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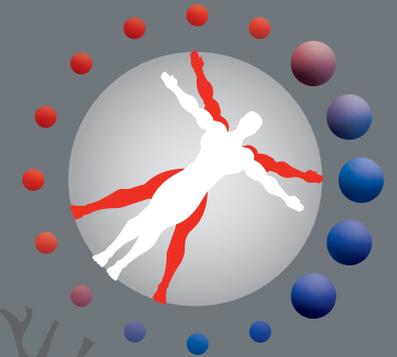


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# WIDENING THE PATH OF PRECISION CANCER MEDICINE

HOW DARWINHEALTH'S PROTEIN-HUNTING ALGORITHMS ARE HELPING THIS INNOVATIVE COMPANY ADVANCE CANCER THERAPY AND FILL THE GAPS LEFT BY MORE TRADITIONAL, GENE-BASED METHODS



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by Nicole M. Davis, Ph.D

The biopharmaceutical industry has celebrated some big wins in cancer in recent years, with a wave of new treatments that can rev up the immune system, igniting a fierce, all-out assault on patients' tumors. Yet as impressive as these new cancer immunotherapies are, their benefits are not surefire: only a small percentage of patients respond to them. Even the centerpieces of precision oncology — targeted drugs, such as gefitinib (an EGFR inhibitor) and trastuzumab (which blocks HER2), that are molecularly honed to defuse the actions of a tumor's faulty genes — possess similar weaknesses. Even for patients whose tumors harbor telltale genetic mutations, response is not a guarantee.

This apparent paradox of precision medicine has propelled some scientists to look beyond tumor genes and genomes, seeking a wider,

more unifying lens through which to view cancer and its treatment. For more than a decade, Andrea Califano, PhD, a professor of chemical and systems biology at Columbia University, has led a team to pioneer such an approach.

Using a combination of molecular and computational techniques, the scientists developed a method that can systematically scrutinize protein activity within cells and identify networks of proteins—so-called “tumor checkpoints”—that consistently misfire like a faulty circuit. These faulty circuits, the researchers discovered, not only underpin tumor growth, but also can be toggled on (or off) with drugs.

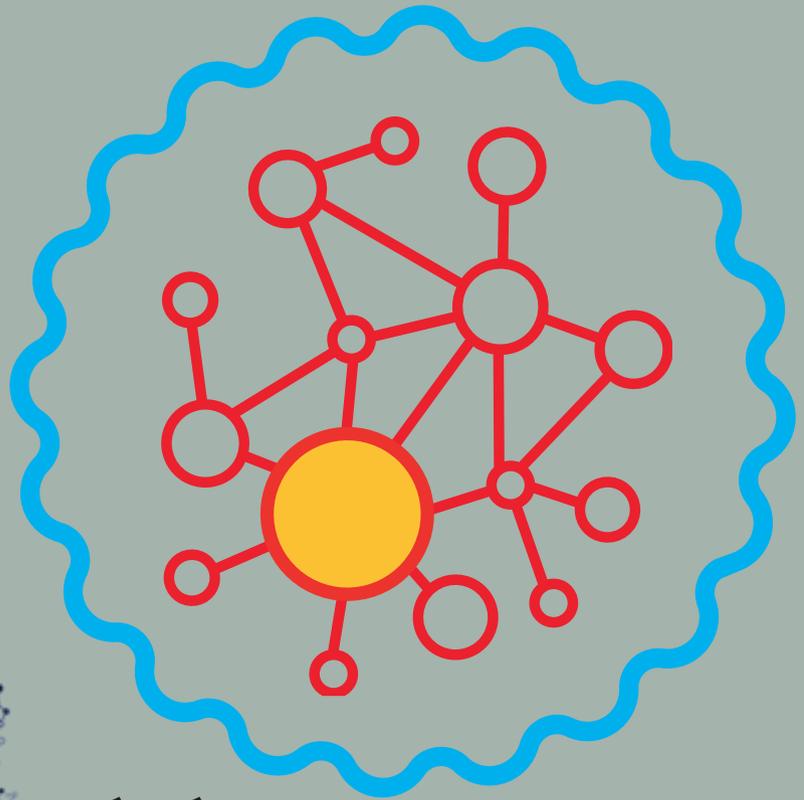
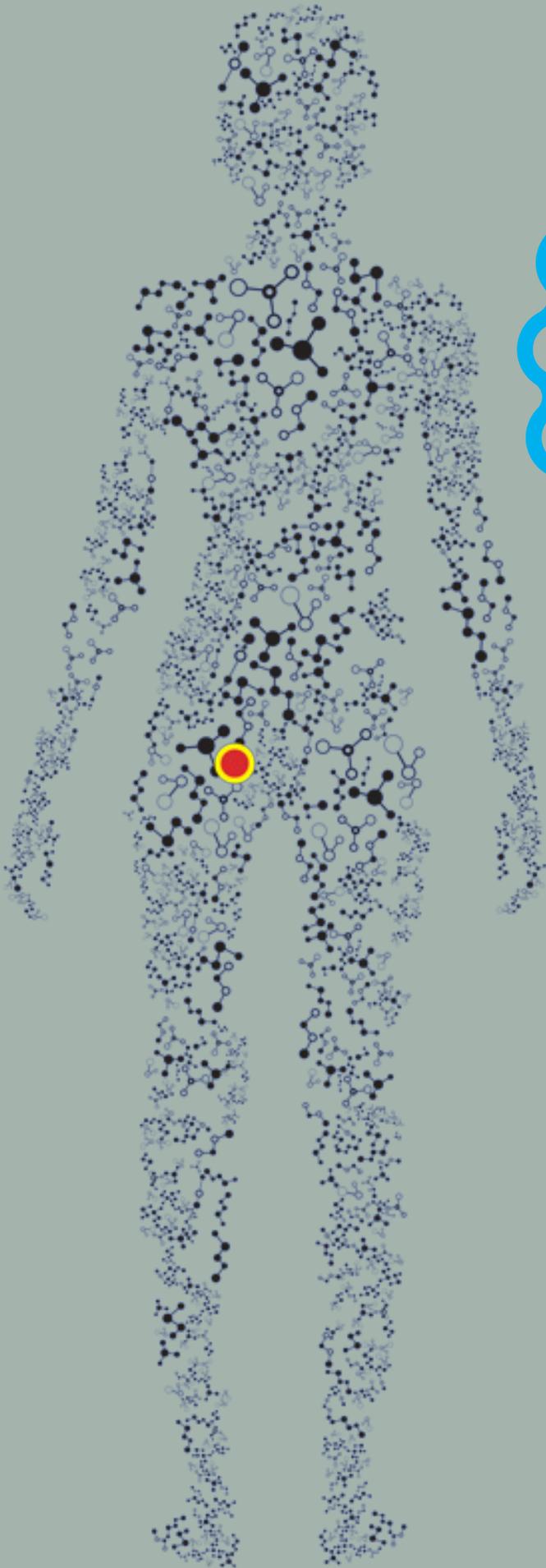
This work now forms the basis of a bold new biotech start-up called DarwinHealth, launched in the Spring of 2016 by Califano and co-founder Gideon Bosker, MD. The company is harnessing its

network-based method to develop a suite of diagnostic tests that can help pinpoint drugs and drug combinations with the potential to tame — and ideally eradicate — patients' tumors. Califano, Bosker, and their colleagues believe their approach could help fill the gaps left by more traditional, gene-centric techniques.

“If you can get to something that's really core — the hub and spokes — that's potentially more rewarding,” says Bosker, who serves as DarwinHealth's CEO. “I think that's one of the distinguishing factors between what we do and what many other organizations are doing, not to minimize the success of finding some magical ligand that stimulates immune cells,”

Unlike genomic-based approaches to cancer, which seek to unearth the so-called actionable





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mutations within a patient's tumor, DarwinHealth's technology reveals a hierarchy of wayward proteins, including the cancer's masterminds. Califano and his colleagues dub these "master regulators," and believe they constitute the molecular heart of a tumor — one that can be rendered lifeless with drugs, including FDA-approved as well as late-stage investigational compounds. Importantly, the researchers have found that these master regulators are often vulnerable to pharmacological intervention even if the genes that encode them are fully intact — in other words, lacking mutations.

"This is an important point," says Califano. "Some of the most exciting drugs that actually cure cancer — for example, glucocorticoids in T-cell ALL — target proteins that are never mutated in the disease." For Bosker and Califano as well as other experts, one of the major failings of precision cancer medicine is not only the abundance of patients who have no actionable mutations, but also the lack of long-term benefit even for those who do. Like conventional chemotherapy, molecularly targeted drugs can fail to fully eradicate patients' tumors, effectively sowing the seeds of disease recurrence by enabling the cancers to persist and spread.

Although DarwinHealth has been in operation for barely two years, it has already inked deals with a handful of pharmaceutical companies, including Daiichi Sankyo, Ipsen, and Karyopharm. Several clinical trials are also underway at major U.S. medical centers, including Columbia University, Mount Sinai, Memorial Sloan Kettering, and MD Anderson Cancer Center. Moreover, DarwinHealth recently secured CLIA certification from the state of New York for two diagnostic tests, DarwinOncoTarget and DarwinOncoTreat, which are now available through Columbia's Laboratory of Personalized Genomic Medicine.

### Beyond Stamp Collecting

Califano trained as a physicist and then spent 13 years working at IBM Research in the dawning days of computational biology. The field appealed to him because of the thorny, unanswered questions that were ripe for exploration. In contrast, "there weren't many large, unsolved problems in physics when I started out," he recalls.

While reflecting on various efforts to decode tumor genomes over the last decade, Califano jokingly cites an adage widely credited to Nobel laureate and physicist Ernest Rutherford: All science is either physics or stamp collecting. Califano believes these mutation-hunting endeavors, while useful in some ways, have largely failed to yield the robust returns many researchers hoped for. "There's been an enormous amount of stamp collecting," he says, jokingly. To be sure, the notion of analyzing genetic mutations in tumors is sound. Several decades of research revealed that the origins of cancer lie in mutated genes. Moreover, sweeping advances in DNA sequencing technologies paved the way for rapid, inexpensive, and reproducible techniques for probing tumor genomes. The methods for interrogating proteins, however, are considerably less mature. "If you want to do something, clinical reproducibility is the name of the game," says Califano. "You can't get approval without extraordinary reproducibility and proteomics simply is not there yet."

To overcome the inadequacies of protein-based technologies, he and his colleagues engineered a creative workaround. Using readouts of gene activity (known as gene expression, or transcriptional, profiles), the researchers developed a suite of algorithms that can home in on the most essential proteins in the cell — including the master regulators. One of these algorithms, known as ARACNe (Algorithm for the Reconstruction of Accurate Cellular Networks), allows the researchers to essentially reverse engineer the connections that exist between different proteins, reconstructing the

pivotal networks that control cells' biology. This work stretches back more than a decade, and includes a seminal paper published in Nature Genetics in 2005, which revealed the regulatory networks present in B cells — the first experimentally validated network in human cells, according to Califano. "Today, our method is basically a de facto standard for reverse-engineering transcriptional networks," he says.

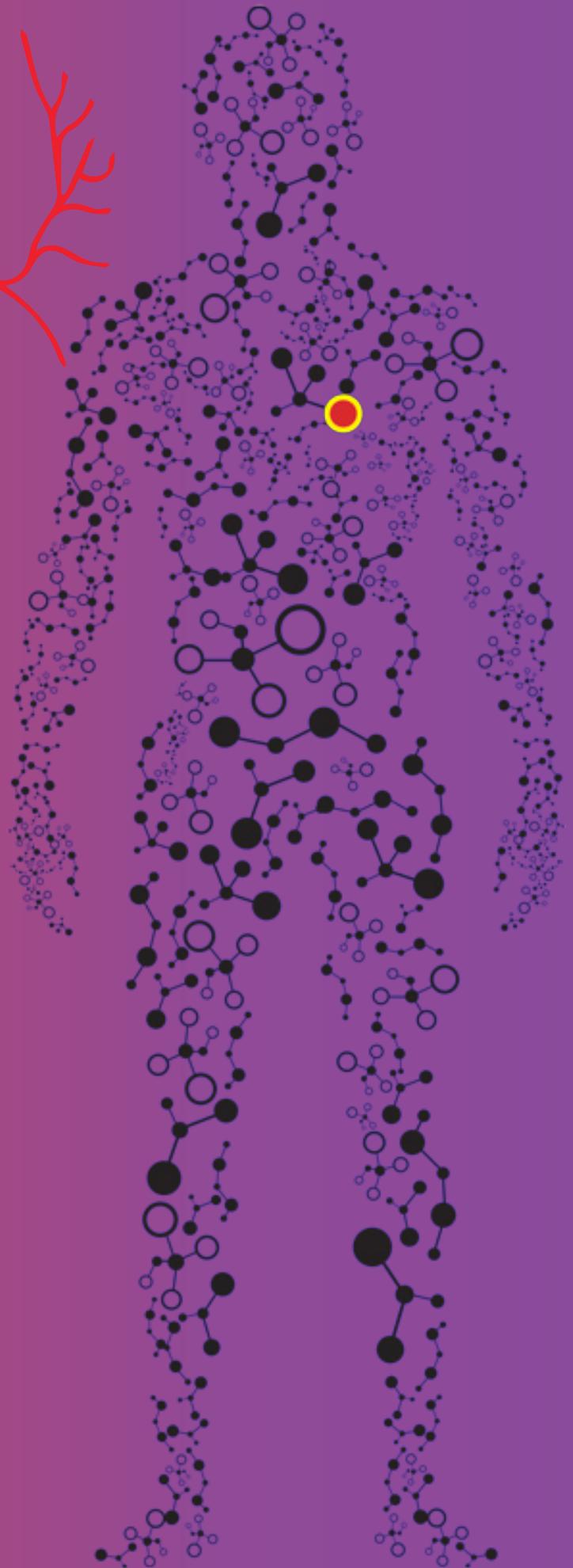
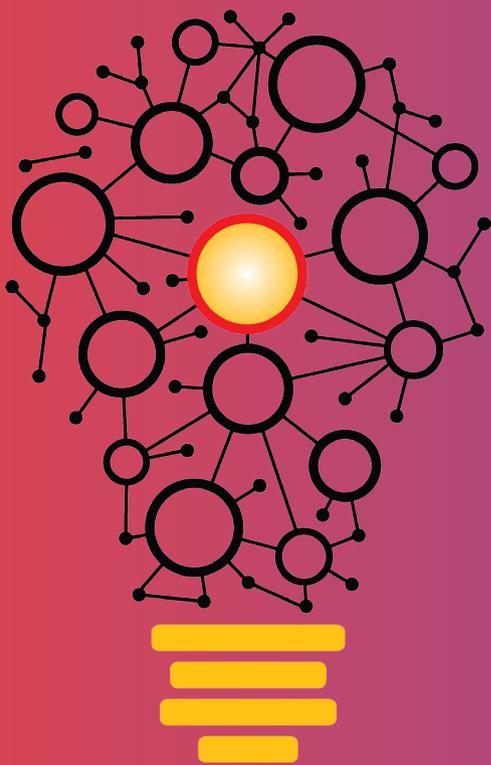
Building on this early work, the researchers developed another critical algorithm that helps pinpoint the most active proteins present in a cell. The tool, known as VIPER (Virtual Inference of Protein activity by Enriched Regulon), provides a rank-ordered list of the proteins within a single sample, ranging from most to least active. It was co-developed by Califano and computational biologist Mariano Alvarez, PhD, who is now DarwinHealth's Chief Scientific Officer. These and other protein-hunting algorithms form the backbone of the company's proprietary technology, including its new diagnostic tests, which can unmask a cancer's most crucial actors and match them up with existing drugs. Bosker and Califano compare their approach to the inference techniques astrophysicists use to discover planets, which are too small to be discerned directly, even with the most powerful telescopes. "Planets are detected by looking at the gravitational oscillations in the stars they orbit — it is an indirect observation, based on an underlying theory that is exact enough to make some key predictions," explains Califano. "We're doing the same thing for biology."

### An Eye Toward the Clinic

Although DarwinHealth is relatively new to the biotech scene, there are already some tantalizing signs that its technology could help improve the status quo of precision medicine in cancer. For example, in a recent study based at Columbia researchers are in the process of recruiting 260 patients with various types of untreatable cancer tumors



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so aggressive that they had failed as many as seven different lines of therapy. The team removed bits of these patients' tumors and then cultivated the cells in dishes or inside mouse "avatars," providing an environment to test the predictions flowing from the algorithms that have recently received NYS Department of Health certification and have been licensed to the company. While results are still preliminary, for each patient, as many as five different drugs predicted by the analyses of aberrantly active proteins induced objective response in tumor transplanted directly into an immunocompromised mouse.

The results of these "N-of-1" trials — so named because each patient constitutes a single test case — proved surprising. Roughly 60% of the predictions yielded what the DarwinHealth team calls an objective response — either stable disease (that is, no net tumor growth) or an overall decrease in tumor mass. Although each predicted drug was tested individually on patients' cells, in many cases, there were compelling drug pairs and trios that could also be drawn based on the algorithms' output.

"Once you reduce the pool of potential drugs to such a small number, the options for combination therapy become almost obvious," says Califano. He and his colleagues are now studying these combinations. Additional clinical trials are also underway that seek to evaluate some of DarwinHealth's other therapeutic predictions, including those for patients with breast cancer.

The company is also extending the reach of its protein-seeking algorithms by discovering drugs with unexpected cancer-fighting potential. This involves systematically searching for compounds that can reverse the activity profiles of different master regulators in different types of tumors — an effort based on Califano's large body of research, which suggests that, across all types of cancer, only a few hundred proteins

make up the full universe of master regulators. The researchers will soon publish a key proof of concept in this area, focusing on a group of rare, difficult-to-treat neuroendocrine tumors.

"Let's consider the real world — you're a patient with cancer, you've been treated with one or maybe two drugs, but you have no actionable mutations. Or maybe you've been treated for a mutation and then you relapse in four months. What target-to-drug model is currently available that would give a therapeutic roadmap for what drug to choose next?" asks Bosker. "There is none."

If his company's endeavors prove fruitful, that sobering answer could become a lot more encouraging.

**Nicole M. Davis, Ph.D.** is a freelance writer and communications consultant specializing in biology, medicine, and technology. With over a decade of experience in science communications, she has worked with leading life science organizations in the Boston area and across the U.S. She holds a Ph.D. in genetics from Harvard University.