

To mimic what happens in actual tumors, researchers utilized a breast cancer cell line that created indolent tumors when xenografted into mice. From the same cell line, they generated a panel of 18 subpopulations, or subclones, by overexpressing in each subclone a different protein linked to cancer progression.

They then compared the phenotypic properties of tumors and clonal expansions in two experiments. In the first, mice were implanted with a single subclone that competed against its parental cells at a 1:18 ratio. In the second, mice were implanted with a mixture of the 18 different subclones. In both experiments, subclones that overexpressed the protein IL11 were able to drive tumor growth. In contrast, a subgroup that overexpressed the protein LOXL3 did not increase cancer growth despite taking over a large portion of the tumor.

“The minor subpopulation of IL11-expressing cells never grew to become a dominant clone, but it was still responsible for driving tumor outgrowth,” says Polyak, adding that IL11 appears to change the tumor microenvironment by recruiting stromal cells and promoting angiogenesis.

Researchers also observed that when all 18 subclones were present in the same tumor, they interfered with one another’s expansion. “Clonal interference can limit tumor growth,” Polyak says. “Decreasing heterogeneity—which sometimes happens in treatment—is not always good because you might be favoring the growth of cancer cells with less favorable properties such as those resistant to treatment.”

The best treatment approach, she says, would be to develop drug combinations based on the heterogeneity of the tumor. Currently available drugs could be applied more effectively if scientists better understood their effects on the tumor, says Polyak.

“Further studies will hopefully help us identify and target the true drivers and potentially slow down the growth of the tumor, even if we cannot cure it,” she says. ■

Regulation May Stifle Research in Europe

The European Society for Medical Oncology (ESMO) is worried that a

proposed European Union (EU) General Data Protection Regulation about the handling of personal data could have unintended consequences for cancer research. Specifically, ESMO is concerned that the wording of the regulation might be interpreted as requiring a patient’s explicit—and repeated—consent prior to using their data or tissue samples in any new studies.

Such a stipulation “may put at stake the survival of retrospective clinical research, biobanking, and population-based cancer registries in the EU,” writes Paolo Casali, MD, author of the official ESMO position paper, published in August and endorsed by nine other European cancer-related organizations (*Ann Oncol* 2014;25:1458–61). Repeatedly needing to seek consent would be “time-consuming, administratively burdensome, expensive, and intrusive into patients’ lives,” he says.

Instead, ESMO calls for a “broad, one-time consent.” This way, fully informed patients could agree from the outset that their data and/or tissues can be used for future research unless they specifically withdraw their consent. This arrangement would mitigate the risk of cancer research grinding to a halt due to the need to obtain explicit consent for each new study.

The paper notes that existing safeguards at biobanks already adequately protect a person’s privacy, and that adapting those safeguards as new situations arise should provide continued protection. Furthermore, Casali says that the publication of research studies involves aggregate data, not individual results or identities.

When it comes to population-based studies, Casali argues that if individual patients are allowed to opt out, “the relevant registry will be incomplete or unrepresentative, and can lead to incorrect conclusions.” Even if the number of patients opting out is small, obtaining consent from everyone in a country or region “would be almost impossible.”

The European Commission, European Council, and European Parliament are still determining their respective positions on the regulation, after which joint negotiations over the final text will begin, likely in 2015. ■

New Grants to Boost Genome Sequencing

The National Human Genome Research Institute (NHGRI), part of the NIH, awarded \$14.5 million in grants in August to eight groups of researchers in industry and academia who are working to make genome sequencing speedier, more accurate, and more informative.

Thanks to next-generation techniques, the cost of sequencing a human genome has plunged by more than 99% in less than 10 years, and now runs as low as \$1,000. Plummeting prices have opened up numerous opportunities for researchers, such as sequencing full tumor genomes to uncover gene variants that drive abnormal growth. But for clinical uses, “it’s still more expensive than you want it to be for an individual patient,” says Mark Akesson, PhD, of the University of California Santa Cruz Genomics Institute, who received one of the grants.

The awards are the most recent—and the last—from the NHGRI’s Advanced DNA Sequencing Technology program, which began in 2004. Over the last 10 years, the program “has in my opinion been just critical for advancing sequencing technology,” says Jay Shendure, MD, PhD, of the University of Washington in Seattle, who’s also a grant recipient.

Four grants went to researchers who are seeking to improve what may be the next big thing in genome sequencing: nanopore sequencing. Next-generation sequencing involves breaking up DNA into small chunks that can be less than 100 bases long. Copying and sequencing the pieces produces “reads,” and software assembles the jumble of reads into a full genome. Nanopore sequencing, in contrast, works by reeling DNA strands through tiny holes, or nanopores, in a lipid layer or other material. An electrical current passes through each nanopore, and as the DNA strand moves through the pore it causes characteristic changes in the current that allow researchers to determine the identity of the DNA bases.

Research labs already perform nanopore sequencing, and the first commercial device, the size of a flip phone, is being beta tested. The advantage of nanopore sequencing is that it

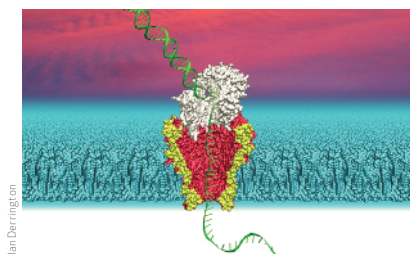


Illustration of a nanopore derived from a genetically modified bacterial membrane channel being used to sequence DNA.

provides longer reads that are easier to assemble into a final sequence.

Akeson's lab plans to test how well nanopore sequencing recognizes DNA methylation and other epigenetic modifications in the human and mouse genomes. Changes in the pattern of these modifications can have key roles in cancer—for example, tumor suppressor genes are often heavily methylated in cancer cells. However, standard next-generation methods remove the modifications, Akeson notes.

Shendure's team is developing techniques that fill in information that next-generation sequencing skips. For instance, next-generation sequencing can't reveal the haplotype, or which gene variants occur together on the same chromosome copy.

However, he and his colleagues were able to reconstruct the haplotype for the entire genome of the famous HeLa cell line by sequencing a library containing large DNA fragments. With their grant, Shendure's team hopes to make techniques like this one cheaper and easier to use. "Thousand-dollar genomes are only 90% complete," he says. "What we are trying to do is get you that last 10%."

NHGRI is planning future grants that could fund more work on DNA sequencing technologies. ■

HPV Testing More Reassuring than Pap

Pap tests have long been the cornerstone of cervical cancer screening in the United States, but a negative test for human papillomavirus (HPV) may better predict a woman's risk for cervi-

cal cancer than a negative Pap test, according to a study by NCI researchers published in July (*J Natl Cancer Inst* 2014;106:dju153).

The researchers analyzed data from more than a million women between ages 30 and 64 in the Kaiser Permanente Northern California health care system. Every 3 years between 2003 and 2012, the women were screened for cervical cancer with Pap and HPV tests. After analyzing the outcomes, the researchers concluded that a woman's 3-year risk of developing cervical cancer following a negative HPV test was just 11 per 100,000, roughly half the 20 per 100,000 for women who'd had a negative Pap test.

The researchers weren't particularly surprised by the results. "We expected to find that HPV testing was superior [to Pap testing] because we know that a persistent infection of cancer-causing types of HPV is the causal agent of cervical cancer," says Julia Gage, PhD, MPH, first author of the study. "In the absence of HPV, a woman's risk of cervical cancer is extremely low."

Currently, the U.S. Preventive Services Task Force and many professional societies recommend two strategies for cervical cancer screening: either Pap tests every 3 years or both HPV and Pap tests every 5 years. Although the optimal screening interval for primary HPV testing has not been determined, based on current screening guidelines, a negative HPV test might provide reassurance against cancer for 5 years, compared to 3 years for a Pap test. Using those intervals, the researchers estimated that in a hypothetical population of 1 million women, changing from giving Pap tests every 3 years to giving HPV tests every 5 years would result in nearly 2 million fewer tests over a 15-year period.

If the interval for primary HPV testing is set at every 3 years, it "might provide as much, if not more, reassurance against precancer and cancer, compared to primary Pap testing every 3 years," the researchers note. Determining the ideal screening interval is a critical next step, they say. ■

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- **The NIH launched ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials) to identify patients with early-stage lung tumors that harbor genetic changes in *ALK* and *EGFR*** and evaluate whether drugs targeted against those changes can improve survival. Those with the genetic changes will be eligible for one of two treatment trials; all screened participants, regardless of their tumor's mutations, will be followed for 5 years.
- **The FDA issued final guidance on the development, review, and approval or clearance of companion diagnostics**, which are tests used to identify patients who will likely benefit from treatment with a particular drug. The tests are commonly used to detect certain types of gene-based cancers.
- On July 31, **the FDA also notified Congress of its intent to publish a proposed risk-based oversight framework for laboratory-developed tests**, which are designed, manufactured, and used within a single laboratory. The agency must wait at least 60 days from that date to publish the document.
- UK-based **Wellcome Trust announced that it will invest £27 million in a state-of-the-art genome-sequencing hub for Genomics England**, the government's project to decipher 100,000 complete genetic codes. The funding will allow Genomics England to become part of the Wellcome Trust Genomics Campus in Hinxton, which is also home to the Sanger Institute, the European Bioinformatics Institute, and several small biotech companies.
- **The FDA approved Exact Sciences' Cologuard, the first stool-based colorectal screening test** that detects the presence of red blood cells and DNA mutations that may indicate the existence of cancer or a precursor to cancer.
- **Ohio's Cleveland Clinic unveiled plans to build a \$276 million, seven-story cancer center**, which will bring all cancer-related services, including imaging, under one roof. The additional space will also allow the institution to increase the number of patients it can accommodate in clinical trials. Groundbreaking was anticipated at the end of September, with completion slated for early 2017.

For more news on cancer research, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.