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.[1] After the breakthrough development of imatinib mesylate for the treatment of newly diagnosed chronic myeloid leukemia,[2] 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

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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.[3,4] Vemurafenib induced an overall response rate of 81% (26 of 32) in patients with melanoma bearing the V600E *BRAF* mutation,[3] and crizotinib induced an overall response rate of 57% (47 of 82) in patients with ALK-rearranged non–small cell lung cancer.[4]

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.[5] 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%; C*KIT,* 3.4%; *TP53,* 35.8%; and HER2, 5.5%. Overall, 882 patients received treatment on phase I studies.[6] 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.[6] 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 ($p < 0.0001$).[6] 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 IN 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.[7]

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

No. of Aberrations	Therapy	No. of Patients	CR+PR+SD ≥ 6 Months (%)	P	Median PFS (months)	p	Median Survival (months)	p
1	Matched	306	113/293 (39)	<0.0001	4.9	<0.0001	11.2	0.006
	Not matched	360	52/337 (15)		2.2		8.6	
2	Matched	101	21/82 (26)	0.30	3.7	0.13	9.9	0.31
	Not matched	68	10/57 (18)		2.6		6.6	
≥ 3	Matched	33	9/26 (35)	0.71	3.7	0.09	7.7	0.63
	Not matched	14	3/12 (25)		1.9		7.8	

Abbreviations: No., number; CR, complete response; PFS, progression-free survival; PR, partial response; SD, stable disease.

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; proportion of cancer cells; 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.

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.

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.[8] Furthermore, molecular profiling of primary renal carcinomas and associated metastatic sites demonstrated intratumor heterogeneity, which is associated with heterogeneous protein function.[9] 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.[9] 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.

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,[10] 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[11] 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 premalignant 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.[13] 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.[14] It is hoped that further collaborations of this sort will address other novel molecular markers as they become widely available. A recent example is *BRAF*V600E mutation testing to select vemurafenib treatment for patients with melanoma. The drug is labeled for use in patients with melanoma harboring a *BRAF*V600E 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 throughout the country. For example, patients with nonsquamous, 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 patients 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.[13]

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.

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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

1. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature.* 2001;409:860-921.
2. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031-1037.
3. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med.* 2010;363:809-819.
4. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363:1693-1703.
5. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res.* 2012;18:6373-6383.
6. Tsimberidou AM. Personalized medicine: molecular profiling and therapy for patients with advanced cancer. Presented at: Accelerating Development and Advancing Personalized Therapy (ADAPT) Conference; 2012; Washington, DC.
7. Jönsson B. Technology assessment for new oncology drugs. *Clin Cancer Res.* 2013;19:6-11.
8. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
9. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012;366:883-92.
10. Cho S-H, Jeon J, Kim SI. Personalized medicine in breast cancer: a systematic review. *J Breast Cancer.* 2012;15:265-272.
11. Ringborg U. The Stockholm declaration. *Mol Oncol.* 2008;2:10-11.
12. Mendelsohn J, Ringborg U, Schilsky RL. Personalized cancer medicine: a strategy to counteract an increasing cancer challenge. *Mol Oncol.* 2012; 6:109-110.
13. Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther.* 2012;91: 426-437.
14. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;25:118-145.