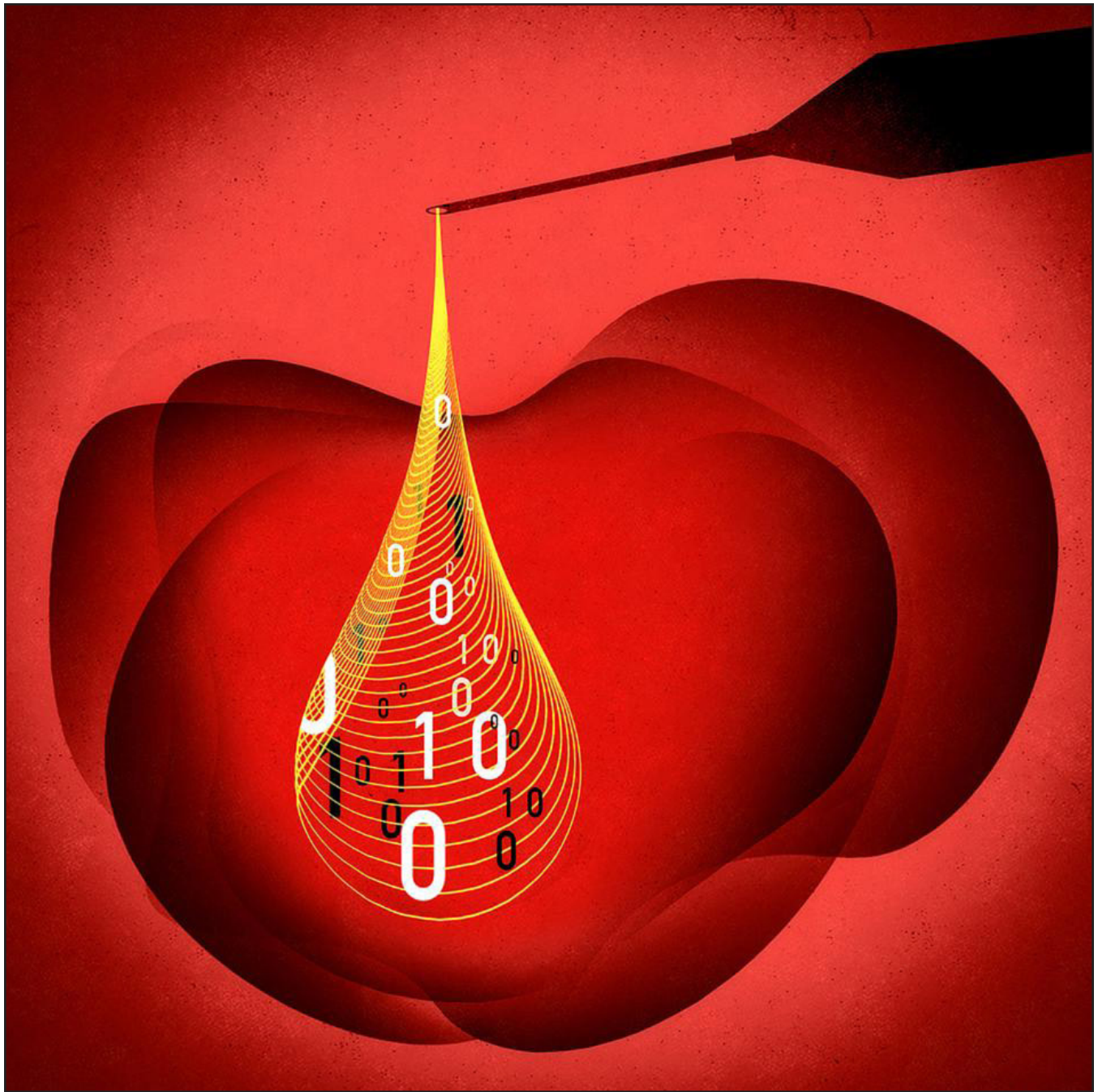


# Can Math Crack Cancer's Code?

New quantitative models focus on the hidden architecture of tumor cells



By ANDREA CALIFANO and GIDEON BOSKER

## Can Math Crack Cancer's Code?

At some point in their lives, about half of all Americans will hear the frightening words, “You have cancer.” For patients and families, the personal burden of cancer is staggering, and many scientists and physicians, though working heroically on new treatments, remain unsatisfied with the care that they are able to provide.

Much attention and excitement has focused lately on “precision medicine”—the targeted deployment of drugs to counter specific “driver” mutations in tumors and also to activate the body’s own immune system against cancer cells. These strategies have resulted in some real success stories, but not enough patients—especially those with metastatic breast, colon, lung and prostate cancer—are achieving the kind of lasting remissions that were expected. Worse, most tumors cannot be treated this way.

Researchers are continuing to refine these targeted treatments, but new approaches are needed—and here, as in many other fields, the answers may lie in the information revolution.

Disappointed with the slow pace of discovery and inclined to look for elegant, universal explanations for nature’s conundrums, many cancer researchers have increasingly been asking: Is there some sort of “Da Vinci Code” for cancer? And can we crack it using mathematics?

Quantitative modeling has been extremely successful in disciplines as diverse as astronomy, physics, economics and computer science. Can “cancer quants”—scientists applying quantitative analyses to the landscape of cancer biology—find the answers we seek? And, if so, what would the new paradigm look like?

This approach has been in the works for years at Columbia University (in the lab that one of us directs), and we are attempting to develop it commercially at the company that we co-founded, DarwinHealth. The idea is to integrate robotics and supercomputers to identify more universal tumor vulnerabilities, within a much larger segment of cancer patients, and to use single drugs and novel drug combinations to target them.

We are not alone on this track. An increasing number of systems biologists— Franziska Michor and Peter Sorger at Harvard University, Gordon Mills at the MD Anderson Cancer Center and Trey Ideker at the University of California, San Diego, among others—are also embracing this sort of strategy, with growing support from the National Cancer Institute.

As a result of this evolution, the focus in many labs has shifted from genes to proteins—the molecular machines that govern cell behavior, including cancer. But while genes can be readily sequenced, proteins are much harder to observe and measure.

There is mounting evidence that virtual, computation-based methods are particularly effective in detecting aberrant proteins in this hidden layer of cancer control. In our own labs, we rely on computational methods to pinpoint the “dark” proteins that constitute the command center of the cancer cell. Abnormal activity in these “master regulators” can result in rapid tumor growth and devastating propagation of cancer cells.

Perhaps most important, these proteins form tightly-knit modules—or “tumor checkpoints”—that represent the ultimate on-off switches in the cancer cell’s engine room, providing a new class of targets for anticancer therapy. There is already compelling evidence, widely published in scientific journals, to support the existence of such universal on-off switches for cancer.

Indeed, the more we use quantitative models, the more we understand that cancer isn't the result of a single gene going rogue—the premise of the mutation-based therapy approach. Rather, cancer develops when an entire gang of rogue proteins work in concert to thwart the defense mechanisms that cells use to keep cancer at bay.

This is no mere hypothesis. Clinical trials at Columbia, in patients with metastatic and drug-resistant breast cancer, have already started to evaluate how well novel, multi-drug regimens can target the aberrantly activated proteins in a tumor checkpoint. And in “N of 1” studies, also at Columbia—that is, studies in which a single patient is the entire trial—tumor checkpoints are being used to select the best therapy for 260 patients across 14 different kinds of previously untreatable tumors.

To identify master regulator proteins and tumor-checkpoint modules, DarwinHealth is using sophisticated tools such as the VIPER algorithm, which we presented recently in the journal *Nature Genetics*. Like astronomers and physicists discovering “dark” planets indirectly, from deviations in the trajectory of the stars around which they gravitate, we are able to use VIPER to begin to decode the hidden “oncotecture” of cancer—that is, the universal regulatory architecture of cancer cells.

It might seem counterintuitive to employ a virtual world to decode something as real as cancer, but predictions made by these methods are already undergoing rigorous clinical evaluation. These studies are geared to finding the specific drugs and drug combinations that, by short-circuiting the regulatory logic of the cancer cell, can help turn these tumor switches to the off position—permanently.

Setbacks are inevitable in this line of research. This is cancer, after all, and developing and testing new checkpoint-based drugs or innovative combinations is an expensive process that can take years.

But we are already seeing hopeful developments. Our individualized “N of 1” studies at Columbia suggest that toggling these on-off cancer switches may not require new drugs. Rather, it may be accomplished by drawing from a large tool kit of drugs already approved by the FDA—many of them inexpensive and no longer under patents—and from compounds available from late-stage clinical investigations. We are currently conducting a trial in collaboration with Drs. Kevin Kalinsky of Columbia and Jose Silva of Mount Sinai in New York to test how well a new combination of two FDA-approved drugs can shut down the tumor checkpoint of breast-cancer patients who no longer respond to conventional therapy.

Cancer researchers are only now beginning to appreciate how much they can learn by applying these new tools to one of medicine's most elusive challenges: disabling, reversing or subverting the aberrant regulatory programs that ignite perfectly normal cells and morph them into monsters that explode with destructive fury.

Over the centuries, and across countless areas of human need, we have seen the power of numbers to improve our lives. Increasingly, it looks as if this will hold for cancer, too. It may just be a matter of getting the math right.

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