in HIC and LMIC. The second most important obstacle in HIC was lack of time or competing priorities and in LMIC, it was regulatory issues.

Table 1. Major Obstacles to Cancer Research.

	Average Rank	HIC (n=41)	LMIC (n=39)
Competent authorities procedures	4.25	4.61	3.87*
Ethics committee procedures	4.55	4.80	4.28*
Insurance/indemnification coverage	4.55	4.54	4.56
Lack of patients/patient accrual	5.43**	5.27**	5.59**
Lack of funding	3.16***	3.15***	3.18***
Lack of research materials (eg, drugs)	4.49	4.49	4.49
Lack of trained personnel	5.00	4.90	5.10
Lack of time or competing priorities	4.58	4.24	4.92

*marks change in obstacle distribution when stratified by country income; ** patients versus rest (except personnel) significant; ***fuding versus significant.

Future Global Cancer Research

According to Richard L. Schilsky, MD, University of Chicago, Chicago, Illinois, USA, cancer is a systems issue that encompasses biological, healthcare delivery, clinical trial information, and patient support systems. Researchers are recognizing that every tumor has a unique profile, with multiple molecular subtypes within each histologic type. A schema of personalized medicine developed by MacConnaill and Garraway [*J Clin Oncol* 2010] based on DNA profiling and targeted therapies is being challenged by emerging data on intra-patient tumor heterogeneity [Gerlinger M et al. *N Engl J Med* 2012] and evolution of histologies and genotypes.

The vision of personalized care faces many challenges, including the need for molecular pathway analysis, validated biomarker assays, an information infrastructure able to support decision-making and patient monitoring, multiple effective therapies, and increasing regulatory complexity. The success rate of bringing drugs to market is 5% to 8%, resulting in great inefficiencies and costs.

To address these challenges, new learning structures are needed, including global research consortia, community-based networks, and learning healthcare systems. There is a need to move toward trials that have the greatest potential to provide benefits for patients, with selection of participants based on molecular characteristics. Pragmatic clinical trials in community clinical practice are also important. Patient-centered, rapid-learning cancer care systems, such as ASCO Cancer-LINQ, that incorporate data collection and comparative effectiveness research with implementation, assessment, and refinement of new evidence are needed.

Targeted Therapy Issues in the Age of Personalized Medicine

Biomarkers and Oncology Drug Development

Elizabeth Mansfield, PhD, US Food and Drug Administration (FDA), Silver Spring, Maryland, USA, discussed the use of biomarkers and biomarker tests for prediction, prognosis, and patient selection in targeted drug development trials. Once identified a test must be developed that measures the biomarker in a useful way. Some biomarkers are both prognostic and predictive, but trials must be designed to demonstrate the marker's value for one or the other. Selective biomarkers are neither prognostic nor predictive but are used to select a treatment population.

In 2011, the FDA published the Companion Diagnostic Draft Guidance, announcing that if a companion diagnostic test is necessary to find a drug to be safe and effective, the FDA must approve at least one instance of that test. Table 1 shows examples of pairs of diagnostic tests and biomarkers. Test selection and development must take into consideration appropriate measurement characteristics, be analytically validated, be uniformly used in registration trials, and be available for approval together with the drug.

Table 1. Types of Companion Diagnostic Tests.

Use	Type
Identify patients likely to respond or not respond to a partiuclar therapeutic product	**Predictive**
Identify subgroups of the larger population with poor prognosis who are likely to benefit from a particular therapeutic product	**Prognostic**
Identify patients likely to be at increased/decreased risk for serious adverse reactions from a particular therapeutic product	**Safety**
Monitor response to treatment for the purpose of adjusting treatment (schedule, dose, etc) to achieve improved safety or efficacy	**Monitoring**
Individualize the dose of particular therapeutic product	**Dosing**
Use as integral part of therapeutic clinical trials conducted to support market approval of a therapeutic product	**Selection**

Preselection is difficult, because all or most included patients are marker-positive and different tests with different performances are likely to have been used. External or non-Clinical Trial Assay tests may bias an enrolled population. In addition, no negative markers are available to validate the test or drug performance.

To gain approval, patients with acceptable benefit-to-risk profiles should be selected and any serious safety

signals should be removed or avoided, the population should be narrowed to those who are most likely to benefit, and the biomarker test must work and be available at drug approval.

Challenges in Targeted Agent Development

Patient selection is key in developing targeted agents that offer real patient benefits. Selecting the right patients for a drug involves understanding the tumor biology and using the appropriate diagnostics, endpoints, and trial design. Gwendolyn A. Fyfe, MD, San Francisco, California, USA, used human epidermal growth factor receptor (HER) 2, epidermal growth factor receptor (EGFR [HER1]), and VEGF as examples to illustrate the challenges in developing targeted cancer therapies.

Although development of trastuzumab seemed difficult at the time, a great deal was known about HER2, including the fact that breast cancer patients with HER2 overexpression had shortened median survival. To target HER2, a well-characterized therapeutic and a diagnostic for selecting patients were needed. HER2 was unusual, in that there was almost a dichotomous response to trastuzumab, with dramatic growth inhibition in overexpressing cell lines and no effect in normal cell lines. When only marker-positive patients were treated, longer survival resulted.

EGFR was more difficult. It was assumed that overexpression should be targeted, but the value of EGFR overexpression as a prognostic marker remains unclear. Survival curves from erlotinib-versus-placebo trials are not as straightforward as those observed in trastuzumab studies. Simulations show that clinically significant separation of Kaplan-Meier curves in a randomized trial requires an effect in at least 30% to 50% of patients. The current poor understanding of EGFR biology makes it difficult to select patients who might benefit from erlotinib.

Choosing the right endpoint is important, as illustrated with anti-VEGF therapy development. Early bevacizumab single-agent trials reported varying response and survival rates. With a drug that targets tumor infrastructure but not the tumor itself, the response rate can be dangerously misleading. When bevacizumab was combined with chemotherapy for colorectal cancer, both responders and nonresponders had a survival benefit.

Selecting the right patients for the right drug is key in the development of drugs that offer real benefits. Targeted therapy generally takes longer and is more expensive than standard drug development, but may identify important new therapeutics.

Hits and Misses in Targeted Therapy

Karen A. Gelmon, MD, University of British Columbia, Vancouver, British Columbia, Canada, discussed the current confusion about targeted therapy among clinicians. The hope has been that agents that target the fundamental molecular changes of malignancy would yield treatments that reduce normal tissue toxicity and increase survival and cure rates.

Successful targeted agents include imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors and trastuzumab for HER2-positive breast cancer. Other agents looked promising but did not deliver anticipated results, including sunitinib for renal cell carcinoma, bevacizumab for breast cancer, and iniparib for triple-negative breast cancer.

Targeted therapies have been successful when the abnormal target is a critical driver of the malignancy, is associated with poorer outcomes and can be successfully targeted without significant toxicity, and when the mechanism is known. So far, every effective targeted agent, with the exception of VEGF, has a response-prediction biomarker, but finding it or proving it has been challenging.

In the past, anticancer drug development focused on patient response. Current and future development depends on determining the molecular profile of the tumor and finding the most appropriate drug to target that profile. Researchers are looking at predictive, intermediate endpoints and other molecular biomarkers to find the right biomarker for the right drug for the right patient. This must be done early, or there will be increasing numbers of negative Phase 3 trials.

Molecular profiling shows that each tumor may be associated with many mutations. Defining driver versus passenger mutations is a challenge that requires functional studies, which require a good link between preclinical and clinical work. The intratumor heterogeneity model [Yap TA et al. *Sci Transl Med* 2012] proposes that ubiquitous driver events may provide more tractable biomarkers and targets than heterogeneous events that may lead to drug resistance and treatment failure.

Personalizing anticancer therapy requires a process that includes patient referral, surrogate tissue or archived tumor analysis, patient allocation to trials that is based on molecular characteristics, patient monitoring, and reanalysis of the tumor and other tissues for resistance mechanisms upon disease progression [Yap TA et al. *Nat Rev Cancer* 2009].

Dr. Gelmon concluded that the oncology community needs to understand both the promise and the limitations of the targets. They also need to be alert to new toxicities of novel targeted agents, and not rush to assume benefit or lack of benefit prior to Phase 3 testing and mechanistic studies to define the target.