tions, sensors for gas seeping out of ocean sediments and volcanoes, and satellite-borne remote-sensing tools. Overlapping techniques are needed, says Diana Roman, a volcanologist at the Carnegie Institution for Science in Washington, D.C., who helped organize the workshop. For example, a burst of seismic unrest at a volcano could mean a fresh injection of magma—or not. The only way to tell is to compare seismic observations with simultaneous measurements of surface deformation and gas emissions.

Seafloor instrumentation will also play a key role in the SZO. GPS doesn't work underwater, but researchers can measure crustal motion using ship-based sonar to track the locations of acoustic transponders on the seabed. Another approach involves installing pressure gauges that can precisely measure water depth, a proxy for how the sea floor rises and falls during slow slip events. Some hope the SZO might enable the development of these and other novel instruments, like autonomous ocean "gliders" for acoustic surveys or seafloor cables for real-time data collection.

Basing the instrument network at least partly in the United States—for instance, along the Cascadia subduction zone in the Pacific Northwest—would provide an opportunity to collaborate with USGS, which is developing a parallel project, informally called the Ring of Fire, to monitor and forecast natural hazards in subduction zones.

On the other hand, many scientists—and NSF—recognize that studying subduction zones outside the United States would offer different lessons, and an incentive for international participation and funding. "Why not put it in three different places?" asks Kerry Sieh, a geologist and the director of the Earth Observatory of Singapore. For example, he suggests choosing one U.S. location, one along the Peru-Chile Trench in South America, and one along the Sunda Trench in Indonesia. Others, including Gomberg, say the SZO could be made up of much smaller pilot projects, or could even be an umbrella organization that merely facilitates collaboration and data sharing.

The different options imply wildly different price tags. At the upper end of the spectrum would be something like EarthScope, which cost roughly $200 million to build, was subject to a lengthy review process, and had to survive congressional budget negotiations.

In the next few years, pressure on the MREFC budget will ease up, with the completion of other major projects, such as the Large Synoptic Survey Telescope in Chile. It's too early to say whether the SZO will follow the same funding model as EarthScope, says Anne Meltzer, a seismologist at Lehigh University in Bethlehem, Pennsylvania, who helped spearhead the project. Although the MREFC could fund construction, a big project would need to find other ways to support ongoing science and operations. The payoff would be powerful, she says. "If we could marshal something on that scale we could really advance our understanding of subduction zone dynamics." ■

Julia Rosen is a writer in Portland, Oregon.

Earth's conveyor belts

Geoscientists are planning the Subduction Zone Observatory, which could place a diverse suite of sensors across the regions where ocean crust sinks below continents.

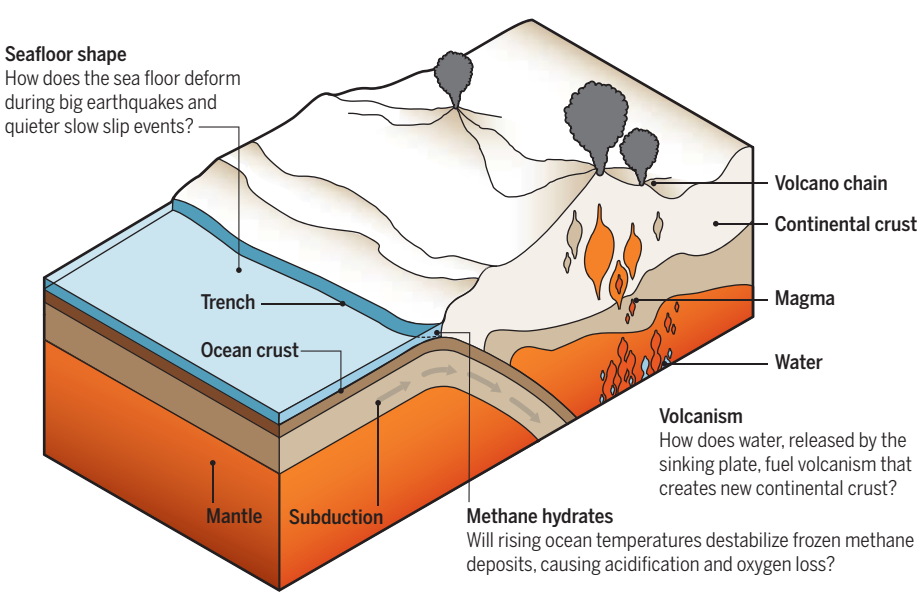


DIAGRAM: G. GRULLÓN/SCIENCE

CANCER

Using DNA, radiation therapy gets personal

Gene-based tests aim to predict who will benefit from radiation, or suffer

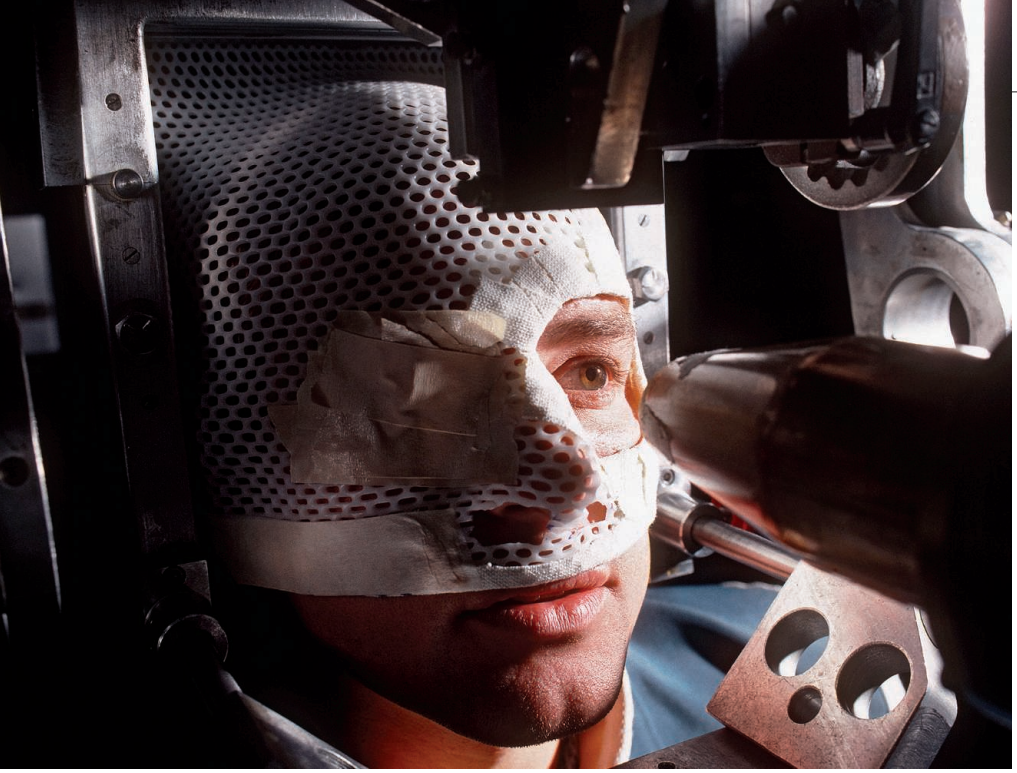
By **Elie Dolgin**

At most cancer hospitals today, medical oncologists routinely order genetic tests that help guide their treatment decisions. If the tumor has a certain DNA mutation, the patient may be a good candidate for a targeted drug therapy; if it overexpresses a series of genes, chemotherapy might work well. But down the hallway in the radiation ward, cancer patients typically get a one-size-fits-all course of radiotherapy, regardless of their genetics or those of their cancer.

A small but increasing number of radiation oncologists is hoping to change that. At the annual meeting of the American Society for Radiation Oncology (ASTRO) next week in Boston, researchers will describe their hunt for gene activity profiles in tumors that can help determine how susceptible the cancer will be to radiation. Others are looking for variations in patients' normal DNA that explain why some people tolerate radiation well, whereas others experience severe and lasting side effects ranging from trouble swallowing and memory loss to impotence and incontinence.

The work is still far from the cancer clinic, and some observers think it may be slow to realize its promise given the many false starts experienced by past gene signature tests for other conditions and the unique financial and logistical challenges of radiation oncology. "The process of advancing this might be like a wave lapping on the beach—a foothold here, a foothold there," says Siraj Ali, director of clinical development at Foundation Medicine, a cancer diagnostics company in Cambridge, Massachusetts.

But those looking for genetic predictors say there's an urgent need to personalize radiation therapy: Nearly two-thirds of people with cancer receive it, which means that anything that helps boost cure rates or mitigate



Unlike cancer drug therapy, radiation therapy for head and neck cancer is rarely guided by analyzing DNA.

toxicity problems could be a boon to patients. Most radiation oncologists, however, have focused almost exclusively on improving the machines and the targeting. "As a field, we've done very well on the technology side," says Judy Keen, director of scientific affairs at ASTRO in Arlington, Virginia. "Now is the time for the biology to really explode more."

One approach now under investigation is to look at gene activity in the tumor itself. That's the strategy of a University of Michigan (UM) spinoff company called PFS Genomics in Vancouver, Canada, which used breast cancer cell lines to identify a 51-gene expression signature of radiation sensitivity. Validation of the signature in patient tumor samples suggests it could help determine which women undergoing lumpectomies will benefit from radiation, which would do fine without it, and which patients won't respond and might thus need additional interventions.

Nearly all women get radiation after this kind of breast-conserving surgery, yet close to three-quarters of them may not need it, notes UM Ann Arbor physician-scientist Corey Speers, a PFS co-founder. "We're overtreating patients," says Speers, who will discuss the firm's risk-stratifying strategy at the ASTRO meeting. Felix Feng, another PFS co-founder, will also describe a 24-gene test for men with prostate cancer, designed to predict who will benefit from radiation after surgery.

Also at ASTRO, Javier Torres-Roca of the Moffitt Cancer Center in Tampa, Florida, will present a new concept he has dubbed the "genomic-adjusted radiation dose," which takes advantage of gene expression data from the tumor to indicate how much radiation each patient should receive. In recent years, Torres-Roca has published papers showing that a 10-gene test—which includes genes involved in DNA damage response, cell-cycle control, and epigenetic regulation—could retrospectively predict survival rates in patients undergoing radiation for a variety of cancers, including those of the brain, pancreas, and breast. Torres-Roca has founded a company called Cvergenx, which aims to market a system to help oncologists fine-tune radiation dosing to account for a person's genomic features. He argues that those whose gene expression test predicts low survival should get greater than average radiation doses. Some of his peers, however, express concern that the test doesn't account for radiation effects such as toxicity.

> ***"Now is the time for the biology to really explode more."***
>
> **Judy Keen**, American Society for Radiation Oncology

Many researchers are also hunting for gene variants that predict adverse reactions to radiation. Members of the international Radiogenomics Consortium, an effort backed by the National Cancer Institute in Bethesda, Maryland, are searching across the genomes of thousands of cancer patients for common polymorphisms linked to problems after radiotherapy. In July, they reported two new gene variants tied to urinary troubles such as incontinence in men whose prostate cancer had been bombarded with radiation. So far, half a dozen variants linked to radiation toxicity have been tallied—typically in "genes that control some aspect of the tissue or organ impacted by the complication," says consortium co-leader Barry Rosenstein from the Icahn School of Medicine at Mount Sinai in New York City—but the group may need at least twice as many to create a useful test.

Tim Ward in Manchester, U.K., a patient advocate with the consortium who suffers from rectal bleeding as a consequence of his own radiation treatment for prostate cancer 4 years ago, says that such a test could help people with cancer make more informed decisions. "Certainly, a lot of patients who have severe [gastrointestinal] problems say to me, 'If I'd known this was going to happen I may not have had the radiotherapy, because my life is completely blighted,'" he says.

But bringing a genetic test for radiation response to market will not be easy. "The number of hurdles we need to jump through to achieve that are not trivial," says Feng, who moved from UM Ann Arbor to the University of California (UC), San Francisco, earlier this year. Other DNA-based predictive tests—for drug responses, for example—often don't survive replication attempts by independent groups or in large populations. And evidence that tests to guide radiation therapy actually work could be slow in coming.

For starters, radiation is often given to cancer patients in the earliest stages of the disease, which means that it could take years to know whether genomic data can boost long-term survival or limit toxicity. In contrast, most new cancer drugs are tested in people with metastatic disease who often have just months to live. The centers that conduct radiotherapy (and the companies that manufacture the equipment) also have little financial incentive to weed out potential clients with such tests, so it's hard to attract the investment needed to validate any of these products.

Joanne Weidhaas, a radiation oncologist at UC Los Angeles, hopes to drum up commercial interest for the DNA test she's developing through a startup called Mira Dx by considering genetic biomarkers that can predict responses both to radiation and to certain drug treatments, including the cancer immunotherapies that have taken the pharmaceutical industry by storm. "For me, I need to make what's best for patients, and for the business people they need to make money," Weidhaas says. "And if you can do both, that's a path forward." ■

Elie Dolgin is a writer based in Somerville, Massachusetts.

PHOTO: RGB VENTURES/SUPERSTOCK/ALAMY STOCK PHOTO

Using DNA, radiation therapy gets personal
Elie Dolgin (September 22, 2016)
Science **353** (6306), 1348-1349. [doi: 10.1126/science.353.6306.1348]

Editor's Summary

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.