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Economic, Health Delivery, and Other Factors Affecting Adherence with Cancer Treatment

Therese Mulvey, M.D.
Physician-in-Chief
Medical Oncologist
Southeast Health System
New Bedford, Massachusetts

Ann H. Partridge, M.D., M.P.H.
Associate Professor of Medicine, Harvard Medical School
Founder and Director, Program for Young Women with Breast Cancer
Dana-Farber Cancer Institute

Dr. Mulvey reviewed the potential benefits of oral chemotherapy agents, including ease of administration, ability to reduce time in the clinic, and potential to spare healthy tissue. However, said Dr. Mulvey, there are significant challenges associated with administering the right dose of oral cancer drug at the right time on exactly the right schedule. There is also the matter of patient responsibility for management of the side effects of oral chemotherapy. Of serious concern to Dr. Mulvey are the financial toxicities associated with oral cancer drugs. Patients are confronting the aggressive use of utilization tools for oral cancer drugs, including prior authorization requirements and disease management programs. The greatest limit on utilization is the significant cost-sharing that may accompany some oral cancer therapies.

Dr. Partridge reviewed a number of studies on adherence to oral cancer therapies. She said that, contrary to assumptions that cancer patients would have high rates of adherence because of the seriousness of their condition and benefits of many drugs, there are serious challenges to adherence to therapy by cancer patients. Poor adherence to tamoxifen has been particularly surprising to oncologists, because use of tamoxifen is clearly associated with better survival. In adjuvant breast cancer trials, hormonal therapy was prematurely discontinued in 23-28% of participants. In prevention trials, tamoxifen was prematurely discontinued by 20 to 46% of participants.
Improving adherence requires predicting and identifying non-adherence. Unfortunately, healthcare providers are not good at this task, and the literature is inconsistent and primarily addresses sociodemographic and medical factors. This is a problem because behavioral determinants are probably most important in predicting non-adherence. In the future, predicting non-adherence and improving adherence will require knowing the signs and predictors of poor adherence and utilizing a multi-pronged approach for improving adherence that focuses on behavioral and psychosocial elements of adherence.

“Do-Less” Recommendations: Do They Suggest We are Over-testing and Over-treating?

Barnett Kramer, M.D., M.P.H.
Director
Division of Cancer Prevention
National Cancer Institute

Lowell Schnipper, M.D.
Clinical Director
Beth Israel Deaconess Medical Center Cancer Center

Peter Bach, M.D.
Director
Center for Health Policy and Outcomes
Memorial Sloan-Kettering Cancer Center

Regina Vidaver, Ph.D.
Executive Director
National Lung Cancer Partnership

Dr. Kramer described physicians in the United States as poorly trained for medical uncertainty, a fact that has led to the systematic overuse in clinical practice of tests, procedures, and treatments. Dr. Kramer then discussed the possibility for overdiagnosis of cancer. There are two requirements for overdiagnosis: 1) existence of a silent disease reservoir and 2) activities, particularly screening, that lead to its detection. He analyzed the possibility for overdiagnosis of prostate, thyroid, and breast cancer. The screening technologies for these cancers are resulting in diagnosis of disease that is “in the body of the iceberg.” As a result, we are diagnosing many more new cases of prostate cancer and yet have seen no corresponding increase in deaths from this cancer, which suggests an overdiagnosis of prostate cancer. He also suggested overdiagnosis of melanoma, with the rapid rise in incidence rate driven by early-stage cases.

Dr. Kramer ended with the observation that we may be close to the day of reckoning in terms of screening that contributes to overdiagnosis.

Dr. Schnipper reviewed a wide range of activities that are underway at the American Society of Clinical Oncology (ASCO) to address the crisis in health care spending. The work has been undertaken by a task force charged with considering ways to bend the cancer care cost curve and has been coordinated with the Choosing Wisely campaign of the American Board of Internal Medicine (ABIM). The five ASCO
recommendations that are incorporated into the Choosing Wisely campaign are: 1) do not give chemotherapy to patients with poor performance status, 2) do not provide PET, CT, or bone scans to breast cancer patients with low risk of metastases, 3) do not provide PET, CT, or bone scans to prostate cancer patients with low risk of metastases, 4) do not use advanced imaging tests and routine blood tests for biomarkers to screen for cancer recurrences in individuals who have completed curative treatment for breast cancer and who have no symptoms of recurrence, and 5) limit use of white blood cell stimulating factors.

Dr. Schnipper reported that oncologists have said that the Choosing Wisely guidelines are useful. Reporters have focused on the end-of-life recommendations, payers have been quietly supportive, and biotechnology companies have placed general inquiries about the impact of the recommendations. According to Dr. Schnipper, Choosing Wisely is just a start and the goal must be a redesign of the system of care to one that emphasizes quality of care and value.

Dr. Bach reviewed the results of three major lung cancer screening trials and discussed whether lung cancer screening can and should be implemented. In the National Lung Screening Trial (NLST), there was an absolute decrease in lung cancer death of 0.33%, or about 3 lung cancer deaths avoided per 1,000 screened. There was no statistical difference in deaths from other causes. In DANTE and the Danish Lung Cancer Screening Trial (DLCST) there were no differences in lung cancer and other cause mortality.

When the NLST results were released, there were immediate claims that screening would prevent deaths from emphysema and heart diseases. Dr. Bach recommended a close look at the potential harms associated with screening. In the NLST, there were complications from the diagnostic procedure, including 3.4 deaths per 10,000 individuals screened by low-dose computerized tomography (LDCT) and 33 major complications per 10,000 individuals screened by LDCT.

The only group for which benefit of lung cancer screening has been seen is the population of high-risk smokers. In NLST, the only group where benefit was seen were those ages 55 to 74 with >=30 pack years of smoking who quit<=15 years prior to the study entry (if they had stopped smoking). However, Dr. Bach noted that compliance in the NLST was very high and not easily achievable in a real world setting. The NLST was conducted in large academic centers, including NCI-designated centers. Compliance was very high with follow-up screening, and the doctors involved in the study probably had more expertise than average doctors. Dr. Bach recommended that we consider the difficulties of replicating trial conditions in practice in addition to evaluating the risks of screening.

Dr. Vidaver focused on the failure to incorporate molecular testing of lung cancer into current practice. She noted first that, although there is a National Comprehensive Cancer Network (NCCN) guideline for EGFR testing for all advanced adenocarcinoma cases, the pathology guidelines for testing are still in development after two years. There is no drug labeled in the United States for directed first-line therapy for EGFR mutation-positive patients, and there is a challenge getting all advanced adenocarcinoma tumors tested for EGFR.

There are, according to Dr. Vidaver, a number of challenges to improving utilization of tumor testing:

- The need to address patient misconceptions. Patients typically think the tests are genetic and resist them.
• Need to address provider misconceptions. Providers sometimes believe that there are insufficient data to show benefit, and they also may believe that testing and targeted therapy won't help much in high-mortality cases.

• Need to address knowledge gaps. Providers may have insufficient knowledge about which tumor types should be tested and when, and they also may not understand the potential impact of testing and targeted treatment on overall survival or progression-free survival.

• Need to address an inconsistent testing system. Testing may occur on-site or at a commercial lab, and the choice affects time to result and therefore start of care.

Dr. Vidaver identified several key responsibilities for patient advocacy organizations:

• Translate science and medical findings to lay-friendly descriptions
• Conduct patient and provider education and outreach
• Provide information about transitions in the field as well as clinical trial and treatment successes
• Serve as “honest brokers” among academia, industry, and regulators

Cancer Research and Therapeutic Development: What Do Recent Developments Mean for Cancer Patients?

Douglas R. Lowy, M.D.
Chief, Laboratory for Cellular Oncology
Center for Cancer Research
Deputy Director
National Cancer Institute

Patricia Cortazar, M.D.
Clinical Team Leader
Breast Oncology Group
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Tatiana M. Prowell, M.D.
Medical Officer Breast Oncology Group
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

The goals for the Cancer Genome Atlas (TCGA) and TARGET are to: 1) discover the spectrum of genes implicated in a specific form of cancer, 2) learn how specific combinations of genes work together in the cancer, and 3) apply this information to suggest new uses for existing drugs and development of new drugs. In the initial phase of TCGA, there was to be a comprehensive genomic analysis for 25 tumor types (analysis of 500 tumors per type). In 2012, the Rare Tumor Project was launched as part of TCGA. TCGA is a large, community-based effort linking scientists who adhere to standards and processes for tissue samples, quality control, computational analysis, and comprehensive characterization.
Dr. Lowy described the movement from cancer genetics to cancer genomics as a shift toward a broader sort of analysis. Cancer genomics produces a catalog of the DNA and RNA differences between the patient’s cancer cells and his or her normal cells. The DNA analysis identifies mutations in the tumor, and the RNA analysis identifies the loss of genes whose expression is increased or decreased. The challenge of cancer genomics is to determine which mutations are important and which changes in gene expression are important.

The landscape for cancer genomics is evaluating rapidly. It is now possible to do genomic analysis with less tissue and even with formalin-fixed paraffin-embedded tissue. The cost of sequencing continues to go down, and the $1,000 genome may soon be a reality. However, the cost of analysis is still high. Genomic analysis is being incorporated into clinical trials, but there are challenges with integrating it into patient management.

The progress in cancer genomics is real, but expectations must be managed. Most improvements will probably benefit only a subset of patients with a particular tumor type, rather than all patients. Finally, determining the actual benefit of a new treatment of a disease that is not rapidly lethal will take a long time.

Dr. Cortazar described the distinctions between neoadjuvant and adjuvant trials. She described neoadjuvant trials as having these characteristics: smaller sample size, pCR fast assessment, in vivo assessment of tumor response, short drug exposure, necessity for prior safety information, and the ability to identify unresponsive tumors rapidly. In contrast, adjuvant trials have bigger sample size, permit assessment of long-term outcome, result in longer drug exposure, and are the best design for studying long-term safety.

Dr. Cortazar said that FDA hopes that the use of pCR as an endpoint to support accelerated approval in the neoadjuvant setting will encourage industry innovation and expedite the development of breakthrough therapies to treat high-risk, early-stage breast cancer. She also said that adjuvant trials will still be necessary because they will provide confirmation of long-term efficacy and safety. Also, many breast cancer subgroups will need extended post-neoadjuvant therapy.

Dr. Prowell offered the rationale for neoadjuvant treatment and the reason for FDA to focus on a guidance that might encourage clinical trials in the neoadjuvant setting. She said that such therapy may: 1) render locally advanced breast cancer operable, 2) permit breast conservation in patients who would otherwise require mastectomy, and 3) enable real-time assessment of tumor response in an early-stage population.

The goals of the draft guidance on pCR are to: 1) describe subgroups of breast cancer patients with unmet medical need and for whom pCR is expected to predict clinical benefit, 2) propose a standard definition of pCR, 3) outline a neoadjuvant trial design for accelerated approval and conversion to regular approval, and 4) discuss safety concerns and how best to address them.

One of the serious challenges of the guidance is to select the appropriate patients. The goal was to identify patients at high risk of recurrence and death despite best available systemic therapy. But how should high risk be defined? Those who are triple negative and HER2+ have the highest likelihood of pCR. The most compelling data to date that pCR predicts clinical outcome are in this population. Finally, there is a clear unmet need in the triple-negative subset, making the risk-benefit balance of this approach appropriate.
Those who are hormone receptor-positive are both less likely to attain pCR and more likely to have long-term survival. As a result, pCR is less likely to predict clinical benefit.

The pros of the neoadjuvant pathway are: 1) earlier access to novel agents for high-risk patients, 2) incentive for drug development in high-risk subtypes, and 3) opportunity to improve outcomes for patients with residual cancer after neoadjuvant therapy. The cons of the approach are: 1) risks unrecognized or long-term safety concerns, 2) the fact that some high-risk patients would have been cured with existing therapy and 3) the risk of loss of public confidence in the approval process if cancer drugs given accelerated approval require subsequent withdrawal of approval.

Technology to Guide Cancer Treatment: Issues Related to Their Development. Regulatory Review, and Reimbursement

Vincent A. Miller, M.D.
Senior Vice President
Clinical Development
Foundation Medicine

Andrew Fish
Executive Director
AdvaMedDX

Lee Newcomer, M.D.
Senior Vice President, Oncology
United HealthCare

Angela Bradbury, M.D.
Assistant Professor of Medicine
Perelman School of Medicine
University of Pennsylvania

Alberto Gutierrez, Ph.D.
Director
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
Food and Drug Administration

Dr. Miller identified the current challenges of clinical genomic analysis in oncology. The challenges related to the sample include limited tissue amounts from small biopsies, DNA damage from routine fixation, and low tumor purity. The challenges associated with the assay include the heterogeneity of relevant alterations (including point mutations and copy changes), which compound the cost of using single analyte tests. The process challenges include the logistics of routing samples to many different labs for different tests, the difficulty of managing clinically relevant turnaround times, and the integration and interpretation of results.
Because various genes are mutated in individual tumors and cancer cells often contain combinations of mutations, it is critical to understand entire pathways which incorporate many genes. To understand these pathways, next generation sequencing should be utilized. The advantages of next generation sequencing are the ability to sequence the entire coding region of cancer-related genes, the ability to simultaneously identify all classes of DNA alterations, and the ability to achieve high coverage and clinical grade sensitivity and specificity.

At Foundation Medicine, the underlying principle is the development of a test with 99%+ sensitivity to detection a mutation with allele frequency of >5%, with no false positives. Dr. Miller described the advantages of targeted sequencing, including its ability to cover all classes of DNA mutations, links to more treatment options, ability to complete with small amounts of DNA, and flexibility to add content as knowledge increases. He suggested that this technology holds the promise of giving researchers and clinicians the tools to understand the patient’s genomic makeup and the molecular characterization of the patient’s cancer cells. This technology is what is necessary for oncologists to travel the changing landscape of cancer.

Dr. Fish concentrated on the big challenge of securing appropriate payment for diagnostics. He said that diagnostics are a value proposition, as they ensure appropriate diagnosis and targeting of therapies. However, the current environment is one in which diagnostics are undervalued. The lab fee schedule that is used by private payers has not been fundamentally changed since the 1980s. The payment system is based on time and materials, with no emphasis on innovation and its value.

It is absolutely critical, said Dr. Fish, to move away from the time and materials model for payment for tests. He suggested that the most comprehensive reimbursement solution might be a legislative one, such as the plan included in the Diagnostics Innovation Act/MODDERN Cures Act. There is a wide range of payer policies on diagnostics. Dr. Fish articulated the need for common analytical principles regarding the value of diagnostics, which would lead to consistency in assessment, payment, and utilization.

Payers are looking at diagnostic utilization to make sure their spending on diagnostics is rational and sensible. They realize that if they are smart and drive utilization of certain diagnostics, they can achieve savings and the proper selection of therapies. The problem for innovative diagnostic companies is that different payers are using different models. BIO has completed a survey of payment for diagnostics that could potentially be used to rationalize payment for diagnostics.

Dr. Newcomer identified the three components for securing coverage of diagnostic tests.

- **Analytic validity** – does the test really measure what it is supposed to? The kits that were manufactured for HER2 achieved analytical validity, but when they were used in community pathology sites, they were not measuring what they said they did.
- **Clinical validity** – is the test statistically associated with the condition? You will find aberrant genes in everyone. Is the aberrant gene associated with a disease? Is the association real? The current reimbursement system is not adequate for making sure that tests have clinical validity, yet we have to have this validity.
- **Clinical utility** – will the test results change outcome or clinical behavior? If a doctor uses the uveal melanoma risk predictor, he may produce information that the physician or patient wants. However,
the information will not change the patient’s clinical treatment. On tests with this kind of impact, payers will have to say no coverage.

UnitedHealth Group is proposing the 10 percent solution. This means that where a test developer’s test shows there is a 10 percent improvement in survival or a reduction in morbidities or a reduction in cost of 10 percent, that test is worth pursuing and will be paid for.

Dr. Bradbury described the three big challenges that DTC advertising presents for cancer care:

- The evidence dilemma – DTC testing challenges current thresholds for introduction of medical innovations. The availability of commercial genetic tests should be based on professional recommendations founded on empirical evidence, not merely on the technical feasibility of a test or its commercial potential.
- DTC activities bypass conventional channels of expert sources, yet many consumers share test results with providers and believe it is a physician’s duty to help interpret DTC test results.
- The quality and claims of DTC activities have been questioned. Claims regarding DTC genetic tests may be exaggerated or unsupported by scientific evidence, and this is problematic for both physicians and patients.

DTC advertising creates a burden on providers to:

- Order tests of questionable clinical utility
- Explain tests already obtained
- Correct inaccuracies or expectations
- Understand a variety of services
- Rely on company materials

Overall, DTC tests can have a negative impact on the patient-clinician relationship, create time and cost burdens to the health care system, and compromise patient care.

Among the possible solutions to the DTC crisis are regulatory efforts to ensure quality and claims, provider education about DTC tests, and practice guidelines about the use of genetic tests.

According to Dr. Gutierrez, the exercise of FDA enforcement discretion is not unique to laboratory developed tests, or LDTs. The exercise of enforcement discretion does not change the fact that the law applies. The decision to exercise enforcement discretion may be influenced by a number of different reasons, including risk, history, resources, and other factors. Enforcement practices may change, often because of changes in the risk profile of products.

Many LDTs of today are similar to the LDTs of 1976 – they are for unmet needs and rare diseases and still need expert interpretation. But LDTs of the current day are also much more. The volume and types of LDTs have grown significantly, and the development of an LDT is often just a mechanism for market entry of novel tests. Today, as compared to 1976, a higher proportion of LDTs are developed in commercial labs and by biotechnology companies. Often, there is no clinician-pathologist-patient relationship with regard to the LDT.
The tests are developed for broad, commercial use and are broadly advertised and aggressively marketed to clinicians. In addition, the tests are also advertised direct-to-consumer and sales are made on the internet with overnight shipping. The tests have national or even international reach. LDTs of the current day often require complex software, incorporate automated interpretation, and rely on complex statistical methods. The clinical validity of these tests is not well-understood. Many of the tests are for predicting drug response and risk of disease. These novel LDTs are often developed by companies and licensed to a lab.

According to Dr. Gutierrez, enforcement discretion becomes a loophole. Many LDTs are now dependent on components assembled and marketed by others; business models leverage enforcement discretion for rapid market access and avoid FDA oversight, and there is a parallel industry with traditional IVD manufacturers.

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**Affordable Care Act: Implementation by the Federal and State Governments**

*Katherine Jett Hayes, J.D.*  
*Associate Research Professor*  
*Department of Health Policy*  
*George Washington University School of Public Health and Health Services*  

*Joshua Sharfstein, M.D.*  
*Secretary of Health and Mental Hygiene*  
*State of Maryland*

According to Ms. Hayes, states have made a range of decisions related to exchange implementation. States are: 1) still studying exchange options, 2) have made decisions NOT to create state exchanges, 3) are planning for partnership exchange, 4) have established state exchanges, or 5) have taken no significant steps toward implementation.

At the time of Ms. Hayes’s presentation, CMS had indicated that states may opt in and opt out of Medicaid expansion and receive the enhanced match for its expansion. Additional guidance on questions of Medicaid expansion, including the potential for a partial expansion, was anticipated at the time of the meeting.

Some consumer and patient advocates have been critical of CMS for its failure to adhere to the notion of a single federal standard on essential health benefits or other issues. Ms. Hayes suggested that the approach of CMS was superior to the expectations of advocates, because it seeks to encourage partnerships and participation in the Affordable Care Act system.

Ms. Hayes commented on the impact on insurance coverage of the decisions of states NOT to expand Medicaid. She suggested that the lack of coverage in non-expansion states will have a negative impact on population health. In the 11 states that have said “no” or “leaning to” Medicaid expansion, an estimated 7 million people will be without coverage if the states make a final decision not to expand Medicaid. A recent study concluded that Medicaid expansion to low-income adults in NY, ME, and AZ were associated with a 6.1 percent reduction in mortality and increased access to care.
Dr. Sharfstein is the chair of the Maryland exchange board, which has proceeded with implementation tasks in three stages. The board has addressed issues of governance, policy, and funding. He described the composition of the nine-member board: 1) three government employees, 2) three people with specific expertise in health care, and 3) three smart people without specific expertise.

In the first 18 months of work of the exchange board, there have been no contested votes. Meetings occur every month or every other week, and there are generally about 50 to 75 members of the public at the board meetings. There are lots of people interested in exchange implementation, and the discussion of health reform in Maryland is very different from the discussion at the federal level.

The exchange board has addressed the structural framework and is turning its attention to the policy framework. The board is also studying what should be done to finance the exchange. The cost will be in the $30 million per year range, and in terms of economic benefits the $30 million investment is a good one.

There is already a good sense of how the selection and enrollment process will work in Maryland. Individuals will go online where they can receive assistance from a navigator or assister. The online system will assess what the individual is eligible for. If one is eligible for Medicaid, they will be enrolled. If not eligible for Medicaid, one can make a private insurance choice and determine whether eligible for a subsidy. Small businesses may also choose to purchase through the exchange.

The state of Maryland has chosen the state employee plan as the benchmark but will still have to make some decisions about substitution.

The choice is Maryland is to set up the exchange and let it work without attempting to micromanage it. One issue that will require monitoring is the issue of networks of care. The ACA will provide individuals with insurance coverage, but it will be important to understand if newly insured individuals have access to care networks. It is important to realize, said Dr. Sharfstein, that adjustments and modifications to the exchange system will be necessary. The system will not be perfect in its first year.