Published in final edited form as:

Trends Genet. 2013 January ; 29(1): 6–10. doi:10.1016/j.tig.2012.09.004.

Can we deconstruct cancer, one patient at a time?

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Abstract

Patients with cancer face an ever-widening gap between the exponential rate at which technology improves and the linear rate at which these advances are translated into clinical practice. Closing this gap will require the establishment of learning loops that intimately link lab and clinic and enable the immediate transfer of knowledge, thereby engaging highly motivated patients with cancer as true partners in research. Here, we discuss the goal of creating a distributed network that aims to place world-class resources at the disposal of select patients with cancer and their oncologists, and then use these intensively monitored individual patient experiences to improve collective understanding of how cancer works.

Keywords

cancer; personalized medicine; N-of-1; omics; longitudinal monitoring; learning loops; research

Cancer treatment in the age of omics

Although genomic, transcriptomic, proteomic, and metabolomic (here collectively referred to as ‘omic’) technologies are dramatically improving understanding of health and disease, the goal of exploiting this information for the benefit of patients is only beginning to be met. Cancer research is especially well positioned to benefit from advances in omic technology, and next-generation sequencing (NGS) has already yielded profound new insights into cancer biology. We now know that each cancer arises from a distinct combination of genomic alterations and, thus, is unique [1]. Cancers are also remarkably heterogeneous within individual patients, and subclones expand and contract in response to selective pressure [2–5]. These discoveries pose significant challenges to the design of clinical trials in patients with cancer. Two strategies reflect diametrically opposite frameworks for advancing cancer treatment: (i) an established paradigm that compares outcomes between groups of patients randomized to different treatments and implicitly deals with cancer as a black box; and (ii) a nascent mechanistic approach that aims to understand cancer within individuals. Fully capitalizing on the opportunities that omic technologies provide requires that we acknowledge the limitations of randomized trials and develop next-generation trials that rigorously evaluate intensively monitored individual patient experiences. An essential

feature of this new approach is the involvement of patients with cancer as active partners in discovery-based research.

Cancer as a black box

Despite their lack of molecular tools, early pioneers in cancer therapeutics were remarkably successful in developing treatments for childhood acute lymphoblastic leukemia (ALL), Hodgkin's disease, and testicular cancer. These gains were achieved through a largely empirical process culminating in the evaluation of drugs and drug combinations in randomized clinical trials. Randomized trials assign patients to two or more groups that are designed to be comparable. Patients within groups receive the same treatment, whereas patients assigned to different groups receive different treatments, and the outcomes between groups are compared. To achieve comparability, the randomization process can be adjusted to balance groups according to recognized prognostic factors, such as tissue of origin, age, clinical status, microscopic appearance (grade), and extent of disease (stage). The assumption inherent in randomized trials is that patients assigned to different treatment arms are sufficiently similar as to allow for a valid comparison between treatments. This assumption withstands scrutiny either when a large fraction of tumors responds to an empirically defined regimen (e.g., childhood ALL), or when a molecular marker strongly predicts treatment responses, as occurs with the breakpoint cluster region-*c-abl* oncogene 1 (BCR-ABL) translocation in chronic myeloid leukemia (CML), human epidermal growth factor receptor 2 (HER2) amplification in breast cancer, or point mutations in *v-kit* Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (c-KIT) or *v-raf* murine sarcoma viral oncogene homolog B1 (BRAF) that occur in gastrointestinal stromal tumor (GIST) and melanoma, respectively. A significant advantage of randomized trials is that they allow effective therapies to be developed even when the disease is not well understood. For example, randomized trials demonstrating the efficacy of lenalidomide [6] and bortezomib [7] in patients with myeloma represented significant advances even though the molecular basis for their efficacy is not well understood.

However, randomized trials can encounter difficulty in the face of increasing knowledge about cancer mechanisms and the rational development of therapeutic drugs. One well-publicized example, reported in the *New York Times*, described two cousins that both had metastatic melanoma bearing the BRAFV600E mutation, and they both enrolled in a randomized clinical trial comparing an investigational BRAF inhibitor and a toxic and largely ineffective standard therapy (DTIC) [8,9]. The cousin assigned to the BRAF inhibitor responded and served as pallbearer at the funeral of his DTIC-assigned relative, who died rapidly. The significance of this example rests not in an 'N-of-2' notion that one treatment was superior to the other, but rather in the implication that randomized trials may subjugate the best interests of individual patients with cancer to the best interests of science. This perception is especially unwelcome in view of the widespread complaint that fewer than 5% of all adult patients with cancer enroll in clinical trials [10]. One might ask why patients with cancer should be expected to participate in trials for which they are not intended beneficiaries? However, it should be noted that, fortunately, many randomized trials have provisions for crossing over to the other arm if the initial treatment fails.

Randomized trials have other limitations. They can be nonsensical in situations where interventions are so obviously effective that control arms defy reason, as with parachutes and bulletproof vests [11]. On the other end of the knowledge spectrum, randomized trials can be insensitive to detecting biologically (and clinically) relevant signals because of noise attributable to the heterogeneity of the population examined. The fact that cancer cures are notoriously more prevalent in mice than in humans is attributable in large part to the relative homogeneity of inbred mouse strains that allows for experimental repetition, in contrast to the heterogeneity of germline and tumor genomes that makes each human subject a unique object of investigation. Thus, whereas randomized trials provide the foundation for wide adoption (and often regulatory approval) of a new treatment, they are insensitive to new discoveries.

Despite their limitations, randomized trials are likely to remain the gold standard for defining the safety and efficacy of new therapies for many years to come, because even the best characterized cancer therapies fall short of the parachute standard. Nevertheless, continuous improvements in understanding of cancer, combined with increasingly sophisticated interventions, may one day make randomized trials difficult to justify.

Deconstructing cancer, one patient at a time

Increasingly, randomized trials will be forced to share the stage with innovative trials that deeply investigate cancer within individuals. These new investigations are being enabled by advances in omic technologies, which allow for the comprehensive characterization of a patient with cancer and his or her tumor. NGS results show that cancer genomes contain small numbers of recurrent mutations accompanied by much larger numbers of mutations that are rarely or never found in the tumors of other patients [12]. Whereas recurring mutations are probably involved in disease pathogenesis, rare or unique mutations likely represent mixtures of driver mutations that collaborate to promote tumor growth and passenger mutations that are uninvolved in cancer genesis or progression [13,14]. Distilling this vast information into a cohesive framework that describes how a cancer operates within an individual, and unveiling its potential vulnerabilities, is one of the grand challenges of our time. Deciphering the general operating principles of cancer will require methods for converting the results of omic testing into candidate networks, and then monitoring how these networks evolve and respond to treatment over time. Success requires discerning biologically relevant signals from vast backgrounds of noise. A major challenge is a phenomenon known as ‘overfitting’ [15]. Overfitting occurs when a statistical model is confounded by random noise instead of revealing true biological relationships, and it is inevitable when the number of measured parameters outstrips the number of observations. In other words, efforts to synthesize the massive data sets that omic studies generate into a cohesive framework will invariably lead to large numbers of seemingly reasonable solutions, most of which will be wrong. In the context of single-patient studies, overfitting presents an enormous challenge, and developing approaches for meeting this challenge represents a crucial avenue of investigation.

A second challenge is that the results of omic studies provide a signal average: a summation of measurements generated from all cell types present within the tumor. Many tumors are

highly heterogeneous, comprising multiple morphologically distinguishable cell types, and different types of cells can cooperate to sustain tumor growth [16,17]. Even tumors that are morphologically homogeneous comprise subclones that differ in their mutational content. Deconvoluting these relationships presents a significant challenge that will require methods that can use omic data from unfractionated tumors to infer the number and size of subpopulations [18] as well as from single-cell approaches [19].

Additional technical challenges include identifying and accounting for systematic errors that pervade omic data arising from batch effects [20], and assuring that tissue specimens are collected in a manner that safeguards the integrity of information that they contain, because factors such as ischemia time can dramatically influence results [21].

Approaches for discriminating signal from noise can be broadly classified into two categories: static and dynamic.

- Static approaches: cancer in snapshot. Several reports have described the use of omics to identify the potential vulnerabilities of a cancer. Although strong predictions and effective interventions based on the aberrant regulation of a single gene have been described [22,23], unambiguously favorable outcomes are likely exceptions to the rule [24]. In most cases, strong evidence for dependency on a particular pathway will be lacking, and confidence levels for any given prediction will need to be assessed using a variety of approaches. For example, testing multiple independent samples from the same patient at a given time point to assess the reproducibility of key findings across specimens may increase confidence, although heterogeneity in the mutational content of tumor subclones is an important caveat. Another approach relies on developing intersecting lines of experimental evidence. Corroboration of a genomic result (e.g., upregulation of a receptor tyrosine kinase by RNA-Seq) with a proteomic result (phosphorylation of the corresponding substrates by reverse phase protein arrays) would provide valuable additional evidence. Placing the cancer under investigation into a broader context of prior knowledge using publicly available databases will also be a useful tool to identify candidates. For example, understanding where a particular cancer fits within the constellation of all other previously characterized cancers should prove increasingly valuable as omic profiling extends to all cancer clinical trials, thereby establishing associations between omic profiles and treatment responses. Similarly, the genetic diversity of at least some cancers appears to condense around a limited number of known signaling pathways [25], thus improving interpretability. Finally, correlating omic information with clinical information will be critical to interpreting these types of data. For example, in patients with metastatic cancer undergoing treatment, disease stabilization sometimes occurs at one or more sites whereas progression occurs at other sites. Comparing omic results at sites of growing versus stable disease might point to mechanisms that tumors use to resist treatment.
- Dynamic approaches: cancer in motion. Whereas static measurements are encumbered by the enormous challenge of discriminating signal from noise, repeated assays over time can significantly improve the ability to resolve

correlations between data points and discern underlying biological relations. A landmark example was recently described by Chen, Snyder, and colleagues, in which a single healthy individual (the senior author of the study) was monitored by extensive omic testing involving 20 separate assessments of peripheral blood mononuclear cells over 400 days, totaling more than 3 billion data points [26]. Results across genomic, transcriptomic, proteomic, and metabolomic platforms were normalized and integrated, revealing clusters of temporally correlated measurements that segregated into biologically plausible pathways. A serendipitous yet striking discovery involved abnormalities in the insulin regulatory pathway that arose after the second of two viral infections, and further testing led to a new diagnosis of diabetes that resolved following a strict regimen of diet and exercise. Might a similar approach be applied in patients with cancer? Deeper insights into how cancer functions will require similar systems approaches that convert omic data into presumptive regulatory networks and point to candidate vulnerabilities. Confidence in any particular model can be gained or lost by treating the patient with those drugs predicted to be most likely to disrupt key nodes within the network. Although many predictions will prove wrong, embedding mechanisms for learning into the process should, through iteration, improve accuracy. Monitoring the omic profiles of tumors before and following treatments designed to interfere with tumor growth could provide information that is valuable both to science and to patient care. It will provide insight into whether interventions designed to target specific signaling pathways worked as intended. For example, if a targeted therapy designed to interrupt a presumptive driver signaling pathway fails to interfere with tumor growth, it would be important, both scientifically and for patient care, to discern whether the targeted signaling pathway was blocked as intended. Furthermore, serial monitoring will provide a means for examining how networks respond to perturbations [27], thereby providing insight into how the networks work.

Establishing this type of learning loop is challenging to implement because of concerns that patients should not be exposed to research methods that have not been extensively validated. At center stage is a widely publicized scandal at Duke University, which involved pervasive scientific misconduct in clinical trials that used omic data to guide therapy in patients with cancer [28]. In response, the Institute of Medicine (IOM) of the National Academy of Sciences recently recommended that a ‘bright line’ separate testing that is done in the discovery phase of research from clinical studies in which only fully specified and validated tests with ‘locked down’ computational procedures are used to direct patient care [29]. The core question is: should fully informed patients with cancer, under appropriate clinical and ethical circumstances, be allowed to participate in discovery-based research? Answering ‘no’ places a firewall between patients with cancer and the latest scientific discoveries. Although this may help to protect patients from misconduct or less nefarious mistakes, such a firewall could also prevent them from accessing the latest scientific and technological discoveries. As a consequence, highly motivated patients with cancer with no good alternatives would be prevented from participating as true partners in advancing cancer research.

The road ahead

Fully exploiting the opportunities that technology creates requires a reassessment of the approach to cancer. Whereas many of the challenges described above are scientific and technical in nature, other important limitations (listed in Box 1) are self-imposed.

Overcoming another major challenge to implementation (the recovery of costs) will ultimately require a restructuring of reimbursement patterns, but this issue is beyond the scope of this article.

Partners in Personal Oncology as a paradigm for advancing cancer research and treatment

One of us (CAB) co-founded Partners in Personal Oncology, a not-for-profit organization, based on the belief that a new patient-centered framework is needed to optimize understanding and treatment of cancer (<http://www.personaloncology.org>). By building a network of linked partnerships, Partners in Personal Oncology is developing an approach that can be summarized as ‘all for one, and one for all’: placing world-class technology and expertise in the service of individual patients with cancer and their oncologists (all for one) and using individual patient experiences to advance our collective understanding of how cancer works for the benefit of future patients (one for all). There are several noteworthy aspects of the cycle of Partners in Personal Oncology (Figure 1). First, patients will enter the cycle repeatedly over the course of their disease, with serial biopsies and longitudinal monitoring enabling the creation of ‘molecular movies’ of how cancer evolves within individual patients over time. Second, the cycle of Partners in Personal Oncology will foreshorten the ‘learning lag’ that separates science and medicine, intertwining discovery-based research and clinical care in a more intimate and immediate manner than exists currently. Researchers will benefit by testing their hypotheses directly in patients with cancer, and patients will benefit by gaining access to world-class technology and expertise that aims to understand the molecular basis of their disease and treat them accordingly. Third, the network of Partners in Personal Oncology is distributed, both with respect to aggregating technology and expertise irrespective of institutional boundaries, and by allowing patients with cancer to access world-class resources irrespective of their geographic location. Fourth, patients with cancer who choose to participate in this program will be made aware of the highly experimental nature of this approach and, as such, will be true partners in discovery-based cancer research. Finally, by combining intensively monitored individual patient experiences with mechanisms for learning, it should be possible, through iteration, to increase the accuracy of our predictions over time.

Box 1

Some proposed changes in the current approach to cancer

- i. Increase longitudinal monitoring. Sequential biopsies provide an important means for understanding how cancer works, but are rarely performed because until now, they have had only a limited role in clinical care. Sequential biopsies could be performed in significant subsets of patients with cancer, and might eventually be replaced by evaluating circulating tumor cells.

- ii. Improve quality control in tumor acquisition. Tumor specimens are generally not processed in accordance with the tightly controlled conditions necessary for reliably assessing RNA and protein. More attention must be paid to acquiring tumor samples in a manner that retains the integrity of the information they hold.
- iii. Improve access to investigational drugs. Regulatory approval of a new drug by the US Food and Drug Administration (FDA) requires clinical trials that begin with dose-finding (Phase I) studies and end with one or more randomized controlled trials. Outside this framework, single patient investigational new drug (IND) applications can allow patients with cancer who would not otherwise qualify for clinical trials to access investigational drugs on a 'compassionate use' basis. Given that the results of omic studies may suggest unanticipated vulnerabilities, patients need a path for rapidly accessing those drugs to which their tumors are predicted to respond, even if an established clinical trial is not available. Single patient INDs are labor intensive and require the consent of the manufacturer. Pharmaceutical companies are often reluctant to grant compassionate use access because of the risk of adverse events (which must be reported to the FDA, potentially delaying regulatory approval), and the lack of upside benefit (for the company) from anecdotal responses. Combining 'compassionate use' access with intensive longitudinal monitoring might enable drug companies to learn more about the molecular contexts in which their investigational drugs work, thereby improving the probability of success in later trials.
- iv. Allow patients with cancer to participate in discovery-based research. The rigidity of the clinical trials system risks constraining innovation. For example, the aforementioned IOM report recommends that only tests that have been extensively validated preclinically should be used in patients [29]. The uniqueness of cancer threatens to make such an approach impractical. Do we always need to know that a test is valid before applying it in a patient, or are there circumstances under which we can evaluate the validity of a test in a patient? Better ways of balancing access to innovation while protecting patients from avoidable errors need to be identified.

Both (iii) and (iv) point to a need for increased regulatory flexibility as we work to find the optimal path for translating omic information into clinical practice.

Concluding remarks

It is transformative to consider the possibility of linking the efforts of physicians, researchers, and patients in advancing cancer research. On the one hand, researchers cannot progress unless the hypotheses that they develop can be tested. On the other hand, patients with cancer who are not curable by available therapies are poorly served by clinical trials that ignore tumor-specific characteristics and by physicians who have only their intuitions to guide therapy. Cancer research is also poorly served because of the many existing clinical trials from which we currently learn almost nothing. The careful and comprehensive

documentation of the molecular and clinical changes that occur within a patient with cancer and their tumor at baseline and following interventions designed to interfere with tumor growth would contribute immensely to understanding of cancer. Even if the interventions initially fail more than they succeed, the approaches described aim toward a new definition of ‘doing our best’. This new type of clinical trial is likely to be a necessary step on the road to deconstructing cancer.

Acknowledgments

We thank Lee Huntsman, George Stamatoyannopoulos, Stan Fields, Junfeng Wang, and Zhijun Duan for helpful comments and discussions. Supported through R01 CA 135357 and gifts from Norman Metcalfe and the Tietze Family Foundation.

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Figure 1.

The Partners in Personal Oncology cycle. Partners in Personal Oncology will provide: (i) optimized methods for biospecimen collection and banking; (ii) access to state-of-the-art testing using omic and other technologies; (iii) a databank that will house the results of testing annotated with the patient's clinical information; and (iv) a panel of medical and scientific experts that will examine the results of testing and convey a recommendation for treatment back to the patient and their oncologist.