

## Using Patient-Initiated Study Participation in the Development of Evidence for Personalized Cancer Therapy

Laurie Fenton Ambrose<sup>1</sup>, Jamie Freedman<sup>2</sup>, Kenneth Buetow<sup>3</sup>, Stephen Friend<sup>4</sup>, and Richard L. Schilsky<sup>5</sup>

### Abstract

Personalized cancer therapy offers the promise of delivering the right treatments to the right patients to improve patient outcomes and quality of life, while reducing exposure to ineffective therapies and the cost of cancer care. Realizing this promise depends in large part on our ability to generate timely and sufficiently detailed information regarding factors that influence treatment response. Generating this evidence through the traditional physician investigator-initiated clinical trial system has proved to be challenging, given poor recruitment rates and low compliance with requests for biospecimen collection. As a result, our current understanding of treatment response is inadequate, particularly for cancer therapies that have been in use for many years. Patient-initiated study participation may offer a new model for evidence generation that capitalizes on strong patient interest in furthering research to inform better and more tailored cancer therapies. In this approach, patients are engaged and recruited directly by the sponsor of an Institutional Review Board–approved study, and patients subsequently drive the participation of their health care providers to facilitate collection of required data and tissue samples. The ultimate goal of these studies is to generate evidence of sufficient quality to inform regulatory decisions (i.e., labeling changes for marketed therapies to reflect populations most likely to respond) and treatment selection. Here, we describe a hypothetical prospective observational study in non–small cell lung cancer that could serve as a model for patient-initiated study participation applied to understand molecular determinants of treatment response. Key elements discussed include study design, patient engagement, and data/biospecimen collection and management principles. *Clin Cancer Res*; 17(21); 6651–7. ©2011 AACR.

### Introductory Note

At the 2010 Conference on Clinical Cancer Research, co-convened by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution, participants explored 4 pressing challenges in the field. Articles summarizing the panel's recommendations on each of these topics are featured in this issue of *Clinical Cancer Research* (1–4).

### Predicting Response or Non-Response to Approved Oncology Therapies

Approval of new cancer drugs by the U.S. Food and Drug Administration (FDA) relies upon safety and efficacy data from population-based trials. To date, such trials have

typically employed tumor classification systems that do not fully account for the growing body of genomic knowledge regarding tumor diversity (5). When drugs evaluated in these trials are approved and become standard of care, the implications of failing to account for tumor diversity become apparent. Standard-of-care cancer therapies may benefit only one in four patients, leaving upwards of 75% of patients without effective initial therapies and at risk of experiencing only toxic effects (6).

The goal of personalized cancer therapy can be achieved through the development of new therapies or the selective use of existing therapies in patients more likely to benefit. Designing new targeted therapies requires a clear understanding of the tumor biology and how it varies in the patient population. In cancers for which this understanding is still developing, an alternative approach is to study variations in response to available treatments in search of biomarkers that predict favorable outcomes. In cases where adequate evidence can be developed, a primary goal would be to modify the label of a marketed drug to specify the patient subgroups most likely to benefit or those unlikely to benefit. Such a post-approval labeling change happened recently in the case of cetuximab, a member of the class of cancer drugs known as epidermal growth factor receptor (EGFR) inhibitors (7).

For older drug products, existing data may not contain the needed genomic information to identify markers of response

**Authors' Affiliations:** <sup>1</sup>Lung Cancer Alliance, Washington, District of Columbia; <sup>2</sup>GlaxoSmithKline, Collegeville, Pennsylvania; <sup>3</sup>Bioinformatics and Information Technology, National Cancer Institute, Bethesda, Maryland; <sup>4</sup>Sage Bionetworks, Seattle, Washington; and <sup>5</sup>University of Chicago Comprehensive Cancer Center, Chicago, Illinois

**Corresponding Author:** Richard L. Schilsky, Biological Sciences Division, University of Chicago Medical Center, 5841 S. Maryland Avenue, MC 2115, Chicago, IL 60637. Phone: 773- 834-3914; Fax: 773-834-3915; E-mail: rschilsk@medicine.bsd.uchicago.edu

**doi:** 10.1158/1078-0432.CCR-11-1110

©2011 American Association for Cancer Research.

or nonresponse. Moreover, in the traditional physician investigator-based patient recruitment model, the clinical trials necessary to expand our knowledge are plagued by low enrollment and poor compliance for biospecimen collection (8). When genomic data are to be collected in pivotal trials, the current practice relies on optional genomic patient consent (either prospective or retrospective), which results in convenience, and potentially biased, genomic sample data collection (9). The genomic consent rates vary from trial to trial, making study results very difficult, if not impossible, to interpret when the compliance rates are low (10).

One potentially promising avenue for developing such evidence rapidly lies in directly engaging patients to participate in studies that collect detailed information about their tumors, treatments, and clinical outcomes. We define patient-initiated study participation as a model in which patients are engaged and recruited directly by the sponsor of an Institutional Review Board (IRB)-approved study, and patients in turn drive the participation of their physicians and other health care providers to facilitate collection of required data and tissue samples. As part of such a study, patients who receive cancer care from their usual providers would volunteer to donate certain biospecimens and clinical information to the study sponsor prior to treatment initiation and over the course of treatment. The goal of these studies is to use patient biospecimens and other data to identify molecular markers of treatment response that can be used to select treatment for future patients.

Recognizing the promise of this approach, advocacy groups such as the Love/Avon Army of Women, the Lung Cancer Alliance and others have begun to mobilize their networks to generate data through patient-initiated participation (11–15). For example, the Love/Avon Army of Women Initiative is attempting to recruit one million healthy women (including breast cancer survivors and women at risk for breast cancer) to participate in breast-cancer related studies (11). As of May 2011, over 354,000 women and men had registered online and 50 studies have been launched after successful matches were made

between interested participants and researchers (16). These initiatives speak to the motivation and commitment of patients and their families to advancing cancer research in general and personalized cancer care in particular. By providing patients with tools to enroll themselves and their providers in studies (thereby flipping the traditional provider-initiated approach), these efforts demonstrate the promise of patient-initiated participation for rapid accrual of large amounts of detailed exposure and outcomes data to answer a range of important questions in cancer care, including how to better target therapies. To ensure that these efforts result in actionable information, what is needed now is a clearer understanding of how such data can be most effectively collected (e.g., through improved education for involved parties) and used to inform the decisions of doctors, patients, regulatory authorities, and payers.

### Data Required to Identify Patient Subsets

Developing evidence to support targeting available treatments to a subgroup of patients requires collecting detailed and high-quality data. These data can be thought of in layers of comprehensive, longitudinally linked information so that treatments can be tracked over time and within subgroups of patients. In addition to basic information like demographics, clinical laboratory results, and medical history, needed layers will likely include normal tissue samples, tumor and other biological specimens, detailed information on treatment exposure, adverse events, and clinical outcomes (Fig. 1).

Few data sources currently have the breadth and depth of information necessary to support analyses with sufficient statistical power to identify biomarkers of response or nonresponse. Furthermore, changing FDA-approved labels and recommended standards of care requires robust evidence built on high-quality data and an acceptable study design. We envision collection of these data through post-approval studies in which genomic data from biospecimens

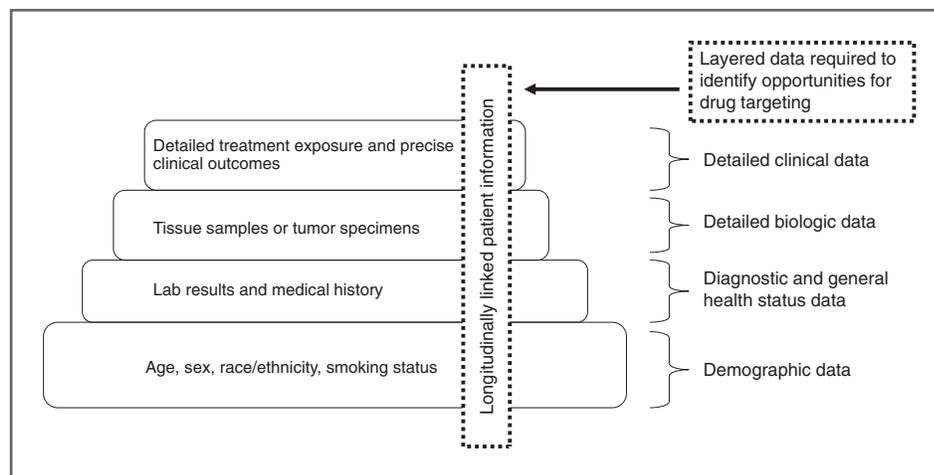


Figure 1. Layered data required to assess patient subsets.

are used to identify biomarkers predictive of clinical outcomes. Several factors can affect the ability to generate useful data from a genomic biomarker trial: (i) the prevalence of the target biomarker in the population; (ii) the prognostic impact of the biomarker to distinguish clinical outcomes in the population; (iii) concordance of biomarker expression between primary and metastatic tumor tissue; (iv) qualification and validation (analytical and clinical) of the biomarker assay; (v) availability of tissue specimens containing the biomarker; and (vi) quality and quantity of the tissue samples for biomarker analysis. Each of these factors will need to be addressed in any study of this nature.

### Hypothetical Proposed Study

To help illustrate the issues, challenges, and potential solutions in using data generated through patient-initiated study participation for the purpose of informing labeling changes for existing cancer therapies, we examine study design considerations within the context of treatment for non-small cell lung cancer (NSCLC). First-line treatment for NSCLC typically consists of chemotherapy with a 2-drug regimen containing either cisplatin or carboplatin and another agent, which is typically vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed. Experience with these regimens indicates that only approximately 30% of patients respond favorably (17).

To identify molecular signatures that explain variation in treatment response, several initiatives, including the Sage Bionetworks Non-Responder Project, are working to design studies that identify predictive markers of nonresponse. The Non-Responder Project has chosen several candidate tumors to study, including NSCLC, with an initial pilot study in acute myelogenous leukemia (5) based on 4 "first principles" for tumor selection (Fig. 2).

Informed by this and other related efforts, the objective of the proposed study is to identify one or more molecular

markers of nonresponse to first-line platinum-containing therapies for metastatic NSCLC, with the goal of supporting the revision of FDA-approved labels and recommended standard of care for these drugs.

The proposed study would begin when a patient with NSCLC is nearing a treatment decision and becomes aware of the opportunity to participate in the study by means of a website description or other form of outreach. This patient would approach his or her physician for support to enroll in the study. After enrollment, biospecimens would be collected from the patient at a designated research center and then the patient would return to the care of their oncologist. Meanwhile, tumor specimens would be analyzed in a Clinical Laboratory Improvement Amendments–certified laboratory for known and clinically actionable genetic variants. If clinically actionable results are identified from the research analyses, they would be returned to the patient and treating oncologist. Within the context of this hypothetical study, the study sponsor would determine what constitutes clinically actionable information on the basis of currently available evidence. Only clinically actionable results would routinely be shared with patients and providers; however, full results would be available upon request. Together, the patient and oncologist would select the most appropriate treatment approach (which may or may not rely on the results of tests performed in the study) from among the standard targeted or platinum-based therapies, and the provider would collect and report additional data on clinical outcomes over time. These longitudinal data would eventually be compiled, linked to other sources of electronic clinical data, and made available to qualified researchers.

Details regarding the proposed study design, including population characteristics, sample size, and key endpoints, are provided in Fig. 3. Analyses would be prespecified in the IRB-approved study protocol. Included in this study design would be the necessary and appropriate statistical analysis along with the network-biology modeling done to identify

Figure 2. Sage Bionetworks Nonresponder Project: First Principles for Tumor Selection.

<b>Sage Bionetworks Nonresponder Project: First Principles for Tumor Selection</b>
<ul style="list-style-type: none"> <li>▪ The treatment under investigation should have substantial response and nonresponse rates (&gt;20% in either group).</li> <li>▪ The disease must have clear, robust definitions of response and nonresponse that are clinically important. (A nonresponse biomarker should have the potential to change clinical practice.)</li> <li>▪ Routine clinical management of the disease guarantees access to high-quality tissue specimens. (Use of archival tissue from diagnostic samples introduces risk when assessing treatments given at relapse.)</li> <li>▪ The nonresponse group should ideally be defined as patients refractory to treatment rather than those who respond then relapse early. (If early relapse is caused by a resistant subpopulation at diagnosis, genomic analysis of tissue at diagnosis may or may not be informative, depending on the size of the resistant pool.)</li> </ul>

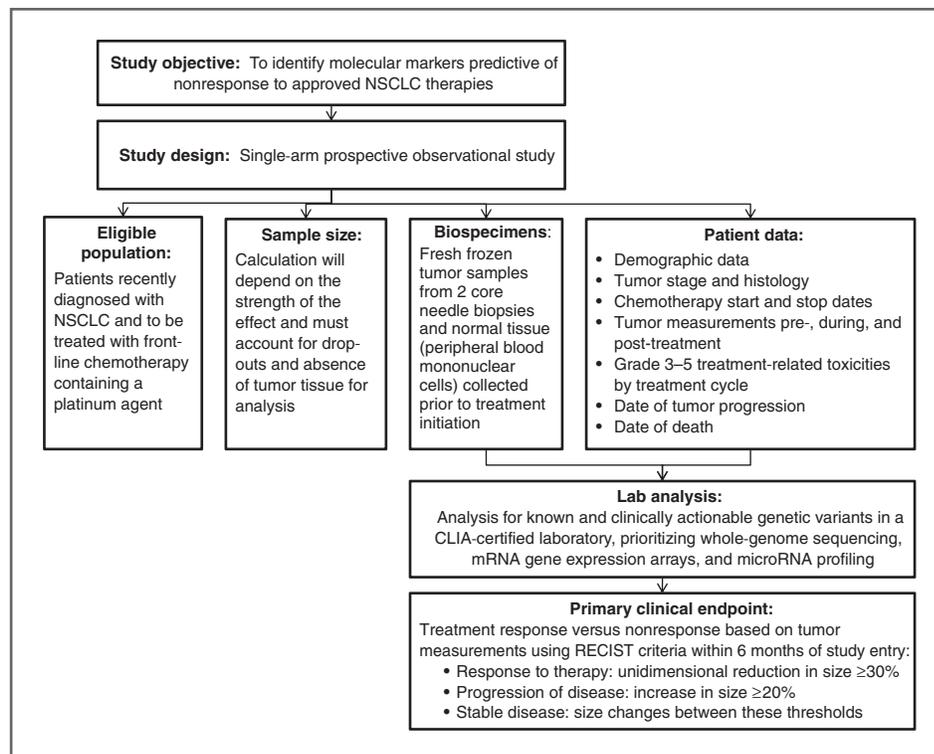


Figure 3. Design for hypothetical observational study. RECIST, Response Evaluation Criteria in Solid Tumors.

not just isolated markers for nonresponder populations but also sets of genes or "gene signatures" capable of identifying nonresponders. The goal for lung cancer might be to identify patients who have more than an 85% chance of not responding with a certainty of this outcome of 90%. This certainty around the likelihood that a patient may not respond would need to be set at a predetermined level of stringency to enable clinicians to use this information to determine whether to forego the original approved therapy and instead provide the patient an opportunity to receive an investigational regimen. The criteria for foregoing standards of care would be tumor and regimen specific and would need to be agreed to upfront with regulators and clinicians before the study is started.

### Feasibility of Patient-Initiated Study Participation

While patient-initiated study participation offers promising opportunities for more efficient and dynamic clinical trial enrollment, a number of feasibility issues must be considered during data collection so that resulting data are relevant for regulatory and other forms of decision making.

#### Patient engagement

Patient-initiated study participation begins with raising awareness of participation opportunities, achieving patient/family engagement, and supporting patients/families through the process of enrolling in the study. Patient advocacy groups are positioned to play a key role in edu-

cating patients and their families regarding the importance of study participation and how the clinical research process works. In order to ensure optimal patient participation, we recommend that patient-initiated study participation efforts do not impose any sort of fees on patients. Instead, organizers of such efforts should absorb any associated costs or such costs should be incurred as part of routine cancer care.

As with any biomedical study, sponsors of studies employing patient-initiated participation must be careful to identify potential ethical concerns, address them as much as possible through study design, and ensure they are clearly communicated during the consent process. In some ways, a study such as the one proposed poses a narrower range of ethical concerns because it is not a treatment trial, but rather an observational study intended to enhance our understanding of response to established treatments. Even so, important issues to consider may include, but are certainly not limited to, the timing and nature of informed consent (e.g., if consent is obtained by study sponsors without the patient's provider present to offer guidance), clear communication of what results will and will not be returned to patients and providers, and anticipated risks of biospecimen donation that are above and beyond those associated with routine cancer care.

#### Role of health care providers

Health care providers can help to inform patients of the importance of study participation, streamline the consent and biospecimen collection process, and counsel patients

regarding potential health risks. In addition, health care providers assume certain formal responsibilities in the context of patient-initiated study participation. Once a patient decides to participate, they rely on their health care providers to provide the sponsor with medical records and possibly to perform relevant procedures, such as biopsies. As described above, the costs associated with these procedures should not be imposed on patients, and they also should not fall to providers. These costs should be covered as part of routine cancer care or should be absorbed by the study sponsor, as appropriate. To facilitate effective provider cooperation, organizations leading patient-initiated study participation efforts should consider proactively identifying interested providers and providing them with detailed information about the initiative and what level of provider involvement is expected.

### Sample collection

When necessary, collection of biologic samples must address specific challenges. In general, normal tissue (e.g., blood, skin, or hair follicles) is easier to collect than tumor specimens. However, even these samples may require more complex sample collection schemes (e.g., peripheral blood mononuclear cells from whole blood) that call upon specialized collection methods and expertise at the clinical sites. Tumor samples are generally more difficult to collect because they require invasive procedures and because the quality of the specimens may be highly variable. Certain anatomic sites (e.g., skin or lymph nodes) are more amenable than others for collection of tumor specimens. Primary lung cancer specimens are very hard to collect because of location. If an assay for archival tissue is available from the original surgically obtained tumor specimen, such a sample might allow the highest yield if deemed scientifically appropriate to meet the study objectives.

During sample collection and all subsequent phases of storage and analysis, great care must be taken to ensure that biospecimens are of high quality. In an effort to improve the quality and standardization of biospecimens collected for cancer research, the Office of Biorepositories and Biospecimen Research within the National Cancer Institute (NCI) has launched several initiatives, including the development of best practices for biospecimen collection, processing, storage, retrieval, and dissemination (18). Although adherence to these best practices is voluntary, these standards and recommendations should be consulted in any patient-initiated study participation effort that involves biospecimen collection.

### Sample compilation and storage

After samples and other data are obtained from patients, processes must be developed to efficiently compile and integrate them. Efforts that rely on patients to directly transfer data (e.g., computed tomography scans) to the study organizer will be more direct and simple to accomplish. Obtaining biospecimens from

patients may be more challenging because patients are typically not the "owners" of these samples and coordination must occur with health care providers. Such coordination may be more feasible if sample collection occurs at designated collection facilities and if relationships have been previously established with a core set of providers. As patient data/samples are collected, they should ideally be stored in a way that preserves the ability to link to other sources of electronic clinical data (e.g., from electronic health records) while protecting confidentiality. This measure is critical to creating the type of layered data necessary to identify markers of response and nonresponse.

### Data access

To fully realize the goal of patient-initiated study participation, we recommend that data be compiled and made available free of charge in a standardized electronic format to all qualified researchers, rather than restricting access to a particular investigator or team. This availability will enable the widest possible access to patient data, and therefore the greatest possibility for important discoveries.

### Patient privacy and data security

Ethical use of the data and samples requires review to ensure protection of human subjects, as well as assurance of patient privacy and data security. To this end, it is necessary to establish a "trust fabric" that grants access only where appropriate and only to data components that have been authorized [Health Insurance Portability and Accountability Act (HIPAA)] or consented to (Office for Human Research Protections) by the patient. Patients should be clearly advised that their donated data would be accessible to researchers and that the product of the research may be commercialized. The level of identification risk associated with donating their data must be transparently communicated to the participating patients and informed consent obtained. Because HIPAA assigns responsibility for protections to local groups that hold patient information, this trust fabric should recognize the need for local control of data release.

Patient privacy should be protected by removal of all HIPAA "identifiers" and by agreements that no parties may seek reidentifying information except for research covered by the informed consent. Double deidentification may provide further privacy protection with the use of 2 levels of coding between HIPAA "identifiers" and information relevant for research purposes (e.g., health outcomes or genetic/genomic test results). Use of this approach increases the stringency of privacy protection, while retaining the potential for future analyses building upon the collected data, which is not the case with other methods (e.g., total anonymization).

Patient-initiated study participation efforts should allow controlled access to patient-level data, and researchers seeking such data would have to make appropriate commitments including the following: (i) use only for approved

research; (ii) no sharing of data/samples with others without such sharing having been referenced in the consent form; (iii) no effort to reidentify; (iv) return of unused biospecimens to the repository; and (v) the repository would be obligated to confirm that the proposed research is consistent with the scope of the consent forms and to track the disposition of all specimens.

### **Governance**

Governance policies are required to establish oversight of data collection and use. This is essential to maintain aspects of compliance, privacy, and access to data and models within the project. Existing projects involving clinical/genomic data set generation by structures such as the Cancer Biomedical Informatics Grid (caBIG), The Cancer Genome Atlas, and trials such as the BATTLE trials and the I-SPY trial network provide precedents for establishing these governance rules and processes. Relevant policies may pertain to the use of data collected and how to ensure that the effort uses a sustainable funding model, among other topics.

### **Regulatory submissions**

One potentially important issue involves the types of entities that might bring data forward to a regulatory agency as a result of patient-initiated study participation. Given that such efforts may be spearheaded by nonprofit as well as commercial organizations, it is possible that a nonprofit organization, not affiliated with a commercial product sponsor, might develop and submit data on molecular markers associated with response/nonresponse to an approved drug for review by a regulatory agency. It is unclear whether there is a pathway for evidence to be brought to the FDA by these nontraditional sponsors. If the evidence pertained to a biomarker for treatment response in general and without reference to a particular drug under development, one potential pathway might be through the FDA's recently proposed qualification process for drug development tools. In such cases, if the biomarker is qualified, it could be incorporated into any future drug development based on the qualified context of use. However, the process for translation of evidence from patient-initiated study participation into labeling changes may still require clarification and consideration regarding whether data arose from a specific drug development program as opposed to a postmarketing study. Such changes might occur independently of the product sponsor and possibly without the sponsor's agreement. Arguably, these changes would likely be in the interest of the patient community and society in general, but they might not always be in the interest of product sponsors.

### **Principles for Effective Management of Patient-Initiated Data Collection**

As with any clinical research, it is essential that data be of a standard form for analysis. In traditional research settings, standardization of multiple data sources is accomplished

through use of common data collection forms and adherence to common practices in form completion. Years of practice in the oncology community have produced a large library of these common data elements using terminologies and ontologies that are national and international standards. In a partnership among academia, industry, and the FDA, these elements and ontologies have been used to create a common information model that supports electronic regulatory submission. Wherever possible, data collection should leverage these and other standard information representations.

Data generated through patient-initiated study participation is unlikely to arise solely from the clinical research arena. Instead, data will arise from health care encounters in settings using a variety of information representation standards. In addition, clinical information represents only a single dimension among the multiple diverse types of data that must be captured, managed, and interconnected. Similar considerations exist for biospecimens, imaging data, and the molecular data that will be used to characterize the individual participants. This information must have common representation across the diverse organizations in multiple disparate locations acquiring and sharing variant dialects of data often captured in unstructured (narrative) form. The NCI's caBIG program has created such representations and a collection of tools, accessible as Web tools, which utilize them. However, as is the case for clinical information, the caBIG Integration Hub permits disparate types of information to be cross-mapped to a common representation. Researcher-generated data can then be collected in a standardized manner and captured in an infrastructure that can support reuse by other investigators as authorized by patients.

Aggregation and analysis of the complex, multidimensional data also requires novel infrastructure. The caBIG community has created data mart/data warehouse tools that facilitate the collection and effective use of the multidimensional clinical and molecular data through its caIntegrator capabilities. These tools effectively manage the large volume and complexity of data for projects such as The Cancer Genome Atlas.

### **Next Steps**

Patient-initiated study participation is a potentially promising way of rapidly generating evidence to support better targeting of previously approved cancer therapies. Cancer patients, caregivers, and their advocates have demonstrated strong enthusiasm for improving the efficiency of clinical research. It is possible that better patient education will enhance the quality of data collected through patient-initiated participation in clinical studies. However, some limitations should be acknowledged and addressed, including potential issues in selection of patients for these types of studies. For example, it is possible that certain highly motivated patients may be disproportionately represented, which could influence results obtained.

We have proposed a model that leverages the motivation and commitment of cancer patients to overcome some of the challenges in the collection of data and biospecimens that can be used to identify biomarkers predictive of nonresponse to previously approved chemotherapeutic agents. Care should be taken to ensure that such studies are designed with broad-based input from all stakeholders so that patients are informed appropriately, the correct types of data and biospecimens are collected, information is compiled and managed efficiently, the resulting database is made available to researchers with appropriate protections and security features in place, and that the data are analyzed in a way that yields evidence of sufficient quality to inform regulatory decisions and clinical practice.

In order to determine the true potential of patient-initiated study participation, pilot efforts are an important first step. These pilot studies will necessarily be informed by the ongoing data collection efforts of advocacy organizations. To inform pilot studies, a Guidance from FDA regarding what data will be considered actionable for labeling changes would be helpful. This information could be gathered unofficially as part of meetings that convene regulatory

authorities, industry representatives, patient groups, and academia around this issue.

### Disclosure of Potential Conflicts of Interest

Dr. Schilsky reports having served as a member of the Board of Directors for Universal Oncology, Inc. and as a member of the Scientific Advisory Board of Foundation Medicine, Inc. No potential conflicts of interest were disclosed by the other authors.

### Acknowledgments

The authors gratefully acknowledge the contributions of several individuals. Sue-Jane Wang (U.S. Food and Drug Administration) offered valuable insights during the development of the concept for this paper and participated in the panel presentation at the 2010 Conference on Clinical Cancer Research. Roy Herbst (Yale School of Medicine), Annie Martin (GlaxoSmithKline), and Ignacio I. Wistuba (The University of Texas MD Anderson Cancer Center) provided targeted advice as the authors refined the concept. Joshua S. Benner, Erin Karnes, and Ed Walters (all from the Engelberg Center for Health Care Reform, The Brookings Institution) as well as Elaine Khoong (medical student at Washington University School of Medicine) helped to coordinate panel discussions and provided research and drafting assistance throughout the process.

Received May 6, 2011; revised July 5, 2011; accepted August 25, 2011; published online November 1, 2011.

### References

1. Roberts SA, Karnes EK, Allen JD, Benner JS, Sigal EV, McClellan M. Achieving the goals of effective, safe, and individualized cancer care. *Clin Cancer Res* 2011;17:6632-3.
2. Scher HI, Fuld Nasso S, Rubin EH, Simon R. Adaptive clinical trial designs for simultaneous testing of matched diagnostics and therapeutics. *Clin Cancer Res* 2011;17:6634-40.
3. Turteltaub KW, Davis MA, Burns-Naas LA, Lawton MP, Clark AM, Reynolds JA. Identification and elucidation of the biology of adverse events: the challenges of safety assessment and translational medicine. *Clin Cancer Res* 2011;17:6641-5.
4. Cleeland CS, O'Mara A, Zagari M, Baas C. Integrating pain metrics into oncology clinical trials. *Clin Cancer Res* 2011;17:6646-50.
5. Friend SH, Golub T, Radich J, Sawyers C, Schilsky R. Identification of non-responders to approved cancer drugs through patient-oriented sample and data collection: Strategic Summary and AML Pilot. Overview for NCI Meeting, Sep 23, 2010. [cited 2011 Oct 13]. Available from: [http://sagebase.org/downloads/NRP\\_Appendices.pdf](http://sagebase.org/downloads/NRP_Appendices.pdf).
6. Friend SH, Schilsky RL. Sage Project: finding non-responders to approved drugs through patient oriented sample/data collection and hosted in the public domain. Mar 2010.
7. Cetuximab (Erbix) and panitumumab (Vectibix) [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. [cited 2011 Mar 21]. Available from: <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm>.
8. Comis RL, Colaizzi DD, Miller JD. Barriers to cancer clinical trials (CCT) participation: "We have met the enemy and he is us." ASCO Annual Meeting Proceedings (Post-Meeting Edition). *J Clin Oncol* 2007; 25(18S): abstr 6567.
9. Wang SJ, Cohen N, Katz DA, Ruano G, Shaw P, Spear B. Retrospective validation of genomic biomarkers—what are the questions, challenges and strategies for developing useful relationships to clinical outcomes—Workshop Summary. *Pharmacogenomics J* 2006;6:82-8.
10. Wang SJ, O'Neill RT, Hung HMJ. Some statistical considerations in evaluating pharmacogenomics confirmatory clinical trials. *Clin Trials* 2010;7:525-36.
11. Love / Avon army of women [homepage on the Internet]. [cited 2010 Sep 23]. Available from: <http://www.armyofwomen.org/>.
12. Health of women study [database on the internet]. [cited 2010 Sep 23]. Available from: [http://www.armyofwomen.org/HOW\\_Study](http://www.armyofwomen.org/HOW_Study).
13. Lung Cancer Alliance. What is Give a Scan? [cited 2010 Sep 23]. Available from: <http://www.lungcanceralliance.org/giveascan>.
14. The Clarity Foundation. [cited 2010 Sep 23]. Available from: <http://www.clarityfoundation.org>.
15. About the MMRC [homepage on the Internet]. [cited 2010 Sep 23]. Available from: [http://www.themmr.org/about\\_mmr.php](http://www.themmr.org/about_mmr.php).
16. Reimer S. Dr. Love builds an anti-cancer army [monograph on the Internet]. Baltimore (MD): The Baltimore Sun; [updated 2011 May 12; cited 2011 Jun 29]. Available from: [http://articles.baltimoresun.com/2011-05-12/health/bs-hs-love-profile-20110512\\_1\\_breast-cancer-cervical-cancer-susan-love](http://articles.baltimoresun.com/2011-05-12/health/bs-hs-love-profile-20110512_1_breast-cancer-cervical-cancer-susan-love).
17. Scagliotti GV, De Marinis F, Rinaldi M, Crinò L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285-91.
18. National Cancer Institute best practices for biospecimen resources. Bethesda, MD: National Cancer Institute; 2007. [cited 2011 Jun 20]. Available from: [http://biospecimens.cancer.gov/global/pdfs/NCI\\_Best\\_Practices\\_060507.pdf](http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf).