Bringing personalized medicine into the real world

Outcomes of the annual National Cancer Institute/Accenture panel

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Scientific advances of this last decade in the medical environment have allowed us to identify the underlying causes of major diseases with increased understanding—leading the way towards personalized medicine. In this new era, each patient requires adapted treatments, drugs and therapies tailored to his or her unique disease and medical traits. Cancer is the most advanced arena in which personalized approaches to therapy are being addressed.

With this in mind, Accenture and the National Cancer Institute held an event at the ASCO Annual Meeting focusing on the critical steps to allow the delivery and administration of specific drugs for specific diseases. Two panels were convened to discuss the challenges of this new era in depth. The first panel was on diagnostic tools and how they are used in the real world, with a focus on efforts coordinated at the national level. The second panel focused on contemporary models of observational trials and their potential. Both discussions utilized a moderated panel format with qualified experts from academia, industry and public agencies and further augmented with questions and insights from the diverse group of session attendees. These conversations are summarized in the following pages.

Assay development and their real-world utilization

In this age of personalized medicine, the first step is to identify patients whose cancers have specific mutations that can be targeted. Our goal is to deliver the right drug to the right patient at the right time. In order to do this, cancer centers globally must address multiple stakeholders with different needs, including patients, researchers, and treating physicians.

The amount of data generated within those cancer centers means collecting and maintaining the results can be a challenge. At the center of this data flow, clinical platforms are in charge of delivering the data to patients and their physicians for use in the clinic and then fed into a data repository for further research and analysis. Determining the significance of a given mutation in a given cancer is one issue, but there is also a need to determine the threshold for a positive result. In addition, for cancers with multiple mutations, which actionable targets take precedence over others? Which biomarkers have merely prognostic significance, and which are truly predictive of response to a given therapy?

Looking beyond the treatment centers, it’s clear that diagnostic results benefit the whole community and must be integrated in a much more complex ecosystem than the one limited by the confines of the academic cancer centers. In this new era of scientific discoveries, one test—one drug will not serve the needs of individual patients as well as multiple assays on a single specimen, since the prevalence of each molecular abnormality may be low, and there may be several “actionable” molecular abnormalities in a single disease.

The new opportunities in diagnostically-driven clinical trials have led to a variety of national efforts globally. In France, most molecular tests are already coordinated and performed at the national level. Indeed, following the initiative of the French government’s National Cancer Plan, all cancer patients in France get offered, through core national laboratories, a molecular diagnostic of their tumor in order to improve the treatment outcomes. In the United Kingdom, national leaders have implemented a diagnosis initiative for the last three years and are expanding. UK leaders are currently focusing on defining the molecular characteristics of selected cancers. One challenge has been having the right infrastructure to support database management and research allowing the optimal delivery of personalized therapies. In the United States, a variety of clinical trials have begun in order to take advantage of the revolution in cancer diagnostics. In particular, the US National Cancer Institute is helping fund the Lung Master Protocol (LUNG-MAP), NCI MATCH, and M-PACT. All of these trials, and several others, are essentially basket protocols in public-private partnerships which allocate patients to specific treatment arms based on the status of mutations or protein over-expression. Regulatory authorities have been consulted to ensure that diagnostic assays are appropriately utilized and validated and that the specific treatment allocations do not pose significant risks to enrolled patients.
Once the proper systems are in place, experts will have to build and improve decision-making mechanisms and encourage payers to support the integration of new assays into clinical laboratories as a standard procedure. This final aspect is critical in improving the standardization of future therapies. Reimbursement strongly determines the care patients receive. From a public policy perspective, the next major shift will be to successfully integrate molecular testing as a routine practice as part of each nation’s health services. In Europe for example, approval for a diagnostics test is still regulated on a country-by-country basis. In the United States, co-development of therapeutics and diagnostics is a model being promoted by the FDA to take advantage of the molecular revolution in medicine.

Predictive biomarkers may allow prescribers to identify biomarkers that will exclude patients from ineffective treatments and identify therapies which may be of benefit. A clear success of this strategy will be found if trials which used to require thousands of patients to identify a small subset of responders can be downsized by identifying potential responders a priori through enhanced molecular diagnostics.

**Contemporary models of observational trials**

Payers and regulators are increasingly expecting pharmaceutical companies to prove that their drugs work not only in controlled clinical trials, but in the real world as well. As a new field of investigation, observational trials are still not completely defined and formatted. To successfully measure the impact of cancer drugs in real life settings, specific rapid learning systems, such as CancerLinq (http://www.asco.org/quality-guidelines/cancerlining), are being developed. The goal of such databases is to bring individual patient EHRs into large data warehouses, transform the data into a common model, aggregate and de-identify the data, and then share the data with various users for different purposes.

The initial use of these databases will be to evaluate the quality performance of practices against established benchmarks. These systems will allow the healthcare community to go beyond current limitations of oncology practice initiatives and demonstrate the relevance of certain therapies while showcasing the lack of usefulness of others. This can result in an improved understanding of real world diseases, more efficient clinical trials and shortened drug approval times.

Furthermore, observational trials may be the best tool to address the issue of off-label drug use. Current off-label use is not always substantiated by sufficient evidence. Real world data can directly fill this knowledge gap. This use of observational trials to document the impact of off-label use is the most cost-efficient and effective method of capturing as much information about the activity of these drugs as possible.

Although making sense of some mutations or assay results when deciding on a patient’s treatments can be difficult, observational trials and their associated analysis in major repositories can actually help physicians make more informed decisions.

Observational trials and more specifically longitudinal observational studies can help address the 3 biggest challenges around cancer care today:

- Tumor heterogeneity where limited clinical trial populations cannot successfully meet researcher requirements and where there is rapid drug resistance emergence
- The evolution of patients across long periods of time where a standard clinical trial would be too costly and impractical
- Finally, the identification of populations with higher likelihood of complications and comorbidities cannot be done outside of observational trials as these represent too small a population to be statistically representative in economically viable standard trials

Observational trials can provide very high quality evidence to allow patients, clinicians and health administrators to make wise choices among options for improved patient outcomes. At present, financial incentives encourage the use of the newest therapies, even when there may not be a significant benefit may not be proven to support their use. This is a particular concern in a given rare histology, for which given targets may exist, but prevalence of the tumor may not justify an industry-sponsored clinical trial. If coordinated, the implementation of observational trials in these settings can ultimately minimize off label use and wasted effort. Capturing information in a registry-based trial can help researchers analyze an initial cohort of off-label patients. Once sufficient evidence is present, novel indications can be more rigorously studied in a clinical trial with a preliminary understanding of efficacy.

New, evidence-based data can be a cornerstone of drug reimbursement as well. Novel payment models that incorporate treatment-based registries should be explored by the industry, regulatory agencies and payers alike. As it stands, many patients are locked in payment models in which therapies are reimbursed regardless of evidence. For other patients, payment is denied despite reported efficacy in a given rare histology. By coordinating novel payment models that incentivize the evaluation of efficacy, patients who may derive benefit from a given therapy can be evaluated more quickly. In this way, evidence from a registry can be more quickly implemented in the real world.
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