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Editorial

A game-changer in cancer treatment

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Editorial

A new platform is matching the best existing anticancer drugs with the patients whose cancer will actually respond to them. Today, overall cure rates for advanced lung, breast, and pancreatic cancer are typically less than 50%;[1] most patients with these cancers will need a plan B after all the standard treatments have failed. We need a way to match approved or experimental cancer drugs to the patients whose tumors are likely to respond to them. Right now, though, deciding what treatments to try is largely guesswork, and success rates, when surgery fails to remove the entire mass, are depressingly low. Consequently, selecting the right drug for a specific cancer patient, particularly those who don't respond to initial treatments, has largely been a guessing game, akin to trying to navigate a maze in the dark. It is a fantastically complicated maze, too: there are 250 FDA-approved cancer drugs and 200 different types of cancer, resulting in tens of thousands of possible drug-cancer combinations and literally billions more if you combine multiple drugs.[2]

However, a glimmer of hope is appearing on the horizon, thanks to new approaches powered by circulating cell-free mRNA (cfmRNA).[3] Although still in its early stage, this technology is already showing promising results-accurately pairing patients with their most effective treatment. The PGA (Patient-derived Gene expression-informed Anticancer drug efficacy) platform enabled clinicians to infer patient's own gene expression signature, which can act as a matchmaker for the best anticancer drugs, irrespective of any genetic markers or mutations.[4] The PGA approach takes advantage of patient-specific gene expression pattern which captures tumor and non-tumor signals, in contrast to other tumor-only techniques which miss a large fraction of tumor microenvironment (TME) insight. To remedy this, scientists used circulating cell-free transcriptomic profiling to establish cancer type-specific biomarker panels. The PGA platform then applied those panels to each individual patient to obtain a patient-derived gene expression fingerprint, which helped to find the most effective anticancer drugs among hundreds of existing drugs. With the high levels of missing relevant TME data in mutation-only NGS sequencing tests, this is like solving a crossword puzzle. PGA is both the dictionary and puzzle-solver that tells us which letters go with which words. PGA highlights the potential to use treatments targeting cancer pathways that aren't necessarily linked to mutations, the most common basis for many expensive targeted cancer therapies.

PGA, which targets current non-responders-based on a model of cancer biology called "oncomap". It takes measurable data of gene expression profiles, and uses it to make precise inferences about drug efficacy, which are not directly measurable but can be deduced using an *in silico* biological-twin model. Indeed, such a roadmap is already leading to real world impacts. The confirmation that the PGA platform can predict a drug's effectiveness will be presented at American Association for Clinical Chemistry (AACC) 2023 annual meeting.[5] The pilot trial showed that treatment strategy supported by PGA had better outcome compared with the standard of care, demonstrating PGA's clinical utility and validity. This is a critical feat because a tumor-just like cancer itself-is not all the same. A single tumor can harbor dozens of molecularly different subpopulations with different drug sensitivities, a phenomenon also known as cancer heterogeneity. Patients with lung, breast and pancreatic cancers, lacking targetable genetic mutations (non-responders for targeted therapy or immunotherapy) may especially benefit here, working their way around the roadblocks affecting currently available precision medicine.

Trillions of dollars, countless lives: We believe the high cost and slow progress of cancer medicine today are, in part, rooted in the flawed assumption that genetics hold all the keys. While this is true for rare heritable diseases, the story is much more complicated for complex diseases, including most cancers, where gene-encoding mRNA/proteins and pathways play a much more critical role. Unfortunately, with few notable exceptions, even a precise understanding of a cancer's genetic makeup-a routine test performed on people with cancer every day-can't fully determine which drug or therapy will be most effective. For individuals with cancer, this often results in costly and physically debilitating cocktails of multi-drug interventions, many of which prove to be stabs in the dark that provide only marginal and transient benefits.

PGA's breakthrough lies in its ability to optimize the usage of existing drugs, freeing us from the costly process of new drug development, by connecting patients to FDA-approved drugs that can target the overexpressed drivers of their tumors. The new paradigm empowered by PGA bridges the gap between patients and the drugs best suited to treat them, based on signaling networks known as "cancer pathways". If this approach scales and is widely adopted, we believe this strategy could save trillions of dollars and countless lives by predicting more effective treatments for specific patient populations. The improved drug-tumor alignments made possible by these *in vitro* and *in silico* approaches immediate cost savings. They promote the usage of approved, affordable, readily available drugs-but just importantly, they identify effective drugs early, when they're most likely to work, reducing costs and toxicity from subsequent treatments when initial therapies fail.

Cancer care is dynamic and rapidly evolving, and it has been inspirational to contribute towards that evolution, but even more

so it has been inspirational to see the real impact personalized and precision treatments are having on the lives of patients and their families. While traditional approaches to treating cancer have focused on an increasingly sophisticated arsenal of drugs targeted against various mechanisms of tumor cell growth, immunotherapy represents a paradigm shift by activating anti-tumor immune responses broadly and independently of tumor growth mechanisms. Nonetheless, many patients do not respond to immunotherapy, and therapy failure is difficult to predict. Since PGA has the potential to identify candidate therapeutic drugs and sensitivity/resistance mechanisms across tumor types, it also represents an opportunity to tailor precise combinations of complementary drugs for patients who do not respond to current targeted treatments for other conditions beyond cancer. Taken together, PGA platform represents an opportunity to tailor future combination therapies at the single-patient level. In principle this can be extended even beyond cancer treatment to identify drugs with complementary immune effects across any number of medical contexts-even including the efficacy of vaccines.

Recently, cancer treatments have been moving toward more personalized and targeted approaches. Individual mutations and other biomarkers have been used to guide the choice of one treatment over another, but biomarkers for immunotherapy remain crude, and often exclude many patients who might otherwise benefit. This is why a deeper understanding of the effects that both immunotherapy and conventional therapies exert on the immune microenvironment is needed to find more precise, rational combinations of complementary drugs. Whether we understand them fully yet or not, these drugs all have an effect on the immune cells inside of a tumor in addition to whatever their intended effect may be on the tumor cells themselves. Additionally, tailored combination therapies and immune effects of cancer drugs have been difficult to study. This is because preclinical cancer drug testing has traditionally been done in immune-deficient mouse models, assessing only drug toxicity against tumor cells, with no testing for effects on the immune system prior to large-scale clinical trials. Our greatest hope for the future of its research is to translate predicted drug combination discoveries back to the design of new clinical trials and patient care.

While a comprehensive theory explaining cancer's complexities remains elusive, we may be turning a corner with these pathway-centric approaches. Scientific breakthroughs like PGA could help us save lives, improve the quality of those lives, improve clinical trials' accuracy, and reduce cancer's projected multi-trillion-dollar cost over the next three decades. This new strategy, more akin to a "Cancer Starshot" than a "Cancer Moonshot," offers a path forward in our ongoing battle with this devastating disease.

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Conflicts of interest

The authors declare no conflict of interests.

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