Four Important Steps Toward 21st Century Care for Patients with Cancer

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Disclosures: Mark McClellan: None; Joshua S. Benner: Honoraria: Pfizer, Novartis.

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INTRODUCTION
Between 1990 and 2005, 920 cancer compounds underwent clinical trials, yet only 32 were approved [1]. The uncertain fate of products in the pipeline for new oncology treatments and the apparent opportunities for improving its productivity are sources of frustration for everyone in the cancer community.

The current situation doesn’t reflect a lack of effort. The average amount of time spent in development and approval for those 32 therapies was 9.1 years [1], but the development process is not focused on treatments that actually work: half of the cancer therapies that ultimately failed reached expensive and time-consuming late-stage clinical testing before being abandoned [2]. At the U.S. Food and Drug Administration (FDA), new oncology treatments represent a disproportionately high share of priority reviews, of orphan drug designations at approval, and of drugs that were granted inclusion in at least one of the agency’s expedited access programs. But while FDA approval times are 6 months shorter for oncology drugs than for other categories on average, clinical development times are 1.5 years longer than for other therapies.

The problems of inefficient and uncertain development are not new, but they have become more urgent in an era that should be defined by clinically meaningful advances in genomics and proteomics and the promise of personalized cancer therapy. With more effective ways to predict and demonstrate the safety and effectiveness of such targeted therapies, this new era of cancer therapy could arrive much sooner.

To identify some promising and concrete actions that could address the productivity challenge in the clinical development of cancer therapies, the Engelberg Center for Health Care Reform at the Brookings Institution hosted a Conference on Clinical Cancer Research, with support from Friends of Cancer Research, the American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR). The September 26 meeting convened cancer experts from academia, the National Cancer Institute (NCI), the FDA, patient advocacy groups, and the medical products industry with the aim of identifying consensus-driven solutions to critical questions regarding the future of clinical cancer research.

Thanks to the efforts of four expert collaborative panels and a room of more than 150 thought leaders who joined in the discussion, a set of concrete steps emerged to help usher in 21st century care for patients with cancer. The shared vision, as articulated by John Niederhuber of the NCI and others, is for a more quantitative and systematic process for determining the safety and efficacy of cancer therapies.
linked to more comprehensive and consistent evidence from collaborative trials and clinical practice. By combining insights from genomics, systems biology, and other emerging fields with consistently collected empirical data in support of these emerging models, this approach will enable better prediction of which patients will respond to treatments or combinations of treatments, and faster and more certain conclusions about when there is a response, or lack of response, or important safety problem. To achieve this vision, the conference identified four specific steps that can be taken by the clinical cancer research community now, without waiting for new laws or new funding. These steps all amount to paying more attention to the science of demonstrating safety and effectiveness, as well as the studies of particular treatments themselves.

**ADOPT CONSISTENT DATA SUBMISSION STANDARDS FOR CLINICAL STUDIES**

Because of uncertainty about the details and scope of data that are required to demonstrate the safety and efficacy of a cancer therapy, sponsors often exercise an “abundance of comprehensiveness” by collecting a great deal of data on a large number of subjects. Moreover, there is wide variability in how measures are collected and analyzed across clinical development programs. Although more data might seem to be better, inconsistent data and additional data that have little or no value in reaching conclusions about safety and effectiveness tend to add to the burdens, costs, and time of clinical studies without clear benefits. Thus, the absence of clear evidence requirements and data submission standards means longer and more burdensome trials, fewer centers and patients participating in a timely way, and ultimately fewer insights about safety and effectiveness. To address this problem, the FDA has issued guidances on data collection in registration trials for cancer therapies and on how to conduct safety reviews [3–5]. However, because these are not prescriptive and do not include specific details on key issues, many opportunities to improve submission standards and evidence requirements exist.

Perhaps the most straightforward opportunities for addressing this problem involve data collection for additional indications, rather than initial approvals. Streamlined data collection for treatments about which much is already known will make trials faster, less costly, and less burdensome on volunteers.

As part of an expert panel led by ASCO President Richard Schilsky, experts representing the FDA, NCI, academia, patient advocates, and the industry have contributed to an issue brief on this topic [6] and are currently working to develop an evidence-based decision tree to help investigators and sponsors develop protocols that will collect necessary data efficiently. Efforts to standardize data collection will pave the way for standardized analytic methods and expanded electronic data submissions—all of which can increase the efficiency of both clinical trials and regulatory review. To support such efforts, clinical investigators should strongly consider using the NCI’s cancer Bioinformatics Grid (caBIG), an open-source, open-access, open-development, and federated platform that makes possible standardized data capture and secure data sharing across 56 NCI cancer centers and 16 community health centers [7].

**INCORPORATE VALID AUXILIARY ENDPOINTS IN CLINICAL STUDIES**

Auxiliary endpoints were the second topic of discussion at the Brookings conference, with the expert panel led by AACR President Ray DuBois. As defined by the panel, these are endpoints other than overall survival that may be used to learn about the benefits and risks of cancer therapies in clinical trials [8]. These may include progression-free survival (PFS), patient-reported outcomes, and tumor biomarkers. Auxiliary endpoints are not intended to replace overall survival, but they offer the potential to learn more about therapies—and faster—than if the only outcome is overall survival. However, there is a need to ensure that auxiliary measures are validated and interpreted consistently across trials.

The challenges associated with validating and interpreting auxiliary endpoints are clearly illustrated in the ongoing debate about the appropriate use of PFS, which has been deemed acceptable by the FDA as a measure of efficacy for new cancer drug approvals. Because a progression endpoint is usually reached sooner than a survival endpoint, PFS offers the hope of increasing the ability to target clinical trial effort and resources to therapies that are most likely to demonstrate a clinically meaningful benefit. But, although employing PFS may result in shorter trials, PFS rates have not correlated consistently with overall survival. It is unclear whether this is because progression and survival are not always causally related, whether potential biases in the measurement of PFS may be confounding the association, or both. The potential for bias is of particular concern in open-label trials, when cancer progression is determined based on investigators’ interpretation of radiographic images. This concern has prompted significant discussion and further work on assuring consistently valid measurement of PFS—in particular, whether and to what extent auditing of tumor progression via blinded independent central review (BICR) is needed. Investigators at the NCI and within the industry are conducting statistical simulations on data from several completed PFS trials involving
CREATE A CLEAR PATH FOR THE CODEVELOPMENT OF DIAGNOSTICS AND THERAPEUTICS

Diagnostic tests to identify patients more likely to benefit from cancer treatments are an essential part of progress toward better-targeted therapies. However, as panel chair Dan Hayes pointed out at the Brookings conference, many scientific, regulatory, and reimbursement barriers may be slowing the development of effective cancer diagnostic tests. Challenges in translational research include the identification and validation of predictive biomarkers and technical difficulties in creating clinically useful, reliable tests. An unclear and inconsistent regulatory path for cancer assays has also hampered their development. Diagnostics can reach the market in one of several ways—via the FDA approval process, the “home brew” rule, or the clinical laboratory improvement amendments—all with differing kinds of regulatory scrutiny and evidence. Finally, public and private payers’ poor reimbursement for diagnostic tests has also slowed innovation and investment in potentially high-value tests.

Opportunities exist to help improve the efficiency of translational research on markers of likely patient response or side effects from treatment. ASCO and AACR, which are sponsoring ongoing initiatives on tumor marker development and use, can provide a foundation for this effort. A number of academic centers have predictive medicine programs in oncology that are generating data across a range of cancers. Merck is one of several product developers to invest heavily in the validation of biomarkers by pooling genetic and outcomes data over large populations, and in the development of cancer diagnostics based on those biomarkers. Coordination and collaboration across these stakeholder groups can lead to more efficient development of diagnostics and companion therapeutics.

To clarify and remove uncertainty from the regulatory approval process for diagnostic tests, and to support more efficient development of these potential markers, coordination and consistency among FDA centers is necessary. The Oncologic Drugs Advisory Committee (ODAC), which assesses safety and effectiveness data for new cancer drugs and makes non-binding recommendations to the FDA, can serve as a useful model in this case. An ODAC-like committee should be established to improve intra-agency cooperation and increase the consistency of the regulatory process for tumor markers. This committee should include a diverse array of clinicians, trialists, laboratorians, statisticians, and consumer and advocacy groups. Such broad representation is crucial to ensuring that the committee’s recommendations are based on sound policy and science [9]. Potential initial activities for this committee and FDA staff include defining the level of evidence required to qualify a diagnostic test as having clinical utility, as well as the level of evidence necessary to show clear impact on treatment and outcomes. The latter is likely to require prospective evaluation to support FDA-approved clinical labeling. The committee could also provide a forum for evaluating progress and gaps in the available evidence on markers.

However, when diagnostic tests and therapies need to be codeveloped, achieving any level of evidence for a diagnostic test involves a “chicken and egg” problem: Demonstrating impact on treatment and outcomes requires that the test be used in conjunction with an effective drug (or drug combination), yet proving the efficacy and safety of the drug is more likely if its use is targeted based on a test. Many diagnostic tests in use today are stuck at this stage, where the evidence is suggestive but not definitive (i.e., based on well-designed, prospective studies). To stimulate discussion of methods for codevelopment of tests with therapeutics, Ray Woosley and the Critical Path Institute have proposed using a retrospective data-driven disease model to assess whether a particular marker can predict which patients will benefit from a hypothetical treatment (i.e., the initial level of evidence). If simulations indicated that the marker had potential clinical value, the marker would be “qualified for use” in developing drugs similar to the hypothetical treatment. Once a clinical trial confirmed the marker’s value, the FDA could consider approving the marker for use with its companion treatment. This is only one of several possible codevelopment models that should be evaluated before the FDA issues its guidance on codevelopment.

MODERNIZE THE FDA’S APPROACH TO CANCER PRODUCTS

Common to all of these activities is a need for applying new scientific capabilities, such as those in genomics, systems
biology, and analysis of large and complex databases, to improve the science of demonstrating that innovative cancer therapies and combination treatments are safe and effective for particular patients. The FDA has a critical role to play in leading this effort. The FDA has already demonstrated its commitment to expedited review and approval of new cancer therapies that fill a therapeutic gap. Increasing the productivity and efficiency of clinical cancer research is an extension of these efforts.

Of course, these efforts would be enhanced through an increase in FDA resources. Although broad-based efforts to support the FDA have resulted in increases in the FDA’s appropriations in the past year [10], more support is needed. To justify the allocation of more resources to the FDA, officials there should make clear how additional resources will specifically affect the FDA’s capabilities and activities. In particular, the agency should demonstrate how it will incorporate quantitative evidence into its decision-making processes and develop greater expertise in systems-based biology and other relevant fields.

Although additional resources would enable faster progress, neither this vision for more efficient and productive clinical cancer research nor the steps to its implementation require the passage of new laws, budget appropriations from Congress, or an overhaul of the FDA to become reality. Instead, real progress requires motivated stakeholders representing academic and government researchers, patient advocates, product developers, and regulators to adopt and share the vision for improving the science of developing cancer therapies. Now is time to do it. This recent conference identified collaborative opportunities and concrete next steps to fulfill them, and we expect to see further progress thanks to all of these organizations working together.

REFERENCES