Pricey cancer genome project struggles with sample shortage

When the ambitious Cancer Genome Atlas was announced in December 2005, the project's leaders said they would examine scores of tumors for mutations that promote cancer, which could then help develop targeted treatments.

But more than a year into the venture, they have found only a fraction of the tumor samples they need.

The three-year pilot phase of the project, pegged at more than \$100 million, aims to analyze 2,000 genes from 1,500 lung, brain and ovarian tumors. The full project is supposed to catalog the genetic changes in 50,000 samples representing more than 100 types of cancer.

That's a lot of samples—and scientists warned that this might be more than what the project would be able to find (*Nat. Med.* **12,** 719; 2006). At the same time, many researchers hailed this aspect of the study, saying that mutations associated with cancer often vary between individuals, making it difficult to identify the important, recurring changes.

"The samples in this project are key," says Daniel Haber, director of the Massachusetts General Hospital Cancer Center, who is not associated with the project.

"Each tumor seems to have mutations in different genes—in other words, not too many recurrent ones," Haber says. "To find the genetic commonalities you must have a large set of tumor samples."

So far, at least, things seem more complicated than researchers had hoped.

Based on 210 tumor samples, for example, scientists at the UK's Wellcome Trust Sanger

Institute have found nearly 1,000 different mutations, but all at low frequencies (*Nature*, **446**, 153–158; 2007).

"The end result is you need a larger number of samples," says Michael Stratton, one of the lead investigators of that study, which is unrelated to the atlas.

Even finding 210 samples that met the strict criteria was difficult, says Stratton. For example, 80% of each sample had to be comprised of tumor cells.

After scouring the US for two years the US National Institutes of Health (NIH), which oversees the atlas, in September 2006

chose three tissue banks to each supply 500 tumor samples. The banks have gathered about a third of that request.

Of 500 requested squamous cell lung tumors, for example, the Lung Cancer Tissue Bank of the Cancer and Leukemia Group B has 20 that meet the criteria, says Richard Schilsky, the bank's chairman.

The bank has more tumors, Schilsky says, but they were collected before the genome project began, and patients were not asked for the proper consent. To make the samples eligible, the bank would have to go back to each donor and explain that their genetic information would be entered into a public database. The bank collects about six or seven new samples each month but



Long haul: The Lung Cancer Tissue Bank has only 20 of the 500 samples required.

at that rate, it would take at least six years to meet the goal.

The Gynecologic Oncology Group, one of the three chosen banks, was asked to supply a subset of ovarian tumors and estimates that it has about 500 in its Columbus, Ohio, bank. Most of those are likely to qualify but about a third don't have the proper consent from donors, according to Michael Birrer, the group's vice-

The bank will have to revise consent forms and get them approved by the hospitals or other sources that supplied the tumors. But those sources may not approve the new forms because of the ethical implications of sharing the donors' genetic data, Birrer says.

Fewer samples won't make the genome project impossible, but it will diminish the value of the results. If existing samples aren't enough, tissue banks may begin collecting large numbers of tumors for the project's next phase.

"I personally think it's not worth doing unless they have large numbers," says Haber. "The Sanger study looked at hundreds of tumors, so the next logical step is to look at a broader set of genes in thousands of tumors."

Emily Waltz, New York



documents the long-term persistence of the islets or their production of [pig] insulin in primates," she notes.

LCT's chief executive, Paul Tan, told *Nature Medicine* that the company has unpublished research showing statistically significant differences in insulin requirements between control and experimental groups of eight monkeys.

Sykes says the trial poses risks to the subjects and to society at large because of the potential for undetected pig viruses carried by the implants to mutate into forms that cause illness in people. Long-term effects of the method should be assessed in non-human primates before it is tested in people, she says.

The implants come from hygienically housed pigs descended from animals introduced by whalers to sub-Antarctic islands in the 19th century. Pigs on the islands have been found to be free of many viruses, bacteria and parasites commonly found in pigs elsewhere, according to the company.

Sykes says Russia does not have rules governing xenotransplantation. "It seems possible that Russia may have been chosen as the location for these studies precisely because its national health authorities do not have such standards for oversight and monitoring of xenotransplantation trials," she says.

LCT provided Nature Medicine with a list of journal articles

attributed to Skaletsky and says he has performed 1,500 xenotransplants in Russia, where the therapies are already commercially available.

But Skaletsky is unknown to many in the xenotransplantation research community, says Tony d'Apice, immediate past president of the International Xenotransplantation Association. "Literature searches suggest that he has not reported his vast experience so that it can be critically reviewed," d'Apice says.

The company's general manager, Paris Brooke, acknowledges inaccuracies in its online citations and says they will be remedied. Brooke adds that a paper due to appear in the journal *Xenotransplantation* in March will show the continued production of pig insulin after ten years in a human diabetic who received a prototype implant in a trial approved in New Zealand.

Although the trial will be conducted in Russia, Brooke says, it has been designed to meet criteria set by the US Food and Administration

"LCT would not have proceeded with this application if the company was not confident that all regulatory and ethical standards would be adhered to," she says. The company is awaiting approval for another human trial in New Zealand and for trials in the US.

Simon Grose, Canberra