CLINICAL TRIALS

Strategies to Overcome Clinical, Regulatory, and Financial Challenges in Implementation of Personalized Medicine

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Strategies to Overcome Clinical, Regulatory, and Financial Challenges in the Implementation of Personalized Medicine

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OVERVIEW

This article highlights major developments over the last decade in personalized medicine in cancer. Emerging data from clinical studies demonstrate that the use of targeted agents in patients with targetable molecular aberrations improves clinical outcomes. Despite a surge of studies, however, significant gaps in knowledge remain, especially in identifying driver molecular aberrations in patients with multiple aberrations, understanding molecular networks that control carcinogenesis and metastasis, and most importantly, discovering effective targeted agents. Implementation of personalized medicine requires continued scientific and technological breakthroughs; standardization of tumor tissue acquisition and molecular testing; changes in oncology practice and regulatory standards for drug and device access and approval; modification of reimbursement policies by health care payers; and innovative ways to collect and analyze electronic patient information that are linked to prospective clinical registries and rapid learning systems. Informatics systems that integrate clinical, laboratory, radiologic, molecular, and economic data will improve clinical care and will provide infrastructure to enable clinical research. The initiative of the EurocanPlatform aims to overcome the challenges of implementing personalized medicine in Europe by sharing patients, biologic materials, and technological resources across borders. The EurocanPlatform establishes a complete translational cancer research program covering the drug development process and strengthening collaborations among academic centers, pharmaceutical companies, regulatory authorities, health technology assessment organizations, and health care systems. The CancerLinQ rapid learning system being developed by ASCO has the potential to revolutionize how all stakeholders in the cancer community assemble and use information obtained from patients treated in real-world settings to guide clinical practice, regulatory decisions, and health care payment policy.

The human genome project has enabled sequencing of human DNA and led to advancements in technologies that detect genomic, transcriptional, proteomic, and epigenetic changes. After the breakthrough development of imatinib mesylate for the treatment of newly diagnosed chronic myeloid leukemia, the concept of “personalized” or “individualized” medicine for patients with solid tumors emerged. Now, a plethora of studies are invested in improving our understanding of the pathophysiology of various tumor types and the role of molecular aberrations in carcinogenesis. Advances in technology, including next-generation sequencing, that enable fast, accurate, inexpensive, and efficient tumor molecular profiling to detect genetic aberrations in tumors combined with the clinical development of agents inhibiting the function of driver genes have enabled the use of personalized medicine in selected patients with targetable tumor aberrations.

Despite these advances, however, personalized medicine is available to very few patients, and the discovery of new anticancer therapies remains complicated and lengthy. Although the use of tumor molecular profiling to guide treatment decisions is envisioned as an important strategy in cancer therapy, the policies of institutions, regulatory agencies, and insurance companies often limit patient access to personalized treatment. To more fully implement personalized medicine, the methodology of laboratory and clinical research must be improved, the available resources must be used more efficiently, and policy and practice must be harmonized.

REWARDS: THE PROMISE OF PERSONALIZED MEDICINE

During the last decade, tumor molecular profiling has revealed various DNA sequence or structural alterations, gene deletions, duplications, or amplifications, and transcriptome and epigenetic changes in individual patients with cancer. This knowledge has led to the development of novel agents with antitumor activity in molecular subtypes of certain tumors. Our understanding of tumor biology has optimized the
selection of treatment in subgroups of patients, resulting in improved clinical outcomes. This practice results in more efficacious use of resources because it limits patients’ time receiving ineffective treatments and because the use of targeted therapy is associated with decreased toxicity.

Two major developments provide evidence that the concept of personalized medicine can become a reality: (1) The BRAF inhibitor vemurafenib in patients with BRAF-mutated melanoma and (2) The ALK inhibitor crizotinib in patients with ALK-rearranged lung cancer. Vemurafenib induced an overall response rate of 81% (26 of 32) in patients with melanoma bearing the V600E BRAF mutation, and crizotinib induced an overall response rate of 57% (47 of 82) in patients with ALK-rearranged non—small cell lung cancer.

In 2007, the University of Texas MD Anderson Cancer Center initiated a personalized medicine program through the exploratory, nonrandomized IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy) study. Tumor molecular profiling (polymerase chain reaction—based sequencing, immunohistochemistry, and fluorescent in situ hybridization in a Clinical Laboratory Improvement Amendments (CLIA) environment) was performed in patients with advanced cancer, and patients with targetable aberrations were treated with matched targeted agents in phase I clinical trials, if feasible. Within a 4.5-year period, 2,282 patients with advanced cancer of any tumor type who had previously undergone treatment, whose disease was refractory/nonresponding to or incurable with the standard—of-care treatment, and who were seen in the Department of Investigational Cancer Therapeutics at MD Anderson underwent tumor molecular analysis. The median number of prior therapies was three. Overall, 1,191 patients (52.2%) had one or more molecular aberrations detected (one, two, and three or more aberrations in 892 [39.1%], 242 [10.6%], and 57 [2.5%] patients, respectively). Proportions of aberrations detected were as follows: PIK3CA, 10.1%; AKT, 1.7%; PTEN, 15.6%; KRAS, 20.6%; NRAS, 7.2%; BRAF, 12.1%; EGFR, 6.1%; MET, 4.6%; ALK, 0.2%; GNAQ, 1.7%; CKIT, 3.4%; TP53, 35.8%; and HER2, 5.5%. Overall, 882 patients received treatment on phase I studies. Best responses by Response Evaluation Criteria in Solid Tumors (RECIST), progression—free survival, and overall survival by number of aberrations and type of therapy are shown in Table 1. In addition, time to treatment failure (TTF) with matched phase I therapy was longer than that with prior systemic therapy (median, 4.0 vs. 3.1 months, respectively; p = 0.0008). TTF with unmatched phase I therapy was shorter than that with prior systemic therapy (2.0 vs. 3.2 months; p = 0.0001). In multivariate analyses, matched therapy was an independent factor predicting response (p < 0.0001) and TTF (p < 0.0001). Taking into consideration that there were several limitations to this exploratory, nonrandomized study, these striking findings support use of a personalized molecular approach for patients with cancer.

Further research is needed to develop the technology to identify molecular aberrations in all patients with cancer and to understand driver aberrations, resistance mechanisms, and tumor heterogeneity. Prospective, carefully designed clinical trials taking into consideration the antitumor activity of targeted drugs and specific tumor molecular aberrations in certain tumor types will bring new treatment paradigms to light.

**KEY POINTS**

- Clinical trials have demonstrated that the use of targeted therapy against targetable molecular aberrations in tumors is associated with improved outcomes in certain tumor types, but this approach is available to very few patients.
- Implementation of personalized medicine requires continued scientific and technological breakthroughs and collaborations between molecular pathologists, bioinformaticians, oncologists, clinical investigators, and other professionals involved in making clinical decisions.
- Increased harmonization across discoveries, policies, and practices will expedite the implementation of changes in oncology practice, will improve access to drugs, and will help modify the reimbursement policies of health care payers.
- In Europe, the EurocanPlatform has established a complete translational cancer research program covering the drug development process and strengthening collaborations among academic centers, pharmaceutical companies, regulatory authorities, health technology assessment organizations, and health care systems.
- Innovative informatics systems that harness diverse types of information from diverse sources to build rapid learning systems that both collate data and use sophisticated algorithms to learn from each patient, such as the CancerLinQ rapid learning system being developed by ASCO, will help guide clinical practice, regulatory decisions, and health care payment policy.

**CHALLENGES TO THE IMPLEMENTATION OF PERSONALIZED MEDICINE**

Implementing a personalized cancer medicine program requires the following: (1) adequate tumor tissue available for molecular profiling, (2) a standardized, high—quality laboratory for molecular profiling to ensure the accuracy, reliability, and timeliness of patient test results: CLIA—certified in the United States and International Organization for Standardization (ISO)—certified in Europe and other countries, (3) identification of tumor “targetable” molecular aberrations, and (4) availability of a targeted agent known to inhibit the function of the molecular aberration (Table 2).

The most limiting factor in the implementation of personalized medicine appears to be the slow progress of translational research resulting from limited funding and regulatory constraints. We need to constantly evaluate the status of clinical, laboratory, regulatory, and financial challenges and discuss strategies to expedite drug approval and the implementation of personalized medicine in patients with cancer.
Some other challenges in implementing personalized medicine are the cost of a tumor biopsy, the lack of optimal tumor tissue to perform molecular analysis (adequacy of core biopsies vs. fine-needle aspiration; paraffin-embedded tissue vs. fresh biopsy), and the development of resistance to targeted therapy after disease control is obtained for a period of time.

The development of vemurafenib and crizotinib involved molecular screening for a single aberration. In July 2011, before the approval of these drugs, the U.S. Food and Drug Administration (FDA) issued a draft guidance that defined in vitro (IVD) companion diagnostic devices as analytic tests that are required for the safe and effective use of a drug. However, the sequential single-aberration screening used for vemurafenib and crizotinib has already been replaced worldwide by next-generation sequencing, which enables more efficient selection of the appropriate targeted drug.

A central issue that remains unaddressed is the dynamic relationships among molecules, pathways, and networks in the primary tumor and metastatic sites. Evidence suggests that the prevailing molecular pathways are altered after the use of targeted therapy against a specific gene. For instance, the genotypic and histologic evolution of cancer resistance to targeted agents, such as epidermal growth factor receptor inhibitors for lung cancer, emphasizes the need for repeated molecular profiling throughout the course of the disease. Furthermore, molecular profiling of primary renal carcinomas and associated metastatic sites demonstrated intra-tumor heterogeneity, which is associated with heterogeneous protein function. This heterogeneity may foster tumor adaptation and therapeutic failure, and suggests that a single-tumor biopsy may be suboptimal to fully characterize the molecular profile of a tumor. Many other features of the tumor, including relative hypoxia and metabolic activity, likely contribute to the fine-tuned regulation of molecular aberrations.

The implementation of personalized medicine is a complex, but not unfeasible, process that requires some critical steps: (1) Exploring how to best implement advanced technologies for tumor tissue molecular profiling, (2) Reassessing the value of IVD companion diagnostic devices in the emerging era of next-generation and whole-exome sequencing, (3) Understanding how to integrate molecular, clinical, regulatory, and economic data to expedite drug development, (4) Raising awareness of existing issues and stimulating coordinated participation of molecular pathologists, bioinformaticians, oncologists, clinical investigators, and other professionals involved in clinical decisions, and (5) Increasing the harmonization among research, policy, and practice.

Newer information about the molecular pathophysiology of cancer has amplified interest in the field and holds the promise of enriching the therapeutic arsenal for the treatment of cancer. A shift in the current therapeutic paradigm toward an increased emphasis on treating patients uniquely, taking into consideration the molecular biology of each patient’s tumor, will expedite the cure of cancer.

### TABLE 1. Clinical Outcomes by Number of Aberrations and Type of Therapy

<table>
<thead>
<tr>
<th>No. of Aberrations</th>
<th>Therapy</th>
<th>No. of Patients</th>
<th>CR + PR + SD ≥ 6 Months (%)</th>
<th>P</th>
<th>Median PFS (months)</th>
<th>p</th>
<th>Median Survival (months)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Matched</td>
<td>306</td>
<td>113/293 (39)</td>
<td>&lt;0.0001</td>
<td>4.9</td>
<td>&lt;0.0001</td>
<td>11.2</td>
<td>0.006</td>
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<tr>
<td></td>
<td>Not matched</td>
<td>360</td>
<td>52/337 (15)</td>
<td>2.2</td>
<td>8.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Matched</td>
<td>101</td>
<td>21/82 (26)</td>
<td>0.30</td>
<td>3.7</td>
<td>0.13</td>
<td>9.9</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Not matched</td>
<td>68</td>
<td>10/57 (18)</td>
<td>2.6</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>Matched</td>
<td>33</td>
<td>9/26 (35)</td>
<td>0.71</td>
<td>3.7</td>
<td>0.09</td>
<td>7.7</td>
<td>0.63</td>
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<tr>
<td></td>
<td>Not matched</td>
<td>14</td>
<td>3/12 (25)</td>
<td>1.9</td>
<td>7.8</td>
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Abbreviations: No., number; CR, complete response; PFS, progression-free survival; PR, partial response; SD, stable disease.

### TABLE 2. Requirements for the Implementation of Personalized Medicine Related to Molecular Profiling and Targeted Therapy

1. **Molecular Profiling**
   - Development of a universal complete molecular profiling platform
   - Advancement of technology to identify molecular aberrations in 100% of patients
   - Identification of driver versus passenger aberrations
   - Access to an interventional radiologist or surgeon to perform an adequate biopsy in a timely manner
   - Access to CLIA-certified pathology laboratory
   - Bioinformatics; Interpretation of results in a CLIA-certified environment
   - Decision support tools to assist physicians in understanding the implications of multiple, complex molecular aberrations
   - Rapid turnaround time (from time of ordering a tumor biopsy to reporting of results)
   - Standardization of operating procedures
   - Telepathology or central pathology review

2. **Targeted Therapy**
   - Identification of new drug targets
   - Selection process among multiple targeted agents in a class
   - Availability of and access to a clinical trial
   - Reimbursement for off-label drug use
   - Access to broad formulary of targeted agents
   - Review board including experts in molecular pathology, bioinformatics, and oncology

Abbreviation: CLIA, Clinical Laboratory Improvement Amendments.
BACKGROUND

Concerned with the increased burden of cancer, European Commissioner for Research Philippe Busquin established in 2004 a scientific working group to look at the fragmentation of European cancer research and to identify barriers. As a result of this consultation, the Eurocan+Plus project was launched in 2006 within the framework of the specific program titled “Integration and Strengthening of the European Research Area” in the domain “Life Sciences, Genomics and Biotechnology for Health in Framework Programme 6 (FP6).” The intention was to identify areas in which lack of coordination was especially detrimental to the progress of scientific knowledge and quality of care.

Despite a better understanding of the molecular mechanisms underlying cancer and reasonable funding, benefits that improved patients’ lives were difficult to achieve. Epidemiologic analyses clearly indicated an increasing cancer problem; incidence and mortality trends projected a 60% increase during the next two decades. In particular, the number of patients living with a cancer diagnosis was projected to increase still more (i.e., cancer has become one of the main chronic diseases in Europe). Therefore, the project was requested to propose new strategies to address the increasing burden of cancer.

The Eurocan+Plus project confirmed that fragmentation of cancer research was a major drawback and offered several reasons for the fragmentation that included, in part, the fact that the European Union is not a federated state and embraces several countries with different cultures, health care systems, funding organizations, and priorities. The latter is not helped by the fact that health is not a competence of the European Union, whereas research is. There is increasing complexity in both cancer care and research, and the critical mass of expertise and resources is lacking in single centers, even in the large cancer research centers. As a result, translational cancer research is suboptimal. Europe has strong basic and preclinical research centers, but there are suboptimal links to the clinical centers. Many cancer research centers are located in universities with a governance and structure that add to the fragmentation of cancer care and research. There are, however, a few independent comprehensive cancer centers, but collaboration across borders is not easy. Research funding is mainly national, with iteration of research projects instead of international competition and collaboration.

An important conclusion of the Eurocan+Plus project was that collaboration between research groups would not solve the problems. There was instead a need for collaboration between centers to guarantee infrastructure support, including the availability of patients, biologic materials, and technological resources, as well as competencies. Such collaboration is also important to be able to improve the coordination of cancer research. With this background, the Eurocan+Plus project suggested the establishment of a European platform for translational cancer research by linking comprehensive cancer centers and basic/preclinical research centers.

THE EUROCANPLATFORM PROJECT

Following the recommendations of the Eurocan+Plus project, the European Commission (EC) released a call for proposals in the seventh frame program for European research funding: “Structure translational cancer research between European cancer research centers to develop innovative research in prevention, early detection and therapeutics.” Representatives of 18 European centers had earlier committed themselves to collaborate and filed an application to develop a network of excellence to structure translational cancer research. The EurocanPlatform project was approved by the EC in 2010. The project, which has a duration of 5 years, aims to develop a consortium for translational cancer research by linking 23 cancer research centers and five European cancer organizations. One of the most important goals is to develop personalized cancer medicine that is based on the understanding of the biology of the tumor and normal tissues so treatment can be applied at an early stage of the disease. Moreover, prevention strategies should be rooted in cancer biology to identify and target high-risk individuals. The project includes 16 work packages covering the entire cancer research continuum. Sustainability, quality assurance of centers, and the development of a designation procedure for identifying research centers of excellence are a part of the program. Parallel to the EurocanPlatform project, a funding structure, TRANSCAN, was initiated to support international collaborations in translational cancer research.

A challenge for the EurocanPlatform is to organize translational cancer research for personalized cancer medicine. Several centers have strong cancer biology research programs for the identification and validation of new targets for therapy. The drug development program involves discovery and validation of prognostic and predictive biomarkers. Experience so far indicates that more than one molecular pathway should be targeted, and as a result, bioinformatics and systems biology approaches need to be implemented in clinical research. Prospective validation of predictive biomarkers is an important task for early clinical trial units. The complexity of clinical trials will increase with the implementation of pharmacology, methods to assess target saturation, and molecular imaging for assaying heterogeneity of metastatic disease and early therapeutic response. Repeated biopsies will be needed to follow molecular changes in the tumor and adapt the treatment. Clinical databases and biobanks of tumor and normal tissues for biomarker discovery and retrospective validation, as well as for biologic studies of tumor cell heterogeneity and resistance mechanisms, must have a high priority. This is also the case for pharmacogenomics for the prediction of acute and late adverse effects, a problem particularly when combining targeted drugs. With the increasing number of subgroups identified within each tumor type, stratification of patients will lead to new clinical trial strategies. Comparative randomized clinical trials will be replaced successively by clinical effectiveness assays and by observational studies using quality-assured clinical registries. High-quality structures for outcomes research will bridge the
late translational research gap and support health economics research. The EurocanPlatform aims at creating a comprehensive structure to provide researchers with a complete infrastructure and strategy to develop personalized cancer medicine. In the end, personalized cancer medicine is a strategy to achieve improved patient outcomes as well as cost-effectiveness.12

A problem for Europe is the sharing of patients, biologic materials, and technological resources across borders. All regulatory issues have not yet been addressed for optimal collaboration, such as the need to transport patient data and biologic materials across borders. There is also a need to increase patient participation in clinical trials in foreign countries. We have today increasing drug development costs, and the adoption of new treatment modalities is suboptimal because introduction into clinical care is not systematic and clinical effectiveness studies are lacking. The cost of new anticancer agents is high for health care systems because few patients respond and the remission duration in most cases is short. Consequently, health care systems are often unwilling to pay. In Europe, health technology assessment organizations are numerous, and there is a need to organize health technology assessment at the European level. We see increasing difficulties with providing regulatory authorities with the traditional information regarding the risks and benefits of new anticancer agents when moving toward personalized cancer medicine. Moreover, quality assurance of the infrastructures needed for different diagnostic technologies such as molecular pathology/cytology, molecular imaging, genomics, and proteomics is becoming an increasing problem for regulatory authorities.

NECESSARY COLLABORATIONS FOR DEVELOPMENT OF PERSONALIZED CANCER MEDICINE
Academic Research Centers

The EurocanPlatform aims to develop new types of collaboration between cancer research centers to reach the critical mass needed to implement complete translational cancer research, including drug development. Infrastructures in centers should be harmonized to permit data collection and sharing of information. We need to share structures for discovery of prognostic and predictive biomarkers and collaborate regarding prospective validation of biomarkers. Clinical trials should be harmonized and bioinformatics implemented to develop molecular pathway–driven clinical trials. Molecular imaging, pathology, and omics technologies (theranostics) will be crucial. To cover late translational research, cancer research centers must build harmonized outcomes research structures for evaluation of clinical effectiveness and health economics. To ensure the sustainability of the consortium, quality assurance of centers and the development of a designation procedure for identification of research centers of excellence are part of the program. Collaborations will aim to increase independence from the pharmaceutical industry when conducting innovative clinical trials.

The EurocanPlatform projects have been active during the last 2 years. Examples of ongoing activities include:

Kinome analysis of high-grade serous-type ovarian cancer. All kinases and an additional 80 genes related to the kinome are being studied regarding mutations, deletions, duplications, RNA expression, and phosphorylated kinases with the aim to identify novel kinase targets. The next step will be validation in clinical trials.

A phase II clinical trial with a focus on lobular breast cancer and phosphoinositide 3-kinase (PI3K) inhibition has been designed and is expected to be activated within 3 to 4 months. Biologic studies will be linked to the trial: identification of pretreatment predictive biomarkers, pharmacodynamic biomarkers, biomarkers for early response, and drug resistance mechanisms.

For collection of detailed information about clinical effectiveness of innovative anticancer agents, work has started to build clinical registries in several centers for compilation of clinical data. This is a first step toward a comprehensive outcomes research structure.

Studies are ongoing for biomarker discovery for early detection of breast and lung cancer, including relevant pre malignant lesions for breast cancer as well as early invasive and metastatic disease. Analyses involve micro-RNAs, circulating tumor cells, and proteomics.

Pharmaceutical Industry

Collaboration between academic centers and the pharmaceutical industry must be improved. Academic centers will very soon expand genomic screening to cover the whole cancer genome, include analyses of RNAs and proteomics, which will allow the identification of tumor-driving molecular pathways. Academic technological platforms can be used to identify relevant patients for clinical trials, and the benefits and risks of new anticancer agents will be studied in parallel with predictive biomarker validation. For studies of combinations of targeted drugs and biomarker research, it will be important for academic centers to collaborate with more than one pharmaceutical company.

Health Care Systems

Translational cancer research for drug development is highly dependent on the health care system. Several infrastructures must be established in collaborations between academia and the health care system: clinical trial structures, clinical cancer registries, biobanks, molecular pathology and imaging, genomic structures for stratification of patients, structures for outcomes research, and studies of health economics. In the comprehensive cancer center, the health care delivery activities should function as an infrastructure for translational research.

Regulatory Authorities

Because we are moving toward personalized cancer medicine and the clinical trial strategy is changing, we need to identify the relevant clinical data for assessment of benefits and risks for approval of new anticancer agents. Therefore, academic
centers, industry, and regulatory authorities must achieve consensus. To make the drug development process more effective, conditional or progressive approval should be considered. Relevant data for evaluation of treatment effects must be identified by the academic centers. With a high-quality infrastructure for clinical effectiveness analysis, it will be natural to integrate the early and late phases of drug development.

Health Technology Assessment and Payers
If clinical efficacy, which is the outcome of comparative clinical trials, can be replaced by data on clinical effectiveness (i.e., effects of treatment of a total population of patients, or “real-world data”) collaboration with health technology assessment organizations can start during the drug development process. The EurocanPlatform is currently working to establish a European structure for outcomes research that includes clinical effectiveness. Through collaboration between several centers, it will be possible to collect data within a short time period and subject it to health economic analyses to determine cost-effectiveness. This is an important part of late translational cancer research. Payers will quickly have information on cost-effectiveness for decisions regarding the adoption of new anticancer agents in the health care system.

FUTURE RESEARCH
The EurocanPlatform aims to establish a complete translational cancer research program covering the whole drug development process in an effort to implement personalized cancer medicine in health care systems. The translational cancer research process is highly complex and requires infrastructure support and coordination; a sustainable collaboration between major cancer research centers is essential. To make the entire drug development process more effective, collaboration between academic centers, the pharmaceutical industry, regulatory authorities, health technology assessment organizations, and health care systems is essential.

BREAKING DOWN BARRIERS IN THE IMPLEMENTATION OF PERSONALIZED MEDICINE
The potential rewards and significant challenges of implementing personalized cancer care have been well described in the preceding pages. What is the path forward? Modifying existing paradigms of clinical research and health care delivery will require not only continued scientific and technological breakthroughs but also cultural changes in the way medical practitioners work together that are stimulated by new practice guidelines; changes in regulatory standards for drug and device access and approval; modification of reimbursement policies by health care payers; and new ways of collecting and analyzing patient information by using electronic medical records linked to prospective clinical registries and rapid learning systems. Underpinning every facet of personalized cancer medicine must be comprehensive and accessible informatics systems that integrate clinical, laboratory, radiologic, molecular, and economic data to not only guide and support clinical care but also provide a seamless infrastructure to enable clinical research. Professional societies, government agencies, pharmaceutical and device companies, payers, practitioners, and patients must all contribute their expertise and resources to overcome the obstacles noted earlier in this article.

Currently, developing a personalized medicine plan for a patient with cancer requires interrogation of a tumor biopsy for “actionable” molecular aberrations such as gene mutations or overexpression that can direct a specific therapeutic approach. Yet, few guidelines exist regarding the minimum standards for tissue acquisition, handling, preservation, transport, and storage to ensure that each patient has a specimen of suitable quality available to guide their medical care. Professional organizations such as the College of American Pathologists (CAP) are well positioned to issue such guidelines because they possess the necessary expertise and influence to ensure adoption by the pathology community. Indeed, beyond standards regarding tissue acquisition, clinical practice guidelines should specify the molecular workup of tumors, including the relevant molecular aberrations, appropriate testing platforms, definitions of positive and negative test results, reporting standards, and a description of the limitations of the test. CAP and ASCO have already collaborated to issue practice guidelines on HER2 testing for patients with breast cancer that have set national standards for test performance, interpretation, and reporting. It is hoped that further collaborations of this sort will address other novel molecular markers as they become widely available. A recent example is BRAFV600E mutation testing to select vemurafenib treatment for patients with melanoma. The drug is labeled for use in patients with melanoma harboring a BRAFV600E mutation detected by a specific FDA-approved test. Yet, within a month of the drug/test approval, at least six laboratories began to offer non–FDA-approved versions of the test. The analytic validity, performance characteristics, and clinical utility of these tests are largely unknown, and a clinical practice guideline on BRAF mutation testing in melanoma would be of great value to the medical community, to the patients who rely on such tests to select their treatment, and to the payers who are asked to cover the costs of tests of unproven value.

As more frequent and complex molecular profiling of tumors is introduced into clinical practice, countries will need to assess the optimal strategy for supporting molecular profiling within the context of their health care systems. In the United States, such testing is typically done by hospital or commercial laboratories and is regulated by the FDA or the Centers for Medicare & Medicaid Services (CMS) under the terms of CLIA. Physicians often struggle to find a suitable lab that performs the appropriate tests with acceptable analytic validity and turnaround time. By contrast, France, under the auspices of its National Cancer Institute, has implemented 28 regional molecular genetics testing centers that perform necessary molecular tests on tumor specimens for patients with
cancer across the country. For example, patients with non-squamous, non–small cell lung cancer now routinely have their tumors tested for mutations in EGFR, KRAS, BRAF, and PIK3CA, as well as for HER2 amplification and ALK translocations, using well-standardized testing protocols. Plans call for introducing testing for ROS1 and MET aberrations as well. Such centralized approaches have the potential to ensure widespread access to standardized tests of acceptable quality, to provide uniform decision support tools to physicians to aid interpretation of test results, and to enable the capture of information on test use and patient outcomes that can inform both practice guidelines and health care policy.

As molecular profiling of tumors becomes more widespread, clinical trials such as the MD Anderson IMPACT trial described previously are being undertaken to match drugs to patients whose tumors harbor particular molecular profiles. Although it remains to be proven conclusively that such approaches produce superior patient outcomes, patients and physicians are increasingly interested in using the information from tumor molecular profiling to guide clinical decisions. It will become necessary, then, to devise strategies to provide access to drugs that have the potential to benefit patients whose tumors harbor specific aberrations. Drugs might be available in several scenarios, including use within the labeled indication, off-label use of a marketed product, access to a drug within a clinical trial, or even compassionate use of a drug that is going through regulatory review. Reimbursement for off-label use of expensive targeted therapies is a potential obstacle to patient access that could be addressed through innovative reimbursement models such as the Coverage with Evidence Development model available through CMS, wherein CMS agrees to reimburse the intervention if certain data collection goals are met documenting the impact of the intervention on physician decision making or patient outcomes.

Matching of patients to clinical trials will likely require a new model for clinical trial design and implementation. Rather than testing a single drug against a single molecularly defined tumor type, such as vemurafenib in BRAF-mutated melanoma, it will become necessary to design trials that either test a variety of drugs against the “actionable mutations” detected in a specific tumor type or that test a single drug against a single aberration that occurs in several tumor types, so-called “histology agnostic” clinical trials. Examples of both types of trials already exist. The U.S. National Cancer Institute, for example, is developing the MPACT trial (Molecular Profiling based Assignment of Cancer Therapeutics), a pilot trial that seeks to demonstrate that matching patients with advanced cancer to treatments determined by molecular profiling improves outcomes. Implementing such trials requires assembling a formulary of targeted agents under the regulatory umbrella of a single investigational new drug application, centralized or at least standardized molecular profiling protocols, and a plan for providing trials to patients rather than to trials that will require a central institutional review board so patients with rare aberrations can access a trial quickly after the profiling results become known.

Using the results of what will essentially become a series of “N of 1” trials to seek regulatory approval for use of a drug in a new indication will require ongoing engagement with the FDA and regulatory authorities worldwide. Issues to be considered are the level of evidence required to label a drug for use in treating tumors that harbor a particular molecular aberration, regardless of histology; the data that are necessary to demonstrate the clinical utility of complex molecular profiling tests such as next-generation sequencing; the definition of a “breakthrough drug” in a given clinical situation, such as a molecularly defined tumor subtype; and whether regulatory decisions could follow an “adaptive licensing” approval process, as some have advocated.

Underpinning all aspects of personalized cancer medicine will be sophisticated informatics systems that harness diverse types of information from diverse sources to build rapid learning systems that both collate data and use sophisticated algorithms to learn from each patient. The CancerLinQ rapid learning system being developed by ASCO is one example of such a tool that has the potential to revolutionize how all stakeholders in the cancer community assemble and use information obtained from patients treated in real-world settings to guide clinical practice, regulatory decisions, and health care payment policy. For example, a rapid-learning system can be used to track rare side effects, identify exceptional responders to treatment, detect drug interactions, assess the impact of off-label drug use, and examine the utility of molecular tests to guide treatment.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

References

Targeted Therapies in the Acquired Resistance Setting: Considerations for Trial Design and Clinical Practice

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Mechanisms of Resistance to RAF Inhibition in Melanomas Harboring a BRAF Mutation

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OVERVIEW

Treatment of V600E/K BRAF-mutated melanomas with RAF inhibitors (either vemurafenib or dabrafenib) results in rapid and dramatic responses in most patients—results that are associated with improved progression-free survival (PFS) and in the case of vemurafenib, overall survival (OS). However, resistance develops at a median time of approximately 6 months. Understanding the mechanisms of resistance is critical to develop strategies to prolong PFS and OS. Negative feedback mechanisms inherent in the MAPK pathway serve to modulate responses to these drugs. However, genetic changes develop within the tumor, which lead to reactivation of the MAPK and resistance to these drugs. The mechanisms that have been demonstrated in many patients by multiple investigators are (1) development of an activating mutation in NRAS, and (2) appearance of a BRAFV600E splice variant that encourages RAF dimerization. Several other mechanisms of resistance have also been described in individual patients or in preclinical models of resistance. In addition, there is evidence that activation of parallel pathways, such as the PI3K/AKT pathway, may represent another mechanism of resistance. Understanding the various mechanisms of resistance will inform our attempts to prevent resistance to RAF inhibitors.

Forty percent to 60% of melanomas harbor a driver mutation in BRAF, most commonly V600E or K. This leads to constitutive activation of the MAPK pathway and increased activation of ERK, which drives proliferation of the melanoma. Inhibitors of RAF kinases, such as vemurafenib or dabrafenib, effectively shut down ERK activation and lead to rapid tumor shrinkage in the majority of cases. Randomized trials have shown that both of these drugs improve PFS compared with dacarbazine chemotherapy; vemurafenib has also been shown to improve OS. Both of these drugs show remarkably similar response rates and improvements in PFS. New RAF inhibitors are in development, such as LGX818, and would be expected to have similar clinical efficacy.

Although 80% of patients with BRAF-mutated melanoma show some degree of tumor shrinkage when treated with a RAF inhibitor, and approximately 50% of patients achieve a formal partial response, clinical trials with both vemurafenib and dabrafenib show that most tumors develop resistance within 6 to 7 months, and approximately 10% are primarily refractory. Therefore, it is critical to understand the mechanisms of resistance to RAF inhibitors. I will review the current state of understanding of these mechanisms. It should be noted that many investigators are working on this problem, and the state of knowledge is currently in flux. Currently, there are some mechanisms that have been confirmed by multiple laboratories, some mechanisms that have been reported by individual investigators but not yet confirmed by others, and some mechanisms that are speculative.

MECHANISMS THAT REACTIVATE THE MAPK PATHWAY

Confirmed Mechanisms of Resistance

Almost all the mechanisms described so far lead to reactivation of the MAPK pathway. One mechanism that is active in all tumors and which leads to modulation of the antitumor effect by RAF inhibitors is the inherent negative feedback mechanisms of the MAPK pathway. Inhibition by vemurafenib leads to decreased activation of ERK. This decreases the level of negative regulators such as Sprouty proteins and relieves the suppressive effects on RAS activation. With increased RAS activation, BRAF kinases dimerize which allows vemurafenib to induce trans-activation of RAF. This leads to reactivation of MEK and then ERK. The final result is that, after a period of maximal suppression of ERK, the pathway regulates itself to maintain a low level of ERK activation. This can be seen most readily in vitro experiments. This observation probably explains why most clinical responses are partial responses.

Several other resistance mechanisms have been described that result from genetic changes in the melanoma (Table 1). NRAS mutation. It is clear from the observations of several investigators that melanomas treated with vemurafenib can
acquire an activating mutation in NRAS. This leads to activation of the pathway. It would also be expected that this would lead to enhanced dimerization of RAF and that continued treatment with vemurafenib would result in trans-activation of RAF dimers and further ERK activation. Whether the NRAS mutation preexists in the tumor or arises under the pressure of vemurafenib treatment remains unclear.

**BRAFV600E splice variant.** Another resistance mechanism is the development of a splice variant of the mutated BRAF mRNA. This splice variant results in a truncated form of the mutated BRAF kinase in which interaction with RAS is enhanced. This leads to dimer formation between the truncated, activated BRAF kinase and wild type RAF kinases. Once dimerized, vemurafenib induces trans-activation and subsequent reactivation of the MAPK pathway.

**Other Resistance Mechanisms of Uncertain Frequency**

There are a variety of other resistance mechanisms that have been identified in individual patients. There are others that have been described using in vitro and mouse models. The frequency by which these mechanisms cause resistance in patients remains uncertain.

**Activation through RTKS.** Melanoma is known to express a large variety of RTKs that signal through the MAPK pathway. Activation of these would be expected to lead to resistance. Several investigators have conducted kinase screens that point to MET activation as a potential resistance mechanism. Activation of other RTKs have been proposed as potential resistance mechanisms, including IGF-1R and PDGFRβ. Supporting data from clinical samples are not yet available.

**Increased expression of mutated BRAF kinase.** By transferring human melanomas to immunosuppressed mice and treating with vemurafenib, investigators developed resistant melanoma clones with enhanced transcription and translation of the mutated BRAF kinase. These melanoma cells appeared to be addicted to the BRAF mutation in that withdrawing vemurafenib led to decreased tumor growth. In four of 20 vemurafenib-resistant BRAFV600E-mutated melanomas, Lo et al. found an increased copy number of the BRAFV600E allele.

**Increased expression of COT.** COT (encoded by the MAP3K8 gene) activates ERK through a MEK-dependent mechanism. In a screen that overexpressed a library of kinase overexpression in a BRAFV600E melanoma, investigators found that overexpression of COT led to vemurafenib resistance. It has been difficult to determine how frequently this mechanism occurs in patients treated with vemurafenib, although the investigators were able to show that in two of three resistant tumors tested, increased transcription of MAP3K8 developed in vemurafenib-resistant melanomas.

**MAP2K1 mutations.** Mutations in MAP2K1 (encoding MEK1) are detected in some BRAF-mutated melanomas and would be expected to lead to vemurafenib resistance. An in vitro mutagenesis screen demonstrated that P124L and Q56P mutations in MAP2K1 led to resistance to an analog of vemurafenib. Clinically, a patient has been described in which a MAP2K1C121S mutation was identified in a resistant metastasis. This was an activating mutation and was associated with resistance to vemurafenib.

**NF1 loss.** NF1 inhibits RAS activation. Loss of NF1 would be predicted to result in resistance to vemurafenib. A recent

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**TABLE 1. Mechanisms of Resistance to RAF Inhibition in V600 BRAF-Mutated Melanoma**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Clinical Evidence</th>
<th>Other Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRAS mutation</td>
<td>Observed in resistant melanomas</td>
<td>In vitro models</td>
</tr>
<tr>
<td>Splice variant of BRAFV600E mRNA</td>
<td>Observed in resistant melanomas</td>
<td>In vitro models</td>
</tr>
<tr>
<td>Activation of RTKs</td>
<td></td>
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<tr>
<td>MET</td>
<td>In vitro models</td>
<td></td>
</tr>
<tr>
<td>IGF-1R</td>
<td>↑ expression has been seen in resistant tumors</td>
<td>In vitro models</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>May be associated with short PFS</td>
<td>In vitro models</td>
</tr>
<tr>
<td>NF1 loss</td>
<td>↑ copy number of BRAFV600E allele observed in some resistant tumors</td>
<td>In vitro models</td>
</tr>
<tr>
<td>↑ Transcription of BRAFV600E mRNA</td>
<td>↑ COT transcription observed in two cases of resistant melanomas</td>
<td>In vitro models</td>
</tr>
<tr>
<td>↑ COT expression</td>
<td></td>
<td></td>
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<tr>
<td>MEK1 mutation</td>
<td>Observed in one case of resistant melanoma</td>
<td>In vitro models</td>
</tr>
</tbody>
</table>

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**KEY POINTS**

- Most BRAF-mutated melanomas respond to vemurafenib but develop resistance.
- Feedback mechanisms in the MAPK pathway make complete responses unusual.
- There are multiple possible mechanisms of resistance, all of which so far involve reactivation of the MAPK pathway.
- NRAS mutations and splice variants of BRAFV600E mRNA are the two most common mechanisms identified so far.
- Concomitant strategies to inhibit the PI3K pathway may be required to prevent resistance.
analysis of melanoma exon sequencing showed 16/121 melanomas harbored a \textit{NF1} missense or nonsense mutation.\textsuperscript{11} This analysis, and another recent data set,\textsuperscript{14} showed that \textit{NF1} mutations often occur in \textit{BRAF}-mutated melanomas. Although one might expect \textit{NF1} loss to be a mechanism of resistance to vemurafenib, this has not yet been clearly demonstrated clinically. In one patient, a \textit{NF1} nonsense mutation found in the initial tumor was associated with a short PFS.\textsuperscript{15}

**PARALLEL PATHWAYS LEADING TO RESISTANCE**

Given that \textit{RAS} activates both the MAPK and the PI3K/\textit{AKT} pathway, the latter has received special attention as a potential parallel pathway. Indeed, it has been long known that \textit{PTEN} is frequently deleted from \textit{BRAF}-mutated melanomas\textsuperscript{16} and recently, \textit{PTEN} deletion was shown to be required for the malignant phenotype in a \textit{BRAFV600E} mouse model.\textsuperscript{17}

In human \textit{BRAF}-mutated melanoma tumors, 44% also contained a mutation or deletion of \textit{PTEN}.\textsuperscript{11} In \textit{BRAFV600E} cell lines treated with \textit{RAF} inhibitor, upregulation of certain RTKs, such as \textit{MET}\textsuperscript{5} or IGF-1\textit{R},\textsuperscript{6} leads to AKT activation suggesting the possibility that the PI3K/\textit{AKT} pathway can serve as a rescue pathway for \textit{RAF} inhibition. These observations suggest strongly that a subset of melanomas rely on activation of the PI3K/\textit{AKT} pathway and that successful therapy will require inhibition of this pathway as well as the MAPK pathway.

Other pathways have received less attention but could play a role in vemurafenib resistance.

**CONCLUSION**

The challenge going forward is to obtain tumor biopsies pretreatment and at the time of tumor progression so that we can determine the mechanism of resistance in the individual patient and to catalog these mechanisms. The range and frequency of these mechanisms of resistance will guide future strategies to prevent and overcome resistance to these drugs.

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**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**

CLINICAL TRIALS

The New NCI Community Oncology Research Program (NCORP) and ASCO's Community Research Forum: What Every Clinician Needs to Know

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The NCI Community Oncology Research Program: What Every Clinician Needs to Know

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OVERVIEW

Research in the community setting is essential for the translation of advances in cancer research into practice and improving cancer care for all populations. The National Cancer Institute is proposing a new community-based program, NCI Community Oncology Research Program (NCORP), which is the alignment of two existing programs, the Community Clinical Oncology Program, Minority-Based Community Clinical Oncology Program, and their Research Bases, and the National Cancer Institute’s Community Cancer Centers Program. NCORP will support cancer control, prevention, treatment, and screening clinical trials and expand its research scope to include cancer care delivery research. Cancer disparities research will be integrated into studies across the continuum of NCORP research. Input from current NCI-funded community investigators provides critical insight into the challenges faced by oncology practices within various organizational structures. Furthermore, these investigators identify the resources, both administrative and clinical, that will be required in the community setting to support cancer care delivery research and to meet the requirements for a new generation of clinical research. The American Society for Clinical Oncology (ASCO) has initiated a forum to focus on the conduct of clinical research in the community setting. Resources are being developed to help practices in managing cancer care in community settings.

The National Institute (NCI) has supported cancer research within community settings for nearly three decades. The participation of community oncologists and primary care physicians in cancer treatment and cancer control and prevention trials has facilitated the translation of research advances into practices throughout the United States and Puerto Rico. Cancer research and care in the community setting face increasing challenges from emerging science and technology and a rapidly changing health care environment. The era of genomics and molecular-targeted therapy requires molecular-based delivery systems for the application of these advancements in the new health care world.

In April 2012, NCI leadership recommended that NCI support one community oncology research program. The proposed new community oncology program, the NCI Community Oncology Research Program (NCORP), will integrate two existing community-based programs: the Community Clinical Oncology Program (CCOP), the Minority-Based Community Clinical Oncology Program (MBCCOP) and their Research Bases and the NCI Community Cancer Centers Program (NCCCP). The three-component Community Clinical Oncology Program is a clinical trials network that contributes 30% to 40% of enrollment to treatment trials in the NCI Clinical Trials Network (NCTN). Academic investigators develop and conduct the clinical trials with scientific and feasibility input from community oncologists and their research teams. The CCOP network has successfully engaged primary care physicians into the recruitment of individuals at risk of cancer and as partners in both research and the care for patients with cancer. Since the inception of the CCOP network, over 250,000 patients have been enrolled into NCI-sponsored trials, with 112,860 enrolled in cancer control and prevention trials. The NCI Community Cancer Centers Program began in 2007 as a pilot program to support a platform for basic, clinical, and population-based research in community hospitals across the cancer continuum. It is a public-private partnership of the NCI with 21 currently funded community hospitals in 16 states. The goals of the program are to enhance access to care, improve the quality of care, and expand infrastructure to support research for informatics, biospecimen collection, cancer disparities, and clinical trials.

NCORP will build on the strengths of the CCOPs/MBCCOPs and NCCCP programs and expand the scope of research to include cancer care delivery research. NCORP will serve as a network to support clinical trials, cancer care delivery, and cancer disparities research.
Core principles of NCORP include the following:

- Including community-based organizations with a variety of research capacities linked to the NCI’s Clinical Trials Network
- Providing support to oncology practices with varied organizational settings as a collaborative network
- Engaging patients within and outside of clinical trials, organizations, and clinicians as research subjects
- Encouraging commitment of management within organizations to support the research agenda
- Integrating cancer care disparities, care delivery research, and clinical trials

NCORP will consist of three community components: NCORP and NCORP-Minority/Underserved sites. Awardees are required to enroll participants into treatment, cancer control, and prevention trials, as well as other studies that are included in the research portfolio for clinical trials. Sites will be required to have a minimal infrastructure to support cancer care delivery research and cancer disparities research. However, not all components of a community program are required to perform all of the research components. At least one component of a community program must participate in the identified areas of cancer care delivery research. All sites are required to participate in clinical trials. Multisite partnerships are encouraged and thought to represent the most competitive applications to support cancer care delivery research and cancer disparities research.

The NCI Working Group for NCORP has defined cancer care delivery research as the following:

**Cancer care delivery research is the multidisciplinary field of scientific investigation that studies how social factors, financing systems, organizational structure and processes, health technologies, provider and individual behaviors affect cancer outcomes including: access to cancer care, quality and cost of cancer care, and ultimately the health and well-being of cancer patients. Cancer care delivery research focuses on individuals, families, organizations, institutions, providers, communities, populations, and their interactions.**

Research goals for cancer care delivery research are to assure that optimal evidence-based therapies and system supports are available in routine practice; build evidence base for how clinical practices and organizational processes improve patient outcomes; and build data capabilities to assess organizational approaches to improve care for the underserved. The structure of oncology care delivery is changing with practice mergers and increased practice acquisitions. Evidence to support the best quality of cancer care is not readily available for many of the practices performed in the community setting. It is the goal of the research expansion into cancer care delivery to conduct research that will benefit the participating institutions within NCORP.

Cancer disparities research will be facilitated by the use of existing NCI programs (e.g., National Outreach Network and Community Network Centers) to promote participation of underserved populations in clinical trials and cancer care.
The potential opportunities to address research questions related to disparities are abundant across the entire cancer continuum. Research ideas should be considered at the concept level for clinical and cancer care delivery research as both primary and secondary outcomes.

NCORP research will be peer-reviewed, and expertise from clinical trials and cancer care delivery researchers will be used for development and review of research concepts. Review of cancer care delivery research will be modeled after the existing Steering Committee conducted by the NCI Coordinating Center for Clinical Trials.

Clinical trials will continue to be the core foundation of NCORP with additional research opportunities in health services, behavioral, dissemination, and outcomes research. The development of NCORP affords an opportunity for NCI to be responsive to the new challenges in cancer research and care in the community setting. The challenge to design a program that is successful in the community and that contributes to the advancement of both science and patient care is paramount and is a work in progress. The effort to develop such a program is a collaborative one with the NCI Division of Cancer Prevention, Division of Cancer Control and Population Sciences, the Division of Treatment and Diagnosis, the Center to Reduce Cancer Health Disparities, and with the many community investigator, academic, patient, and advocacy stakeholders, all of whom are committed to a common mission of advancing the science that improves cancer outcomes in the community setting.

THE NEW NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM: PERSPECTIVES ON NCORP FROM A COMMUNITY ONCOLOGIST

Since 1982, the NCI’s Community Clinical Oncology Program and Minority-Based CCOP have succeeded in

- facilitating evidence-based and innovative patient care in community settings;
- augmenting the number of protocol participants including minority and medically underserved populations;1,2
- accelerating the completion of large phase II and phase III protocols, including cancer control and large-scale risk-reduction trials;
- contributing biospecimens and other ancillary materials that optimize the information that can be gained from patients’ participation in clinical research studies;
- providing educational opportunities for CCOP physicians and staff via attendance at cooperative group meetings; and
- creating a mechanism for communicating the “community perspective” in cooperative groups, as members of disease, modality, and administrative committees, so that protocols and group initiatives are implemented in a manner that is feasible in local settings.

From the community-based physician’s viewpoint, a CCOP/MBCCOP grant reflects positively on the physicians, their staff, and the administration of the programs. Financially, a CCOP grant provides funding for indirect costs and greater potential for independence from hospital operating budgets. Some of these successes and honors are shared by community-based investigators who are unaffiliated with a CCOP and who participate in cooperative group research independently or as an affiliate of an academic center.

Issues of Concern among Community-Based Clinicians

Clinicians associated with CCOPs, as well as those who are unaffiliated with CCOPs, could face significant new challenges if the new community oncology program is designed in a way that it devalues the previous strengths of the existing CCOP program or diverts resources from it.

Historically, many CCOPs exist as coalitions of practices and institutions within a geographic region. Otherwise competing hospitals identify common ground in the conduct of costly and increasingly complex clinical research. Hospitals and practices may be unwilling to share information about how their cancer care is delivered or impacted by the presence or absence of certain resources that they may regard as “proprietary.” Cancer research may be one thing; cancer care–related data may be quite another. Depending on the defined metrics for a successful NCORP grantee, a community could have several NCORP grantees with duplicative research processes at a time when funding from all sources (federal, practice-based, and hospital operations) are stretched thin.3

NCORP will require that grantees perform health care delivery research, in addition to clinical trials research. How health care delivery research will be funded and the metrics by which success will be measured are undefined at present. These uncertainties are particularly concerning at community-based programs, given the narrow profit margins associated with private practice and the economic realities faced by community hospitals, including pressures to implement cost-saving measures related to the Affordable Health Care Act.

As currently described, NCORP sites will be participating in a partnership with the NCI, with a commitment from local management to coinvest in the program. In view of the challenging and uncertain aspects of the NCORP proposal that are enumerated above, it is difficult for potential local NCORP leaders to request explicitly financial coinvestment by local institutions and practices.

Key challenges confront the practice of oncology in the community settings and among them is the assurance that cancer-care delivery research can be accommodated in routine practice. Nurse navigation, electronic records, genetic counseling, and survivorship programs are available in some community-based practices. Access to these supports has not been necessary heretofore for a practice or CCOP/MBCCOP to successfully accrue to NCI-sponsored clinical trials. Many hospitals are already responding to market and regulatory pressures to provide these services, but developing these supports could be challenging for community practices that have heretofore focused their resources only on those that would enable them to manage data accurately and efficiently for clinical trials.
Building the evidence base for how institutional policies can improve care outcomes for patients in routine practice has not been the traditional purview of clinical cancer research programs. Community-based hospitals and private practices, in general, lack the expertise to conduct systems-based research of this type. Mechanisms for affiliation with (and providing incentives to) Comprehensive Cancer Centers and other entities that have these specialized capabilities are not immediately apparent in the initial descriptions of NCORP.

Understanding the knowledge, attitudes, and behaviors of clinicians, clinical teams, and patients and their families to improve outcomes of cancer care delivery is important and may help community-based physicians utilize information from the large number of patients who choose not to participate in clinical trials. However, once again, this type of research is unfamiliar to otherwise successful community-based clinical trials offices. There will be challenges associated with staffing these important (and potentially informative) efforts in practice settings. However, accurate assessment of patient outcomes in the clinical setting is vital, especially when findings from clinical trials are extended to the broad populations of patients in community settings. However, the mechanisms, accuracy, and rigorousness with which community- and academic-based clinical programs assess outcomes in routine practice are variable.

Development of infrastructure, implementation of rigorous post-trial assessment of outcomes, and the funding of these efforts in community practice will be major challenges. A related challenge is establishing criteria for success of NCORP sites that is as unambiguous and simple as “clinical trial accrual,” “timely and accurate data submission,” and “satisfactory data audits.”

Steps to Consider by Community Practices and Current CCOPs/MBCCOPs in Preparation for NCORP
Preparation for the possibility of an eventual grant application is essential (even for currently funded CCOPs). There are several intuitive steps that could be undertaken in the period before issuance of the NCORP RFA:

1. Clinical and administrative leaders should review which components of the delivery system attributes, linkages to community resources, outreach efforts to underserved populations, clinical research program, research infrastructure, quality of care measurements, and continuity of care components (e.g., survivorship, palliative care, and hospice) currently exist, which components are accessible to the research enterprise, and which components need to be modified or amplified in order to participate meaningfully in the local NCORP research program.

2. Because not every institution or practice within an NCORP needs to have every resource in place, logical affiliations with new local or regional partners should be explored, including linkages to primary care practices for care coordination efforts.

3. If there are academic institutions in the community or region that can help provide components of research (e.g., genetics, palliative care, psychosocial, or navigation services) that will be required within the local NCORP grantee, those relationships should be enhanced and partnerships should be forged.

4. If there are new certifications (e.g., ASCO’s Quality Oncology Practice Initiative [QOPI] or the Rapid Quality Reporting System [RQRS]) or community partnerships (including resources that have access to medically underserved populations) that were planned for either the clinical research or clinical care program, the opportunity to apply for an NCORP grant may serve as a stimulus to proceed with those certifications or partnerships, so that relevant experience can be gained.

5. Existent coinvestment by practices and hospitals in the current clinical research program or CCOP should be quantified, as precisely and completely as possible.

6. Since smoking cessation and obesity-reduction efforts will likely be part of community-based cancer risk-reduction efforts, those programs and practices that do not currently routinely record tobacco use and body mass index (BMI) in their patients’ electronic health records should begin to do so.

COMMUNITY RESEARCH FORUM: AN ASCO INITIATIVE
The Cancer Research Committee of the American Society of Clinical Oncology, under direction of the Board of Directors, initiated the concept of a Community Research Forum (CRF) in the fall of 2010. Conscious of the challenges involved in conducting good-quality research at nonacademic organizations, ASCO aimed to sponsor an annual meeting to convene community-based research teams where selected projects designed to facilitate the management of clinical research programs would be discussed.

An online survey was submitted to principal investigators at Community Clinical Oncology Program, NCI Community Cancer Centers Program, and Clinical Trial Participation Award sites, along with investigators at Sarah Cannon Research Institute and US Oncology. A total of 92 respondents completed the survey. Of the projects identified by the respondents, which were not already addressed by the ASCO Board of Directors, the CRF members selected the “Workload Assessment Tool” and the “Quality Assessment Tool” for further development.

Managers and administrators struggle with the proper staffing of research personnel, and data regarding the optimal number of patients that can be safely handled by a research coordinator are lacking, especially given the differences in complexities among trials. In this context, the main goal of the workload project is to develop an instrument that provides benchmarks for research personnel in community-based programs.

The ability to maintain timely and credible data is essential to any research program. Unfortunately, many community-based programs do not have the resources to support an active internal quality assurance (QA) program and rely exclusively on external audits, which, while valuable, are by nature retrospective, and do not always translate into...
structural modifications or prevent further deviations. The CRF committee developed a manual to assist programs to create their own QA program, as discussed below.

Workload Assessment Tool
Various research programs that have begun the process of developing workload measurement tools employ the utilization of complex scoring formulas that often encompass measurements of time associated with individual trial-related tasks and/or detailed ranking options. Despite these efforts, neither a validated measurement tool nor a recommended maximum metric (i.e., number of research participants to staff ratio) has been established for research workload.

The ASCO Workload Assessment Working Group determined that any future tool must consider its simplicity, reproducibility, and long-term usability. Specifically, if a workload measurement tool is too complex and requires too many layers of measurement, and therefore too much time and effort, it will not be utilized. Furthermore, the tool must endure changes in the design of clinical trials and the flexibility to adapt to new requirements in the long-term. The Wichita Protocol Acuity Tool (WPAT) utilized by a single oncology-focused research program for over 10 years, was selected as the model on which the ASCO Workload Assessment Tool would be based. Elements of the WPAT were modified by the Working Group to serve as the template for the ASCO Workload Assessment Tool.

An important next step in the development of ASCO’s Workload Assessment Tool is to test its effectiveness in a small group of community-based oncology research programs. The primary objective of the validation process is to establish preliminary workload benchmarks reflected as acuity scores and the numbers of patients per research nurse and CRA FTE to serve as references for oncology community-based practices.

Quality Assessment Tool

“Every clinical research organization, facility or site carries the obligation to ensure that the conduct of the research is carried out with a high-level of quality in order to protect the patients’ safety, rights and welfare, the data captured are accurate and the participation is meaningful.”

In today’s environment, the need for a quality assurance program within clinical research departments cannot be overstated. The safety and welfare of patients are paramount. In addition, research data are only meaningful if accurate. Although external audits are an essential component of the research process, they cannot identify issues prospectively and tend to be more focused on specific protocol deviations rather than processes. An active QA program is an important investment for a research site because it encourages ongoing evaluations and identifies areas of weakness in a more comprehensive fashion.

Few programs in the community have ongoing QA components, which was identified as an unmet need by the ASCO CRF and selected as one of the projects for 2012–2013. The Quality Assessment Tool is designed to be a practical manual to help community research programs (1) implement the basic elements of a QA program; create and develop a plan for continuous review of standard operating procedures to standardize processes, including training of research personnel, credentialing and data management; and, to adhere and comply with good clinical practice (GCP) guidelines. Mechanisms to ensure quality include but are not limited to random chart reviews, which serve as internal audits, and corrective action plans, which ensure that problems are appropriately addressed in a timely manner.

The Quality Assessment Tool was presented at the September 2012 Forum, and suggestions from the attendees have been subsequently incorporated. CRF members are finalizing the manual, which ASCO plans to publish by the fall of 2013 to serve as a roadmap for community research programs to implement a QA program.

The First ASCO Community Research Forum
The first annual CRF was held in September 2012 and included over 50 participants from a variety of research sites and programs including principal investigators, research nurses and coordinators, and other key stakeholders. An overview of the Workload Assessment Tool and the Quality Assessment Tool was presented, and participants provided feedback and ideas for future products of the Forum. The meeting also included presentations on topics of interest such as insurance coverage of clinical trials and what lies ahead for the National Cancer Institute’s support for community-based research. Results from a meeting evaluation survey were very positive, with over 90% of respondents indicating that they would recommend the meeting to colleagues.

In summary, the ASCO CRF aims to provide community-based investigators from different practice settings (e.g., private practices, the Clinical Trial Participation Awards, and the proposed NCI Community Oncology Research Program) with a venue to discuss and develop solution-oriented projects, which will be made available as ASCO-sponsored products to the membership at large. The Forum also allows ASCO to obtain better insight on the challenges associated with conducting research in a community setting and enables the organization to better fulfill its mission of supporting members at community sites.

Disclosures of Potential Conflicts of Interest
The author(s) indicated no potential conflicts of interest.
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