On the Eve of Personalized Medicine in Oncology

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Introduction

The future of cancer care and treatment lies in the concept of "personalized medicine," a model that focuses on the individual, not just the disease. Personalized medicine in cancer care will need to use molecular signatures to *match* the right patients to the right drugs, first in clinical trials, then in clinical practice. This is a new paradigm in which information technology, science, and clinical treatment are combined to improve health outcomes and patient satisfaction. It will require unusually large databases, relating both molecular and clinical data, such that patients can be proactively selected for the most appropriate therapies.

There is consensus building among clinicians, scientists, and information technology professionals on seven principal areas that could dramatically affect the way therapeutics are developed and delivered to patients.

Whole Genome Profiling/Sequencing

Largely limited in the past by cost, both whole genome sequencing and gene expression analyses now hold promise in helping classify patients and their tumors. This segmentation can be leveraged and exploited to target the right drug therapy for individual patients.

New technologies will likely reduce costs (ultimately less than an estimated $1,000 per genome assessment) and times in the near future, making sequence analyses of somatic tumors and human genomes, on a population basis, feasible. Candidate gene and exon sequencing approaches will dominate first, but whole genome sequencing will have value in pharmaceutical development and clinical trial matching (the right drug for the right patient). Other technologies, including microRNA, epigenetic, and proteomic analysis, may also have value on a whole genome basis.

Diagnostic and Prognostic Testing

Molecular tests, such as Her2Neu amplification or c-Kit or Ras mutation assessments, that will assist and guide physicians in therapeutic decisions, are now becoming commercially available. These tests are expected to proliferate rapidly over the next 5 years, particularly as companion diagnostics to therapeutics. Use of these tests may ultimately be driven by insurers desirous of reducing health care costs for therapies without predictable benefit.

Commercial signatures are already available to predict outcomes for breast cancer patients (1). Soon, a lung cancer signature will be available to predict the best chemotherapy doublet for the patient (2). And the ability to predict individual tumor radiosensitivity, for example, is central to the development of personalized treatment strategies in radiation oncology. Scientists have developed and biologically validated a systems biology model of tumor radiosensitivity in 48 human cancer cell lines. The implications of a successful radiosensitivity predictive assay are broad and significant because it will allow for better selection of patients for radiation protocols and, thus, could potentially improve the ability of physicians to individualize therapy.

Molecular Imaging

Molecular imaging is an emerging field in which molecular and cell biology are joined to modern technology for noninvasive imaging. This involves developing the necessary assays and technologies for the smallest molecular changes in specific molecular pathways *in vivo*. Molecular imaging will allow us to better understand the biological processes of cancer and other diseases, leading to improved diagnosis and disease management.

Current imaging technologies have substantial room for improvement. Newer hardware and wetware solutions will be required to metabolically image tumors such that responses can be evaluated in hours to days, rather than months. The use of biosensors that precisely monitor the timing of cell division may allow for the screening of more anticancer compounds and allow scientists to observe and measure cellular processes in real-time rather than through after-the-fact images. Using these newer techniques, clinicians can see not only where a tumor is in the body, but also observe specific molecular and biological processes (proliferation, apoptosis, and angiogensis) that influence tumor behavior and responses to therapy. This could play a critical role in cancer detection, drug development, and individualized treatment.

Information Technology

Personalized medicine requires substantial information technology solutions that support storage and linkage of large amounts of clinical, research, and genomic data. This will require the development of solutions that target the complete data pipeline, including collection, storage, and delivery.

To realize the promise of personalized medicine, it is essential that physicians standardize how they evaluate patients and how they represent this information in the medical record, preferably in an electronic format. A first step is establishing both common data sets and a common vocabulary for describing the data. An ontology is a type of vocabulary that not only describes preferred terms and their meanings but also how these terms relate to one another semantically. Using an ontological representation of health data

Note: Based the first Total Cancer Care Summit: The Future of Personalized Medicine, hosted by the H. Lee Moffitt Cancer & Research Institute and held Oct. 24 to 28, 2007, in the Bahamas. The conference focused on the current practice of cancer patient care, the vision for the next 5 years, and the development of "blue sky" opportunities for the future of personalized medicine.

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will allow physicians to infer relationships in the data that are not explicitly defined in the database record. The Open Biomedical Ontologies Foundry is assuming a set of these ontologies, built upon a common set of design principles, which cover entities for the entire biomedical domain, including anatomic structures, cells, genes, proteins, chemicals, diseases, and clinical findings. These universal approaches will be a key step toward linking databases and data sources from multiple hospitals. Linking data across hospitals has always been a major challenge and is currently the subject of national projects such as CaBig.

Drug Development

Currently, there is a prolonged timeline for drug development because of a lack of preclinical systems that accurately predict efficacy and toxicity, as well as the frequent failure rate of new drugs. About 5% of investigational new drug (IND) applications for new molecular entities (NME) submitted to the Food and Drug Administration (FDA) progress beyond the investigational phase, and there is more than a 50% failure rate of agents in phase III trials. The cost of an NME is estimated at >$800 million, which, combined with the cost of patient and professional resources for drug development, certainly encourages the development of novel, cost-, and resource-conscious trial approaches.

A recent approach to improving the efficiency of drug development, initiated and supported by both the FDA and the National Cancer Institute, is an exploratory IND that allows the conduct of "phase 0" trials. These trials require up-front development of robust and validated pharmacokinetic (PK) and biomarker assays that are used in studies in which low doses of the drug are escalated to achieve the desired drug exposure or target modulation over a limited dosing period. Phase 0 trials require fewer patients, have as their end points target modulation and PK analyses, and may allow for earlier Go/No Go decisions.

Although phase 0 trials are not yet widely accepted, they have the potential to allow investigators to collect a wealth of PK and pharmacodynamic data regarding molecularly targeted agents that will better inform subsequent phase I and II trials; examine the schedule or sequence effects of drugs in combination trials; facilitate the selection of a lead agent for clinical development among a group of candidates; and allow the early application of molecular-imaging studies.

Gene-Based Clinical Trial Matching

Substantial changes in the way clinical trials are designed, reviewed, opened, accrued, and closed will be required to effectively offer patients the best genetically matched trial opportunities. Trial matching holds promise to radically change the method and timing of early phase I/II clinical trials.

A not-too-distant approach to personalized cancer care is matching the patient to a molecularly targeted drug. In Florida, there is a massive translational project under way, called "Total Cancer Care," designed to obtain demographic, clinical, and tumor gene expression profiles from tens of thousands of cancer patients. These patients will be followed for life, and all of their clinical and genetic information will be entered into and stored discretely in a data warehouse. Although ideally, these patients would be accrued to a regimented clinical trial with strict entry and exclusion criteria, this approach is not truly feasible on a large scale across multiple tumor types, and does not recapitulate the "real world" practice of oncology, where many patients are treated with variations of rigorous trial standards. There is still considerable value in collecting accurate data from a very large population of patients treated with standard of care approaches. As the number of patients in this trial increases, there will be a steady-state number of patients with a specific malignancy that could be matched to a drug that has shown preclinical efficacy associated with a specific gene expression profile. A significant number of patients with this predictive profile could be rapidly available for an early-phase trial with a new agent, with perhaps a greater assurance of response than is seen with the traditional early phase trial approach.

Industry and Academic Partnerships

No one academic institution or industry has the capacity or capability to single-handedly accomplish the mission of personalized medicine. A "syndicate" of interested and willing parties must meet the challenges ahead in this new paradigm of care.

New approaches to sharing data, biospecimens, and intellectual property will be required if such a syndicate is to be successful. A contract research organization, for example, could be established to function as the infrastructure to facilitate multicenter research, from hypothesis to publication. The CRO could bridge the best of the critical elements of successful clinical research, including connecting sponsors-investigators, research sites, and funding entities. Although this infrastructure is crucial, it must be scalable to meet the requirements of the various types of research it will manage, and the variables of its operation must be carefully considered. In addition, a comprehensive information system, accessible by researchers, clinicians, and patients, which will contain molecular analyses results paired with clinical outcome data are being constructed. The goal is to develop personalized therapy, identify molecular signatures for prognoses, and establish an evidence-based approach for cancer treatment.

One example of how personalized medicine can is through the Molecular Analysis Directed Individualized Therapy trial for patients with non–small cell lung cancer, which tailors the selection of chemotherapy drug combinations to fit a patient's distinctive genetic profile. The trial uses standard treatments but with chemotherapy assigned according to a novel algorithm. Investigators have seen tumor response rates in excess of 50%.

The future for personalized medicine—not just for cancer care, but other diseases as well—is bright. Commercially available diagnostic and prognostic molecular tests are available. Prescreening for clinical trials is becoming more commonplace. Molecular imaging initiatives are becoming more prevalent.

One thing is clear—the patient experience will continue to benefit from these personalized medicine approaches, particularly as each patient becomes more closely involved in his or her own care. This is being achieved, in part, through streamlining the consent process by means of secure patient Web portals. There, a patient can schedule appointment, renew prescriptions, etc. This allows collection of data into the corresponding database in real-time, thus streamlining all processes, and making information accessible for future use in clinical studies. It is also believed that Web portals designed for patients will augment the

participation of patients in the data collection processes key to making personalized medicine a success story.

And although such things as trial matching using a population-based approach and "signatures of response" that can help select patients for therapy may take several years to make their way into the mainstream of medical care, we continue to overcome challenges one at a time.

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Disclosure of Potential Conflicts of Interest

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