NATIONAL COALITION FOR CANCER SURVIVORSHIP
CANCER POLICY ROUNDTABLE
APRIL 9-10, 2014

Wednesday, April 9

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

Tanisha Carino, PhD
Executive Vice President
Avalere Health

Ms. Carino offered an update on Affordable Care Act enrollment, citing the Obama Administration announcement that 7.1 million people have enrolled in exchange plans. The number may not be final, because it does not include those who are in line to be enrolled but whose enrollment process is not yet complete. As of the date of this Administration announcement, there were not many details about the demographics of the enrollees.

The enrollment figures are a bit surprising, based on the early experience with the exchanges and especially the shortcomings of the federally facilitated exchange. The early enrollees were skewing to older enrollees, but there is an expectation that the later enrollees will be younger. Whether enrollees chose plans through state exchanges or the federally facilitated exchange, silver and bronze plans were there most frequent choices.

Ms. Carino presented data that underscored that there is significant variation across the states in terms of premiums, with premiums in some states significantly higher than the average federally facilitated exchange premium.

Exchange plan deductibles have also 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. This decision to narrow networks has resulted in the exclusion of certain leading cancer centers. Issuers still seem to be adjusting their networks, which means that some problems with narrow networks could be addressed. 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 provided an overview of 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 – all important protections for cancer patients.

She also stressed the provisions of the law that address adequacy of coverage and discussed the ways in which plans in 2014 may fall short for cancer patients. There are possible issues for cancer patients related to network adequacy, access to clinical trials, and the essential health benefits definition.

Ms. Volk stressed that the law provides opportunities to revisit the adequacy of coverage. 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 influenced the quality of plan choice. More choices do not necessarily lead to optimal choices. Ms. Volk recommended 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. Experts from Massachusetts advised that two hours of in-person assistance may be necessary to ensure that a consumer makes a wise enrollment decision.

Emily Mueller, MD
Child Health Evaluation and Research Unit

University of Michigan

Dr. Mueller described pediatric cancer survivors and their access to health insurance before and after enactment of the Affordable Care Act.

There are currently 320,000 pediatric cancer survivors in the United States. Two-thirds of them have a chronic medical condition, and one-third of them have serious or life-threatening conditions. Much of the information about pediatric cancer survivors comes from the Childhood Cancer Survivor Study, coordinated by researchers at St. Jude. The study permits tracking of more than 20,000 childhood cancer survivors in 27 participating sites across the country, who are compared to a 4,000-person control sibling cohort.

Half of adult survivors of childhood cancer had a cancer-related health care visit in the last two years. However, those who are at greatest risk are least likely to get care. Those who do not receive care include cancer survivors who are black, of older age, and uninsured.

In 2005, before enactment of the Affordable Care Act, survivors of pediatric cancer who are under age 18 had insurance rates comparable to those of their siblings. Over the age of 18, the rate of insurance for survivors of childhood cancer goes down. Among survivors of childhood cancer, 29% said they had difficulty receiving insurance. They reported exclusions and restrictions, and extra premium charges related to their cancer diagnosis.

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) state-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. In addition to preventive benefit gaps, there are likely

shortcomings in essential health benefits that will prevent childhood cancer patients from receiving the care they need for late and long-term effects of cancer and cancer treatment.

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

Ms. Stern said that, with the open enrollment period ended, there is now an opportunity to assess the lessons learned about enrollment. Additional lessons will come as people start to use their coverage.

At the end of the enrollment period, 7.1 million individuals were enrolled in exchange plans. The Congressional Budget Office in February 2014 had modified its projected enrollment to 6 million. That goal was easily met and exceeded.

There was a 5% enrollment growth in Medicaid, which represents additional enrollment of 3 million individuals. This total reflects Medicaid enrollment to February, and there is an expectation that the numbers will go up with the final month of enrollment is considered.

How did we do it? 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. They need to be reached at an enrollment event and then 3 or 4 subsequent times. 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.

There remains a lack of awareness about plan affordability and financial help. Consumers who would be eligible for premium support or cost-sharing assistance were completely unaware of that assistance.

Although there was an expectation that in-person assistance would be critically important, it was still surprising that those who had in-person assistance were twice as likely to enroll as those who attempted to enroll online without assistance. 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.

What is next? Although the open enrollment period is closed, there is much more work to be done. Medicaid enrollment is open year-round, so there can be a focus on that effort. There must be an educational effort to be sure that people understand that they need to report income to the exchanges. There are also important advocacy opportunities to make the consumer experience better.

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 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 movement to limit the number of probes reimbursed, often at odds with practice guidelines or practice standards, may adversely affect quality of cancer care.

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

Dr. Fish, of AdvaMed DX, the association within the AdvaMed association that represents manufacturers of diagnostic tests, stated that the key challenges that manufacturers confront in bringing diagnostics to the patient relate to regulatory and payment challenges.

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?

Currently, it is the role of FDA to make decisions regarding analytic and clinical utility. However, as Dr. Vance noted, FDA has not extended its authority to LDTs. There has been much discussion around what FDA should do with regard to LDTs. AdvaMed takes the position that all tests have some potential for impact on patients when put into use and therefore require some review.

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.

Dr. Fish shifted his focus from FDA regulation of molecular tests to payment for diagnostics. He noted that when he has spoken to previous Roundtable meetings, he has focused on the fact that Medicare payment for clinical laboratory services has not changed since the 1994 clinical laboratory fee schedule. The Institute of Medicine (IOM) concluded in 2000, more than a decade ago, that the payment system was out of date at the time the IOM reported.

Since the IOM report, the situation for reimbursement of molecular diagnostics has gotten worse. AdvaMedDX and other stakeholders have been working very hard for a number of years to overhaul payment. Fortunately, the Medicare "doc fix" that was recently approved includes some important policy reforms, including changes in Medicare diagnostic reimbursement.

A major change was the replacement of the fee schedule under which CMS and its contractors make payments. In 2017, labs will have to report their private payment rates. Medicare will collect data and set Medicare payment at the median of those payments. Medicare will set the median rate for each test, and those rates will remain in place for three years. After that period, there will be an updating. In the short-term, payment rates for most tests will go down. It still remains to be seen how deep the reductions in payment will be. However, the fee schedule will not be static.

There are other key provisions of the law. New tests for which there is currently no private payment will be set according to the current system but re-priced after three years.

In addition, an expert advisory panel on molecular diagnostics will be established at the Centers for Medicare & Medicaid Services (CMS). This responds to the long-standing concern about the inability of CMS to set payment rates.

There are also provisions the require transparency, which means that CMS must explain how it got to a payment decision.

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. It is incredible the number of tests that have been developed and it is an exciting field to be part of. 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 noted that others on the panel have already identified the issues that go along with a dual regulatory pathway for diagnostics. For more than 20 years, diagnostics have been reviewed according to the "commercially distributed test" pathway or according to an LDT pathway. In the last two decades, the number of tests reviewed and approved by FDA has increased dramatically. However, the number of LDTs has also increased.

There is no "research phase" with an LDT. Analytic validity is established by post hoc sampling, and there is no clinical validation, or validation that a test can be used effectively in a clinical setting. The research phase for an LDT is a decision by the lab developer that the test is ready to use.

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 in circulation. 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?

In 2011, FDA released a draft guidance document on development of companion diagnostics. That guidance does not fully reflect the development of mult-plex tests. That guidance will likely be delayed until a final decision is reached on the LDT guidance.

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

Dr. Cox introduced himself as a practicing medical oncologist in Dallas. His other frame of reference for the molecular diagnostics issues at hand is as a consulting oncologist for a payer in Texas.

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 now 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.

The horizon for the profession is very exciting, with an ability to target therapies. However, according to Dr. Cox, 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.

Dr. Cox also suggested that clinical trials need to be redesigned to ensure that doctors are identifying patients properly by molecular defect and then properly targeting their therapies.

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.

The fundamental goal is coordinated, team-based care for all services related to a specific condition.

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 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.

However, there was a change to payment methodology. We said to providers, "This is the way you will be paid if you are part of our network." Spaulding said that the targets were set conservatively, and as a result no providers opted out of the networks. Under the program, there is a review of claims from the performance period to identify a principal accountable provider (PAP) for each episode. Payers calculate average cost per episode for each PAP. Everyone CAN get incentive payments.

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.

Spaulding said that the numbers are still too new to know if the new payment system is working. Each payer assesses the historic provider costs and seeks to compress the rates of payment. There is an effort to compress the variation by creating incentives. There is an expectation that the compression will occur at the end of the first year.

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.

Providers will be able to look at costs and see what is causing them problems.

What does this mean for principal accountable providers (PAPs)? There can be many winners. In fact, the system aims to have as many providers as possible gain. The risk/reward levels are set to make this a reality. Average costs are what count. Episode costs are risk-adjusted to ensure fairness, and outliers are removed.

John Sprandio, MD
Chief of Medical Oncology and Hematology
Consultants in Medical Oncology and Hematology
Dr. Sprandio explained that the patient-centered oncology medical home seeks to provide high value care, and he defined value as quality/cost.

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.

Dr. Sprandio described cancer care as a microcosm of the US health care system. It is system that relies on high technology and expensive drugs and is plagued by fragmented care. Each year, 1.6 million Americans are diagnosed with cancer. Cancer care is a low-volume, high-cost situation. As an industry, cancer care is going through a transformational change. It is not smooth or linear. New value propositions are being demanded – by patients, payers, and providers – to increase the value of care that is provided.

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 as desired by patients and families. These principles are access, engagement, process standardization, coordination, and communication. There also needs to be an alignment of provider compensation with principles of quality and desired outcomes. There is in addition the pressing need to address out-of-pocket expenses.

Dr. Sprandio is attempting to implement these principles for reform through the oncology patient-centered medical home model, which is an integrated delivery model for hematology and oncology. The oncology model is built on the patient-centered medical home principles of access, engagement, coordination, communication, and accountability.

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 fundamental conclusion of the group was that bundled payments for cancer care are doable, but the payments will not bundle themselves.

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.

The global payment for the bundle may be prospectively or retrospectively paid, usually at a discounted rate. The number of services included in the bundle is variable, and the provider risk may also be variable. Alternative payment models in oncology raise two fundamental questions: the degree to which payments will be bundled across providers and the extent to which physician payments will be case-based. Dr. O'Shea indicated that, even in a bundled payment system, it is possible that some payments to physicians will remain fee-for-service payments.

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

Dr. Yu referenced the failure of Congress to move the sustainable growth rate bill, which would have initiated a process of specialty payment reform, as a signal that physicians must take responsibility for payment reform.

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 in 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.

Another component of the ASCO payment reform effort relates to ensuring care of high quality. It has already been said by previous speakers, but it is worth repeating that there must be an effort to ensure quality of care.

According to Dr. Yu, ASCO is also focused on other efforts to assess and influence the quality of care. He generally described the work of ASCO to define a value-based framework that will determine the value of a cancer drug to the patient. ASCO is also considering the cost of imaging and its value. Finally, ASCO is involved in efforts that relate to appropriate pricing policies for drugs.

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 temporary 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.

The Office of Hematology and Oncology Products believed that Iclusig was a drug with very important clinical benefits. The office wants drugs out as fast as possible so that patients may enjoy their benefits. However, the office also realizes that the adverse event rate will increase when a product is on the market. The key question is whether the increase represents an acceptable rate of adverse events.

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.

Still, a critical issue remained: How could ponatinib be made safer? The problems with ponatinib are in the arteries and not in the veins, and those problems are quite difficult to treat.

Even as the investigation of the safety issues continued, FDA and the sponsor engaged in discussions about how to provide access to patients who really need the drug. The decision was to provide single patient access through the compassionate use process. Ariad determined how to respond to requests and send out supply, and the company ensured that there would be 24/7 coverage for emergency INDs.

Beth Galliart
Co-Founder, Iclusig Patient Group

Ms. Galliart expressed her gratitude in being included on the panel to provide the patient perspective on ponatinib. She said that although patients appreciated that FDA was caught between a rock and a hard place with assessing risk and benefit of ponatinib, they also thought that FDA had defined ponatinib adverse events in an unnecessarily broad manner.

It was not clear to patient advocates if FDA had achieved the right balance of risk and benefit or if the agency understood that patients saw the choice as death without the treatment versus the adverse event. 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 is whether the 15 mg 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

Ms. Selig shared the history of the Melanoma Research Alliance (MRA), which has a mission of accelerating the pace of scientific discovery and clinical translation to eliminate suffering and death due to melanoma. The MRA has awarded $51 million in research grants to date, with an additional $8 million in grants due in 2014.

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. Through an academic-industry partnership strategy, MRA receives matching funds from industrial partners that might also collaborate scientifically in research projects, financially supports academic researchers who are the primary drivers of research projects, and selects projects and provides programmatic oversight of them.

MRA currently has eight academic-industry partnerships, partnerships with Stand Up to Cancer, and co-funding collaborations with additional foundations and professional societies.

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 regarding 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.

MRA has also been engaged in conversations with FDA and industry to encourage expanded access, and the results have resulted in expanded access to at least one PD-1 drug.

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.

The Best Pharmaceuticals for Children Act and the European pediatric investigation plans have moved the needle on when industry beings to talk to pediatric researchers about drug development, but the European regulatory requirements have had some unintended adverse consequences.

Years ago, said Dr. Adamson, we looked at ways to conduct adult phase I trials in order to improve the timeline of studies. A critical goal was to determine the recommended dose in order to get to the phase II trial. 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 also accomplishing that.

The National Cancer Institute has also played a positive role in persuading companies to work together on trials. Slowly, the concerns of companies about working together are lessening.

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

Mr. Erwin began his comments with an observation about previous presentations about therapeutic development, which he said provide great reason for enthusiasm. However, he said that there are also lingering frustrations with the pace of development. He suggested that more should be done to shorten the timeline for access to new drugs. For example, the development of diagnostics has been frustratingly slow.

The failure to match the right therapy to the right patient must be addressed. We all – patients, industry, regulators – need to realize that every patient counts and every day counts. We have an opportunity to use drugs that already exist in new ways.

Mr. Erwin said that there must be clarity of regulatory standards and processes. Clarity is more important than the specific points that are clear. Without clarity, corporations will not make investment decisions related to cancer therapeutic development.

FDA has done an impressive job of clarifying the standards for expanded access, from 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.

The recent case of parents using social media to campaign for their child's access to an anti-infective was an important wake-up call to us about strategies and options for providing patients access to unapproved therapies. Use of the social media has brought about a dynamic change in expanded access efforts. In the opinion of Mr. Erwin, it is problematic to leave it to social media to decide who will gain access to unapproved therapies. In the case of the anti-infective drug, the limitations were not regulatory.

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 provide answers related 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.

Audience members raised the issue of cancer patients who are not eligible for any trials and who have limited treatment options. There was a plea for special attention to those patients and how they might gain expanded access.

FDA's Dr. Reaman commented that initiation of expanded access protocols early can be a good idea. With some planning, it is possible to achieve balance in expanded access between over-regulation and a complete lack of oversight. Dr. Reaman argued for some control and for expanded access NOT to be left to social media decision-making.

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

Dr. DeMichele said that she was speaking on behalf of her colleagues at I-SPY. She opened with the observation that the I-SPY trial is designed to address many of the issues that had already been raised by panelists.

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.

If we move chemotherapy to the pre-surgical setting, then do surgery, and then follow the patient, there is a one-year knowledge turn. The use of a surrogate endpoint is not perfect and varies with the biology of the tumor. However, using a surrogate gives investigators a handle on activity and permits the identification of active agents.

In the I-SPY trial, a screening MRI, blood draw, and biopsy permit stratifying up front. Lower risk patients can be screened out and remaining patients are randomized to standard chemotherapy or standard chemotherapy plus investigational agents.

There are also early, inter-regimen, and post-chemotherapy MRI and blood draw before surgery. These efforts are critical to profiling every tumor and determining who is responding to the investigational agents. The development of biomarkers hand-in-hand with drugs is a critical element of the I-SPY trial.

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.

The I-SPY 2 trial also includes a common platform for data sharing.

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.

What are the benefits of breakthrough designation? 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. Umbrella trials test the impact of different drugs on different mutations in a single type of cancer. Some examples are BATTLE, I-SPY 2, and the SWOG Squamous Lung Master trial. Basket trials test the effect of a single drug on a single pathway or mutation in a variety of cancer types. Examples are the imatinib basket trial, the BRAF+ trial, and the NCI MATCH trial.

Dr. Reaman reviewed the advantages and challenges of each type of trial. Umbrella trials permit comprehensive study of a single disease. There can be a uniform multiplex screening platform with analytic validation approved by CDRH. There is a low screen failure rate, and randomization within a sub-study provides prognostic information of a given biomarker-defined subgroup. An umbrella trial can leverage the network of research centers to identify rare subsets that would not be feasible to study in a single institution.

The challenges of umbrella trials include the fact that there is overlap in biomarker positivity-assignment based on prevalence and not necessarily oncogenic driver. We also have limited knowledge of the functional significance of some aberrations. Drugs may be entered into umbrella trials at various stages of development, and that may result in limited data to enter a registrational trial. Finally, umbrella trials are big and logistically challenging.

Basket trials can function as a series of single arm studies and can rapidly screen for agents with large effect sizes and those with breakthrough impact. These trials are more appealing for home runs than for singles and doubles. These trials are especially appealing for drugs with established safety profiles and demonstrated efficacy in other diseases. In basket trials, it is necessary to interpret the response rate in the context of the disease and other available therapies. In such trials, there may be limited data on prognostic information about a given biomarker subset, limited toxicity data, and limited information on biomarker negatives. Also, although local testing provides flexibility, it may also raise questions about analytic validity.

In the future, said Dr. Reaman, the single drug/single test/all-come clinical trial model will not be sustainable in a genomic era. 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.