New Biorepository Guidelines Raise Concerns

A new framework intended to guide management of cancer biological specimen resources has generated as many questions as answers since it made its first public appearance in May.

The National Cancer Institute guidelines spell out the best practices for collecting, storing, and disseminating human cancer tissue and related “biospecimens,” a loose term covering any biological material collected from an individual.

Most biobank managers appreciate the need for more standardization, which was first recommended by the Institute of Medicine. But the details of the expanded informed-consent procedures, new operating systems, and expected increased costs to make recommended upgrades have some wondering whether it will be too much for some banks to handle.

“I think if these first-draft federal guidelines become the standard for all NCI-supported biorepositories, a lot of them are going to go out of business,” said Virginia LiVolsi, M.D., a pathologist at the University of Pennsylvania in Philadelphia and principal investigator of the eastern division of NCI-funded Cooperative Human Tissue Network. “In reading the guidelines there were several issues where I said, ‘This will close us down.’”

Carolyn Compton, who leads the NCI effort as director of Office of Biological and Biospecimen Research (OBBR), said she expected the guidelines would generate concerns, which is why they are discretionary. At this point the guidelines are intended to help biorepository managers see where NCI is headed with its funded banks.

“We are going to give [existing biorepositories] a grace period because these are high-level guidelines that have to do principally with good laboratory management, and most of our biorepositories already do these things,” said Compton. “But for those biorepositories that don’t, this may come as a bit of a rude awakening, and they will require some adjustment. We are going to give people time to make financial and infrastructural adjustments required to meet these guidelines.”

**Behind the New Rules**

The NCI guidelines are the culmination of 2 years of effort, starting with a 2004 survey by the National Cancer Advisory Board that showed NCI-supported biorepositories are operating in an ad hoc manner, making it difficult to coordinate and share resources.

Compton said that the guidelines reflect a complex process that involved surveying managers of all NCI-funded biorepositories, convening meetings to gather input, and circulating drafts among administrators both nationally and internationally.

Many tissue bank directors got their first look at the guidelines when they appeared in the *Federal Register* in May for a 30-day public-comment period. Many investigators applauded NCI for its effort in putting together the guidelines, and most agreed that uniform procedures were long overdue.

“If you do not have these guidelines in place and you are not following these guidelines, then simply you are not operating a credible bank,” said Peter Geary, director and CEO of the Canadian Tumour Repository Network (CTRN).

Geary reviewed the proposed rules, discussed them with NCI administrators, and circulated them among members of the CTRN before they were made public. He says they closely mirror Canadian regulations, which are compulsory for members of CTRN, and are similar to guidelines being developed through the Marble Arch Working Group, a group of biobank leaders from 15 countries who are working to harmonize tissue banking internationally.

But other tissue bank directors wonder how the guidelines would apply to existing tissue resources. Most of the concerns raised revolve around whether retrofitting older banks, which have evolved their own operating systems, will be too onerous. Their issues included an informed-consent procedure that some perceive as too burdensome, worries about the increased financial burden, and the feasibility of reaching some of the recommended clinical parameters.

LiVolsi outlined her main objections in a letter to the OBBR, stating that some of the first-generation guidelines “seem draconian.” Specifically, she is concerned about a draft informed-consent procedure that would require patients to give detailed instructions on how their tissue may be used, including whether data from their medical records may be associated with the tissue and whether the tissue may be used for
I think it is a very unfortunate policy to have donors dictate what their tissue samples could and could not be used for,” said David Korn, M.D., senior vice president of the American Association of Medical Colleges. Korn argues that it is impossible to predict advances in technology, so tissue donors should not dictate specific uses for their tissue. He says that he “argued strenuously” against the policy at an NCI-sponsored meeting convened to discuss the issue. “They decided to go another way,” he added.

LiVolsi said that she believes asking patients to specify in detail how their tissues are used could harm both the research and the patients themselves. “They have already been faced with numerous forms to fill out and sign, and in their somewhat concerned state or distressed state, administering consent—even if it were physically feasible—would probably not reflect true informed consent,” she wrote in her letter to OBRR. Also, the patient admissions system at Penn involves more than 100 points of access, making a uniform consent procedure difficult, she said.

Grace Period

Compton said the guidelines are intended to anticipate the future needs of researchers using technologies to probe the cancer genome and proteome on a large scale, such as the NCI’s cancer genome atlas project. Such projects, she said, will require tissue samples that have detailed clinical annotation, a feature of few current tissue banks. For example, new guidelines call for “a high level of biospecimen annotation, consistent across NCI-sponsored biorepositories, recording key data, such as time to banking, time of ischemia (loss of blood supply to the tissue), time of biospecimen excision, character of chemical preservation, time of fixation, etc.” The guidelines also state that all such data should be tracked in an approved, secure bioinformatics system.

However, William Grizzle, M.D., Ph.D., immediate past president of the International Society for Biological and Environmental Repositories, points out that the NCI is aiming for what he calls “platinum specimens.” “I question the demand for these platinum-level specimens,” said Grizzle. “These specimens will be very expensive. When you get above $100 per specimen, only big pharma can afford it. The individual investigator can’t afford these types of specimens.”

Grizzle wonders what will become of the Cooperative Human Tissue Network, a network of six NCI-funded repositories that provide biomedical researchers with access to human tissue for laboratory-based research.

LiVolsi said the guidelines might spell the end of banks that serve many individual investigators. “What happens to the other thousands of researchers around the country that don’t have access to the infrastructure required to maintain this kind of bank?” she asked. “Obviously, if they are not going to get NCI funding or NIH funding, that’s it. Private funding is not going to hold these banks together. It’s far too expensive.”

The question of who will pay for the required upgrades and maintenance of biorepositories remains open. There is no existing NCI program that would cover the new infrastructure.

“From the research perspective it is probably going to be terrific [to have these biospecimens available], but who is going to bear the cost?” asked Sarah Dry, M.D, director of the Tissue Procurement Core Laboratory Shared Resource at UCLA’s Jonsson Comprehensive Cancer Center. “I don’t make money on my bank; I lose money on my bank. I think that’s true of banks across the country. We’re already losing money on these banks, so to add on the additional costs that are going to be required, I think that’s asking a lot.”

For example, the new guidelines direct biorepositories to “eliminate unsecured, ad hoc databases, such as those recorded in Excel, Access, and FileMaker Pro, and manage data by the central informatics system.” But Dry points
out that many tissue banks across the country have spent substantial time and money to implement their own data management systems.

“There are a lot of excellent home-grown systems out there,” says Dry. “Is the NCI going to grandfather those in, and how are they going to determine whether to grandfather those in? If you are only going to allow a certain limited group, people might have to fork out several hundred thousand dollars for a system. It’s a big expense and it’s not clear who is going to pay for that.”

The NCI’s Compton says that the guidelines will continue to evolve and that public comments will be carefully considered. There is no timetable in place yet to make the guidelines mandatory, but Compton said that ultimately the NCI plans to develop an accreditation program for all NCI-funded biorepositories.

“The second mechanism, which is even further down the road, and which will have even bigger teeth, we hope will be linked to the granting mechanism,” said Compton. “Ultimately the NCI would like to be able to say, ‘If your research is scientifically meritorious, we will fund it if and only if you are using biospecimens from an accredited biorepository that follows NCI guidelines.”

Christopher Fletcher, M.D., director of surgical pathology at Brigham and Women’s Hospital at Harvard Medical School in Boston is circumspect about how long it will take to get the two large institutional banks he runs into compliance.

“An awful lot of what is in [the NCI guidelines] is something we are currently trying to put in place for [Brigham and Women’s Hospital and Massachusetts General Hospital], and we are beginning to appreciate that in order to do it properly we are talking certainly in excess of $1 million a year. Unless the NCI is suddenly going to start giving out huge grants to facilitate this, then I don’t think many people will be able to do it. Compliance will be a big problem.”

—Karyn Hede

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