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# Next-Generation Sequencing May Be Key to Personalized Treatments [1]

Discovery [2]
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In 2008, The Cancer Genome Atlas (TCGA) Research Network published its first paper — an article in *Nature* that documented the DNA sequences of some 600 genes in 91 brain tumor samples.

“It was a herculean effort,” says Wendy Winckler, then a member of TCGA and now executive director of Next Generation Diagnostics at the Novartis Institutes for BioMedical Research [3] in Cambridge, Mass. “It took almost a year to generate all that data.”

Now, she says, just five years later, that same experiment would take less than two weeks. And scientists would not be limited to looking at just 600 genes. They could look at every gene — about 21,000 — in the entire human genome.

Why are scientists so intent on examining all these genes, a process known as “sequencing”? It is because understanding genes on a deep level may help to unlock many of the mysteries surrounding our most intractable diseases, including cancer, heart disease and degenerative conditions such as Alzheimer’s. Ultimately, the information gained from such studies may lead to new and far more effective treatments.

The dramatic increase in sequencing speed is thanks to the development of new methods and technologies. Conventional sequencing equipment reads long chains of DNA “letters” — the building blocks of genes — linearly. Researchers reimagined this process, departing from the plodding approach of the past. The latest equipment performs thousands, if not millions, of sequencing reactions at the same time.

“The cost of sequencing has declined exponentially, and the amount of information you can get has increased a lot,” says Jordi Barretina, who runs a lab in Oncology Translational Research at Novartis. “That’s what is allowing the current explosion of genomic data in cancer and other diseases.”

So how is this acceleration in researchers’ ability to examine genes affecting cancer research and drug development? And, most importantly, what does it mean for patients?

## Benefits of Speed

“One of the main advantages of modern sequencing technologies,” says Barretina, “is that you can actually detect many different types of genetic alterations at once.” This gives researchers greater insight into the range of genetic faults characteristic of cancer.

The new technologies also improve the sensitivity of sequencing, allowing researchers to detect low-level genetic variants, which is particularly important when analyzing cancer samples, Winckler says. “When you take a piece of tumor, you have a mixture of normal cells and tumor cells. Depending on the patient and the tumor type, that ratio can differ quite a bit,” she says. With previous sequencing methods, if the ratio of tumor cells to normal cells were too low, researchers would miss mutations.

Teams also missed mutations because they sequenced a subset of genes rather than all genes to save time and money. In TCGA’s study of a brain tumor known as a glioblastoma, for example, “We missed what we now know to be one of the most commonly altered genes in glioblastoma: a gene called IDH1,” Winckler says. The gene simply “wasn’t on our list.” It was only through a later, more comprehensive sequencing study that IDH1’s role in glioblastoma was discovered. The finding spurred a new drug discovery effort in the field.

## Potential  Beyond Drug Discovery

Such next-generation sequencing approaches are used by pharmaceutical companies such as Novartis, as well as many academic centers, some of them involved in cancer genome sequencing consortiums, to generate lists of genes that are frequently mutated in certain cancer types, explains Barretina. “Once you are armed with that knowledge, you can start designing drugs that will actually target those genetic alterations in particular cancers.”

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>
> **Wendy Winckler**, Executive Director of Next-Generation Diagnostics at Novartis Institutes for BioMedical Research

Cataloging genetic alterations of cancer cells was one of the principal goals behind the Cancer Cell Line Encyclopedia — a massive undertaking and collaborative project between Novartis and the Broad Institute, also based in Cambridge, Mass. The encyclopedia provides genetic information on approximately 1,000 different cancer cell lines originally derived from patients’ tumors. The data is released publicly so that researchers around the world can mine it. Cell lines are easy-to-use cancer models that allow researchers to investigate cancer biology and test the effectiveness of potential drugs against various types of tumors. The Cancer Cell Line Encyclopedia also contains corresponding data detailing which cell lines respond to which drugs.

Giordano Caponigro, one of the leaders of the Cancer Cell Line Encyclopedia collaboration, is now senior director in Oncology Translational Research at Novartis. He explains how next-generation sequencing is increasing the value of this resource. “When the Cancer Cell Line Encyclopedia started, next-generation sequencing hadn’t really hit its stride, but as it went on we realized this was an important technology,” he says. “Shortly, whole-genome sequencing of the full set of cancer cell lines will be complete, which will help with the development of

highly accurate diagnostic tools and effective new cancer treatments.”

## Tailoring  Trials and Treatments

Such characterization of cancer cell lines allows researchers to home in on possible targets for new drugs and also helps them determine which patients will respond to an existing drug. Should a patient carry similar mutations to those in one of the 1,000 cell lines in the encyclopedia, for example, the pharmacological data for that line might predict which drugs would be appropriate for the patient, and even steer the patient to suitable clinical trials in which he or she can participate.

“More and more patients, or their primary care physicians, are understanding that rapid sequencing of their tumor DNA can point them immediately towards clinical trials where they might derive the greatest benefit,” says Caponigro. “I think it’s really empowering for the patient.”

Additionally, patients who have been through clinical trials already are informing further drug development, says Winckler. “We are doing retrospective research, after the trial has been conducted, running our genetic test, and asking: What is going on in the people for whom a drug does not work?”

Winckler says her ultimate dream is that the research will lead to personalized, targeted therapies becoming the standard way that most cancers are treated. “As soon as a patient is diagnosed, we should quickly determine what’s driving the cancer and use that information to select an appropriate therapy,” she says. Importantly, this will “hopefully spare a lot of the pain and suffering associated with the current standard of care,” she adds.

In the meantime, spending one’s days working toward the goal of tailored treatments is a deeply rewarding privilege, Barretina says. “I don’t think you need a lot more motivation than knowing that if you succeed in what you do, you might actually help treat cancer patients.”

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