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Affordable Care Act: Enrollment Update and Adequacy of Exchange Plans for Cancer Patients

Tanisha Carino, PhD
Executive Vice President
Avalere Health

The 7.1 million Affordable Care Act enrollment figure announced by the Obama Administration is a bit surprising, based on the early experience with the federally facilitated exchange and some state exchanges. Whether enrollees chose plans through state exchanges or the federally facilitated exchange, silver and bronze plans were there most frequent choices.

The early data offer some clues about the quality of the coverage that exchange plan enrollees will enjoy. Exchange plan deductibles have been found to be high, compared to employer plans. The average deductible is $1,135 in employer plans. According to metal level, deductibles are: platinum, $1,000; Gold, $1,713; Silver, $3,132; and Bronze, $4,959. There are also differences in utilization management in exchange plans compared to employer plans. In the employer market, roughly 30% of plans have utilization management tools. Among exchange plans, 43% have utilization management. Coinsurance requirements for six classes of oncology drugs are significant, reaching as high as 40%. Another serious problem for cancer patients is the lack of transparency related to physician-administered oncology drugs. These drugs are typically covered under the medical benefit, but the problem for patients is understanding if a specific drug will be covered by a plan and what coinsurance they will be responsible for, if the drug is covered.

As a general rule, exchange plan issuers are narrowing their provider networks, with limits affecting access to cancer center. Issuers seem to be addressing some narrow network issues. On the other hand, there are indications that the narrow networks of exchange plans could bleed into the commercial market.

JoAnn Volk, MA
Senior Research Fellow and Project Director
Center on Health Insurance Reforms
Georgetown University Health Policy Institute

Ms. Volk opened with a reminder about the key issues addressed by the Affordable Care Act: access, adequacy of coverage, and affordability of coverage. She stressed that the provisions of the law related

to access to coverage are critically important to cancer patients. The law prevents discrimination based on health status, guarantees the issuance and renewal of coverage, prevents pre-existing condition exclusions, and prohibits rating based on health status.

The law also provides opportunities to revisit the adequacy of coverage, including adequacy of coverage for cancer survivors. The National Association of Insurance Commissioners is currently seeking to redefine the standards on network adequacy. In addition, there are opportunities to address essential health benefits. The Secretary of Health and Human Services has not defined the "periods" at which she will evaluate essential health benefits adequacy, but there is building pressure on her to consider some changes in benefits and network adequacy.

In addition to problems with the adequacy of coverage, there are issues associated with providing meaningful consumer choice. In the case of some exchanges, the existence of so many plan choices does not necessarily lead to optimal choices. Ms. Volk suggested some actions that might ensure more meaningful consumer choice, including efforts by the states to impose a "meaningful difference" standard that might limit the number of plans offered by issuers but encourage better plan offerings; greater transparency on the part of issuers regarding networks and formularies of their plans; development and use of decision-support tools to aid in choose plans; and availability of in-person assistance for enrollment.

Emily Mueller, MD
Child Health Evaluation and Research Unit
University of Michigan

Dr. Mueller provided an overview of pediatric cancer survivors and described their access to health insurance before and after enactment of the Affordable Care Act. There are several key provisions of the Affordable Care Act that have already helped survivors of childhood cancer and hold the promise of more help in the future. These include: 1) prohibition of discrimination on the basis of health status, 2) coverage up to age 26 years on a parent's insurance plan, 3) no annual or lifetime coverage limits, 4) Medicaid expansion (in states agreeing to expansion, and 5) stat-based exchanges that may permit easier enrollment for survivors of childhood cancer.

Research confirms that childhood cancer survivors minimize their need for health care, and as a result they may not see the importance of insurance coverage. Dr. Mueller recommended that we encourage research on the usefulness of incentives for young adult survivors of childhood cancer to purchase insurance, as the current penalty system may not be adequate to encourage enrollment. There is also a need for research on fundamental awareness of the Affordable Care Act enrollment options, as well as research on whether enrollment in an exchange plan provides access to survivorship care.

We already know that the preventive care benefits that are provided by the Affordable Care Act are not consistent with the guidelines for care developed and published by the Children's Oncology Group. As a

result, there is a need for some reforms of Affordable Care Act benefits to ensure that they are meaningful to childhood cancer survivors.

Sophie Stern, MPH
Deputy Director, Best Practices Institute
Enroll America

At the end of the enrollment period, 7.1 million individuals were enrolled in exchange plans, easily exceeding the Congressional Budget Office projection of 6 million released in February 2014. In addition, as of February 2014, there was a 5% enrollment growth in Medicaid, which represents additional enrollment of 3 million individuals.

Ms. Stern shared some findings from the Enroll America campaign. Enroll America, a coalition-based organization, had 5 million consumer engagements, conversations, texts, and emails during the enrollment period. Of that total, 635,000 were one-on-one encounters. What were some of the key findings? Uninsured consumers, and especially young African American and Latinos, need multiple touches to be persuaded to enroll. Those individuals are twice as likely to enroll if they receive those 3 to 4 touches and if they are consistently engaged throughout the enrollment period. The deadline was also highly motivating for individuals. This was expected, based on the enrollment experience in Massachusetts. Nonetheless, the surge in March 2014 was pretty impressive.

What were the factors that hurt enrollment? The principal factors were lack of funding for in-person assistance and local or state governments that were hostile to enrollment.

Targeted Therapies: Encouraging Regulatory and Treatment Strategies that Will Ensure Patient Access

Gail Vance, MD
Professor of Medical & Molecular Genetics
Director of Indiana Familiar Cancer Program
Indiana University

There is great opportunity for molecular diagnosis of cancer, but regulatory policy and reimbursement policy are not keeping pace with science and medicine. The College of American Pathologists (CAP) met with the Food and Drug Administration in the fall of 2011 to discuss the CAP plan for regulation of laboratory-developed tests (LDTs). The conversation between the parties was productive, and CAP is poised for the release of a guidance document on LDTs. However, the FDA guidance on LDTs represents just one of the uncertainties that pathologists are facing.

Pathologists are looking at the gap-filling process undertaken in 2013, and they are assessing the National Correct Coding Initiative that will effectively cut Medicare reimbursement for FISH testing by 50%. Dr. Vance explained how problematic such a reduction in reimbursement will be. To determine if a patient has the BCR/abl1 translocation, a minimum of two probes are necessary. However,

pathologists typically use three probes to ensure an accurate determination. To assess the HER2 amplification, at least two probes are necessary, but pathologists, per guideline, use more probes. The trend is to limit the number of probes that will be reimbursed, effectively ignoring professional guidelines and practice standards. If payment decisions are made by contractors who do not understand the testing, it is likely that reimbursement will be trimmed too much. Increased costs and decreased reimbursement are placing labs in an untenable position. The possible results are fewer labs and restricted access to necessary testing.

A possible solution is for regulatory agencies to work cooperatively to minimize the burdens on laboratories while ensuring proper oversight.

Andrew Fish, JD
Executive Director
AdvaMed DX

The key challenges that manufacturers confront in bringing diagnostics to the patient relate to the regulatory and payment challenges and not scientific or development obstacles.

To consider the regulatory issues, it is necessary to review the terms for thinking about diagnostic tests. The most fundamental characteristic of a diagnostic is its analytic validity. That is, does it test what it says it does and does it do it as well as it claims? The second issue to consider is a diagnostic test's clinical utility. Does the test influence a clinical decision? What is the value of the test in the course of treatment and to the health care system at large? Are decisions based on the diagnostic going to affect the patient?

When one looks at the diagnostics marketplace, one finds that there are many complex genetic and genomic tests that are being marketed as LDTs. The different pathways to the market seem to affect the way that patients think about their tests. FDA faces substantial challenges related to molecular tests, including the fundamental challenge of getting a handle on the sheer volume of molecular tests. In addition, FDA needs to get ahead of the advancing technologies of molecular tests.

AdvaMedDX and other stakeholders have been working very hard for a number of years to overhaul payment. The Medicare "doc fix" that was recently approved includes some important policy reforms, including changes in Medicare diagnostic reimbursement. Dr. Fish suggested that there will be some dislocations in terms of reimbursement for diagnostic tests as the new payment system is implemented. However, the system is overall an improvement because it ends the static nature of payment and also imposes provisions for review of payment levels and mandates transparency as to the process. It is the position of AdvaMedDX that these payment reforms will benefit patients and provide more predictability for the developers of tests. We have not had a reliable way to value diagnostics, and the new framework begins to address that shortcoming.

Dr. Fish also identified issues that are not amenable to government policy solutions, including the under-utilization and the over-utilization of molecular diagnostic tests.

Alberto Gutierrez, PhD
Director, Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Food and Drug Administration

The field of diagnostics is an exciting place to be. In the last 20 years, there has been a diagnostics revolution with development of promising new tests. However, we lack data to support some of the claims that are being made in connection with diagnostics. As good as the field is, it has spawned people making claims that they cannot back up. The fact that CMS is attempting to reform diagnostics payment is because many labs have been playing the system very effectively for aggressive payment.

Dr. Gutierrez acknowledged that regulation does carry a cost. He offered the example of a recent FDA advisory panel that evaluated a blood and stool test for colon cancer. The blood test was an epigenomics test, and the panel was divided on whether the test was worthy of approval. However, there are already tests of this sort being offered to physicians. How long can the decision of the FDA be sustained, when there are already tests on the market? In the situation where data are analyzed by experts, the strengths and weaknesses of the data and the product can be evaluated. That is a good thing for everyone. If the decision of the regulators is positive, the labeling will help the patient. Just putting the test out via the LDT pathway without transparency does not provide comparable benefits to patients.

In 2010, FDA said it would put out a proposal on LDTs. That guidance is still not published. Without the guidance, the agency has not been willing to move against tests that are perhaps LDTs. Dr. Gutierrez described an LDT that claims to use nipple aspirant to make a breast cancer diagnosis. He said that there are no data at all to support the use of this LDT for breast cancer diagnosis, yet FDA is unable to move against the company because of the lack of clear regulatory standards. What is the harm to the patient from use of this LDT? An immediate problem is that women will choose to rely on the nipple aspirant test instead of mammography may receive inaccurate diagnosis.

If FDA does not move to regulate LDTs, will some other entity do so? Will there be new CLIA regulations? Action by CMS? A public-private partnership for oversight of diagnostics?

John Cox, OD, FACP, FASCO
Texas Oncology
Editor, *Journal of Oncology Practice*

Dr. Cox stated that he had made a decision to no longer see drug reps in his office. He still receives glossy folders that describe drugs and their potential uses. However, the number of drug folders is not exceeded by the number of glossy folders for molecular diagnostics. Some are for multi-plex diagnostic

tests and others are for interpretive tools that give information about the prognosis or treatment of patients.

The tests are very bewildering to the practitioner. Colleagues are diving in and ordering the tests, but they are left with many questions about them. First is the question of what clinical benefit the test provides. There are also questions about the cost of the tests. Some may be expensive tests with substantial copayments, whereas in other cases an institution may agree to supply without payment. Providers may also be misled about regulatory approval, thinking that a test has FDA approval when it does not.

There is a concern that we may be misusing targeted therapies by failing to deliver them to all who could benefit and by using them in certain patients who will not benefit. The practicing physician also needs real-time clinical decision support tools to prevent the over-utilization and under-utilization of diagnostic tests and targeted therapies.

Bundles or Episodes of Care: Are These Payment Models Workable for Cancer Care?

Steve Spaulding
Senior Vice President of Enterprise Networks
Arkansas BlueCross BlueShield

The Arkansas payment reform effort began with a call from the Governor to the CEO of Arkansas BlueCross BlueShield asking if there was enough common ground to change the incentives in the health care system. In the Arkansas system, there is coordinated, multi-payer leadership, combined with episodes of care to reward coordinated, team-based care for all services.

Accountability is achieved by the naming of a provider quarterback or principal accountable provider (PAP) who is designated as accountable for all pre-specified services across the episode of care. Incentives are provided for high-quality, cost-efficient care. Such care is rewarded beyond current reimbursement, based on the PAP's average cost and total quality of care across each episode.

The episodes are not prospective bundled payments. Payments are still based on fee-for-service. If you as a patient are a member of an episode, you do not know it. Patients seek care and select providers as they do today. Providers submit claims as they do today. Payers reimburse for all services as they do today.

The system, says Spaulding, rewards high quality, efficient delivery of clinical care. There is an effort to promote fairness by considering patient access, provider economics, and changes required for improvement. The system acknowledges that poor performance is a reality and should not be rewarded. The payment system seeks to protect quality and access by setting a gain-sharing limit at a reasonable, achievable level. Thresholds will be sustained for a reasonable period to allow for adjustment and learning. There will also be an effort to reduce the rate of increase in the cost of care.

At the end of the day, those whose averages are not acceptable have to share 50% of the excess cost, and those between commendable and the gain-sharing limit get to share 50% of the savings.

John Sprandio, MD
Chief of Medical Oncology and Hematology
Consultants in Medical Oncology and Hematology

The patient-centered oncology medical home seeks to enhance quality by increasing the reliability of delivery. This is accomplished by focusing on the processes of care delivery and by incorporating high reliability principles. In the patient-centered medical home, costs are controlled by reducing unnecessary utilization and targeting potentially avoidable complications. The data from the practice must be transparent, accountable, and support rapid learning.

The Institute of Medicine defined quality as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge. Donald Berwick says that health care costs are driven by failures in delivery, and the patient-centered medical home seeks to avoid such failures.

We need to decrease cost and variation and need to move from a system that is organized around physicians to one that is organized around patients. That means applying to the care system the basic principles of care that are desired by patients and families. These principles are access, engagement, process standardization, coordination, and communication.

The value proposition is to achieve better care, better health, and lower cost. The oncology model is easily integrated with the primary care patient-centered medical home as defined by the American College of Physicians. The oncology patient-centered medical home is also easily combined with accountable care organizations and clinically integrated networks. Dr. Sprandio views this model as a transition to a bundled or budgeted payment system. For patients, there must be a "safety net of processes" in place.

Emily Oshima Lee, MA
Policy Analyst
Center for American Progress

Ms. Lee described an effort of 50 stakeholders to develop a bundled payment system. This effort grew out of a desire of Ezekiel Emanuel and colleagues at Center for American Progress to address the lack of payment reform in cancer care. Dr. Emanuel brought together physicians, oncologists, public and private payers, patient advocates, and others to consider bundled payments in cancer.

The group began its work by addressing some basic questions. Is payment reform for cancer desirable? If so, are bundles a possible payment system? And are bundles feasible? Is payment reform for cancer

desirable? The group said "yes." There are high costs in the cancer care system and varying levels of quality. The Institute of Medicine report on cancer care underscored that cancer care is fragmented and not patient-centered.

Why bundles? Bundles were seen as an opportunity to realign incentives. There are cancer care guidelines – from the National Comprehensive Cancer Network and the American Society of Clinical Oncology – that could be used in bundles. There are a number of different services provided to cancer patients, and it seems possible to organize those services into discrete bundles of care. It also seems that bundles can secure maximum participation, stretching from small practices to an integrated delivery system.

The goal of the group was to think through the outline of a bundled care model and to recommend implementation of the bundles. The basic but difficult goal was to design a model that is comprehensive but simple. To do this, it was necessary to answer a number of questions, including: Who is included in the bundle? How do you identify the patients in the bundle? What is included in the bundle? What is the length of the bundle? Which quality measures should define the bundle?

John O'Shea, MD, MPA, FACS
Research Fellow
Engelberg Center for Health Care Reform
Brookings Institution

Dr. O'Shea reviewed the work of MITRE/Brookings/Rand that is related to alternative payment models in oncology. That work included an environmental scan of oncology payment models that was undertaken by Brookings. As part of that work, Brookings conducted expert interviews, completed a literature review, and convened a technical expert panel to discuss alternative payment models. Rand took the responsibility for designing a payment model. The Centers for Medicare & Medicaid Services (CMS) will undertake a simulation of the model developed out of this project.

Dr. O'Shea identified the reasons to undertake payment reform. Cancer care is costly, likely hitting an overall cost of $157 billion by 2020. The current volume-based fee-for-service payments lead to uncoordinated, fragmented care delivery and inappropriate utilization. There is a belief that the transition from volume-based fee-for-service reimbursement to a system that focuses on payment for episodes of care will improve the overall quality of care and experience of the patient.

For all new payment models, there are some fundamental questions, including the level of comprehensive of care provided through the model and the degree to which the new model shifts away from fee-for-service. Other issues or questions include: 1) will the model be medical oncologist-centered, 2) what will be the role of other specialists, such as radiation and surgical oncologists, 3) what will be the site of service, 4) how will drugs be reimbursed, and 5) what quality measures will be utilized?

There is a range of alternative payment models that might be considered for cancer care, including the patient-centered oncology medical home (PCOMH), the oncology accountable care organization (ACO), a model that focuses on adherence to guidelines, and bundled (episodic) payments. Dr. O'Shea focused on the structure of bundled, or episodic, payments. He said that the bundled system moves payments that were previously reimbursed in the fee-for-service system into a more-global payment. However, some elements of care may still be reimbursed on a fee-for-service basis. The goal of the model is to encourage lower-cost options of equal effectiveness. The most expensive domain included in the bundles is chemotherapy and its administration.

Peter Yu, MD, FASCO
President-Elect, American Society of Clinical Oncology

According to the ASCO analysis, there are essentially two episodes associated with cancer care – human resources and technical resources. According to Dr. Yu, physicians make decisions about the deployment of human resources, but they do not have a valid way to control the use of technical resources. The ASCO episodes of care deal with human resources and exclude the cost of drugs. They also exclude the cost of imaging.

The ASCO model is built on one-month episodes of care, which are defined according to acuity of care. ASCO chose a month as the period of the episode because one can reasonably predict what happens to a patient in a month and can adjust payment at the end of the month. The one-month payment and episode, said Dr. Yu, allows the oncologist flexibility to provide care the best possible way.

In the model, 58 billing codes, including chemotherapy administration codes, are reduced to 11 codes. The codes include the new patient visit, several codes for chemotherapy administration, codes for monitoring patients who are not receiving some sort of chemotherapy, and some codes for transitions of care. There is also a provision for payment for enrolling patients in clinical trials.

The system is built on a value-based adjustment. This adjustment will be based on the use of chemotherapy pathways. ASCO does not have its own clinical pathways product but will recommend pathways that might be used. ASCO wants to assure that efficacy, toxicities, and cost are considered in the determination of the most cost-effective treatment. However, the cost of the drug should NOT be the most important factor in deciding on treatment.

Thursday, April 10, 2014

Balancing Risk and Benefit in Cancer Drugs

Ann Farrell, MD
Director, Division of Oncology Products

Office of Hematology and Oncology Products
Food and Drug Administration

Dr. Farrell provided an overview of decisions related to the removal from the market of Iclusig (ponatinib). She began with the information that when the Food and Drug Administration (FDA) removes a drug from the market, it is not done lightly. The agency looks at all of the available safety information, which may include data from the sponsor as well as hypotheses from the sponsor about why a safety problem is occurring. The agency also looks at its own hypotheses for why a safety problem is occurring. All hypotheses are tested before the agency takes steps to remove a drug from the market.

When Iclusig was approved, the agency believed that all adverse event rates were at an acceptable rate. This included thromboembolism. However, seven months after approval, the rate of adverse events had almost tripled. When the adverse event rate for thromboembolism went from 8 to 10 percent to 27 to 30 percent, the agency determined that was no longer an acceptable risk-benefit equation.

The agency did analyses of the patients who were having adverse events, and older patients with underlying hypertension who had adverse events were less alarming than 22-year-olds who had strokes or clots in arteries. The reports of adverse events in younger patients raised a much more serious bar. Whenever a serious safety finding of this sort occurs, the agency goes back to the original application – all the way back to in vitro data – to try to understand what is happening.

In the case of Iclusig, the agency was presented with the challenge of getting out the message to patients about providers about the risks associated with Iclusig. The agency needed to supply health professionals and patients the information necessary to decide benefit and risk. Although it is relatively easy to get information to physicians via a "Dear Doctor" communication, it is not as easy to get the message about risk to patients. In the case of Iclusig, FDA was concerned about the seriousness of the issue and the fact the agency did not have a complete handle on the data. In order to ensure that it was reaching all affected parties, FDA determined to send out Dear Health Care Provider notices that announced a temporary withdrawal of the product from the market. That approach got the attention of health care professionals and patients.

Beth Galliart
Co-Founder, Iclusig Patient Group

Ms. Galliart said that although patients appreciated that FDA was caught between a rock and a hard place with assessing risk and benefit of ponatinib, the patients also thought that FDA had defined ponatinib adverse events in an unnecessarily broad manner. There were also questions from patients about whether adverse events were in fact related to administration of the drug. Ms. Galliart identified CML patients with clotting issues who had adverse events, but she asked if those adverse events were drug-related or just related to underlying and pre-existing disease. Ms. Galliart said that she developed

high blood pressure on the drug, but she considered that a minimal adverse event in light of the fact that the drug was saving her life.

Ms. Galliart suggested that one of the issues with this drug might be that it is a very potent drug. The 45 mg dose of the drug was probably aggressive, said Ms. Gailliart. The question now is whether the 14mg dose now prescribed will be effective.

Ms. Gailliart said that a key lesson for FDA was to have a very strong transition plan if a drug is withdrawn from the market, even if only temporarily. In the case of Iclusig, patients who intended to pick up a drug one morning found that they could not receive it. This created panic and in some cases it took weeks to resolve access to the drug. For those with CML in the chronic phase, a three-week wait is acceptable. However, some cancers "do not play as nicely." The experience with Iclusig offered significant lessons, including that the agency must take steps to prevent the panic and fear when it makes an announcement related to the adverse events related to a drug that also provides significant benefits.

Getting New Medicines to Patients Faster: Innovative Approaches

Wendy K.D. Selig, MS
President & Chief Executive Officer
Melanoma Research Alliance

Melanoma is leading the way, according to Ms. Selig, in the co-development of drugs and diagnostics. In addition to leading in drug-diagnostic co-development, melanoma is a solid case study because research is at the crossroads of molecular biology and immunology and five new drug approvals since 2011 have both changed the landscape for patients and paved the way for additional new drug development.

The recent clinical advances in melanoma include ipilimumab, an antibody against an immune checkpoint; vemurafenib and debrafenib, for BRAF V600E patients; trametinib for BRAF V600E/K patients; the first combination therapy of debfrafenib and trametinib; and more than 100 drugs in the pipeline and 300 clinical trials underway.

MRA has a wide range of grant mechanisms, including young investigator awards, pilot awards, established investigator awards, team science awards, and academic-industry partnership awards. The focus of all of the grant mechanisms is translational research, to be accomplished by individuals and teams. It is difficult for a small nonprofit like MRA to support clinical trials, but the organization has developed partnerships that permit it to be engaged in clinical trials.

The MRA Scientific Retreat is a signature component of the organization's research program. MRA requires all researchers funded by the organization to attend the science retreat, which is not open to the public or press. In addition to MRA-funded investigators, MRA has recently invited FDA, NCI, and

industry partners to the Scientific Retreat. The retreat engages the global leaders in melanoma research and includes as many as 300 participants in interactive discussions of data, trends, and policy issues. There are also industry roundtable breakfasts as part of the retreat. At recent retreats, participants have identified the need for policy solutions to encourage more collaboration among companies. Investigators have also suggested the need for more guidance from FDA on adjuvant trials.

Peter Adamson, MD
Chair, Children's Oncology Group
Chief, Division of Clinical Pharmacology and Therapeutics
The Children's Hospital of Philadelphia

Whereas the private sector funds 60% of pre-clinical research on adult cancers, the pediatric research sector is fully dependent on the public sector. Pediatric cancer researchers face challenges that are also faced by researchers focused on other rare cancers. Access to drugs for research purposes is a problem in the pediatric sector and has been a challenge for pediatric researchers historically. Pediatric researchers have no problems with accrual, as patients and families are willing to enter trials. It is rather remarkable to have NO accrual problems, but it is troubling to have almost no access to drugs to do trials.

Pediatric researchers have always conducted trials with the goal of administrative efficiency. Typically, we decline to do a single disease trial. Instead, we use different strata for different diseases. In a randomized phase II trial, the approach is to randomize against different targets of the same disease. This is a more efficient way to answer questions about the biology of the disease and the potential efficacy of a drug. However, such an approach necessitates having companies working together. Generally, companies are reluctant to go head-to-head on anything.

The concept of evaluating different drugs in a single trial is slowing gaining traction. The easiest approach is when a single company has drugs against two different targets. The more difficult situation is involving two different companies in the same trial, but Dr. Adamson and colleagues are accomplishing that. The National Cancer Institute has also played a positive role in persuading companies to work together on trials.

The fact that Europe requires a comprehensive drug development plan on the pediatric side can have the perverse impact of slowing pediatric drug development planning in the United States. US regulators have more experience with incentives and how to use them without having them adversely affect development, and European colleagues are less experienced and need to fine-tune their implementation of pediatric development incentives.

Bob Erwin
Marti Nelson Cancer Foundation

FDA has done an impressive job of clarifying the standards for expanded access, for options for the individual to relatively large programs. Less than a year ago, FDA developed a frequently asked questions document that provides additional guidance to industry and others regarding expanded access. FDA is not the problem when it comes to expanded access, despite the criticism of the Wall Street Journal and some industry players. The responses of industry to expanded access requests are widely divergent.

Mr. Erwin suggested that we give more thought to ways to use existing regulatory and policy options to encourage expanded access. He said that rationally designed expanded access program can provider answer to the real world use of drugs. For example, the enrollment of large numbers of patients in expanded access programs provided Novartis valuable pre-approval information about Gleevec. That example can be replicated. He also suggested that breakthrough therapy designation be accompanied by a requirement for a company to design an expanded access program. If an agent is good enough for breakthrough therapy designation, isn't it also good enough for expanded access?

Mr. Erwin suggested that an Institute of Medicine study on expanded access might be in order. Perhaps such a study could leave to guidance to small and large pharma about expanded access programs, whether the drugs in question or small molecules or biologics.

Angela DeMichele, MD, MSCE
Jill and Alan Miller Associate Professor in Breast Cancer Excellence
Abramson Cancer Center
University of Pennsylvania

The current path of oncology drug developed is unsustainable, as new oncology drugs take 10 to 15 years to reach patients. In addition, the typical price tag for a new cancer drug is $2 billion. There has until recently been an absence of innovation in trial design and data collection tools. It is also important to realize that cancer is a subset of diseases and that a blockbuster approach to drug development will not work.

The critical inquiry is how we can test drugs within a disease when we know that the disease is not a single disease. The challenge is testing subsets of diseases in a single "machine."

The I-SPY 2 Trial is a randomized, phase II trial to rapidly assess the benefit of targeted therapies in the neoadjuvant setting. Drugs move in and out of the trial as they are evaluated, and there is no endpoint in terms of the number of patients enrolled. There are five critical components of the I-SPY trial: 1) neoadjuvant setting, 2) molecular and imaging biomarker guidance, 3) multiple drugs tested simultaneously, 4) common platform for sharing data, and 5) adaptive trial design.

The traditional approach to breast cancer treatment is surgery, chemotherapy and/or other therapy, and a long follow-up period. The metastatic approach has a 2- to 4-year knowledge turn, and the adjuvant approach has a 6- to 9-year knowledge turn. I-SPY 2 is a standing trial with one protocol and a

master IND. This permits the seamless addition and release of investigational agents. When an investigational agent is added to or released from the trial, only the appendices require updating. A trial structured in this way permits multiple drugs to be tested simultaneously. In the I-SPY 2 trial, there are drugs that have graduated from the trial, agents that are active, and many that are in the pipeline or queue for the trial.

Finally, a critical element of I-SPY 2 is adaptive trial design. The advantages of adaptive trail design are that investigators can learn if the drug works better or worse than anticipated, as the trial progresses. Investigators can act early to drop drugs quickly if they are ineffective or harmful and graduate agents sooner if they are clearly beneficial. With adaptive trial design, phase 2 conclusions will be more accurate and there will be better treatment of patients in the trial. Typically, follow-on Phase 3 trials can be smaller.

The major accomplishments of I-SPY 2 are that it has demonstrated that endpoints work better by subtype, recruited multiple pharma companies to work together in the same trial, developed an infrastructure for adaptive learning and to distribute credit, and has graduated two agents for future development. In addition, FDA has been encouraged to release accelerated approval guidance for neoadjuvant breast cancer agents. The next step is the I-SPY 3 international confirmatory trial.

Gregory Reaman, MD
Office of Hematology and Oncology Products
Food and Drug Administration

Dr. Reaman reviewed the FDA expedited programs, including fast track, breakthrough therapy designation, priority review, and accelerated approval and then provided a detailed overview of the breakthrough therapy designation.

The breakthrough therapy designation was authorized by the FDA Safety and Innovation Act, or FDASIA. According to the terms of the statute, a breakthrough therapy is a drug which is intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease and preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoint, such as substantial treatment effects in early clinical development. A breakthrough designation brings all of the benefits of fast track designation, including frequent interactions with the review team, eligibility for priority review, and rolling review of the NDA or BLA. In addition, those sponsors with a breakthrough designation receive intensive guidance on efficient drug development and an organization commitment to efficient review. This includes the involvement of senior managers and experienced reviewers and the assignment of a cross-disciplinary project lead.

At the time Dr. Reaman spoke, the Office of Hematology and Oncology Products (OHOP) had received almost one-half of all breakthrough therapy requests (53, or 47%, of 124 total requests). Of the 58 breakthrough therapy applications submitted to OHOP, there have been decisions on 53. Breakthrough

therapy designation has been granted in 14 (25%) of cases, denied in 31 (59%), and withdrawn in 8 (15%).

Dr. Reaman identified the opportunities and challenges associated with implementation of breakthrough therapy designation. The opportunities include the change to optimize early communication between FDA and the sponsor and the ability to improve communication within FDA review teams (clinical, clinical pharmacology, and inspections, among others). The challenges include the resource demands associated with breakthrough therapy designation and management, defining the basis for rescinding the status, fostering the FDA and industry cultural change necessary to maximize breakthrough status, and the fact that manufacturing timelines can be a bottleneck.

The old paradigm of a separate clinical development program for every new drug is expensive and inefficient. FDA is embracing and encouraging innovative trial designs that will accelerated the availability of highly effective anti-cancer therapies. For example, the agency is a collaborating partner in Master Protocol approaches. There are two major new trial designs – umbrella trials and basket trials. In the genomic era, said Dr. Reaman, the single drug/single test/all-come clinical trial model will not be sustainable. FDA will be an active partner with other key stakeholders to facilitate the development of novel, biomarker-drive trials of targeted therapies within network of clinical trialists. Both basket trials and umbrella trials will play critical roles in the new clinical trial ecosystem.