Building a Personalized Medicine Infrastructure at a Major Cancer Center

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ABSTRACT

Our understanding of cancer biology is rapidly increasing, as is the availability and affordability of high throughput technologies for comprehensive molecular characterization of tumors and the individual's own genetic makeup. Thus, the time is right to implement personalized molecular medicine for all patients with cancer. Personalized approaches span the full cancer care spectrum from risk stratification to prevention, screening, therapy, and survivorship programs. Several molecular therapeutics have entered clinical trials creating a huge opportunity to couple genomic markers with this emerging drug tool kit. The number of patients managed in major cancer centers creates a challenge to the implementation of genomic technologies required to successfully deliver on the promise of personalized cancer care. This requires a major investment in infrastructure to facilitate rapid deployment of multiplex, cost-effective, and tissue-sparing assays relevant across multiple tumor lineages in the Clinical Laboratory Improvement Amendments (CLIA) environment. Efforts must be made to ensure that assays are accessible to patients most likely to be enrolled onto molecular-marker-driven trials and that the tests are billable and payable, which will make them accessible to a wide range of patients. As the number of patients and aberrations increase, it will become critical to provide decision support for genomic medicine. Institutional commitment is needed to optimize accessibility and quality of research biopsies and to facilitate novel personalized cancer therapy trials. This article will focus on the challenges and opportunities that accompany the building of infrastructure for personalized cancer therapy.

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INTRODUCTION

Our understanding of cancer biology is rapidly increasing in depth, thus providing a wealth of information that must imminently be translated to patient care. In terms of translation to the patient, high-throughput technologies for comprehensive molecular characterization of tumors, as well as the individual's own genetic makeup, are becoming more readily available and more affordable. Thus, the time is right to implement personalized molecular medicine. Despite the exciting potential of personalized medicine, currently there are only a few selected diseases and molecular subtypes for which there are therapy approaches with proven efficacy. Examples of these include anti-HER2 targeted therapy for HER2-positive breast cancer, EGFR-targeted therapy for EGFR-mutant lung tumors, and the mutation-selective RAF and MEK inhibitors for BRAF-mutant melanoma.¹⁻⁴ In all cases, there is a strong biologic rationale for the therapy and, critically, a clinically approved biomarker that can identify patients likely to benefit. There are several challenges that must be overcome before personalized cancer therapy can be widely implemented—

lack of effective drugs against most genomic aberrations, limitations of molecular tests, tumor heterogeneity and molecular evolution, costs, quality of and potential morbidity of tumor biopsies, and reimbursement and regulatory challenges.⁵ Thus, in large academic centers and cancer centers, it is important to build infrastructure to provide clinical cancer therapy for diseases in which sufficient level of evidence exists to make biomarker-based therapy selection the standard of care. It is equally important to build programs that can support clinical investigational therapeutics and basic and translational research, including preclinical modeling, biomarker discovery, and biomarker validation, that will establish biomarker-based therapy as the standard of care for all diseases.

Personalized approaches span the full spectrum of cancer care. Personalized risk assessment can identify patients at greatest risk of developing specific cancers, so they can be offered more intensive screening and prevention strategies, which will lead to fewer cases of invasive cancer, earlier diagnoses, and improved outcomes. Personalized cancer care needs to be multidisciplinary, with intimate collaborations among members of a team of

Fig 1. The personalized cancer care continuum.

radiologists, anatomic and molecular pathologists, surgeons, medical oncologists, radiation oncologists, genetic counselors, and biomedical informaticians. Ultimately, successful cancer therapy will need to be followed by personalized survivorship programs, with risk-adjusted screening for recurrence and secondary malignancies as well as programs to limit long-term adverse effects of therapy. Indeed, matching therapeutic choices to the patient's own genetic makeup may decrease long-term morbidity. To successfully deliver on the promise of personalized cancer care, major investment in infrastructure will be required to support all of these arenas (Fig 1). This review will focus on the challenges and opportunities that accompany building the infrastructure for personalized cancer therapy and research. Ongoing studies are focused on personalizing cancer therapy on the basis of an analysis of each patient's cancer by integrating information across DNA, RNA, protein, and metabolomics—in the context of the tumor microenvironment, microbiome, and the patient's immune system—with the genetic characteristics of the patient. The role of integrated analysis for therapy selection is still under investigation and has not yet been scaled to a large number of patients. However, it is likely that comprehensive multianalyte analyses will give critical insights into optimum selection of prognostic and predictive markers for clinical implementation. Prognostic markers can identify patients at higher risk of relapse, so that patients at lower risk can be spared the toxicity of adjuvant therapy. In turn, patients at high risk of relapse can be treated with an individualized treatment regimen best matched to the molecular characteristics of the tumor and to the host environment. This approach will involve selection of the most effective systemic therapies, including chemotherapy, targeted therapy, and immunotherapy, either alone or in concert, as well as surgery and radiation, and the optimal sequence of therapy with each. Predictive markers of toxicity can further individualize therapy. Treating the right patient with the right drug combination from the outset will decrease the risk of relapse and toxicity and will ultimately decrease health care costs. Unfortunately, treatment of recurrent/metastatic cancer has remained a chal-

lenge, but even in this situation, personalized therapy can help identify the most appropriate standard of practice or investigational regimen, thus improving response rates, progression-free survival, and quality of life.

Setting up the infrastructure for personalized medicine is a challenge for any health care center. Major cancer centers face the additional challenge of scale; they need to rapidly incorporate new technologies and offer state-of-the-art cancer care to a massive number of patients in the case of large institutions such as The University of Texas MD Anderson Cancer Center, where 30,000 new patients are seen each year. However, cancer centers also have the advantage of having a disease focus; thus, infrastructure developments can be focused solely on cancer care and can be used across different cancer types. Further, larger centers would have a sufficiently large patient volume to (1) initiate multiple biomarker-driven phase I and II trials with novel therapeutics for different targets, which would make multiplexed testing to direct patients to therapy both practical and cost-effective, and (2) conduct pilot trials for less common tumor types as well as rare molecular aberrations. The infrastructure should be aimed at improving patient care, demonstrating that the process leads to better outcomes, and rapidly initiating and completing molecular marker-driven trials that result in the timely approval of drugs and delivery of effective therapies to patients.

Significant infrastructure support is needed to implement personalized medicine approaches for cancer care and investigational therapy. These efforts require evaluation and implementation of molecular technology, optimization of the clinical trial infrastructure, and facilitation of the efforts of basic scientists and clinical trialists to discover new biomarkers. A process needs to be developed to capture information on the impact of biomarker testing on patient treatment selection and oncologic and toxicity outcomes to assess the return on investment for different molecular testing strategies. Finally, strategies need to be designed to demonstrate the clinical utility of personalized therapy approaches to make personalized cancer therapy the standard

of care and ensure that appropriate testing approaches become billable and payable, thus providing access to a wide range of patients.

INFRASTRUCTURE SUPPORT FOR MOLECULAR TESTING

CLIA-Compliant Testing for Clinical Care and Investigational Trial Enrollment and Stratification

With technologic advances, targets and technologies for molecular characterization in the Clinical Laboratory Improvement Amendments (CLIA) environment^{6,7} are rapidly evolving. Thus infrastructure support is needed for continuous research and development in molecular diagnostic laboratories to implement standard-of-care assays. Assays aimed at altering patient management, including integral and integrated markers for clinical trials, need to be performed in the CLIA environment. However, bringing new markers into the CLIA environment is costly and time consuming. Biomarker testing in the CLIA environment also adds significant costs to biomarker-driven trials, with the particular challenge of costly screen failures. An important question to be addressed at the institutional level is whether the required spectrum of assays should be developed and performed in-house or whether they should be outsourced. This decision needs to be individualized on the basis of each marker/test in question and will depend on expected cost of development and implementation and on expected use, once the assay is established. Given the rapid changes in technology as well as in biomarkers linked to new trials and therapies, assay development is accompanied by the need for new equipment and approaches, which can make internal equipment purchase and internal assay development costs prohibitive.

There need to be resources for and commitment to a rapid pre-CLIA process: assay development and implementation of potential molecular markers for retrospective analysis to determine the utility of implementation into the CLIA environment. It is important to have a standardized process to enable faculty at a cancer center to nominate markers for new CLIA-compliant assays combined with an efficient approach to ensure implementation in a short time frame. Consideration should be given to creating a multidisciplinary committee that reviews all requests for new assay development by taking all of these factors into consideration and decides on global and specific strategies for assay development. This needs to be coupled with a commitment to bring needed assays from pre-CLIA to CLIA environment within an expedited time frame.

Approaches to Genomic Testing in the CLIA and Research Environments

Recently, much of the attention in personalized therapy efforts has been directed at genomics, in part because many targeted therapies have entered the market with DNA-based predictive markers. Examples include the predictive value of *HER2* amplification and *EGFR* mutations for *HER2*- and *EGFR*-targeted therapy, respectively, the recent demonstration of the efficacy of *BRAF* inhibitors for treating metastatic melanoma with *BRAF* V600E mutations, crizotinib for lung cancers with *EML4-ALK* fusion genes.⁸⁻¹² Thus, many cancer centers are starting to build infrastructure so they can perform genomic assessment for therapies with proven efficacy and perform genomic testing to facilitate biomarker-selected trials with novel molecularly targeted therapies.

One pressing question is which technology or platform should be used for genomic profiling of the tumor? Technologies that work on formalin-fixed paraffin-embedded (FFPE) as well as on fresh or frozen tissue, and those that can be performed with the limited amount of DNA obtained from fine-needle and/or core biopsies are preferable. The one-gene-at-a-time approach to genomic testing is inefficient, cumbersome, and limited by tissue availability. Recently, many cancer centers have developed or adapted multiplex genomic testing with hotspot mutation assays so they can test for known activating mutations in common oncogenes and selected common mutations in tumor suppressor genes by using commercially available approaches. These approaches include mass spectrometric genotyping (eg, Sequenom), SNaPshot (multiplex polymerase chain reaction [PCR], multiplex primer extension, and capillary electrophoresis), and next-generation sequencing (AmpliSeq, Ion Torrent).^{13,14} The approaches have focused on “actionable” targets in which the consequence of the aberration is known and potential therapeutic options are available.¹⁵ This approach is cost-effective, tissue-sparing, and compatible with FFPE tissue; it can detect mutations present in samples with a large amount of stroma or with multiple tumor subclones (eg, mutations in 5% of the DNA). Selecting targeted gene assays that will be useful in designing management for a variety of diseases throughout a cancer center remains challenging, and different assays may need to be deployed for solid tumors and hematologic tumors, or even for different tumor lineages. However, it is most efficient to minimize the number of platforms used and instead use a common multiplex platform supplemented by disease-specific testing for additional aberrations unique to each disease. This approach also facilitates research studies and clinical trials to be conducted across disease sites. More recently, targeted sequencing of a set of full-length actionable genes has become feasible from relatively small amounts of DNA. This approach may be preferred because of the ability to assay aberrations in the whole coding sequence of tumor suppressor genes and give information on copy number that cannot be obtained from analysis of hotspot mutations. Nevertheless, full-length sequencing of candidate genes is likely to lead to identification of aberrations of unknown significance, because aberrations in known cancer genes can be passengers with no consequences on protein function compared with drivers that are potentially actionable. Ultimately, the approach that will be preferred for routine clinical testing will depend on time required for molecular analysis, informatics support required for data interpretation, quantity of DNA needed, and cost.

Whole-exome and whole-genome approaches are also being pursued for CLIA testing because they can identify aberrations in previously unidentified cancer genes that are relevant, regardless of cancer type. In addition to identifying mutations and indels, these approaches have the potential to provide copy number analysis and identify rearrangements. Managing, analyzing, and interpreting the ensuing data and, in particular, determining the clinical consequences of putative aberrations, are particularly challenging. Implementing whole-exome and whole-genome approaches in the clinical environment would add additional challenges, including the cost of equipment that may quickly become outdated, cost of data storage, and personnel needs for informatics support. Despite optimal data generation and analysis, there will likely be many inaccuracies, and thus CLIA confirmation through orthogonal platforms will likely be needed.

Much of the effort of cancer centers has been focused on implementing genomic testing for DNA somatic mutations and indels, but continued effort is needed to identify strategies for replacing fluorescent in situ hybridization with high-throughput strategies for copy number assessment and on using next-generation sequencing or molecular inversion probe assays. Further strategies to globally detect potentially pathogenic rearrangements are also essential.

Infrastructure Needs for Improved Tissue/DNA Quality and Biomarker Turnaround

Careful assessment of tumor tissue is critical for good-quality molecular diagnostics. One way to accomplish this is to set up a dedicated tissue/DNA quality assessment service to determine the quality and quantity of tumor available in tissue, assist in selecting regions of high tumor cellularity for DNA extraction, determine when laser capture dissection is needed to minimize normal DNA contamination, and determine when new biopsies may be necessary because of poor tumor cellularity or necrosis. Novel approaches such as flow cytometry-guided selection of cancer cells on FFPE need to be explored.¹⁶ Selecting blocks to be sectioned and areas of sections to be extracted often requires significant time and effort from pathologists. Pathologists who have time to dedicate to the process are essential to the timely processing of samples. Recognition of this enormous effort by pathologists in consideration of their other clinical workloads is necessary, as is recognition of their important academic contributions to team science.

Another major issue for molecular diagnostics is minimizing turnaround time. Delays in testing are often attributable to delays in retrieving archival tissue from institutional warehouses or from outside institutions. For new patients, this delay can be decreased by requesting archival tumor samples at the initial visit. Having dedicated “tissue expeditors” and using contract service providers who are committed to tracking down outside samples and ensuring their timely delivery can play an important role in expediting personalized cancer care. It is important to make sure that status information is updated in the electronic medical record, so that clinicians and clinical research teams are kept abreast of progress for testing in individual patients and so that patients can be informed of progress as well as any potential delays in testing. If ordering clinicians or investigators are alerted to tissue or DNA insufficiency, then alternate testing or alternate treatments can be planned. Because of concerns about molecular heterogeneity and tumor evolution, rebiopsy should be considered to ensure that proximal aberrations are used to select appropriate therapy.

Standard-of-Care Markers for Clinical Care Versus Markers for Research Testing

Although it seems obvious that more comprehensive testing would lead to better treatment choices in all diseases, the level of evidence required to make genomic testing standard of care is lacking for many cancer types. Because such multiplex genomic testing may not be reimbursed, strategies are needed to determine which patients testing is most appropriate for, especially with today's concerns for cost-effectiveness. *BRAF* mutation testing is now standard of care for metastatic melanoma so that treatment with RAF inhibitors can be considered, as is testing in colon cancer for *RAS*, a marker of resistance to cetuximab.¹⁷⁻¹⁹ Consideration should be given to developing or using existing multidisciplinary committees to weigh the level of evidence for each biomarker for each cancer type to decide on reflex

testing that would be appropriate for each histology. Electronic order entry can facilitate ordering of only approved markers as standard of care, and documentation of medical necessity would be needed for appropriate reimbursement. Comprehensive testing with research intent (eg, biomarker testing for patient selection for research protocols) can be performed after patients give their consent and can be funded through philanthropic funds, grants, or trial charges. Infrastructure should be set up to track non-standard-of-care testing, to ensure that appropriate parties are billed and to determine the impact of genomic testing on clinical trial enrollment and other clinical care decisions.

Biomarker Testing in the Research Environment for Basic and Translational Research

Biomarker analysis that is performed retrospectively and that does not guide treatment selection or stratification can be done in a research environment (ie, a non-CLIA environment). There is a great need for core facilities for commonly performed research assays in trials and for other clinical-translational research studies. These assays can include hotspot mutation analysis; targeted candidate gene approaches; whole-exome and whole-genome sequencing; methylation profiling; RNA-Seq; messenger RNA (mRNA), micro RNA (miRNA), and noncoding RNA profiling; immunohistochemistry; functional proteomics with multiplex proteomics approaches and reverse-phase protein arrays; and metabolomics.

The important determinants of which technologies should be offered in-house or be outsourced are expected assay volume, expected short- and long-term changes in technologies, and cost to the investigator. Using in-house platforms has many advantages, such as ease of access and facilitation of biomarker analysis across trials. However, outsourcing certain technologies may be necessary or preferable because of the costs of developing valid assays and purchasing expensive equipment. To build a successful program, it is necessary to be nimble in technology assessment and use. Collaborations between academia and industry can be invaluable in gaining access to new technologies, and they should be facilitated through umbrella agreements and expedited material transfer agreements.

Several experienced bioinformatics faculty and professional staff are needed for timely data analysis using multidimensional bioinformatics, computational biology, and systems biology. Data sharing across research projects and trials should be mandated to expedite biomarker discovery, particularly when it is funded by philanthropy or federal dollars. A systematic approach to functional genomic validation of potential drivers of disease and markers of therapy response/sensitivity is needed because many of the aberrations identified will have uncertain consequences. Data sharing with basic and translational researchers through regular disease-focused working group meetings or appropriate Web sites is necessary to expedite functional validation of molecular aberrations and efficient implementation of biomarker-matched personalized treatment algorithms.

DECISION SUPPORT

Personalized Standard-of-Care Therapy

It takes approximately 17 years for new scientific discoveries to enter routine clinical practice, and they have a success rate of less than 15%.²⁰ Molecular oncology is rapidly evolving, often too rapidly for clinicians to keep up with new findings. Studies have shown that

despite published evidence and guidelines for EGFR testing, a third of physicians did not consider EGFR mutation testing in stage IV lung cancer to be part of their standard of practice.^{9,21} This highlights the great need for decision tools to help clinicians leverage new technologies that can benefit patients.

Clinicians at academic centers and cancer centers are likely to be up-to-date with current testing and therapy guidelines. Additional mechanisms can be put in place to ensure that they are able to stay up-to-date, including routine attendance at multidisciplinary and treatment planning conferences where clinicians discuss testing and treatment choices and use of standardized electronic order entry sheets with predesignated testing that has been recommended on the basis of level I evidence or clinical consensus. Additional decision support tools such as electronic reminders need to be explored.

Personalized Investigational Therapy

Some patients are presenting with disks containing their genetic data but with no analytic report or interpretation of clinical implications. At the same time, the published literature on molecular oncology is rapidly expanding, and large amounts of genomic data are accumulating in biologic databases. Even highly specialized oncologists at leading cancer centers typically cannot incorporate the vast amounts of genomic information into clinical decision making and selection of investigational therapy for individual patients. Thus, we need to transform genomic data into clinically useful knowledge and provide decision support for implementing clinical trial-based personalized cancer therapy.

Several important steps are needed to enable use of genomic data in clinical decision making. The first is timely data analysis. This is especially challenging for targeted full-length candidate gene, whole-exome, and whole-genome sequencing. A dedicated team of bioinformaticians is needed to rapidly analyze next-generation sequencing data. A short turnaround time can be facilitated by agreeing on standardized algorithms for mutation calling, strengthened by comparison with normal DNA when possible or, alternatively, bioinformatics approaches based on deep sequencing to distinguish germline and somatic aberrations. Existing and novel algorithms need to be explored, validated, and constrained to identify the best tools for functional prediction of mutation impact. This can be expedited by focusing on nonsynonymous mutations, indels, and rearrangements predicted to alter function and by generating a list of actionable targets/potential targets in advance. Informatics algorithms are needed to prioritize mutations as drivers versus passengers and potentially targetable pathway aberrations. To make genomic information accessible, it is important to provide up-to-date information on what is known about the genes being assessed, the potential roles of the specific aberration identified, and on approved drugs or investigational agents and trials that target the aberration or pathway expected to be activated by the aberration.

Robust clinical data management infrastructure is essential for enabling genotype/phenotype correlation. With rapid accumulation of data at cancer centers, clinically annotated genomic data will provide a significant opportunity for discovery of predictive/prognostic markers as well as pharmacogenomics of toxicity and response. Because of tumor heterogeneity within the primary tumor and differences in molecular findings between the primary and recurrences,²²⁻²⁹ it is critical to track what tissue is being tested for genomic assays (primary *v* metastases or both) as well as temporal consideration

(distant or proximal in time) to determine the extent of molecular evolution seen in each tumor type and with each treatment. It is also important to monitor the impact of treatment based on mutation assessment in primary versus recurrence to determine whether the primary tumor can be used as a proxy for metastatic sites. To deliver effective therapy in the face of heterogeneity and clonal evolution, it may be necessary to determine mutational events in multiples areas of the primary tumor and in clinically extant metastasis, which would lead to increased costs and potential morbidity because of repeat biopsies. We and other centers are exploring whether circulating tumor cells or circulating DNA can be used to reflect the mutational load across metastasis. As technology emerges that allows deep sequencing of tumors, it is important to determine what proportion of tumor cells needs to have an aberration in order to respond to a drug targeting that aberration.

In a major cancer center, the expectation is that all patients will ultimately be eligible for testing and will be treated in a personalized fashion by their own oncologists. This leads to process management challenges in dealing with molecular testing for more than 30,000 eligible patients per year. Incorporation of genomic information into practice may be facilitated by critical input from a team of dedicated oncologists with interest in genomics and molecular therapeutics. Some institutions have put together molecular tumor boards to discuss molecular data and treatment recommendations based on them.³⁰

However, for genomic medicine to be scalable, genomic decision support needs to be automated in many steps. A strong bioinformatics and medical informatics team can help maintain up-to-date information based on published literature, other online biomedical data, and internal data to prioritize targets and treatments. Ultimately, a strong clinical molecular database will be needed to perform comparative effectiveness research by tracking outcomes for all patients who receive molecular testing. The individual's clinical characteristics and previous treatment information along with the cumulative therapeutic experience at the institution can ultimately be used to identify the optimal approved or investigational treatment for a given patient.

RESEARCH BIOPSIES FOR THERAPY SELECTION AND BIOMARKER DISCOVERY

Research biopsies are critical to the implementation of personalized cancer therapy. They can be baseline biopsies of primary tumor or metastases obtained for marker stratification, pretreatment and on-treatment biopsies to assess target inhibition and pharmacodynamic markers of response, or biopsies obtained at progression to assess mechanisms of acquired resistance. The ability to obtain high-quality research biopsies is a critical component for delivering personalized therapy and for performing innovative treatment trials. Several things are needed within an institutional infrastructure to facilitate research biopsies.

First, there needs to be institutional commitment to the importance of research biopsies for gaining the most information from clinical trials and from personalized medicine programs. Treating physicians and research nurses who recognize the scientific importance of research biopsies can positively influence patients' decisions to contribute research biopsies. Institutional review boards (IRBs) need to balance the modest risk associated with obtaining biopsies

with the potential to contribute to improved patient outcomes. Interventional radiology review of each protocol that contains research biopsies can ensure that risks were appropriately considered and disclosed in the informed consent form, and that a standard operating procedure is put in place for sample collection. Even for therapeutic trials that fail to achieve improved outcomes, research biopsies can be scientifically invaluable because they can provide important biologic information, evidence for whether the drug failed for pharmacodynamic reasons or whether the putative target is not a driver and should be discarded as a single-therapy target. Once trials are activated, coordinating research biopsies around other testing and clinic visits is challenging, and an experienced research team that can coordinate schedules along with a dedicated facilitator in interventional radiology will help to alleviate those challenges. Finally, there is a great need for quality control for biopsies. Even with dedicated radiologists and pathologists, research biopsies may be inadequate for the planned biomarker assessment.³¹ Intermittent retrospective assessment is needed to determine the usability of the research biopsies obtained with different approaches in different disease types. Novel approaches are needed to optimize biopsy quality. Two new approaches still under development include optical coherence tomography (prebiopsy) to optimize selection of the biopsy site and tomography of the biopsy sample immediately after it is collected to confirm specimen tumor cellularity while the patient is still in the imaging suite.³²⁻³⁷ Novel functional imaging technologies may also have a role in assessing tumor heterogeneity and guiding biopsies.

UNUSUAL RESPONDERS: AN OPPORTUNITY FOR BIOMARKER DISCOVERY

Characterizing extreme responders may identify unexpected mechanisms of action of drugs as well as markers of response and resistance. Further, tumors may evolve with treatment, and molecular characterization of treatment-resistant or recurrent tumors is likely to provide molecular insights into markers of intrinsic and acquired resistance to therapy.³⁸⁻⁴³ In larger medical centers, many targeted therapy trials are ongoing, each with a few patients who have unusual responses. Characterizing tumors from patients with unusual responses including rare responders in targeted therapy trials, patients with unexpected rapid progression, patients with a mixed response (with one tumor site progressing and another site responding), as well as patients with recurrence after a response can facilitate discovery of markers of intrinsic therapy sensitivity/resistance and elucidate mechanisms of acquired resistance (Fig 2). Indeed, the association between *EGFR* mutation status and response to *EGFR*-targeted therapies was based on identification of somatic *EGFR* mutations in eight of nine patients with gefitinib-responsive lung cancer compared with none of the seven patients with no response ($P < .001$).⁴⁴ An institution-wide initiative can be deployed to support biopsies on these patients as needed and to perform in-depth tumor characterization for markers of resistance or response. This can be followed by larger cohort studies investigating the frequency of the aberrations in specific diseases, preclinical functional validation of putative markers of response/sensitivity, and subsequent biomarker-driven trials testing the marker-response connection that was identified (Fig 3).

Fig 2. Biomarker discovery based on unusual responders on targeted therapy. In-depth molecular characterization of tumors from patients with objective response to single-agent targeted therapy or targeted combinations, patients with unexpected rapid progression, and patients with mixed response can give critical insights into intertumoral heterogeneity (represented by different color clones within the tumors), and mechanisms of intrinsic sensitivity and resistance. Characterization of tumors that relapse after initial response may give unique insights into mechanisms of acquired resistance.

FACILITATING PERSONALIZED CANCER THERAPY TRIALS

Providing infrastructure for clinical trials, optimally by using a clinical research-driven model of clinical care is critical to efficient implementation of personalized medicine. Scientific and ethical review of protocols should be carried out by experienced investigators who are familiar with biomarker assessment and issues in genomic medicine. High costs for CLIA assays and image-guided biopsies remain a major challenge, and consideration should be given to forming dedicated review committees that can determine which investigator-initiated trials are high impact and thus should be prioritized for accrual as well

Fig 3. Leveraging information from unusual responders for biomarker discovery.

Fig 4. Exploring the clinical utility of comprehensive genomic testing. After patient informed consent, tumor and normal DNA is extracted in the Clinical Laboratory Improvement Amendments (CLIA) environment. After targeted somatic mutation testing in the CLIA environment, more extended testing is performed in a research environment. Test results are shared with the treating oncologists, and CLIA validation of research findings is pursued if any clinically relevant research findings are found. Therapeutic decisions are based only on CLIA test results.

as for institutional or philanthropic support. Given that molecular marker-driven clinical trials are a necessary step in implementing molecular testing as a standard of care, and thus billable and payable, consideration should be given to use of institutional funds for trials aimed at validating utility of molecular testing.

Next-generation sequencing approaches are only now being developed in the CLIA environment. Cancer centers need to develop approaches to explore the utility of comprehensive multiplex testing, including multigene next-generation sequencing, to facilitate personalized cancer therapy in different disease types. To that end, MD Anderson Cancer Center has implemented an institution-wide molecular testing protocol with hotspot testing in the CLIA environment followed by next-generation sequencing in the research environment (Fig 4). This is done under an IRB-approved protocol and only after a patient has provided informed consent, with tumor and normal DNA extraction and storage in the CLIA environment. After hotspot testing in the CLIA environment, more extended panel testing is performed in a research environment. Test results are shared with the treating oncologists, and CLIA validation of research findings is pursued if any clinically relevant research findings are found. Therapeutic decisions are based only on CLIA test results. One goal of this approach is to determine which testing approaches and candidate targets should be implemented in the CLIA environment. As CLIA compliant testing is extended, the goal will be to implement exploratory testing approaches into the pre-CLIA environment that complement the CLIA approaches. Ultimately, it is possible that genomic testing may be performed in a more sequential manner clinically, with CLIA targeted genomic testing followed by more extensive genomic testing until actionable aberrations are identified (Fig 5).

A standardized institution-wide multiplexed genomic testing protocol can assist in implementing personalized cancer therapy across the cancer center. This approach is likely to be of greatest value for patients with advanced disease who are likely to participate in

Fig 5. Sequential genomic analysis. Genomic testing may be performed in a sequential manner in the clinical setting, with Clinical Laboratory Improvement Amendments (CLIA) –targeted genomic testing followed by more extensive genomic testing until actionable aberrations are identified.

biomarker-driven trials. In addition, this will determine the frequency of mutations and co-mutations in cancer-related genes in advanced disease in different tumor types; it can also establish a database of somatic mutations and clinical characteristics that can be used to select patients who may be eligible for new targeted therapy trials and can be a resource for future determination of the functional impact of specific mutations. Indeed, the spectrum of mutations in patients with advanced disease who are likely to enter onto clinical trials can be quite different from those in surveys of patients at presentation, such as The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) efforts. Planned review of genomic profiles in different disease types can facilitate identification of unmet needs for investigational trials for specific molecular subtypes and ensure a rich portfolio of biomarker-selected phase I and II trials for clinical trial-driven cancer care.

TRAINING AND EDUCATION IN PERSONALIZED CANCER THERAPY

Training and education of future clinician-investigators and physician-scientists committed to personalized therapy is a major need. Fellowship trainees in multiple disciplines will need training on principles of genomics, molecular oncology, targeted therapy, and biomarker development and on designing clinical trials for personalized therapy. This is best done by incorporating basic lectures into the core training curriculum combined with hands-on training in genomic technologies, experience in genomic data analysis, and use of publicly available databases. Dedicated postdoctoral fellowships and junior faculty awards can provide protected time and funding for

research to strengthen junior faculty with the appropriate training and commitment to succeed as independent investigators and be future leaders in personalized cancer therapy.

THE SINGLE PAYOR ENVIRONMENT

Many of the considerations already discussed relate to particular challenges in the US regulatory and reimbursement environment. However, implementation of personalized cancer care into the single payor environment can pose an additional set of challenges. One challenge is balancing the merits of investment in the development and implementation of molecular marker–driven patient care and research with the demands for funds for other areas of patient care. Research on extensive outcomes must be integrated early in the process of selection and development of molecular testing and implementation of clinical trials. The benefits from personalized cancer therapy remain to be fully demonstrated. Targeted therapy benefits only a subpopulation of patients with biomarkers that indicate sensitivity, and these benefits are frequently transient. Thus, it is difficult to demonstrate the cost benefit of particular approaches. However, it is important to note that molecular marker approaches have the potential to indicate which patients will not benefit from expensive therapies, and that will provide a major opportunity for cost savings. For example, several multivariate assays have been developed that indicate patients who do not need and will not be likely to benefit from chemotherapy, thus decreasing both cost and morbidity.^{45–49} Similarly, patients with KRAS mutations are unlikely to benefit from EGFR-targeted therapy, thus sparing the high costs of targeted therapy. An intriguing approach that has recently been implemented is to link reimbursement of drug costs to demonstrated benefit for the individual patient. This approach, which is currently applied solely to drug costs, could be combined to determine the level of reimbursement for molecular diagnostics.

Although it is clear that extensive outcomes research will be necessary to demonstrate the degree of benefit that will occur from personalized cancer care in both the US and international environments, it remains highly likely that considerable patient benefit will occur as a result of implementation of personalized cancer care. This is most clear in the area of breast cancer, in which directing therapy to patients most likely to benefit by classifying tumors as estrogen receptor–positive or HER2–positive and tailoring therapy accordingly has contributed to remarkable improvements in patient survival. Because much of the cost of cancer care occurs for patients in their last 6 months of life, even small shifts in mortality can result in major cost benefits.

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CONCLUSION

We are entering an exciting era in which it is possible to provide rational therapy to patients on the basis of the drivers of their tumors and the emerging drug toolkit. This may provide the greatest opportunity in history to take giant steps forward in improving patient outcomes. However, as we attempt to move the precepts of personalized cancer therapy into standard of care, there are many challenges that need to be overcome. A concerted effort by major cancer centers acting as consortia and sharing information and best practices will be needed to fulfill the incredible promise of personalized medicine in a rapid and efficient manner.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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