr. Simione, was that different institutions place different demands and restrictions on their samples. "An institution might have specific conditions it applies," he says. Discussions about the national biobank were hamstrung on how to access samples. In the end, the budget for the national biorepository was cut, and the idea has been tabled for the time being.

"It was understandable," Dr. Vaught says. "A national resource like this has a very high long-term cost."

There is still hope, though, that a national network will get off the ground in the future, perhaps through public-private partnerships, notes Dr. Vaught.

"There are economies of scale in creating a network like this, and there are great long-term advantages to having a national network," he says. "It's something that would be better to do in improved budgetary times."

The challenge of keeping a biorepository on good financial footing isn't easy. But it is possible, as the industry devises new strategies that will hopefully ensure financial stability and success.

Ms. Strzelecki is Senior Editor of *Critical Values*.

Dr. Kurtzberg

By Molly Strzelecki

Cord Blood Banking: A Q&A with Joanne Kurtzberg, MD

In the mid-1980s, researchers made the startling discovery that blood from the placenta and umbilical cord—called cord blood—contained the same kind of blood stem and progenitor cells found in healthy bone marrow. Furthermore, cord blood could, in fact, substitute for bone marrow transplants. What's more, the cord blood donor and recipient did not have to be related.

It was an extraordinary discovery for patients in need, as candidates for traditional bone marrow transplants must find an exact match in order for the transplant to be successful, a condition that eludes an estimated 30 percent of Caucasians and 70 percent of African Americans. Stem cells taken from cord blood, on the other hand, do not need to be an exact match to produce a successful outcome.

Now, almost 30 years later, public cord blood banks are an essential repository for patients with blood disorders, genetic diseases, or cancer. Cord blood is donated by mothers who have delivered healthy term babies after uncomplicated pregnancies and who give permission for their baby's cord blood to be collected, tested, stored, and listed on the national registry. It is collected within five to 15 minutes of birth, processed, and stored under liquid nitrogen. These units remain viable for decades.

Joanne Kurtzberg, MD, established the pediatric blood and marrow transplant program at Duke University Medical Center in Durham, N.C. In 1997, Dr. Kurtzberg also founded and still runs the Carolina cord blood bank at Duke, a public facility that collects and stores cord blood units for use. She is the codirector of the cord blood advisory group for the National Marrow Donor Program, a network of public cord blood banks that participate in the Be the Match Registry, and she is part of the Department of Health and Human Services' advisory council for blood stem cell transplantation, advising on policy, cord blood, and other hematopoietic stem cell treatments.

Here, Dr. Kurtzberg talks with *Critical Values* about informed consent, the issues facing public cord banks, and the potential role cord blood banks could play in the future.

***Critical Values* (CV): What are the biggest issues facing cord blood banks today?**

Joanne Kurtzberg (JK): In 2010, the Food and Drug Administration (FDA) decided to license public, unrelated donor cord blood. Licensing began in 2012, and as of right now, only five of the 13 operational public cord blood banks in the United States are licensed.

FDA requires more testing and more quality assurance and more controlled facilities, and they all cost more money. It's making the whole field more expensive, and a lot of banks don't have the staff or resources needed. And nowadays, with healthcare dollars being a hugely visible issue, anything that costs more isn't good.

The second issue cord blood banks face is that now all collected units have to have enough cells to result in a successful transplant. Because of this, there has been a lot of conversation around business modeling and how to make public cord blood banks sustainable. For example, at the end of 2005, federal legislation passed that led to a program within the Health Resources and Services Administration (HRSA) that gives federal subsidization to qualifying public cord blood banks so they can increase the inventory of public units. That money won't be around forever, though, and in return, banks have an obligation under the federal program to become self-sufficient. But because of new licensure laws, and the extras that come along with them, it's hard to get cord blood banks to that point.

There is a lot of research going on right now that is looking at ways to make every cord blood unit useful, even if it's

small. There are new technologies and research happening on expanding cells and growing them in a laboratory before they are given to a patient. And that could change the landscape a little.

CV: Is it possible for public cord blood banks to be financially self-sustainable?

JK: Income for public cord blood banks often comes from payments for units when they're distributed to transplant centers for patients; it's a cost-recovery mechanism from FDA. Other sources of income include philanthropy, fundraising, and the government subsidization program. That program subsidizes roughly 20 percent of our operating costs.

For public banks to be successfully self-sufficient, they have to sell enough units every year to cover their operating expenses. If banks needed only to replace the inventory they distributed, they could be self-sustainable. But if they need to increase their inventory, which is the goal for many, banks need subsidization one way or another.

If cord blood applications increase, banks will sell more units. And when they sell more units they will have more income, and then they will be able to support more extension of inventory with their revenue.

CV: Informed consent is a heated topic in health care today, particularly in the area of biorepositories. Do cord blood banks face the same challenges as other biobanks?

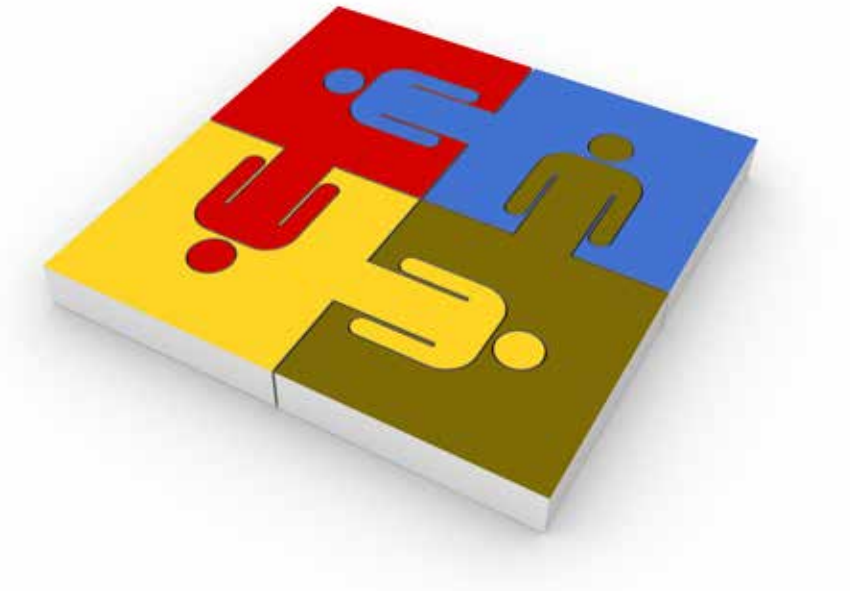
JK: From the start of public cord blood banking, moms who donate their baby's cord blood have always been consented under research protocol. They've given full consent for the collection, storage, and testing of the cord blood, and that also includes consent for the "look forward," which is permission for the bank to contact them in the future if they have additional information about the cord blood that would be important to the family, or if they need additional information from the family to qualify the cord blood.

This has always been done under a research umbrella with a hierarchy of approval of the hospital where the cord blood is collected. And then, because public banks are part of a national donor match program funded through HRSA, the government reviews the consents as well. And since those banks list with the national donor marrow registry in the United States, the Institutional Review Board (IRB) reviews the consent forms, and in some cases FDA reviews the consent forms as well. There is a lot of oversight to the consent forms, and they're very carefully constructed.

When FDA decided to license public cord blood, some hospital IRBs questioned why the consents needed to remain under a research umbrella. Banks like ours collect cord blood, but we don't keep all the units donated because in a transplant setting only the bigger units are effective. Those units that aren't used are distributed to researchers at laboratories who work on blood and stem cells. So because some of the units may be released for research, and because you can't tell before you collect a unit how big it's going to be, most sites have elected to continue to function under a research umbrella, and continue to get a research consent.

CV: What role will cord blood banks play in the future of medicine?

JK: Long term, cord blood is going to have a lot of other applications in medicine. In the areas of blood stem cell transplant, it will expand to include patients with sickle cell disease, of which many are African American and can



really only find a cord blood donor. I think there will be more screening for metabolic diseases, and those babies will be candidates for cord blood transplantation, which will increase its usage.

The bigger advancements will be in applications in cell therapy, or, as some people call it, regenerative medicine, where cells are used to help tissues repair after damage. There are a lot of trials going on now in heart disease and stroke, peripheral vascular disease, brain injury from various causes, cerebral palsy, diabetes. I don't know that cord blood will find a role in all of those disorders, but in some of them there will be a role for cord blood cells in treatments.

The good thing about public cord blood banks is that the units they bank are very well characterized. They're collected with all the appropriate types of donor screening as required by FDA, and they are tested to the highest level possible. They are tissue typed in advance, so if you need to select a matching donor, it's possible. The units have a lot of attributes that would make them readily available to serve patients in need.

Ms. Strzelecki is Senior Editor of *Critical Values*.

ASCP 2013 Chicago: Inspiration, Innovation, and Vision

A bold new vision for the future of health care and laboratory medicine, set forth by an inspiring keynote speaker, Former Secretary of State and Former U.S. Senator Hillary Rodham Clinton, and distinguished presenters, captured the imaginations of more than 1,300 guests who attended ASCP 2013 Chicago, Sept. 18–21.

In this uncertain healthcare climate, ASCP 2013 Chicago's theme, "Beyond the Lab," challenged pathologists and laboratory professionals to exert a strong leadership role as members of multidisciplinary healthcare teams and seek innovative solutions to new predicaments. Three general sessions gathered some of the nation's leading experts on subjects that are of critical importance in pathology and laboratory medicine.

"Our value is based not just on the expertise and accuracy of our diagnoses and test results, but on the importance of guiding cost-effective clinical delivery of health care," says James Crawford, MD, FASCP, who moderated the opening general session, Pathology Leadership in the Patient-Centered Era. Panelist David Nace, MD, immediate past chair of the Patient-Centered Primary Care Collaborative, examined how pathology and laboratory medicine have an unprecedented opportunity in this current healthcare environment to move beyond the laboratory and be recognized for their sustaining impact on the effective delivery of health care.

Forging a New Direction in Testing

Lee Hilborne, MD, MPH, FASCP, DLM(ASCP)^{CM}, a past president of ASCP, led a general session, Choosing Wisely: Appropriate Test Utilization, to identify ways for pathologists and laboratory professionals to engage the clinical team in a dialogue about the clinical utility of the tests they offer. Expert panelists were Gary W. Procop, MD, MS, FASCP, chair of Molecular Pathology at the Cleveland Clinic, and Elaine Jeter, MD, medical director of Palmetto GBH, one of Medicare's largest insurers.

A third general session focused the spotlight on the dramatic advances in pathology informatics and the expanding role that informatics is playing in improving the delivery of health care. Clinical informatics experts Bruce Friedman, MD, FASCP, and Ulysses Balis, MD, both of the University of Michigan, Ann Arbor, Mich., explored these advances and encouraged both pathologists and laboratory professionals to embrace this new technology.

"This is a challenging time in the history of health care, with implications to the practice of pathology and laboratory medicine," says Mark Tuthill, MD, FASCP, a leader in the Association for Pathologist Informatics, who led the informatics general session, Preparing for Seismic Shifts in Pathology Informatics.

Honing Lab Management Skills

This year, ASCP 2013 Chicago brought together the combined expertise of ASCP, the American Pathology Foundation (APF), and the Society for Hematopathology to present specialized content that addresses emerging issues in these respective fields.

ASCP collaborated with APF to provide more than 80 hours of education in laboratory management and offered a special opportunity for attendees to take several sessions as part of the Lab Management University certificate program.

Meanwhile, the world's leading specialists from the multidisciplinary Myelodysplastic Syndromes (MDS) cancer team gathered at ASCP 2013 Chicago to present an interactive symposium to discuss ways that pathologists, oncologists, researchers, and others who care for patients with MDS can improve their communication and more accurately diagnose the deadly blood disorder. The symposium, The Diagnosis, Classification, and Clinical Care of Myelodysplastic Syndromes (DC3-MDS), and a simultaneous live webinar were funded by an educational grant from the Celgene Corporation, based in Summit, N.J.

Travel Grants for ASCP 2013 Chicago

For the first time ever, ASCP provided $1,000 ONELab Travel Grants to five laboratory professionals to attend ASCP 2013 Chicago. The grants, intended to support laboratory professionals in expanding their scientific knowledge and advancing their careers, covered the cost of airfare, hotel accommodations, and incidentals to attend the meeting. The recipients also received complimentary registration.

Implications of U.S. Supreme Court Ruling

The U.S. Supreme Court's landmark ruling on June 13, overturning Myriad Genetics, Inc.'s patent on BRCA1 and BRCA2—gene alterations associated with an increased risk for breast and ovarian cancer—brought hope and relief to many in the healthcare community, according to ACLU attorney Sandra Park, JD.

Ms. Park, who represented ASCP and 19 other plaintiffs in the lawsuit against Myriad Genetics, discussed the case and the implications of the ruling during a special session at ASCP 2013 Chicago.

"I felt strongly that if we got to the U.S. Supreme Court, we would win the case, if it were based only on legal arguments," she says. "It was a long shot because the court only takes on a small number of cases."

With the lawsuit over, millions of women will now have access to affordable testing to determine their risk for the inherited form of breast and ovarian cancer, and men with a family history of the mutation will also be afforded the option of testing by laboratories worldwide for testicular and other related tumors. Researchers now have rights to study the DNA sequence for other potential opportunities to evaluate the BRCA1 and BRCA2 genes' relationship to other cancers.

ASCP Awarded ACCME's Six-Year Accreditation

The American Society for Clinical Pathology in July 2013 received Accreditation with Commendation status for six years by the Accreditation Council for Continuing Medical Education (ACCME). This award reaffirms ASCP's position as the premier CME provider for pathologists. Six-year accreditation is the longest term that ACCME allows. Accreditation with Commendation is based on commendable and exemplary practices and is awarded to only about 8 percent of all accredited CME providers. ASCP has received six consecutive six-year accreditations, beginning in 1983.

ACCME accreditation seeks to assure both physicians and the public that continuing medical education activities provided by ASCP meet the highest standards of the Essential Areas, Elements, and Policies for Accreditation as specified by the ACCME.

Grant Awards Expand Education, Global Outreach

ASCP has been awarded several significant grants this year that will allow the Society to provide improved education and global outreach that will ultimately improve patient outcomes.

The Pfizer Foundation has provided an educational grant to develop a program titled EnGAging an Interdisciplinary Team for NSCLC Diagnosis, Personalized Assessment and Treatment (GAIN): A European Initiative. ASCP is a subcontractor for this GAIN European Initiative, in collaboration with the American College of Chest Physicians and the France Foundation. The initiative, which began in July, is an extension of a program launched last year in the United States to improve the diagnosis and treatment of patients with the deadly non-small cell lung cancer (NSCLC).

The Art and Science of Biopsy

ASCP received an educational grant from Genentech to develop a three-part series of educational sessions at ASCP 2013 Chicago that examined the challenges of gathering a high-quality biopsy to make a diagnosis of breast cancer. The three sessions in the "HER2 Breast Cancer Quality Testing Subtrack" collectively tell a story, identifying the core competency needs of obtaining a high-quality biopsy specimen, best practices of obtaining the specimen, and solutions.

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