

Turning the Tide Against Cancer Through Sustained Medical Innovation: The Pathway to Progress

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Abstract

An ever-expanding understanding of the molecular basis of the more than 200 unique diseases collectively called cancer, combined with efforts to apply these insights to clinical care, is forming the foundation of an era of personalized medicine that promises to improve cancer treatment. At the same time, these extraordinary opportunities are occurring in an environment of intense pressure to contain rising healthcare costs. This environment presents a challenge to oncology research and clinical care, because both are becoming progressively more complex and expensive, and because the current tools to measure the cost and value of advances in care (e.g., comparative effectiveness research, cost-effectiveness analysis, and health technology assessments) are not optimized for an ecosystem moving toward personalized, patient-centered care. Reconciling this tension will be essential to maintaining progress in a cost-constrained environment, especially because emerging innovations in science (e.g., increasing identification of molecular biomarkers) and in clinical process (implementation of a learning healthcare system) hold potential to dramatically improve patient care, and may ultimately help address the burden of rising costs. For example, the rapid pace of innovation taking place within oncology calls for increased capability to integrate clinical research and care to enable continuous learning, so that lessons learned from each patient treated can inform clinical decision making for the next patient. Recognizing the need to define the policies required for sustained innovation in cancer research and care in an era of cost containment, the stakeholder community must engage in an ongoing dialogue and identify areas for collaboration. This article reflects and seeks to amplify the ongoing robust discussion and diverse perspectives brought to this issue by multiple stakeholders within the cancer community, and to consider how to frame the research and regulatory policies necessary to sustain progress against cancer in an environment of constrained resources. *Clin Cancer Res*; 20(5); 1–6. ©2014 AACR.

Introduction

Since the completion of the Human Genome Project, scientific and technological advances in the life sciences have been accelerating at an exponential rate, and much of this progress is now starting to be translated into improved patient outcomes. Armed with advanced knowledge in molecular and cellular biology, and sophis-

ticated bioinformatics tools and technologies, investigators are now unraveling the immense biologic complexity of the more than 200 diseases collectively called cancer (1), and are continuously assessing how these diseases should be classified, diagnosed, and treated. An ever-expanding understanding of the molecular basis of disease combined with efforts to apply these insights to

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Note: In June 2012, in Washington, DC, the American Association for Cancer Research, the Personalized Medicine Coalition, and Feinstein Kean Healthcare, convened a national conference, "Turning the Tide Against Cancer Through Sustained Medical Innovation," to consider the status and future of innovation in cancer research and care. More than 200 stakeholders from across the cancer ecosystem attended this conference on cancer science and policy, where there was a strong call to action for leadership to identify actionable solutions to the challenges of sustaining innovation. (www.TurningTheTideAgainstCancer.org).

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clinical care is forming the foundation of personalized cancer care.

Today, the sheer volume of and access to scientific research and health data are contributing to a growing emphasis in the drug development pipeline toward molecularly targeted agents. Of the nearly 1,000 medicines in the clinical pipeline for cancer, approximately one half are novel biologic and small molecule–targeted agents (2–4); this number is expected to increase dramatically, as 100 % of companies surveyed by the Tufts Center for the Study of Drug Development in 2010 are using biomarkers to facilitate drug discovery and development (5). In addition, the U.S. Food and Drug Administration (FDA) has approved several new biologic entities that are molecularly targeted (6). The early successes of molecularly targeted therapies for some forms of cancer provide a hopeful glimpse into a future in which prevention and treatment strategies will be informed by the molecular makeup of the patient and/or the patient's tumor.

Clearly, emerging innovations in science and in clinical process hold potential to dramatically improve patient care, and could ultimately help address and offset costs (7). Indeed, with continued support for science and innovation, we foresee accomplishing in oncology what has been achieved against other major public health problems, such as HIV/AIDS, in which scientific advances yielded major gains for patients and averted a predicted health spending crisis (8).

At the same time, these extraordinary opportunities are occurring in an environment of intense pressure to contain rising healthcare costs. The cost of cancer research and clinical care is expected to continue growing over the near term due to multiple factors, including increased cancer survivorship (9), an aging population (10), rising direct medical costs, and expanded access under healthcare reform (11). In addition, projections for federal spending under Medicare show the program on an unsustainable long-term trajectory. Together, the projected budget increases for Medicare and Medicaid are the major contributors to projected chronic federal budget deficits (12).

As policymakers seek ways to control rising healthcare costs and overall federal spending, including funding for scientific research and healthcare, we believe it is essential to identify and support policy approaches and proposals that will accelerate the biomedical innovations necessary for improving patient outcomes, care quality, and the value of care for patients with cancer everywhere.

By bringing the stakeholder community together, stimulating dialogue, and communicating with policymakers, we are optimistic that continued scientific progress toward solutions to long-term human and economic challenges can be realized within regulatory and policy frameworks that incentivize innovation and value in healthcare. Themes that have emerged in ongoing discussions among the stakeholder community include the need for policies that foster partnerships and research collaborations; financial support by payers for clinical research (e.g., covering all aspects of treatment that are considered standard of care); adoption of

standards for collection of biospecimens; and sound regulatory and reimbursement policy for molecular diagnostics. Also at the forefront of this ongoing dialogue is the overarching need to reward innovation, as well as the dynamics surrounding patient-centered care for patients with cancer (13).

If the vision of personalized cancer care is to be realized, high-level leadership committed to defining policy approaches that will continue to drive the biomedical innovations necessary for improving the quality and value of cancer care is needed. In this article, we seek to amplify the robust dialogue and diverse perspectives articulated in ongoing discussions and to consider potential next steps for healthcare leaders seeking to sustain progress against cancer.

The Challenges of Innovation in Cancer Research

Strong incentives for sustaining the oncology innovation ecosystem will be vital to realize the tremendous opportunities for "turning the tide" against cancer, despite the pressing issue of cost containment in cancer care. These incentives include preserving strong support for funding basic and applied research in the public and private sectors and promoting policies that encourage innovations in science that will lead to improved patient care and outcomes, and improved healthcare value overall.

However, support for biomedical research, notably federal funding, is under increasing pressure. At the same time, traditional approaches for assessing the value of cancer care and incentivizing delivery of high-value interventions to patients may need to be reevaluated. These approaches, which relied on static, point-in-time evaluations based on broad population averages, seem to be particularly challenged by the emerging science in oncology (14), by the growing emphasis on patient engagement and patient centeredness (15), and by the new era of personalized cancer care that these changes are driving. Developing new approaches is of urgent importance for leaders and stakeholders in the field of oncology. To do this, several key dimensions of value must first be addressed.

Defining value

In healthcare, value is simply defined as health outcomes achieved per dollar spent (16). The application of this equation, however, is anything but simple. Value perceptions and assessments can vary greatly among stakeholder groups and individuals. For example, oncologists and payers define survival benefit of a new cancer drug as extending life by a minimum of 3 months and 10 months, respectively, highlighting a significant discrepancy among these stakeholders (17). Value perceptions also vary greatly among individual patients, depending on their clinical and life circumstances, preferences, and willingness to make risk/benefit trade-offs (14). Workable approaches to a value definition must be responsive to two basic dynamics: the variability of value among individuals and stakeholders, and the variability of value over time. As a starting point, our discussions

focus on *clinical* value, recognizing that economic factors ultimately must be considered as well.

Clinical value is widely recognized as incorporating considerations of both cost and clinical efficacy or effectiveness, as well as broader dimensions such as quality of life, productivity, and patient preference. Establishing policies that recognize and support all of these aspects of value will be essential to sustaining innovation in an era of cost containment. This article addresses some of the elements of clinical effectiveness—such as quality of life—and scientific progress that are leading to personalized cancer care, but have received little attention by policymakers.

The rapid acceleration of science, technology, and big data collection and usage that is taking place within oncology will require an expansion and acceleration of evidence-generation capabilities. However, it is important to recognize the current limitations in how we define value—while innovation, or value creation, must be incentivized, seeking to do so through policies that rest on single, stable, point-in-time definitions of value may be unworkable in the new, rapidly advancing era of personalized cancer care.

Demonstrating value

Understanding the comparative clinical and economic benefits of the various dimensions of cancer care is essential but complex. Although there is an exponential expansion in the amount of information available to guide patient care decisions, current value assessment approaches—including comparative effectiveness research (CER), cost-effectiveness analysis, and health technology assessments (HTA)—are increasingly challenged by the rapid pace of change in science and medical practice, our growing understanding of heterogeneity in cancer, and growing sensitivity to the varying needs of patients. This gap between static value assessment tools and dynamic knowledge base will only widen as we continue to advance into the era of personalized medicine in oncology (18).

Oncology clinical trials, which are carefully designed to meet the FDA's rigorous premarket standards, are necessarily only a starting point for understanding value. Oncology treatments are often studied in narrowly defined protocols specifying, for example, the patient populations, stage of disease, and length of treatment administration. Once the medicine reaches the market, however, it may be used in broader populations, at different disease stages, in combination with other treatments, and over longer periods of time. Thus, a more complete picture of clinical effectiveness and patient value does not emerge until the treatment enters real-world clinical use. Not surprisingly, improvement in patient outcomes is generally observed only over time, through an incremental process, as experience is gained with new treatments and interventions. For example, it only became apparent 5 years after the drug's FDA approval that bortezomib increased overall survival of patients with newly diagnosed multiple myeloma by 13 months (19), and long-term studies have shown that patients with chronic myeloid leukemia who are in com-

plete cytogenetic remission 2 years after starting imatinib mesylate have a normal life expectancy (20). Furthermore, benefits have been demonstrated in additional patient populations beyond the initial approved indication for multiple oncology therapies, including lenalidomide [Revlimid (Celgene); ref. 21], imatinib, and bortezomib (22).

The rapid pace of innovation taking place within oncology calls for increased capability to integrate clinical research and care to enable continuous learning, so that lessons learned from each patient treated can inform clinical decision making for the next patient. Additionally, new approaches are needed in which value assessment models better align with patient-centered care (Table 1). These approaches must enable the rapid conversion of data to knowledge and deliver that knowledge to the bedside in a continuum known as the "Rapid Learning Healthcare System" (23). The promise of such a system is to link research and care seamlessly, allowing for the aggregation and analysis of evidence-based knowledge and its subsequent application to patient care on a national or international level and for monitoring of the evolution of value of a particular drug or diagnostic in the real-world setting over time.

The true value of cancer interventions must be measured over time by following patients throughout their lifetime, beyond the time when they are receiving therapy in a clinical trial. Such tracking—which is far more feasible with the increasing pervasiveness of electronic medical records and emergence of user-friendly digital tools—will ultimately allow clinicians to identify where the "true" value resides based on real-world clinical evidence. Such a shift in the clinical research and care paradigm will address the fundamental mismatch today between the incremental nature of science and the time frame and focus of the public policy process.

Rewarding innovation

As described above, rewarding innovation requires policies that hold two conflicting challenges in balance by recognizing the limitations of defining value in a centralized, population-level manner, yet at the same time providing clear paths through which valuable innovation will be rewarded. Resolving these challenges should result in policies that align with increasingly rapid changes and major

Table 1. Value assessment models need to better align with patient-centered care

- Recognize divergent perspectives on value and center on patient value as defined by patient needs and preferences
- Personalize value measurements, including biologic differences among patients
- Incorporate broader measures of value, including quality of life
- Measure the evolution of value of innovative treatments over time

trends in science and support patient-centered approaches to driving value. Some recently proposed approaches, including "coverage with evidence development" (24) and risk-sharing arrangements (25), could offer effective solutions to the challenge of rewarding innovation.

Potential Paths Forward

Important scientific discoveries are creating new possibilities within the field of oncology; however, these possibilities are being realized during a time of unprecedented pressure for cost containment and increased emphasis on patient-centered care. A recurring theme that has emerged is the need for communication across all stakeholder groups, as well as unity in policy approaches.

Here, we present potential solutions for sustaining innovation that emerged as a result of stakeholder dialogue, and which collectively could begin to define a path forward to turn the tide against cancer (Table 2). The approaches described below are intended to spur discussion of a framework for a sustained, community-wide commitment to solutions.

Support the shift to patient-centered care in oncology

The challenges of defining value at a policy level call for increased commitment to defining and supporting value at the level of the patient with cancer and caregiver. A deliberate and comprehensive shift to patient-centered care is needed. Development of a clear, concrete, and patient-centered research agenda by the Patient-Centered Outcomes Research Institute (Washington, DC), which is currently building the infrastructure for a national patient-centered clinical research network (26), may represent one opportunity to identify specific research that is most responsive to the needs of patients and caregivers, and to support the communication of research findings for improved patient decision support. Patients can become involved in the value equation in more meaningful ways by helping to identify the outcomes that matter most to them, as well as by engaging with physicians in clinical decision making. However, better tools are needed to elicit and capture patient input and to support patient-physician engagement. Physicians, patients, and caregivers should be supported in shared decision making (evidence-based value decisions at the individual level) through the use of clinical decision support tools.

Table 2. Policy suggestions for sustaining innovation in an era of cost containment

- Support the shift to patient-centered care in oncology
- Align CER and HTA with the patient and the science
- Support the development of molecular diagnostics
- Encourage partnerships and collaborations
- Support a continuous learning healthcare system
- Engage society in cost of cancer conversations

Align CER and HTA with the patient and the science

Assessing the comparative clinical benefit of cancer interventions (whether treatments, tests, or services) is essential to controlling costs in ways that sustain innovation. At the same time, it is equally important to move beyond traditional approaches to comparative effectiveness research and health technology assessments to achieve better alignment with patient needs and values, as well as with the emerging science and changing clinical practice of oncology. Work to realign CER and HTA should reflect a commitment to patient engagement and a shift from a retrospective, static paradigm to a prospective, dynamic paradigm to allow for continued learning about innovative new interventions.

It is also essential that CER and HTA recognize and accommodate biologic differences among individual patients and patient subgroups, incorporate a wider range of value measures that particularly matter to patients but are often overlooked—such as quality of life and patient experience—and establish the methods and infrastructure (e.g., linked observational data sets) to guide patient-centered research on real-world clinical effectiveness. Finally, tools must be developed that effectively disseminate meaningful clinical information (e.g., how a particular biomarker may affect treatment outcome) to both patients and physicians.

Support the development of molecular diagnostics

Personalized cancer medicine will not be possible without a flourishing pipeline of molecular diagnostic tests, new diagnostic/treatment combinations, and drug-drug combinations. These advances hold substantial promise for transforming outcomes for patients with cancer and helping control overall treatment costs. However, achieving these goals will require support of coverage and payment policies that provide adequate reimbursement for novel, evidence-based molecular diagnostics and targeted therapies. The current absence of a rational reimbursement approach represents a significant challenge for the development of the molecular diagnostics pipeline (27).

Additionally, within the molecular diagnostics industry, the demands for clinical evidence are not aligned with the rewards for success. To stimulate the development of a more robust diagnostics pipeline and to harness the benefits of personalized medicine in patient-centered care delivery, policymakers and regulators must create an environment that encourages increased investment in diagnostics; enables new advances in patient care that are safe, accurate and reliable; and establishes a viable pathway toward patient access.

Encourage partnerships and collaborations

A highly collaborative multidisciplinary ecosystem is needed in which all stakeholders—industry, academia, government, clinicians, patients, and advocates—are recognized as partners working toward a common vision to translate scientific discoveries into better patient care. The growing volume of scientific and medical data, increasing

need for biomarker identification and qualification, and growing reliance on treatment combinations all favor collaboration as an essential element of continued progress. Regulatory and policy requirements must create a forum and incentives through which these types of partnerships can flourish.

Support a continuous learning healthcare system

Healthcare in general, and oncology in particular, are making strides in moving toward systems for aggregating and analyzing knowledge gained from electronic data sets and applying it to patient care and management of population health (28). Nonetheless, much work remains to be done. Evidence generation should include the ability to follow patients throughout their lifetime for the collection of observational, real-world data after clinical trials have ended. By facilitating system-wide learning and leveraging the clinical experience of all patients with cancer, a continuous learning system will help reduce the cost and accelerate the process of drug development. Realizing the potential of this infrastructure requires solutions that allow for appropriate access to data for research purposes while protecting patient privacy; ensure that analyses are methodologically rigorous; and provide appropriate standards for communication of accurate research findings by entities in the public and private sectors. Policy incentives could stimulate the public-private partnerships and coalitions that are needed to create the foundations for implementation, address concerns associated with the integration of clinical research and clinical care, and facilitate data liquidity in preparation for such a system (Table 3).

Engage in a public dialogue around cost of care

The economic component of value and the controversial issues this topic presents (e.g., cost limits per patient, end-of-life care) are important aspects that cannot be overlooked in policy discussions. Therefore, it is essential that all members of society engage in these critical discussions. It is noteworthy that settings in which all stakeholders are

represented in the debate are the exception, because many gatherings in the research and healthcare arena are conducted by discipline or sector.

Next Steps

Through our work, it became clear that sustaining progress against cancer in an era of cost containment requires commitment, multistakeholder engagement, and strong leadership. This article does not presume to offer a strict set of policy prescriptions. Rather, it is intended as a call for such leadership, and an identification of future directions to guide those leaders willing to step up and make this commitment. We believe there are a range of policy initiatives and activities that can be undertaken to foster innovation, and clear interest has already emerged among various stakeholders in the research and clinical ecosystem to advance these types of endeavors. One such activity already undertaken was the development of cost-containment and deficit-reduction policy principles that do not undermine innovation. Subsequent activities may include additional workshops to delve into more detail about policy frameworks and white papers to delineate and examine policy solutions.

Recognizing the broad array of potential issues to be addressed, we propose four major areas of focus that promise significant impact for the betterment of patients with cancer:

1. Develop evidence-based tools and incentives for patient-centered cancer care. In particular, there are significant, and increasingly important, opportunities to create decision-making tools and care delivery models that support value in oncology by better engaging patients in shared, evidence-based decision making. At the same time, these tools can better elicit and translate real-world patient perspectives on the outcomes that matter to them.
2. Ensure that CER and HTA center on individual patient needs and align with the rapidly advancing science of oncology.
3. Support the continued development of research and clinical data infrastructure needed to foster systems of continuous learning in healthcare.
4. Promote collaboration and integration of all stakeholders seeking sustained innovation in cancer research and patient care in an environment of intense pressure to contain rising healthcare costs. Partnerships will be increasingly important in the new era of oncology and also will be essential to achieving progress across the other three domains.

Disclosure of Potential Conflicts of Interest

J. Mendelsohn serves as a board member with Merrimack Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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Table 3. Policy suggestions to support a continuous learning healthcare system

- Support "meaningful use" programs
- Accelerate the incorporation of research parameters into meaningful use guidelines for electronic health records
- Incentivize the consistent collection of outcomes data in standards-based form
- Develop a policy framework that supports the accessibility of clinical data for researchers and incentivizes data sharing
- Incentivize standards-based data collection and data exchange capabilities in research
- Enforce current provisions that mandate the sharing of data from government-funded research in a timely way

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