Bridging the gap between payer and provider perspectives

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# Evidence-Based Oncology

## THE PERSONALIZED MEDICINE SPECIAL ISSUE

*Provider Perspective*

## Balancing Innovation With Cost in Diagnostic Testing

GNANAMBA VARUNI KONDAGUNTA, MD

Advances in the understanding of cancer biology have presented molecular targets that can prove valuable for prognosis. The use of molecular diagnostic testing has blossomed simultaneously over the past 15 years, and a major area of research has been the development of targeted therapies that can be used to individualize treatment based on molecular profiles. The research has yielded major clinical successes, including the first targeted therapy, imatinib, for patients with chronic myeloid leukemia, and similar efforts are ongoing for other cancers. At the recent 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, a search of abstracts and presentations yielded 842 results for the word *target*. These ranged from papers that studied molecular targets by disease type; by classification (ie, angiogenesis targets, growth factors); and newer immunologic therapeutics, including immune checkpoint-blocking antibodies that boost the patient's immune system to attack malignant cells (ie, anti-CTLA-4 and anti-PD-1 antibodies).

As clinical targets in more common malignancies including breast, lung, and colon cancers emerge, testing and treatment options will increase. Balancing these choices with the high costs associated with the new technology will be the challenge in order to determine value in oncology care.

### THE RISING COST OF HEALTHCARE

As cancer research has made impres-

(continued on page SP425)

*Patient Advocacy*

## The Need to Eliminate Barriers to Personalized Medicine

ALAN BALCH, PHD

Tom Hall had exhausted all the chemotherapy medicines available, and his metastatic lung cancer was spreading. With little hope left, he turned to genetic testing. Based on his genomic profile, 5 off-label medicines were recommended, from which his doctor selected a Medicare Part D drug approved for renal cell carcinoma but not for Tom's lung cancer. This treatment appeared to slow the progression of his disease and gave him more time with his family.

At first glance, genetic testing and subsequent precision treatment seemed to offer hope for Tom, something often hard to come by for patients battling for their lives. However, a vital aspect of his story is missing—the part where Medicare originally denied coverage because the drug would be used off-label. In fact, his doctor appealed twice and was denied. Personalized medicine provided Tom with some new options. The process broke down, however, at a highly crucial juncture—the point at which Tom had to gain timely access to and coverage for his personalized treatment.

Tom sought help and was referred to the Patient Advocate Foundation (PAF), which has provided direct services and support over the past 19 years to more than 750,000 Americans facing chronic, debilitating, and life-threatening illnesses. Ultimately, a PAF case manager submitted an expedited appeal with documents showing the applicability of the off-label use based on his genetic profile. The appeal was successful and Tom finally obtained coverage

(continued on page SP429)

*Reimbursement*

## Alternative Payment Models: *Paving the Way or Building a Wall for Personalized Medicine?*

AMY M. MILLER, PHD; AND ANDREW J. SHIN, JD, MPH

Personalized medicine is rapidly developing as the ultimate weapon for combating cancer. An emerging field that uses diagnostic tools to identify specific biological—often genetic—markers to help determine which medical treatments and procedures will work best for each patient, personalized medicine allows doctors and patients to develop targeted treatment plans. In the decade following the completion of the Human Genome Project in 2003, advances in genome technology have led to an exponential decrease in sequencing costs, and innovative diagnostics and therapies have made what we once thought of as incurable diseases seem treatable and sometimes preventable. We have seen the molecular subdivision of cancer, which when combined with a targeted therapy has produced significant improvements in care. This trend continues to proliferate, with a recent study estimating that more than 70% of cancer medicines in development are targeted therapeutics.[1]

In the midst of this progress begins the trend away from the old fee-for-service system and toward a system that pays for value. Delivery system reform has been a central component in national health system changes since the 2010 passage of the Affordable Care Act (ACA). Furthermore, replacement of the Medicare Sustainable Growth Rate physician payment formula by the Medicare Access and CHIP Reau-

(continued on page SP430)

### WHAT'S COMING IN PERSONALIZED MEDICINE


*Evidence-Based Oncology* speaks with the new president and CEO of Myriad Genetics on existing challenges and opportunities and where he sees the industry's future (**SP409**).

*Also in this issue...*

### FDA PROMOTES PRECISION TREATMENT

The FDA has been a big proponent of precision medicine, recommending parallel development of companion diagnostics for targeted medications. Funding from the Precision Medicine Initiative will further boost the FDA's efforts (**SP398**).

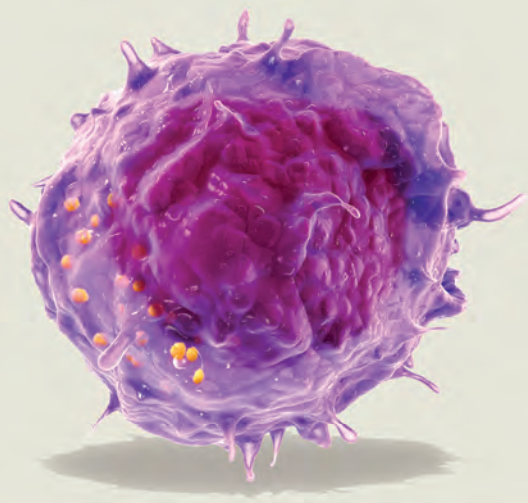
### MARKET ACCESS AND REIMBURSEMENT CHALLENGES

Coverage decisions have been a stumbling block for diagnostic tests. This issue includes market access strategies for diagnostics (**SP404**) and regulatory and coverage policies for laboratory-developed tests (**SP407**).

# THERE'S A NATURAL KILLER INSIDE EVERYONE

## WITH THE POTENTIAL TO TAKE ON MULTIPLE MYELOMA

Natural Killer Cells play an important role in the immune response to multiple myeloma.[1] However, disease burden increases as myeloma cells evolve to evade and suppress the body's natural immune response.[1-9]



Immuno-oncology is a fundamentally different modality under investigation for multiple myeloma and Bristol-Myers Squibb is researching the potential of the **SLAMF7, KIR,** and **CD137** pathways to activate the body's own Natural Killer Cells to target myeloma cells.

## Rethink Multiple Myeloma

Bristol-Myers Squibb is deeply committed to furthering the science behind immuno-oncology by rethinking research and emphasizing the importance of a comprehensive approach to endpoint evaluation in multiple myeloma.

**www.RethinkMultipleMyeloma.com**

**REFERENCES: 1.** Jurisic V, Srdic T, Konjevic G et al. Clinical stage-depending decrease of NK cell activity in multiple myeloma patients. *Med Oncol.* 2007;24:312-317. **2.** Bernal M, Garrido P, Jiménez P et al. Changes in activatory and inhibitory natural killer (NK) receptors may induce progression to multiple myeloma: implications for tumor evasion of T and NK cells. *Human Immunol.* 2009;70:854-857; **3.** Jinushi M, Vanneman M, Munshi NC et al. MHC class I chain-related protein A antibodies and shedding are associated with the progression of multiple myeloma. *Proc Natl Acad Sci USA.* 2008;105:1285-1290; **4.** Carbone E, Neri P, Mesuraca M et al. HLA class I, NKG2D, and natural cytotoxicity receptors regulate multiple myeloma cell recognition by natural killer cells. *Blood.* 2005;105:251-258; **5.** von Lilienfeld-Toal M, Frank S, Leyendecker C et al. Reduced immune effector cell NKG2D expression and increased levels of soluble NKG2D ligands in multiple myeloma may not be causally linked. *Cancer Immunol Immunother.* 2010;59:829-839; **6.** Cook G, Campbell JDM, Carr CE et al. Transforming growth factor beta from multiple myeloma cells inhibits proliferation and IL-2 responsiveness in T lymphocytes. *J Leukoc Biol.* 1999;66:981-988; **7.** Yu J, Wei M, Becknell B et al. Pro- and anti-inflammatory cytokine signaling: reciprocal antagonism regulates interferon-gamma production by human natural killer cells. *Immunity.* 2006;24:575-590; **8.** Nielsen H, Nielsen HJ, Tvede N et al. Immune dysfunction in multiple myeloma. Reduced natural killer cell activity and increased levels of soluble interleukin-2 receptors. *APMIS.* 1991;99:340-346; **9.** Tinhofer I, Marschitz I, Henn T et al. Expression of functional interleukin-15 receptor and autocrine production of interleukin-15 as mechanisms of tumor propagation in multiple myeloma. *Blood.* 2000;95:610-618.

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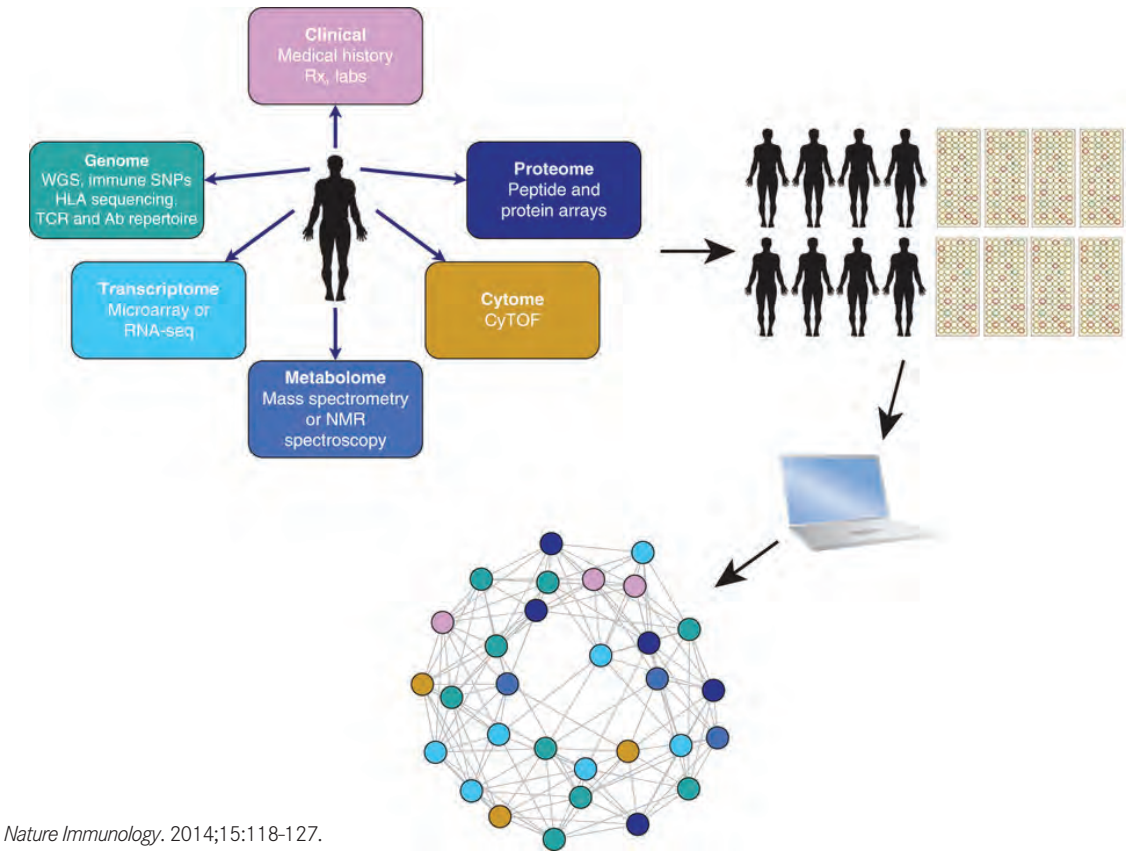


**SOURCE:** *Nature Immunology*. 2014;15:118-127.

***Personalized medicine is transforming patient care–it allows for precise treatment while reducing unwanted side effects. But the field is evolving and problems persist. This issue includes views of diverse stakeholders from the field of personalized medicine.***



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# Integrating Precision Into Oncology Care

MIKE HENNESSY, SR

Personalized medicine has taken a giant leap forward, and while its benefits are visible across all therapeutic areas, it holds particular relevance to oncology. Extensive research has proved beyond any doubt that cancer is a heterogeneous disease with inter-tumoral and intra-tumoral variability, which results in each individual having a near-unique tumor profile. This knowledge makes it imperative that instead of using cookie-cutter treatment plans for patients harboring the same tumor type, we map out the expression of genes and proteins that are either overexpressed or mutated in each tumor. This biomarker-guided treatment approach bears promise of improved outcomes and added value to patient care.

As you will read in this issue of *Evidence-Based Oncology*, healthcare providers, the FDA, patient advocates, and, of course, the manufacturers of diagnostic tests, all believe in the potential of personalized medicine in transforming the cancer treatment landscape. But there are challenges that need to be surmounted before molecular diagnostic tests see widespread use. Some of these problems are more technical in nature, as is evident from the article by Avalere Health on laboratory-developed tests (LDTs) and CMS policies on reimbursement for those tests. Changes are imminent in LDT reimbursement, the authors write, and these changes will reverberate across the healthcare world.

We also hear from manufacturers of these diagnostic tests, Foundation Medicine and Myriad Genetics, on strategies for market access and what payers expect in terms of data when making coverage decisions. Says Mark Capone, CEO of Myriad Genetics, "There are still some uncertainties [with reimbursement], and the best way to deal with that uncertainty is to have very early conversations with payers about what level of evidence they will require for a specific test."

While oncologists appreciate the value of diagnostic tests in guiding clinical decisions, they caution against duplicative and unnecessary care that can increase healthcare costs. In her commentary, Dr Kondagunta from Crystal Run Healthcare writes, "Balancing the appropriate use of diagnostic testing and treatment and ensuring that opportunities for improved survival and quality of life are not missed is the goal of value-based oncology."

The FDA commentary provides testament that the regulatory body is on board and has kept up with the rapid advances in precision treatment—and it will continue to do so, thanks to the budget allocations under President Obama's Precision Medicine Initiative, which has promised $10 million to the FDA for this purpose.

In the meantime, new clinical trial designs complement this growing breed of targeted treatments to accelerate drug development and improve patient access. Trials such as I-SPY2, Lung-MAP, and NCI-MATCH are huge undertakings full of promise.

We'll continue to provide you with updates on current progress in healthcare through our publications, our website www.ajmc.com, and our live meetings, such as Patient Centered Oncology Care (November 19-20, 2015). Thank you for your readership.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

## EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

imbruvica®
(ibrutinib) 140mg capsules

# DISCOVERING HOW FAR THERAPY CAN GO

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**Hemorrhage** - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

**Infections** - Fatal and non-fatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

**Cytopenias** - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

**Atrial Fibrillation** - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

**Second Primary Malignancies** - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

**Tumor Lysis Syndrome** - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

**Embryo-Fetal Toxicity** - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

# IMBRUVICA® (ibrutinib) is the first and only FDA-approved therapy for use in patients with Waldenström's macroglobulinemia (WM)

## IMBRUVICA® is approved for use in 4 indications

**IMBRUVICA® is indicated for the treatment of patients with**

**Mantle cell lymphoma (MCL) who have received at least one prior therapy.**
Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

**Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.**

**Chronic lymphocytic leukemia with 17p deletion.**

**Waldenström's macroglobulinemia (WM).**

### ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia* (57%, 52%, 43%), neutropenia* (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia* (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%†, NA‡), bruising (30%, 12%†, 16%†), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%†, 22%†).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse events.

Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

### DRUG INTERACTIONS

**CYP3A Inhibitors** - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

**CYP3A Inducers** - Avoid co-administration with strong CYP3A inducers.

### SPECIFIC POPULATIONS

**Hepatic Impairment** - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

**Please review the Brief Summary of full Prescribing Information on the following pages.**

To learn more, visit
**www.IMBRUVICA.com**


06/15 PRC-01166

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**Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)**
**IMBRUVICA® (ibrutinib) capsules, for oral use**
See package insert for Full Prescribing Information

## INDICATIONS AND USAGE

**Mantle Cell Lymphoma:** IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in Full Prescribing Information].*

**Chronic Lymphocytic Leukemia:** IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in Full Prescribing Information].*

**Chronic Lymphocytic Leukemia with 17p deletion:** IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

**Waldenström's Macroglobulinemia:** IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

## CONTRAINDICATIONS

None

## WARNINGS AND PRECAUTIONS

**Hemorrhage:** Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

**Infections:** Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. *[See Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

**Cytopenias:** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

**Atrial Fibrillation:** Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3) in Full Prescribing Information].*

**Second Primary Malignancies:** Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

**Tumor Lysis Syndrome:** Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

**Embryo-Fetal Toxicity:** Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

## ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

**Clinical Trials Experience:** Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

**Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Gastrointestinal disorders** | Diarrhea | 51 | 5 |
| | Nausea | 31 | 0 |
| | Constipation | 25 | 0 |
| | Abdominal pain | 24 | 5 |
| | Vomiting | 23 | 0 |
| | Stomatitis | 17 | 1 |
| | Dyspepsia | 11 | 0 |
| **Infections and infestations** | Upper respiratory tract infection | 34 | 0 |
| | Urinary tract infection | 14 | 3 |
| | Pneumonia | 14 | 7 |
| | Skin infections | 14 | 5 |
| | Sinusitis | 13 | 1 |
| **General disorders and administrative site conditions** | Fatigue | 41 | 5 |
| | Peripheral edema | 35 | 3 |
| | Pyrexia | 18 | 1 |
| | Asthenia | 14 | 3 |



**Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Mantle Cell Lymphoma (N=111) (continued)**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | Bruising | 30 | 0 |
| | Rash | 25 | 3 |
| | Petechiae | 11 | 0 |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain | 37 | 1 |
| | Muscle spasms | 14 | 0 |
| | Arthralgia | 11 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea | 27 | 4 |
| | Cough | 19 | 0 |
| | Epistaxis | 11 | 0 |
| **Metabolism and nutrition disorders** | Decreased appetite | 21 | 2 |
| | Dehydration | 12 | 4 |
| **Nervous system disorders** | Dizziness | 14 | 0 |
| | Headache | 13 | 0 |

**Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)**

| | Percent of Patients (N=111) | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 57 | 17 |
| Neutrophils Decreased | 47 | 29 |
| Hemoglobin Decreased | 41 | 9 |

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

***Study 1:*** Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

**Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Gastrointestinal disorders** | Diarrhea | 63 | 4 |
| | Constipation | 23 | 2 |
| | Nausea | 21 | 2 |
| | Stomatitis | 21 | 0 |
| | Vomiting | 19 | 2 |
| | Abdominal pain | 15 | 0 |
| | Dyspepsia | 13 | 0 |
| **Infections and infestations** | Upper respiratory tract infection | 48 | 2 |
| | Sinusitis | 21 | 6 |
| | Skin infection | 17 | 6 |
| | Pneumonia | 10 | 8 |
| | Urinary tract infection | 10 | 0 |
| **General disorders and administrative site conditions** | Fatigue | 31 | 4 |
| | Pyrexia | 25 | 2 |
| | Peripheral edema | 23 | 0 |
| | Asthenia | 13 | 4 |
| | Chills | 13 | 0 |
| **Skin and subcutaneous tissue disorders** | Bruising | 54 | 2 |
| | Rash | 27 | 0 |
| | Petechiae | 17 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Cough | 19 | 0 |
| | Oropharyngeal pain | 15 | 0 |
| | Dyspnea | 10 | 0 |
| **Musculoskeletal and connective tissue disorders** | Musculoskeletal pain | 27 | 6 |
| | Arthralgia | 23 | 0 |
| | Muscle spasms | 19 | 2 |
| **Nervous system disorders** | Dizziness | 21 | 0 |
| | Headache | 19 | 2 |
| | Peripheral neuropathy | 10 | 0 |
| **Metabolism and nutrition disorders** | Decreased appetite | 17 | 2 |
| **Neoplasms benign, malignant, unspecified** | Second malignancies* | 10* | 0 |
| **Injury, poisoning and procedural complications** | Laceration | 10 | 2 |
| **Psychiatric disorders** | Anxiety | 10 | 0 |
| | Insomnia | 10 | 0 |
| **Vascular disorders** | Hypertension | 17 | 8 |

**One patient death due to histiocytic sarcoma.*

**Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1**

| | Percent of Patients (N=48) | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 71 | 10 |
| Neutrophils Decreased | 54 | 27 |
| Hemoglobin Decreased | 44 | 0 |

* Based on laboratory measurements per IWCLL criteria and adverse reactions

***Study 2:*** Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

**Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2**

| System Organ Class ADR Term | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 48 | 4 | 18 | 2 |
| Nausea | 26 | 2 | 18 | 0 |
| Stomatitis* | 17 | 1 | 6 | 1 |
| Constipation | 15 | 0 | 9 | 0 |
| Vomiting | 14 | 0 | 6 | 1 |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 28 | 2 | 30 | 2 |
| Pyrexia | 24 | 2 | 15 | 1 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 16 | 1 | 11 | 2 |
| Pneumonia* | 15 | 10 | 13 | 9 |
| Sinusitis* | 11 | 1 | 6 | 0 |
| Urinary tract infection | 10 | 4 | 5 | 1 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash* | 24 | 3 | 13 | 0 |
| Petechiae | 14 | 0 | 1 | 0 |
| Bruising* | 12 | 0 | 1 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal Pain* | 28 | 2 | 18 | 1 |
| Arthralgia | 17 | 1 | 7 | 0 |
| **Nervous system disorders** | | | | |
| Headache | 14 | 1 | 6 | 0 |
| Dizziness | 11 | 0 | 5 | 0 |
| **Injury, poisoning and procedural complications** | | | | |
| Contusion | 11 | 0 | 3 | 0 |
| **Eye disorders** | | | | |
| Vision blurred | 10 | 0 | 3 | 0 |

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

**Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2**

| | IMBRUVICA (N=195) | | Ofatumumab (N=191) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| Neutrophils Decreased | 51 | 23 | 57 | 26 |
| Platelets Decreased | 52 | 5 | 45 | 10 |
| Hemoglobin Decreased | 36 | 0 | 21 | 0 |

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

**Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| Gastrointestinal disorders | Diarrhea | 37 | 0 |
| | Nausea | 21 | 0 |
| | Stomatitis* | 16 | 0 |
| | Gastroesophageal reflux disease | 13 | 0 |
| Skin and subcutaneous tissue disorders | Rash* | 22 | 0 |
| | Bruising* | 16 | 0 |
| | Pruritus | 11 | 0 |

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**Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63) (continued)**

| System Organ Class | Preferred Term | All Grades (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| General disorders and administrative site conditions | Fatigue | 21 | 0 |
| Musculoskeletal and connective tissue disorders | Muscle spasms | 21 | 0 |
| | Arthropathy | 13 | 0 |
| Infections and infestations | Upper respiratory tract infection | 19 | 0 |
| | Sinusitis | 19 | 0 |
| | Pneumonia* | 14 | 6 |
| | Skin infection* | 14 | 2 |
| Respiratory, thoracic and mediastinal disorders | Epistaxis | 19 | 0 |
| | Cough | 13 | 0 |
| Nervous system disorders | Dizziness | 14 | 0 |
| | Headache | 13 | 0 |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | Skin cancer* | 11 | 0 |

The system organ class and individual ADR terms are sorted in descending frequency order.
* Includes multiple ADR terms.

**Table 8: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)**

| | Percent of Patients (N=63) | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| Platelets Decreased | 43 | 13 |
| Neutrophils Decreased | 44 | 19 |
| Hemoglobin Decreased | 13 | 8 |

* Based on laboratory measurements.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

## DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

**CYP3A Inhibitors:** In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased $C_{max}$ and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

**CYP3A Inducers:** Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib $C_{max}$ and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** Pregnancy Category D *[see Warnings and Precautions].*

*Risk Summary:* Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

*Animal Data:* Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

**Nursing Mothers:** It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

**Geriatric Use:** Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

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**Renal Impairment:** Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

**Hepatic Impairment:** Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

**Females and Males of Reproductive Potential:** Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations].*

**Plasmapheresis:** Management of hyperviscosity in patients with WM may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

**PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial Fibrillation:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.5) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

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# The Vision of an Effective and Equitable Future for Personalized Medicine

In the 1970s there was an optimistic belief that the cure to cancer existed in finding a simple key that could stop all malignant disease. In this quest for the cancer equivalent to the holy grail, new therapeutics like the BCG vaccine, and later interferon, were heralded in publications like *Time Magazine* as the "Magic Bullets" that would upend cancer. This early optimism, however, eventually yielded to a sober sense that cancer was both more refractory and complex than initially suspected. Nearly 40 years later, there has been a profound shift in thinking. The naïve belief that there was an inherent simplicity to curing cancer has resulted in a deeper appreciation of the significant complexities of the molecular biology of cancer.

There are approximately 20,000 genes in the human genome that result in the expression of between 17,000 and 21,000 different proteins that constitute the human proteome. Abnormalities and mutations in many of these molecules can, in turn, individually or in networks, lead to the development, evolution, and metastases of cancer. Diagnostic studies based on gene and protein mutations now form the basis of cutting edge cancer diagnostic and prognostic assessment. These molecular targets also are the basis for precision anticancer therapeutics that are capable of treating, and potentially curing, many previously refractory cancers.

Chronic myelogenous leukemia (CML) was the first malignant disease for which a consistent, stereotypic, disease-defining chromosomal translocation was described. It provides the best model for understanding the clinical, laboratory, and economic implications of this new world of molecular and genomic technology-based cancer management. The presence of the Philadelphia chromosome and the resulting *bcr-abl* fusion gene have provided the molecular basis for profoundly powerful, targeted therapeutic agents that turn a once nearly universally lethal disease into one which, for many patients, can be effectively managed with daily oral treatment. In the management of patients with CML, molecular testing is fundamental to diagnosis confirmation, molecular monitoring of therapeutic effectiveness, mutational analysis for the management of refractory patients, and rational therapeutic escalation between the respective tyrosine kinase inhibitors.

Molecular diagnostic testing and targeted therapies now play an increasingly important role in the management of malignant diseases, including both solid tumors and blood-derived cancers. As molecular-based treatment strategies have become more common, the challenges associated with molecular medicine have become increasingly apparent. How do we ensure the appropriate use of these products? How can the healthcare industry keep up with standards of cancer care that are evolving at an unprecedented pace? How do we grapple with the increasing use of laboratory-based testing methods that are not standardized or FDA approved? How can we deliver care in an economically sustainable manner in the context of increasing expensive molecular-based diagnostic testing and exorbitantly priced targeted therapies? How can we shift from a transaction-based economic model toward one that rewards value delivery?

This issue of *Evidence-Based Oncology* describes the scope of these challenges and attempts to contend with how best to systematically and sustainably deliver cancer care in this era of molecular medicine. Varuni Kondagunta, MD, from Crystal Run Healthcare reviews the many challenges associated with molecular testing and deliberates the appropriate and inappropriate uses of these testing methods. Jerry Conway and Mark Oldroyd, JD, from Foundation Medicine discuss the unique issues related to reimbursement, access, quality, and clinical validation related to molecular testing and therapeutics. Alan Balch, PhD, who heads the Patient Advocate Foundation, reviews the importance of personalized medicine and the need to eliminate barriers to equitable access to this level of care. Other contributors address the need for the development of new payments models that can ensure the economic sustainability of the delivery of omic-based medicine.

**ABOUT THE EDITOR IN CHIEF**

JOSEPH ALVARNAS, MD

**Dr Alvarnas** is associate clinical professor and director of medical quality and quality, risk, and regulatory management, City of Hope, Duarte, CA.

In the most recent State of the Union address, President Obama challenged the scientific and healthcare communities to create a future of novel, personalized medicine solutions to answer unmet clinical needs. Understanding how best to deliver such innovative care in an effective, equitable, and economically sustainable manner is essential if this vision is to be achieved. These contributors help to frame the obstacles that may stand in the way of achieving this vision and also offer insight into how to best move forward toward realizing this future. **EBO**

# *Call for Papers*

The US National Library of Medicine defines evidence-based medicine as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis of clinical decisions. Evidence-based medicine asks questions, finds and appraises relevant data, and harnesses that information for everyday clinical practice."

On this basis, *Evidence-Based Oncology* seeks high-quality commentaries and original research reports on cutting-edge clinical, pharmacoeconomic, and regulatory topics in cancer care. The objective is to provide patients, clinicians, payers, health plans, and the pharmaceutical community, evidence-based information to aid care decisions. The editors are especially interested in papers that promote dialogue and facilitate communication among stakeholders and healthcare policy makers that would potentially impact the efficiency and outcomes in cancer care. *Evidence-Based Oncology* regularly publishes articles that cover:

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# Next-Generation Sequencing: *Are We There Yet?*

Surabhi Dangi-Garimella, PhD

Personalized medicine is here to stay, and the advantages are not lost on anyone, as is evident from the articles in this issue by experts from diverse healthcare fields. In contrast to the traditional method of healthcare, in which a clinical observation is followed by an investigation into the cause, technological advances have now placed the provider a step ahead—based on genomic or proteomic information, a physician or a health system can predict an individual's health trajectory and could even prescribe preventive measures through lifestyle changes.

Bioinformatics research has developed rapid, increasingly specific, and cost-effective tools to analyze and interpret health information. Next-generation sequencing (NGS) is one such tool. Also called massively parallel or deep sequencing, NGS is an advanced technique that can sequence the entire genome in a day, a tremendous leap forward from the Sanger technique, which took over a decade to do so.[1]

NGS can include exhaustive parallel sequencing of individual small nucleotide fragments, with the follow-up analysis requiring bioinformatics to reconnect the puzzle based on the reference human genome. The technology has the flexibility to sequence the entire genome or specific areas of interest, such as the whole-exome (22,000 genes) or individual genes.[1]

**TABLE.** Oncology Diagnostic Panels and NGS Services[2]

| COMPANY | PRODUCT | DISEASE | SCOPE OF COVERAGE | NUMBER OF GENES ANALYZED | INVESTIGATES |
|---|---|---|---|---|---|
| Foundation Medicine | Foundation One | Cancer | Panel | 236 genes, 47 introns from 19 gene rearrangements | Solid tumors: gene alterations |
| | Foundation One Heme | Cancer | Panel | 405 DNA genes, 31 introns from rearrangements; 265 RNA genes; gene fusions | Hematologic tumors: gene alterations, gene fusions |
| Personal Genome Diagnostics | Cancer Complete | Cancer | Full exome | ~20,000 | |
| | Cancer Select | Cancer | Panel | | |
| Ambry Genetics | Exome Next | Cancer | Exome | ~20,000 | Mitochondrial geome mutations, sequence variants |
| | BRCA1 and BRCA2 gene sequencing | Breast cancer | BRCA1 and BRCA2 | 2 | Gene sequencing, deletion and duplication, large rearrangements |
| GeneDx | XomeDx | Cancer | Full exome | ~20,000 | Exon analysis |
| | XomeDx Plus | Cancer | Exome | 20,000 plus mitochondrial sequencing | Mitochondrial genome sequencing and deletions |
| | XomeDx Slice | Cancer | Exome | Targeted test | Regions of the exome or specific genes |
| | Comprehensive cancer panel | Cancer | Panel | 29 | Gene sequence, deletions/duplications/mutations |
| NeoGenomics Laboratories | EGFR Mutation Analysis | NSCLC | EGFR exons 18-21 | 1 | Mutations on target exons, duplications/deletions |
| | NeoSITE Melanoma | Cancer | Panel | 5 | Copy number variants, duplications/deletions |
| | FISH for non-small cell lung cancer | NSCLC | Panel | 2 | Rearrangements, gene fusions |
| | Colorectal cancer panel | Colorectal cancer | Panel | 2 | KRAS and BRAF mutations, mismatch repair defects, microsatellite instability |
| Myriad Genetics | BRCA Analysis | Breast and ovarian cancer | BRCA1, BRCA2 | 2 | Gene mutations |
| Quest Diagnostics | OncoVantage | Solid tumors | Panel | 34 | Point mutations, INDELs |
| Arup Laboratories | Gastrointestinal hereditary cancer panel | Gastrointestinal cancer | Panel | 15 | Targeted capture of coding exons and intron/exon junctions, deletion/duplication analysis |

EGFR indicates epidermal growth factor receptor; FISH, fluorescence in-situ hybridization; INDELs, insertions and deletions; NSCLC, non-small cell lung cancer.

## APPLICATIONS OF NGS

Sequencing panels such as OncoType DX, MammaPrint, and Prolaris have had a tremendous impact on clinical diagnosis, prognosis, and treatment decisions in oncology. NGS gene sequencing panels have also found their place in the National Comprehensive Cancer Network guidelines for patients with ovarian cancer.[2] Despite persistent regulatory and reimbursement challenges, multiple gene panels and NGS diagnostic services are offered by several companies (**TABLE**).

While NGS has helped research scientists identify a number of abnormal cancer-causing genes, targeted drug development against those genes has not kept pace. There are a few success stories, though, including imatinib (which was developed to target the product of the *BCR-ABL* gene fusion) and trastuzumab (which targets *HER2*).

### *Need for whole-genome sequencing*

While whole-exome (the exome is the coding region of the genome) is currently the most popular method of sequencing, there is still a need for whole-genome sequencing funneled by the knowledge that the noncoding regions (introns) of the genome may have direct tumorigenic effects and can cause genomic instability. Individualized whole-genome sequencing offers the potential for personalized treatment and care management.[1] Identifying specific mutations, developing drugs to target those mutations, and individualizing treatment can improve outcomes and simultaneously reduce some of the side effects associated with the use of cancer drugs.

## COST OF SEQUENCING THE HUMAN GENOME

The National Human Genome Research Institute has categorized the expenditures associated with NGS as "production" and "non-production" costs (**FIGURE**).[3] Production costs include:

- Labor, administration, management, utilities, reagents, and consumables
- Sequencing instruments and other large equipment
- Informatics activities directly related to sequence production (eg, laboratory information management systems and initial data processing)
- Submission of data to a public database
- Indirect costs as they relate to the above

The non-production costs include:

- Quality assessment or control for sequencing projects
- Technology development to improve sequencing pipelines
- Development of bioinformatic or computational tools to improve sequencing pipelines or to improve downstream sequence analysis
- Management of individual sequencing projects
- Informatics equipment
- Data analysis downstream of initial data processing.

The sequencing of the first human genome, concluded in 2003, required 13 years and cost a staggering $3 billion.[4] The picture is very different today: Illumina boasts that the cost of sequencing a single genome is around $1000 (see Figure) and requires just days. These advances create an entirely new spectrum of opportunities to exploit.

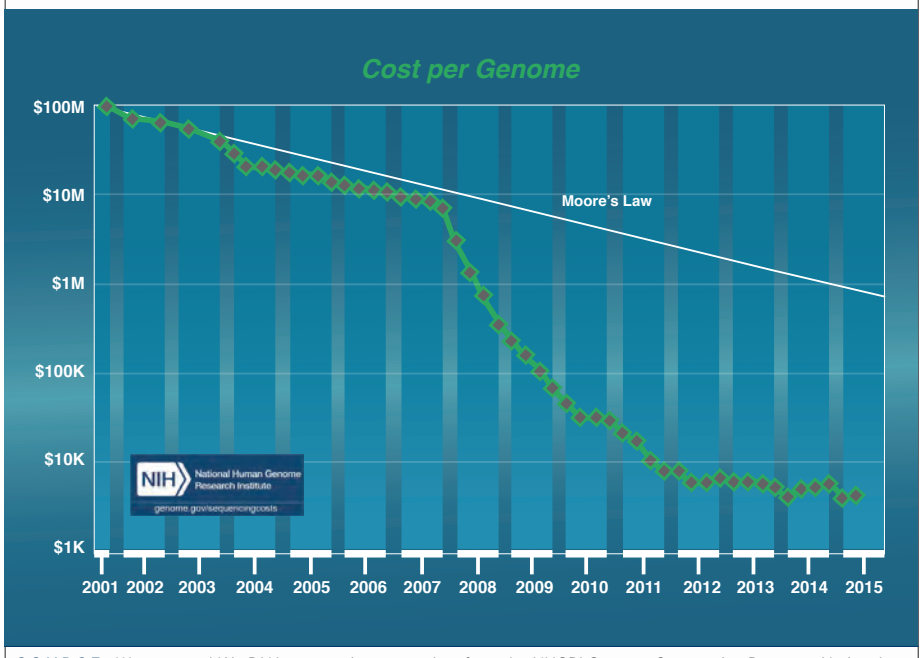
The cost-efficiency boast has a caveat, though: the low price is applicable only for high-volume users that handle huge DNA databases, such as the Broad Institute and the Sanger Institute. Additionally, the up-front cost of the instruments is high, ranging from $50,000 to $750,000.[4]

## POPULATIONWIDE GENOMIC SCREENS

Despite the obvious challenges, there are those who believe in the long-term advantages of NGS. The Department of Health in the United Kingdom has established Genomics England, a company that is currently working to sequence 100,000 genomes of individuals who have provided consent. With an anticipated 2017 completion date, the project is focused on patients with rare diseases and their families, and patients with common cancers.[5]

Closer to home, Regeneron Pharmaceuticals and the integrated healthcare

**FIGURE.** DNA Sequencing Costs[3]




SOURCE: Wetterstrand KA. DNA sequencing costs: data from the NHGRI Genome Sequencing Program. National Human Genome Research Institute website. www.genome.gov/sequencingcosts. Accessed July 28, 2015.

delivery organization Geisinger Health System have initiated a tremendous genetics undertaking—an attempt to improve drug discovery, development, and precision medicine. Announced at the beginning of 2014, the collaboration is aimed at sequencing the genomes of 100,000 patient volunteers and predicting long-term health outcomes by identifying and validating their association with diseases.[6]

David H. Ledbetter, PhD, executive vice president and chief scientific officer of Geisinger Health System, said in a press release, "For Geisinger, this relationship is about the potential to improve individualized patient care. We expect that many of our patients will directly benefit from their participation in this research because of Geisinger's ability to validate and return clinically actionable results to them, and all of our patients will benefit from the knowledge we gain in how to help set the standard for genomically informed care. This collaboration has the potential to provide Geisinger with tools to transform our ability to foresee disease before the onset of symptoms, diagnose chronic and potentially fatal conditions before it's too late to intervene, and determine how best to optimize the health and well-being for each of our patients."[6]

## CHALLENGES WITH NGS

Despite the opportunities envisioned for NGS to identify the right patient population for a specific treatment, the technology has not been adopted extensively, and for a reason—rather, several.

### *Technical*

While scientists surmounted the entire gamut of technical challenges as NGS was being developed, several aspects of the technology remain disputed.

a. **Data storage.** Storage, in a compressed format, of the data generated by a single exome sequencing requires about 10 GB of disk space; at just 3 runs a month, that adds up to 1.4 TB of data. Data analysis requires additional disk space. It all translates into an expensive bargain.
b. **Statistical significance.** Achieving statistical significance for the data may be challenging, with respect to finding as many samples to analyze and the associated cost. Collaboration may be key.
c. **Data safety/privacy.** Patient data may be difficult to keep secret. Safety of patients' genetic information is a prime public concern—information from SNP arrays, exome, or whole-genome sequencing could find its way into wrong hands and be exploited.
d. **Finding samples.** Inter-institutional collaborations may assist with obtaining large numbers of good quality samples. High standards are required to be maintained for sequencing samples obtained by using public funds.
e. **Functional validation.** Genetic information by itself is difficult to sell or make a persuasive argument with, and requires credible support from phenotypic or functional data.
f. **Translation to the clinic.** While several sequencing panels are already being used in the clinic, exome/whole-genome sequencing panels may not be far behind—if challenges with Clinical Laboratory Improvement Amendments (CLIA) certification are overcome.[7]

### *Reimbursement*

Assuming that technical hurdles will be met, how will manufacturers and users ensure that NGS will be reimbursed by payers? Similar to the challenges faced by existing diagnostic panels, analytical validity and clinical utility will top the list of concerns that payers would have with NGS, particularly whole- genome sequencing. Another important concern will be whether the results from an NGS test are clinically actionable to necessitate medical intervention.

The lack of coordinated data generation—based on regulator and payer requirements—has created a difficult-to-cross chasm in the healthcare world. Payers use clinical utility (the impact of diagnostic tests on patient health outcomes) as the gold standard when making coverage decisions. What payers hope to learn prior to making these decisions is whether the test is safe for patients, whether it reliably provides the information needed for clinical decision making, and whether it would add to the rising cost of healthcare.[8]

With the movement toward value-based payment, the other important question that needs to be answered is whether payment for NGS will be based on current reimbursement practices, or a new value-based paradigm will be established, the premise for which would be improved outcomes or reduced spending that results from using the test. While data from diagnostic tests focused on specific disease-associated genes might be relatively easy to analyze and interpret, a broad genomic interrogation by NGS might be complex and would likely require a team of professionals to interpret the results. This would prompt additional questions regarding what is being "valued" when making coverage decisions.[8] Additionally, most NGS-based tests are laboratory developed tests, or LDTs, and fall under CLIA regulations, not those of the FDA. This raises payer as well as provider concerns about the regulatory oversight of these tests, as was indicated by participants in a panel discussion convened by *The American Journal of Managed Care* earlier this year.[9]

Said panel participant Daniel F. Hayes, MD, clinical director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, and president-elect, 2016-2017, of the American Society of Clinical Oncology: "We critically need to take 3 actions: modify the regulatory environment, discuss the analytical validity of a diagnostic test, and identify who really decides the utility of LDTs."[9] **EBO**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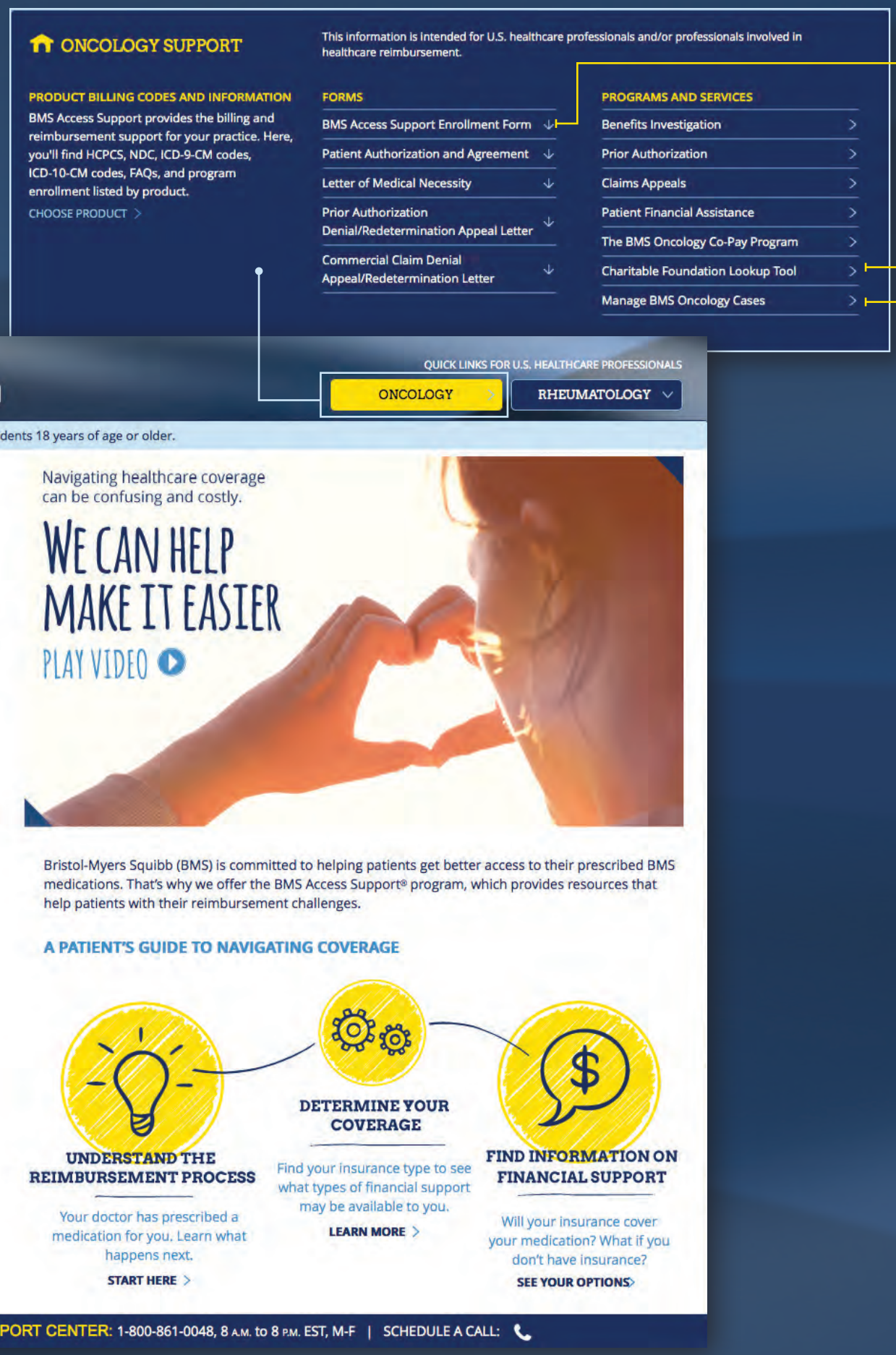

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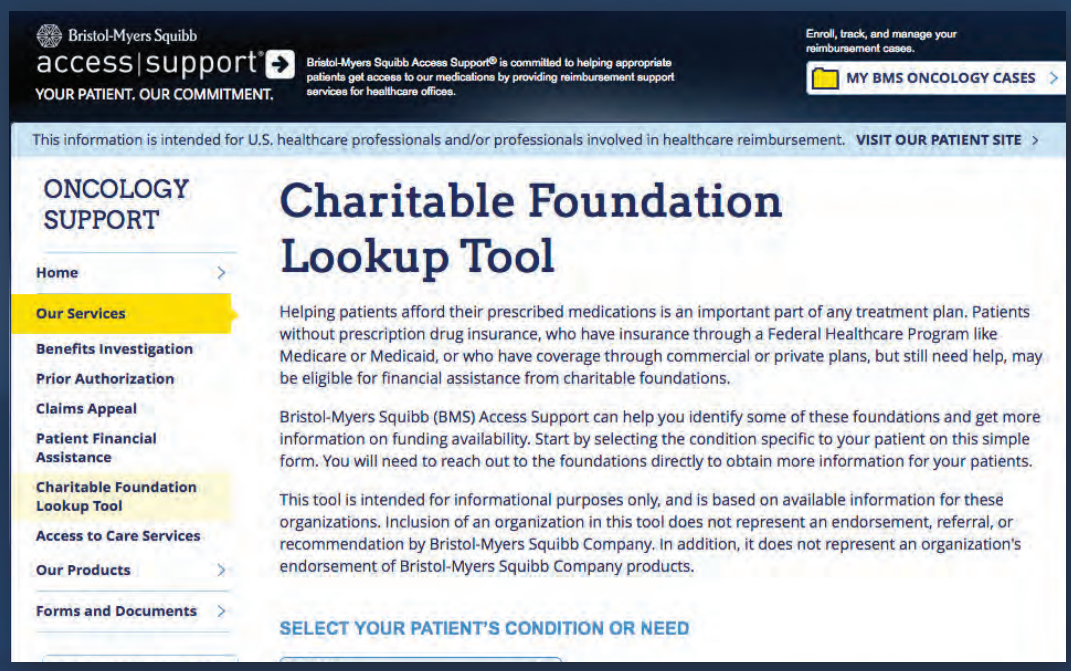


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# Personalized Medicine: *On the Brink of Revolutionizing Cancer Care*

Sean Khozin, MD, MPH; and Gideon Blumenthal, MD


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*The FDA's expedited programs have provided an efficient regulatory framework for accelerating the development and review of personalized therapies. One of the most recent additions to the FDA's expedited programs is breakthrough designation, which was signed into law on July 9, 2012.*

## INTRODUCTION

Personalized (or precision) medicine has been broadly described as the administration of the right therapy to the right patient at the right dose and intensity. The idea behind personalized medicine is not new and the phrase started to appear in the English literature in the late 1800s.[1] Emphasis on the therapeutic patient-doctor relationship was among the earliest strategies for tailoring care to the specific needs of the patient. For example, house calls were a common method for delivering medical care until the early 20th century and allowed doctors to incorporate both quantitative (eg, discrepancies in medication regimens) and qualitative (eg, a patient's performance status and support at home) information into an individualized care plan.[2] Modern concepts in personalized medicine are defined by their focus on utilizing advances in technology for tailoring care. Blood typing to guide transfusions, monitoring the international normalized ratio for dosing warfarin, and predicting hypersensitivity reactions to the antiretroviral drug abacavir based on the presence of the HLA-B*5701 allele are well-known examples of a biomarker-driven approach to personalizing care in modern medicine.[3]

Recently, key stakeholders have articulated widespread support for bringing greater focus to personalized medicine. This commitment is fueled by recent advances in molecular biology, genomics, and health information technology.[4] In his 2015 State of the Union address, President Obama announced the Precision Medicine Initiative. The president's 2016 Budget includes a $215-million investment for the Initiative, the purpose of which will be to "pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients."[5] Important components of this initiative include new funding for the National Cancer Institute to identify genomic drivers in cancer, and for the FDA to create a regulatory framework in support of innovations in precision medicine (TABLE 1).

**TABLE 1.** Key Investments in the President's 2016 Budget to Launch the Precision Medicine Initiative

| INVESTMENT | AGENCY | OBJECTIVES |
|---|---|---|
| $130M | NIH | To develop, in collaboration with other agencies, a voluntary national research cohort of a million or more volunteers.<br>• Sources of information will include medical records, environmental and lifestyle data, patient-generated information, and personal device and biometric sensor data. |
| $70M | NCI | To scale up efforts to identify genomic drivers in cancer and apply that knowledge in the development of more effective approaches to cancer treatment. |
| $10M | FDA | To acquire additional expertise and advance the development of high-quality curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health. |
| $5M | ONC | To develop interoperability standards and requirements that address privacy and enable secure exchange of data across systems for the voluntary national research cohort initiative. |

M indicates million; NCI, National Cancer Institute; NIH, National Institutes of Health; ONC, Office of the National Coordinator for Health.

## ON TARGET

The president's Precision Medicine Initiative underscores the emphasis placed on personalizing care in the fight against the emperor of all maladies: cancer.[6] The field of oncology has recently seen unprecedented activity in this area with the successful development of several targeted therapies, and the FDA has been in the forefront of efforts to ensure timely access to, and the safe and effective use of, these therapies.

Targeted therapy can be defined as a treatment with a molecular target that controls biologically important processes that are central to the initiation and maintenance of cancer. Ideally, the target should be measurable in the clinic and measurement of the target should correlate with clinical benefit following administration of the targeted therapy.[7] Of the 29 FDA approvals by the Office of Hematology and Oncology Products since the beginning of 2014, the majority have been of therapies with specific targets (TABLE 2).

The FDA's expedited programs have provided an efficient regulatory framework for accelerating the development and review of personalized therapies.[8] One of the most recent additions to the FDA's expedited programs is breakthrough designation, outlined in Section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012.[9] Requests for breakthrough designation can be made when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant end points for the treatment of serious or life-threatening diseases such as advanced cancers. Following designation, the FDA mobilizes its resources to expedite the development and review of the designated drug. Since the program's inception, nearly half of the requests have been for oncology drugs, most of which have been targeted therapies. The description in the following section of the approval of the targeted agent ceritinib, the first breakthrough designated drug for the treatment of advanced lung cancer, illustrates the FDA's organizational commitment to the program.

## OPPORTUNITIES AND CHALLENGES IN DEVELOPING TARGETED THERAPIES

### *Small Molecule Kinase Inhibitors*

In the late 1980s, scientists began identifying compounds with inhibitory activity against protein kinases.[10] At the time, evidence emerged on the molecular genetics of chronic myeloid leukemia (CML) underpinning the cytogenetically visible shortening of chromosome 22 (ie, the Philadelphia chromosome) described in prior decades.[11-13] The Philadelphia chromosome is the product of an oncogenic reciprocal translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)], resulting in a fusion protein called BCR-ABL with a constitutively activated tyrosine kinase domain.[14] On May 10, 2001, imatinib, a BCR-ABL tyrosine kinase inhibitor (TKI), was approved by the FDA based on demonstration of exceptional clinical activity and a favorable safety profile in patients with CML.[15] The approval of the drug, heralded as a magic bullet and a new hope for cancer, created significant excitement about the promise of targeted therapies. Commenting on the contributions of his laboratory to the development of imatinib, the 2009 recipient of the Lasker-DeBakey Clinical Medical Research Award, Brian Druker, observed that maximizing the value of targeted therapies in treating cancer would require directing these agents to genetic

**TABLE 2.** OHOP Approvals From January 1, 2014, to May 18, 2015 (excluding 1 biosimilar)

| APPROVAL DATE | TYPE | DRUG | PRIMARY TARGET | INDICATION | CDx |
|---|---|---|---|---|---|
| April 24, 2015 | T | Ramucirumab | VEGF-R2 | In combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer whose disease has progressed on a first-line bevacizumab-, oxaliplatin-, and fluoropyrimidine-containing regimen. | No |
| March 10, 2015 | T | Dinutuximab | GD2 | In combination with granulocyte-macrophage colony-stimulating factor, interleukin-2, and 13-cis-retinoic acid, for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent multimodality therapy. | No |
| March 4, 2015 | T | Nivolumab | PD-1 | Treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. | No |
| February 23, 2015 | A | Panobinostat | HDAC | In combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. | No |
| February 13, 2015 | T | Lenvatinib | VEGF | Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. | No |
| February 3, 2015 | A | Palbociclib | CDK4/6 | In combination with letrozole for the treatment of postmenopausal women with estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. | No |
| January 29, 2015 | T | Ibrutinib | BTK | Treatment of patients with Waldenström's macroglobulinemia. | No |
| December 22, 2014 | A | Nivolumab | PD-1 | Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF V600* mutation–positive, a BRAF inhibitor. | No |
| December 19, 2014 | T | Olaparib | PARP | Treatment of patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. | Yes |
| December 16, 2014 | T | Lanreotide | N/A | Treatment of patients with unresectable, well or moderately differentiated, locally advanced, or metastatic gastroenteropancreatic neuroendocrine tumors, to improve progression free survival. | No |
| December 12, 2014 | T | Ramucirumab | VEGF-R2 | In combination with docetaxel for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. | No |
| December 4, 2014 | T | Ruxolitinib | JAK1/2 | Treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. | No |
| November 14, 2014 | T | Bevacizumab | VEGF | In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. | No |
| November 5, 2014 | T | Ramucirumab | VEGF-R2 | In combination with paclitaxel for the treatment of patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. | No |
| September 4, 2014 | A | Pembrolizumab | PD-1 | Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if *BRAF V600* mutation–positive, a BRAF inhibitor. | No |
| August 14, 2014 | T | Bevacizumab | VEGF | Treatment of persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan. | No |
| July 23, 2014 | T | Idelalisib | PI3Kδ | Treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other comorbidities. | No |
| July 3, 2014 | A | Belinostat | HDAC | Treatment of patients with relapsed or refractory peripheral T-cell lymphoma. | No |
| April 29, 2014 | T | Ceritinib | ALK | Treatment of patients with ALK-positive metastatic NSCLC with disease progression on, or who are intolerant to, crizotinib. | No |
| April 28, 2014 | T | Mercaptopurine | N/A | Treatment of patients with acute lymphoblastic leukemia as part of a combination regimen. | No |
| April 23, 2014 | T | Siltuximab | IL-6 | Multicentric Castleman's disease who are human immunodeficiency virus–negative and human herpes virus-8–negative. | No |
| April 21, 2014 | T | Ramucirumab | VEGF-R2 | Advanced or metastatic, gastric, or GEJ adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy. | No |
| April 17, 2014 | T | Ofatumumab | CD20 | In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate. | No |
| February 12, 2014 | T | Ibrutinib | BTK | Patients with CLL who have received at least 1 prior therapy. | No |
| January 10, 2014 | A | Trametinib/ dabrafenib | MEK/BRAF | Patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation as detected by an FDA-approved test. | Yes |

A indicates accelerated approval; CDx, companion diagnostic; OHOP, Office of Hematology and Oncology Products; T, traditional (regular) approval.

or epigenetic changes in tumors, tumor metabolism, stem cells, and tumor-stroma interactions.[16]

The FDA's accelerated approval in 2011 of the anaplastic lymphoma kinase (ALK) TKI demonstrates the value of the tailored approach articulated by Druker in delivering targeted therapies.[17] While *ALK* gene rearrangement is present in about 5% of patients with advanced non-small cell lung cancer (NSCLC).[18] *ALK* mutations involve oncogenic inversions within the short arm of chromosome 2 with a fusion protein product (most common being EML4-ALK) that bears a constitutively activated kinase domain.[19] The accelerated approval of crizotinib was based on the demonstration of durable overall response rates (ORRs) of 51% and 60% and a favorable safety profile in patients with advanced *ALK*-positive NSCLC in 2 single-arm trials, a treatment effect far superior to traditional chemotherapy's ORRs of 10% to 30% based on historical experience. A companion diagnostic assay based on an ALK break-apart fluorescence in situ hybridization kit was concurrently approved for patient selection. In 2013, crizotinib received traditional (ie, regulator) approval based on demonstration of superior progression-free survival (PFS) in a confirmatory randomized trial against second-line chemotherapy (docetaxel or pemetrexed) in patients with *ALK*-positive advanced NSCLC.[20]

Similar to the EGFR TKIs afatinib and erlotinib, which received traditional FDA approval in 2013 for use in patients with advanced *EGFR* mutation–positive NSCLC, patients taking crizotinib invariably have tumor progression, usually within the first year of treatment.[21] Development of resistance to TKIs occurs via different mechanisms, including emergence of secondary mutations and bypass oncogenic signaling pathways. In early 2013, the FDA granted a second-generation ALK inhibitor, ceritinib, breakthrough therapy designation based on preliminary evidence of clinical activity in patients with meta-

static *ALK*-positive NSCLC previously treated with crizotinib. Ceritinib subsequently received accelerated approval for patients with advanced *ALK*-positive NSCLC based on demonstration of durable ORR and favorable benefit-risk in patients whose disease had progressed on crizotinib.[22] Ceritinib's approval came only 3 years following initiation of the first-in-human trial and 4 months after submission of the new drug application, demonstrating the FDA's commitment to expedite the development and review of promising and breakthrough-designated therapies.

Targeting oncogenic driver mutations by inhibition of constitutively activated kinase products using kinase inhibitors has also been successful in other diseases, such as *BRAF*-mutated melanoma. The BRAF inhibitor dabrafenib was approved in 2013 for treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutation based on superior PFS improvement and a favorable safety profile in a randomized trial with dabrafenib versus a standard chemotherapeutic agent, dacarbazine.[23] As with EGFR and ALK TKIs in advanced NSCLC, resistance to dabrafenib usually develops within the first year of treatment.

### *Monoclonal Antibodies*

Modern recombinant techniques that evolved in the 1990s made it possible to rapidly produce chimeric and humanized antibodies with reduced immunogenicity.[24] In 1997, rituximab, a chimeric monoclonal antibody against CD20, an antigen primarily found on the surface of immune system B cells, became the first monoclonal antibody to receive FDA approval for cancer therapy.[25] The initial approval of rituximab for the treatment of patients with relapsed or refractory low grade or follicular B-cell non-Hodgkin lymphoma was later expanded to include more aggressive subtypes. Evidence of the efficacy of rituximab for the initial approval was based on demonstration of durable ORR of large magnitude. Unlike most kinase inhibitors, the exact mechanism of action of rituximab and newer CD20-directed therapies is poorly understood. Likely mechanisms of action include antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and induction of apoptosis. However, the specific role of each mechanism in vivo remains uncertain, and there is little understanding of the underlying molecular mechanisms leading to resistance.[26]

Greater understanding of the mechanisms of response and resistance to monoclonal antibodies can help in individualizing therapy to maximize therapeutic benefit. For example, selection of patients with breast cancer whose tumors have amplification of the human epidermal growth factor receptor 2 (*HER2*) gene and overexpression of HER2 is the standard and FDA approved method for treatment with the HER2-directed monoclonal antibodies trastuzumab and pertuzumab. Likewise, the discovery of *KRAS* mutations as a negative predictive marker for response to EGFR-directed monoclonal antibodies led to changes in the FDA approved product labels of cetuximab and panitumumab in 2009, restricting the use of these drugs to patients with *KRAS* wild-type tumors. Unfortunately, nearly half of patients with *KRAS* wild-type colorectal tumors do not derive clinical benefit from the EGFR monoclonal antibodies, which highlights the existence of additional predictive markers within a complex signal transduction milieu.[27]

*Given that most cancers may be caused by random mutations arising from stem cell divisions of normal self-renewing cells, application of our evolving understanding of cancer genomics to secondary prevention for detection of early oncogenic events is an important strategy for reducing the burden of cancer-related deaths that can augment personalization of care in the global fight against cancer.*

Efforts to increase the therapeutic benefit of monoclonal antibodies have led to the strategy of combining their targeting properties with the cytotoxicity of chemotherapeutic agents through development of antibody drug conjugates. Gemtuzumab ozogamicin, a humanized IgG4 monoclonal antibody coupled with calicheamicin, in 2000 became the first antibody drug conjugate approved by the FDA under the accelerated approval program for the treatment of acute myeloid leukemia.[28] The drug was, however, withdrawn a decade later due to concerns about the product's safety and its failure to demonstrate clinical benefit to patients enrolled in clinical trials. Brentuximab vedotin (a chimeric monoclonal antibody anti CD-30 coupled with monomethyl auristatin E) and ado-trastuzumab emtansine (the HER2-targeting monoclonal antibody trastuzumab conjugated to the cytotoxic compound DM1) were approved by the FDA for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma in 2011 and for HER2-positive metastatic breast cancer in 2013.

Several new biopharmaceutical technologies, such as cell-penetrating peptides and non-Ig based protein scaffolds, are currently under investigation. Many of these new technologies rely on target-specific internalization of the therapeutic agent, a process that aims to either alter the intracellular environment or deliver toxic payloads to the cytoplasm and/or specific subcellular compartments, with the end result of targeted cell death.[29]

### *Immunotherapy*

Despite over a century of debate on the capacity of the immune system to fight malignant tumors, it was not until the 1960s that immunologists began to recognize the fact that a major function of the immune system is to eliminate malignant cells—a phenomenon based largely on a hypothesis proposed by Frank Macfarlane Burnet.[30,31] Decades later, administration of high doses of IL-2 became the first immunotherapy to show complete and durable responses, its approval by the FDA for treatment of patients with renal cancer and melanoma coming in 1992 and 1998, respectively.[32] However, significant toxicities associated with the administration of high-dose IL-2 have limited its use in clinical practice.

In the early 2000s, accumulating preclinical evidence of the role of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) showed that it acted as an immunologic checkpoint that negatively regulates T-cell responses; further, blocking CTLA-4 was discovered to inhibit interaction of the protein with its ligands, leading to antitumor activity via T-cell activation and proliferation. These findings led to the development of the anti-CTLA-4 antibody ipilimumab.[33] In 2011, the FDA approved ipilimumab for the treatment of unresectable or metastatic melanoma based on demonstration of superior improvement in overall survival (OS) in previously treated patients with advanced melanoma.

Selective blockade of immune checkpoint receptor, programmed cell death 1 (PD-1) or its ligand PD-L1, has also been shown to induce antitumor responses. Unlike CTLA-4, which is expressed exclusively on T cells and normally counteracts the activity of the T-cell costimulatory receptor CD28, the main role of PD-1 is to dampen the activity of T cells in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity.[34] Inhibition of PD-1 or PD-L1 have been successful strategies to illicit clinically significant antitumor responses. Several PD-1, PD-L1, and CTLA-4 antibodies are currently in development, many of which are being investigated in diseases such as lung cancer not traditionally thought to be amenable to immunotherapies. In 2015, the anti-PD-1 antibody nivolumab received FDA approval for the treatment of advanced melanoma in patients previously treated with ipilimumab, as well as in patients with squamous non-small cell lung cancer (SQ NSCLC) with progression on or after platinum-based chemotherapy. Treatment with nivolumab in SQ NSCLC was associated with clinically significant OS prolongation compared with standard second-line chemotherapy.

Emerging data suggest that tumor positivity for PD-L1 expression is a predictor of response to anti-PD-1 and anti-PD-L1 antibodies. However, there is currently no standard definition for PD-L1 positivity. Development plans for immunohistochemical characterization of PD-L1 in tumor tissue can benefit from standardized methods for analytical and clinical validation of companion diagnostic assays for patient selection.

## CONCLUSIONS

Recent technological advances in development of targeted therapies using kinase inhibitors and monoclonal antibodies have paved the way for personalization of therapy in a growing segment of cancer patients. In cases where validated predictive biomarkers are available, administration of targeted therapies such as ALK inhibitors in NSCLC have been associated with unprecedented tumor response and clinical benefit. However, significant challenges remain, and curative interventions for advanced malignancies are extremely rare. Efforts to design tolerable combination therapies involving immune checkpoint and kinase inhibition are rational means of maximizing clinical benefit in the targeted delivery of anticancer therapies.[35,36] These efforts can greatly benefit from appropriate patient selection based on molecular or immunohistochemical characterization of tumors and application of liquid biopsy techniques to supplement traditional disease classification schemes. Given that most cancers may be caused by random mutations arising from stem cell divisions of normal self-renewing cells, application of our evolving understanding of cancer genomics to secondary prevention for detection of early oncogenic events is an important strategy for reducing the burden of cancer-related deaths that can augment personalization of care in the global fight against cancer.[37] **EBO**

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PCOC15 PATIENT-CENTERED ONCOLOGY CARE

# Patient-Centered Oncology Care 2015: *When Personalized Medicine Meets Regulation*

Mary K. Caffrey

The promise of precision medicine puts effective cancer care in closer reach of more patients than ever, but the cost of that care presents hurdles that more patients will face as the nation ages and drug prices escalate.

How stakeholders—payers, providers, policymakers, patient advocates, and leaders from the pharmaceutical industry—address these challenges is the purpose of the 2015 session of Patient Centered Oncology Care, to be held November 19-20 in Baltimore, Maryland, at the Marriott Waterfront. For information and to register, visit http://www.ajmc.com/meetings/pcoc15.

The keynote speaker will be **Julie M. Vose, MD, MBA, FASCO,** the current president of the American Society of Clinical Oncology. Dr Vose is the Neumann M. and Mildred E. Harris professional chair and chief of the Oncology/Hematology Division in the Department of Internal Medicine at the University of Nebraska Medical Center. She is also the associate director of clinical research at the Fred and Pamela Buffett Cancer Center.

Precision medicine will be high on the agenda, including the regulation of diagnostic testing, reimbursement challenges, and how President Barack Obama's initiative will affect oncology practice. Speakers and a panel discussion on immuno-oncology, as well as updates on new payment models and the influence of accountable care organizations will give attendees a cross section of all the elements affecting cancer care today.

"Today's practicing oncologist must follow not only scientific developments but also the changes in healthcare management, reimbursement, and regulation," said Brian Haug, president of *The American Journal of Managed Care* and the conference host. "It's rare to hear at one meeting how all those pieces fit together, but each year we raise the bar with better information from the most important leaders in cancer care."

Discussions at Patient-Centered Oncology Care 2015 will include:

- The impact of FDA regulation on molecular diagnostic testing in oncology, featuring **Bruce Quinn, MD, PhD,** of Foley Hoag; **Michael Kolodziej, MD**, of Aetna; and **Scott Gottlieb, MD,** of the American Enterprise Institute.
- Reimbursement challenges in oncology, featuring Daniel Klein of the PAN Foundation; Syed Yousuf Zafar, MD, of the Duke Cancer Institute; Peter Bach, MD, Memorial Sloan-Kettering; and John Fox, MD, MHA, of Priority Health.
- An examination of the conflict between competing mandates for "personalized medicine" and "population management," featuring Burton VanderLaan, MD, of Priority Health; Debra Patt, MD, MPH, of Texas Oncology; and Joseph C. Alvarnas, MD, of City of Hope, who is also the editor in chief of *AJMC*'s *Evidence-Based Oncology*. **EBO**

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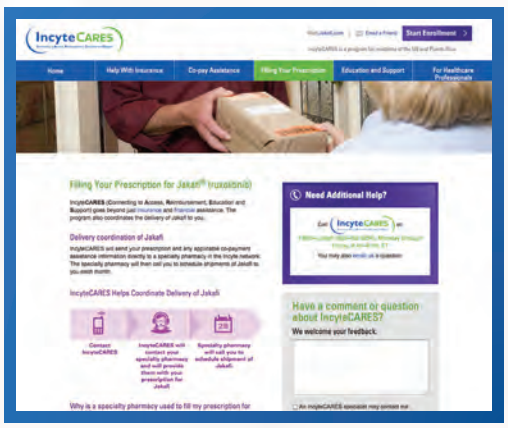


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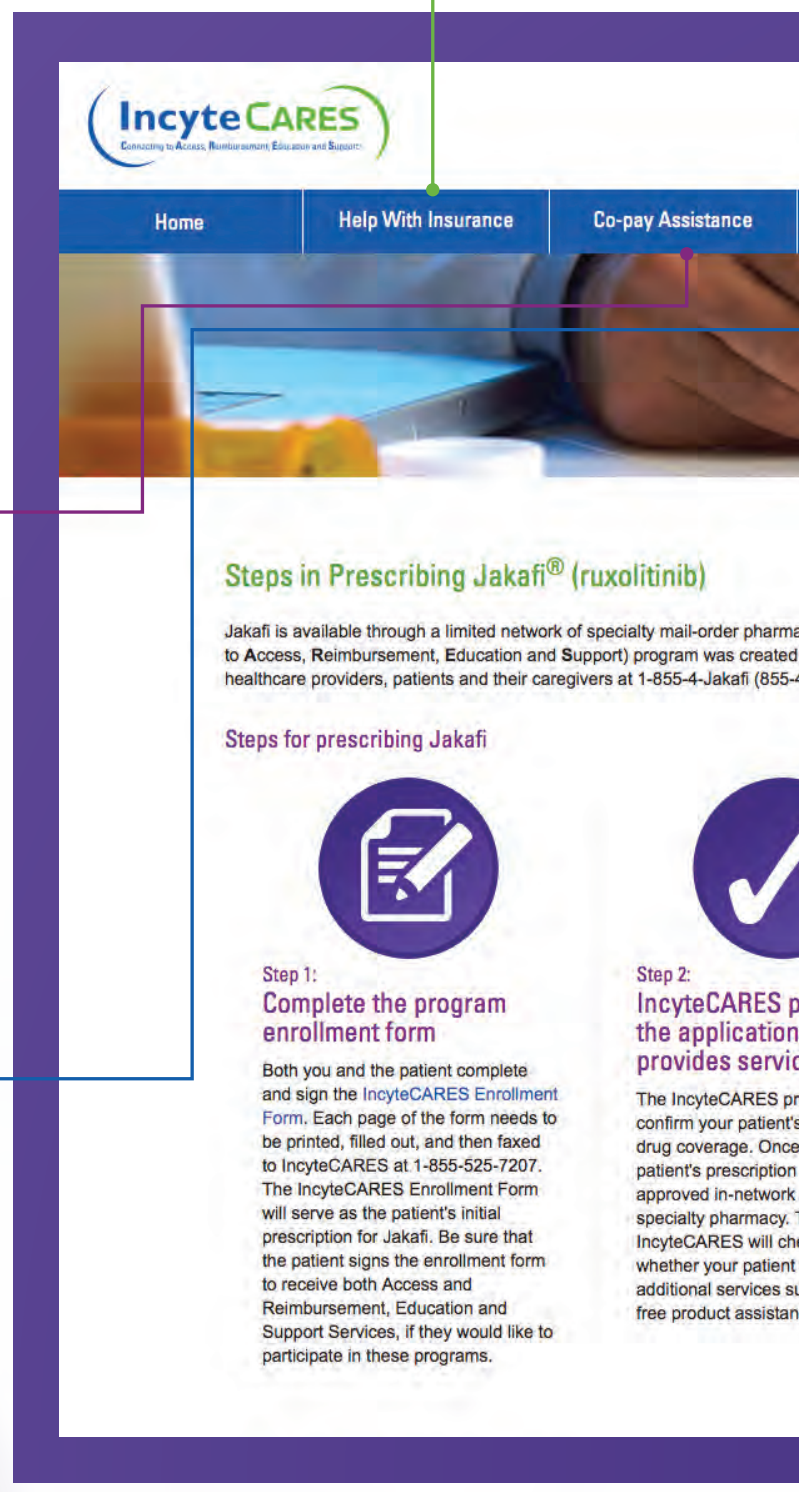


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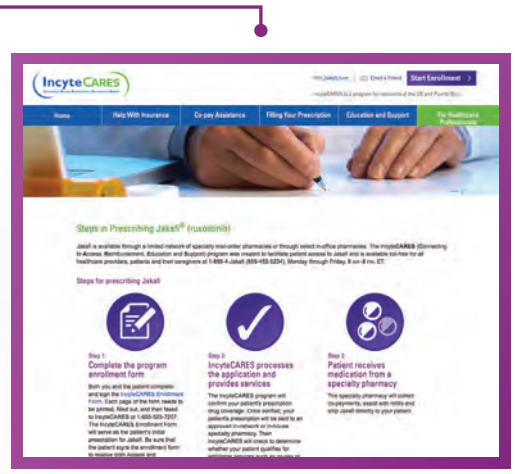


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# Precision Oncology: *Are Payers on the Right Pathway?*

Jerry Conway and Mark Oldroyd, JD


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## A NEW VISION

In 2009, a 58-year-old man diagnosed with poorly differentiated adenocarcinoma of the lung received then standard of care diagnostics and treatment, including neoadjuvant therapy, surgical resection, and postoperative radiotherapy, which stabilized the disease. In 2012, the patient experienced abdominal pain, and a diagnostic workup confirmed relapse of his lung adenocarcinoma. Polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH)–based molecular testing of the *EGFR*, *KRAS*, *BRAF*, *HER2*, *ALK*, *ROS1,* and *MET* genes were each negative. After 2 cycles of standard chemotherapy, the tumor was refractory, and the patient's condition worsened. Additional molecular testing was completed, and a novel *RET/KIF5B* gene fusion, discovered by Foundation Medicine in 2012,[1] was reported. The patient was then started on the *RET* inhibitor vandetanib, leading to clinical remission.[2]

Following the discovery of the *RET/KIF5B* gene fusion by Foundation Medicine, additional data demonstrating clinical responses to another *RET* inhibitor, cabozantinib,[3,4] led the National Comprehensive Cancer Network (NCCN) to include *RET* fusions and cabozantinib treatment in the 2014 guideline update recommending broad molecular profiling for lung adenocarcinoma patients.[5] Thus, within 2 years, a previously unknown genomic alteration (*RET* fusion) and a matched targeted therapy option were identified and demonstrated clinical utility. This progression from discovery to guidelines to standard of care is one of many examples that underscore the rapid evolution from empirically selected cytotoxic treatment to genomically driven, precision oncology care for an increasingly broad population of patients.

## THE UNMET NEED

Payers challenged with the task of managing quality, access, and cost of cancer care struggle to keep pace with the innovations and rapid evolution of precision oncology. The total costs of cancer are rising exponentially; annual costs for cancer care in the United States increased from $104 billion in 2006 to a projected $173 billion in 2020.[6] At the same time, many patients are living longer. Largely due to earlier stage detection, two-thirds of Americans live at least 5 years after a cancer diagnosis, an improvement in survival since the collection of such data began in the Surveillance, Epidemiology, and End Results (SEER) Program in the 1970s.[7] It is estimated that the number of new cancer cases will increase by 45% in the United States by 2030, making cancer the nation's leading cause of death, driven largely by the growing number and aging of patients from the baby boomer generation.[6]

The current standard of care in oncology often results in wasted dollars. Adverse events associated with invasive procedures, non-targeted treatment toxicity and unnecessary testing, as well as emergency department (ED) visits and hospitalizations, all drive substantial human and financial costs associated with comorbidity, reduced quality of life, and even mortality. The idea of 1 empiric treatment approach for every patient with a particular cancer (eg, breast cancer) is not yielding the results required to make meaningful improvements in care. Because of failures with the empiric approach, and the new understanding that cancer is a disease of the genome, treatment is rapidly moving toward precision-based oncology care.

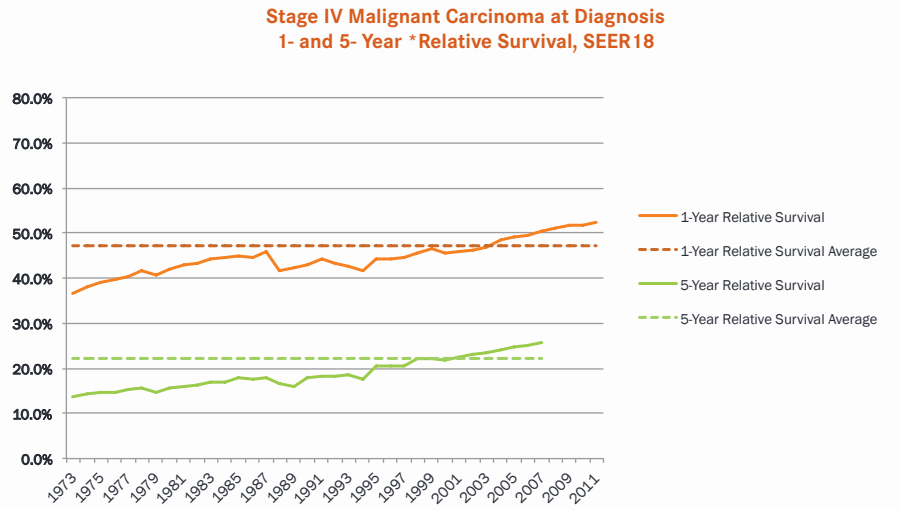
Understanding a patient's cancer at the level of the genomic drivers requires new approaches to diagnostics. Current molecular diagnostic testing platforms are primarily "hotspot" tests (ie, a small segment or segments of the coding region within cancer genes where common alterations—usually only base substitutions and some insertions or deletions—are found). "Hotspot" tests have significant limitations, including the potential for missing clinically relevant genomic alterations, being too costly and inefficient, and using too much tissue. For example, insufficient tissue to complete *all* of the recommended diagnostic cancer tests is a growing problem. Using conventional methods (eg, FISH, immunohistochemistry, PCR), precious tissue is consumed by multiple types of "hotspot" tests. This challenge may affect patient safety, potential treatment efficacy, and cost-effectiveness of care. A recent study reported that the primary reason for not successfully testing all targetable alterations was insufficient tissue for the basic molecular testing itself, in addition to the fact that 2 or more biopsies were often required to complete requisite molecular testing.[8] Insufficient tissue places the patient at risk for additional comorbid and costly procedure(s),[9] which can be avoided with a tissue-sparing approach to testing.

Precision oncology cancer care is becoming routine, with more than 300 identified driver and tumor suppressor genes, hundreds of test options, and more than 40 FDA-approved targeted therapies available.[10] Targeted therapy is primarily used in advanced stages of disease (ie, stage IV) since patient treatment and outcomes in earlier stages are often highly amenable to standard chemotherapy, radiation, and surgical resection. While molecular testing is standard for many advanced tumor types (eg, stage IV breast cancer), payers are reporting enormous costs from overutilization, often in excess of $10,000 per member diagnosed with cancer. And the influx continues—targeted therapy pipelines for commercial development include more than 470 drugs for more than 150 molecular targets in over 950 clinical trials.[10]

Professional organizations like the NCCN and the American Society of Clinical Oncology (ASCO) consider clinical trials to be standard of care for patients with cancer,[11] and many new clinical trial designs are expanding access for patients.[12] When approved by the FDA, targeted therapies are projected to cost in excess of $100,000 per year with the potential for "combination" targeted therapy to multiply this cost impact further.

Unfortunately, in sharp contrast to improved survival in early stage disease, the relative survival rates of patients with advanced cancer remain largely unchanged (**FIGURE 1**). Despite decades of research, promising advances in treatment, and billions of dollars of investment, improved outcomes and quality of life have yet to be realized for most patients with advanced cancer. Additionally, the explosive growth of

**FIGURE 1.** SEER Data Demonstrating Lack of Improvement in Relative Survival Rates




*Relative survival (as distinct from overall survival, and associated with excess hazard rates) is defined as the ratio of observed survival in a population to the expected or background survival rate.

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total US, 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.



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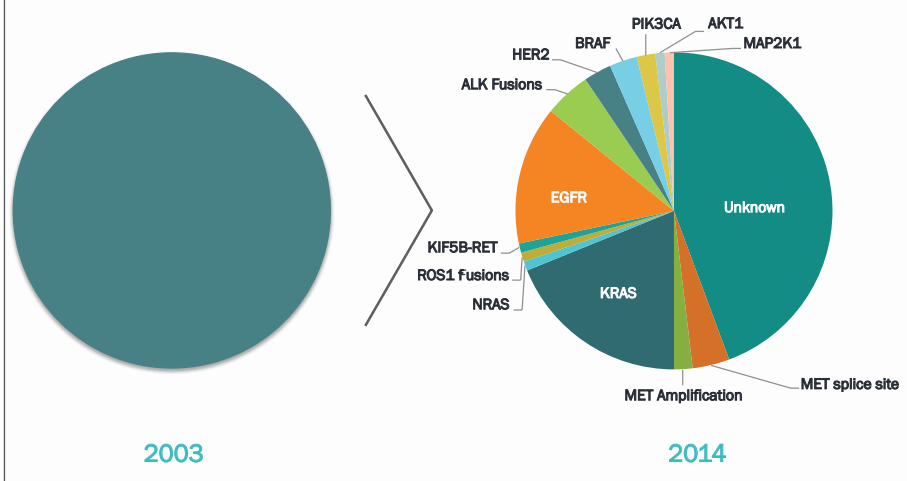
**FIGURE 2.** Paradigm Shift From a Histologic to a Histo-Genomic Diagnosis




SOURCE: Modified and updated from Pao W, Hutchinson KE. Chipping away at the lung cancer genome. *Nat Med.* 2012;18(3):349-351.

molecular tests and related treatment options are overwhelming the payers' ability to review and assess value for coverage and payment. Payers are clearly in need of simple solutions, and a new approach is required to improve outcomes and quality of life through improved safety, efficacy, and cost-effectiveness of diagnosis and treatment in later stages of disease.

## THE PAYER RESPONSE

Payers are responding with a variety of alternative payment solutions to managing the quality, accessibility, and accelerating costs of cancer care. Examples include but are not limited to payer-provider collaborative programs, such as:

- Oncology medical homes
- Pay for performance
- Bundled payment
- Limited provider networks
- Nurse navigators
- End-of-life support
- Survivorship support
- Treatment pathways

For example, UnitedHealthcare, in a pilot initiated in 2009, reimbursed 5 oncology practices a flat fee for physician care and drug infusions in breast, colon, and lung cancer. While total costs were reduced by 34% compared with a control group, surprisingly, drug spending actually increased by 179% versus the same control group.[13] In a recent article, Molly Gamble summarizes this trend by stating: "But more recently, in the move from fee-for-service to pay-for-performance, payers and providers seem genuinely interested in meeting each other halfway when it comes to cancer care and costs. Whether through clinical protocols, provider-patient counseling sessions, genetic testing, or oncology-specific accountable care organizations and bundled payments, oncology presents several collaborative opportunities for providers and payers to better align incentives."[14]

Perhaps more controversial than other approaches, pathway-based programs have been developed and implemented to help streamline oncology decision making in an increasingly complex environment. These programs rely on evidence and provider incentives that reduce options and the trial-and-error approach common in many aspects of cancer care. Pathways align utilization and payment with evidence supporting a reasonable likelihood of improved safety, efficacy, and cost-effectiveness of treatment. Unfortunately, because these programs rely on empirical evidence and consensus opinion that is largely outdated and out of sync with new standard genomic practices, they are likely to yield a poor return on investment in terms of relative survival (**FIGURE 1**) and quality of life. Pathways *may* save some money in the short term, but in the long term may be less successful without the inclusion of precision oncology.

## PRECISION ONCOLOGY: A CORE SOLUTION

Cancer diagnosis and treatment is being transformed with the knowledge that cancer is a disease of the genome,[15-18] and the genomic "blueprint" responsible for driving cancer is unique to each patient, the so-called "malignant snowflake."[19] Data indicate that genomically driven targeted treatment, or precision oncology, is often less toxic, more efficacious,[20,21] and less expensive than traditional cytotoxic chemotherapy, especially when used as a first-line treatment option.[22] Targeted therapies also have the potential to improve patient outcomes and quality of life downstream, in addition to yielding cost savings. Transitioning patients from cytotoxic to targeted treatments is a smart solution that meets the core objectives of payer-initiated alternative payment models—improved outcomes and quality of life through increased safety, efficacy, and cost-effectiveness. As discovered by Newcomer et al,[13] while targeted treatments may initially be expensive, these costs can be significantly offset by the total cost-effectiveness achieved, primarily through:

- Eliminating unnecessary molecular tests
- Eliminating unnecessary biopsies
- Reducing cytotoxic chemotherapy use
- Optimizing targeted therapy utilization
- Reducing ED visits
- Reducing hospitalizations
- Reducing futile treatment

This shift toward precision oncology has been rapidly accelerating due in large part to advancements in our understanding of cancer biology and molecular testing, which better inform diagnosis and treatment decision making. Initially, targeted treatment options were based primarily on single gene "hotspot" or panel tests of 2 or more genes to identify known targetable alterations and "matched" therapies in a very limited subset of tumor types (eg, *EGFR*/erlotinib in non-small cell lung cancer [NSCLC]). However, this "1 target–1 drug" model is unsustainable, and a transition to comprehensive genomic profiling (CGP) of all clinically relevant cancer genes and classes of genomic alteration is already replacing the "hotspot" approach as standard practice for select groups of advanced cancer patients.

*The idea of 1 empiric treatment approach for every patient with a particular cancer (eg, breast cancer) is not yielding the results required to make meaningful improvements in care. Because of failures with the empiric approach, and the new understanding that cancer is a disease of the genome, treatment is rapidly moving toward precision-based oncology care.*

It is increasingly acknowledged that a comprehensive histo-genomic diagnosis (ie, combination of histologic classification by tumor type with subtyping by genomic characterization: **FIGURE 2**) based on a robust knowledge base, with deep analysis of all biologically and clinically relevant genes in cancer, is essential in treatment decision making because it enables a complete understanding of the cellular pathways that drive a tumor's growth. Such a comprehensive approach can provide clinicians with accurate information about treatment sensitivity, resistance, and the need for best supportive care options in the absence of clinically relevant alterations or matched therapies (ie, futile targeted treatment) (**FIGURE 3**).

There are many contributors to the emergence of highly validated CGP and robust decision-support platforms. These include the capability to simultaneously assess, with high sensitivity and specificity, all genes and classes of genomic alteration known to be biologically and clinically relevant in cancer (including base pair substitutions, copy number alterations, insertions/deletions, and select rearrangements), and a growing list of targeted therapeutics that can only be fully utilized with a comprehensive diagnostic approach. Modern medical techniques incorporating smaller, less invasive biopsy procedures cause a scarcity of tissue for diagnostic testing, which requires comprehensive and fully validated testing for patients with advanced cancers, using increasingly minute tissue samples. Test content can be updated daily to reflect the most current evidence supporting clinical utility, which relieves the payer burden of trying to keep pace with the rapidly evolving field of precision oncology.

Evidence supporting analytic validity, clinical validity, and clinical utility of CGP is now well established.[23] To assure quality, validation standards have recently been established by Palmetto MolDX,[24] and their new Local Coverage Determination *NSCLC, Comprehensive Genomic Profile Testing* (L36143) specifically establishes coverage criteria for CGP effective July 6, 2015. Additionally, at the 2015 ASCO meeting, Wheler et al reported on one of the first prospective trials to evaluate patient therapy matching—informed by CGP-improved survival in a group of patients with advanced, refractory tumors that were highly pretreated. Median overall survival was 10.8 months for patients receiving CGP-informed matched therapy versus 7.5 months for patients treated with non-matched therapy.[25]

For select patients with life-threatening advanced cancer, access to a single clinically effective and cost-efficient test is essential. A significant advantage of CGP is the opportunity to eliminate clinical inefficiency, costly use of suboptimal tests, and unnecessary biopsy procedures. Further, CGP enables effective utilization and cost management of

the increasing number of targeted therapies within the patient's medical and pharmacy benefit. As a core navigational aid for payer coverage, payment, and management programs, CGP enables the timely consideration of all available targeted treatment options consistent with relevant guidelines including those from the NCCN and the FDA. As precision oncology becomes more standardized, improved outcomes and quality of life will benefit broader patient populations[25]; and, as reported by Intermountain Healthcare at the 2015 ASCO meeting, the total cost of cancer care is likely to be substantially reduced as cytotoxic therapies, ED visits, hospital utilization, and related costs are replaced by preferential use of targeted therapies with improved safety and efficacy.[22]

## A NEW PATHWAY FOR PAYERS

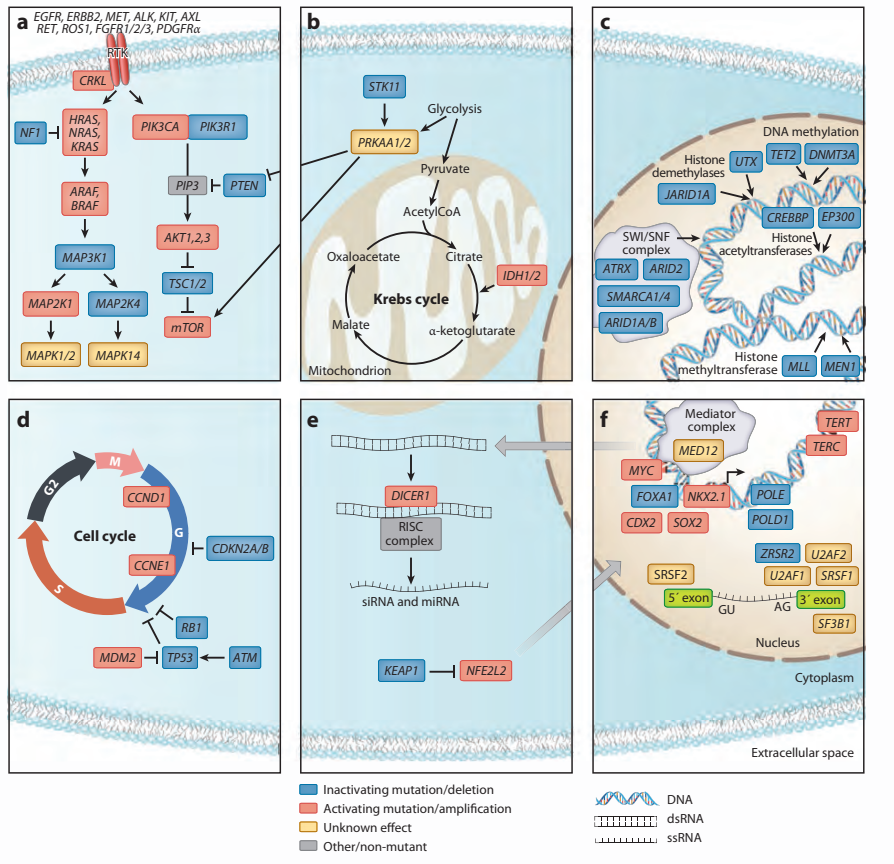
Payers challenged with the task of managing quality, access, and accelerating costs in cancer care are struggling to keep pace with the innovations and rapid evolution of precision oncology. Complicating matters further is the existing medical, coverage, and payment policy framework for diagnosis and treatment. This outdated framework is fundamentally organized around populations rather than individuals and is based on tumor histology that is not supplemented by the comprehensive genomic evaluation of specific alterations associated with the exhaustive universe of cancer genes.

The growth of precision oncology has generated a proliferation of new drugs and tests, with manufacturers and labs clamoring for payer coverage. The shift from a "companion diagnostic" to a "companion therapeutic" paradigm is in high gear; the current armamentarium of FDA-approved and clinical trial agents are now being matched to the patient based on their unique genomic profiles. Unfortunately, the noise and confusion is leading many payers to avoid coverage, missing out on the unique opportunity to proactively collaborate with leading experts by integrating precision oncology into pathways and other programmatic solutions.

Fortunately, payers can now benefit from proactively taking strategic steps to integrate precision oncology into coverage and alternative payment models, as noted below:

1. Acknowledge cancer as a disease of the genome; modify the existing coverage and payment policy framework to align with cancer biology and the N-of-1 diagnostic reality of treatment decision making as a frontline strategy.
2. Recognize CGP as a universal solution for precision targeted treatment decision making; reduce total costs of care by minimizing the use and costs associated with unnecessary biopsies, testing, cytotoxic treatments, and downstream ED visits and hospitalizations.
3. Partner with CGP providers capable of consistently meeting or exceeding high standards of analytic validation, clinical validation, clinical utility, and cost-effectiveness using tailored and efficiently integrated molecular information solutions.
4. Establish a genomic benefit management program that seamlessly integrates highly validated CGP data with expert decision support as the primary navigational tools informing evidence-based utilization and cost management solutions; for example, integrate CGP as the pathway to optimized use of targeted treatments in accountable care organizations, oncology medical home, pay for performance, bundled payment, limited provider networks, nurse navigators, end-of-life support, survivorship support, and/or treatment pathways.
5. Establish strategic advantage with precision oncology coverage and payment policies based on CGP as the "pathway" solution to successfully manage the growing costs in diagnostics and targeted treatment of members with advanced cancer. **EBO**

**FIGURE 3.** DNA Sequencing of Cancer: What Have We Learned?




SOURCE: Adapted from Chmielecki J, Meyerson M. DNA sequencing of cancer: what have we learned? *Annu Rev Med.* 2014;65:63-79.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# The Diagnosis for Diagnostics: *Changes to Medicare Payment and Coverage of Clinical Laboratory Tests*

Adam Borden, MHA; Danielle Showalter, MPH; Geoffrey Storchan, PhD; and Kathleen Hughes, MBA

In the United States, Medicare is the single largest purchaser of clinical laboratory tests, paying approximately $9.7 billion in 2012. Mostly driven by volume increases, Medicare spending on clinical laboratory testing rose by approximately 5.6% between 2003 and 2012.[1] Coding changes for molecular diagnostic and novel tests in recent years have provided CMS and other payers with more clarity regarding which tests are actually being included on claims. This has led to a greater ability to focus on and scrutinize the medical necessity of testing. Recent legislative changes and forthcoming CMS regulation will soon fundamentally change the methodology Medicare uses to determine payment rates for clinical laboratory tests paid under the Medicare Clinical Laboratory Fee Schedule (CLFS). We review the past, present, and future of Medicare payment for clinical laboratory services, which will impact all payers and providers in coming years.

## EVOLUTION OF THE CLINICAL LABORATORY FEE SCHEDULE

Under Medicare Part B, CMS covers laboratory tests that are considered reasonable and necessary when they are furnished in a Medicare participating laboratory and ordered by a physician or qualified non-physician practitioner who is treating the patient. Clinical laboratory tests (excluding most pathology services) are paid for by Medicare under the CLFS, which was created under the Deficit Reduction Act of 1984 (DRA).[2] The CLFS was established for laboratory tests on a regional, state, or carrier basis and was based on what local laboratories charged at that time. The DRA also mandated that the Consumer Price Index for All Urban Consumers (CPI-U) be used annually to adjust for inflation.

Following the DRA, the Consolidated Omnibus Budget Reconciliation Act of 1985 mandated that Congress establish national limit amounts (NLAs) on laboratory payments.[3] Initially capped at 115% of the median carrier rate for each test, the NLA was subsequently lowered by Congress from 1988 to 1998 to 74% of the median carrier rate for each lab test.[4] The payment amount for each test is determined based on the lowest of the provider's charge, carrier rate, or NLA. In order to establish rates for new tests, CMS uses 1 of 2 methods: cross-walking and gap-filling. Cross-walking is used when a new test is determined to be clinically or technologically similar to existing test(s) on the fee schedule. The exact payment amount of the test(s) used in the cross-walk becomes the NLA for the new code. Gap-filling is used when no comparable test is available. Under this method, each Medicare Administrative Contractor (MAC) is instructed to ascertain a payment amount for its geographical area(s) for use in the first year; this subsequently serves as a benchmark for CMS to set an NLA based on the median of MAC rates.[5]

### *A Whole New World Under PAMA*

Until recently, apart from various legislative actions—reducing payments across the entire CLFS, adjustments for inflation and productivity, and the addition of new codes—the CLFS has received little attention since the 1980s.[6,7] However, Section 216 of the Protecting Access to Medicare Act of 2014 (PAMA) will significantly change how Medicare determines payment rates for clinical laboratory tests reimbursed for under the CLFS. All rates for tests on the CLFS will eventually be valued on market-based payment and volume data, somewhat similar to the Average Sales Price (ASP) methodology used for outpatient drugs and biologics. While we are still awaiting the details of implementation from CMS, the law will require applicable laboratories to report private payer (ie, commercial, Medicare Advantage, and Medicaid Managed Care) payment rates, including discounts, and volumes for existing tests beginning January 1, 2016, with those rates to be used to establish a weighted median for payment starting in January 2017. Collection of these data will be driven by unique Healthcare Common Procedural Coding System (HCPCS) codes, although many tests will map to the same code or be reported commonly with unlisted or unclassified codes. The law also allows for tests meeting certain criteria to obtain temporary codes until permanent codes are established. PAMA includes some protections to prevent reimbursement rates from dropping too low: for the years 2017 through 2019, payment amounts cannot be reduced by more than 10% per year; from 2020 through 2022, payments cannot be reduced by greater than 15% per year compared with the preceding year. Other adjustments, such as geographic, budget neutrality, or annual update adjustments, will no longer be applicable.

Following the initial collection and reporting for existing tests, the law separates new tests entering the market on or after January 2016 into 2 categories: advanced diagnostic laboratory tests (ADLTs) and non-advanced diagnostic laboratory tests (non-ADLTs).

Tests that meet the narrow definition of ADLT include those that are offered by a single laboratory and that are either:

(a) an analysis of multiple biomarkers or proteins combined with a unique algorithm to yield a single patient-specific result;
(b) FDA-cleared or approved; or
(c) a test of another type based on other criteria established by the HHS.

To create financial incentives for access to the marketplace, ADLTs will be reimbursed based on the list charge for the first 3 quarters following market entry. At the beginning of the fourth quarter, CMS will transition reimbursement to a weighted median of private payer rates, with the potential for clawback if the list price is greater than 130% of the market-based fee. Reporting for ADLTs will be required on an annual basis, as opposed to every 3 years for non-ADLTs.

Non-ADLTs, which are new tests that do not meet the narrow definition of ADLT, currently account for a majority of the tests on the fee schedule. They will continue to be priced per the gap-fill and cross-walk methodologies until payment rates are established for the tests using private payer data.

In addition, PAMA creates several other provisions to assist with the overhaul of the fee schedule. PAMA calls for an Expert Advisory Panel to be created to comment on payment and coverage processes, and the secretary of HHS may designate 1 or more (not to exceed 4) MACs to establish coverage policies rather than leaving coverage decisions for clinical laboratory tests up to each individual Part A/B MAC. The Congress also directs the Government Accountability Office and HHS Office of the Inspector General to conduct studies to ensure that Medicare cost savings with the new payment methodologies do not harm beneficiary access or clinical decision making.[8]

So, why does this matter to payers other than Medicare? Ultimately, the goal of PAMA is to lower laboratory reimbursement rates based on competitive pricing and contracting to improve Medicare cost savings. This is a significant paradigm shift from current practice where subsequent to tests being reimbursed for based on an antiquated Medicare fee schedule, Medicare often forms the basis of reimbursement for private payers. While PAMA will force the industry


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to prioritize contract negotiations with private payers, the specific approach by private payers and laboratories to adjust their future negotiating and contracting to account for the changes in Medicare payment rates remains undetermined. In the short term, this payment shift may create a volatile marketplace for laboratories and manufacturers due to the uncertainty of consistent or adequate payment, as well as create a hefty reporting burden on laboratories. Most likely, payment changes will vary by test code and we could see downward, neutral, and upward adjustments to future laboratory test payment rates.

### THE RISE OF MOLECULAR TESTING HAS INCREASED PAYER SCRUTINY

In the current healthcare environment, diagnostic developers face ever-growing demands by payers to establish the value of their product to gain favorable coverage. With the rise in the number of multipanel genetic tests and the introduction of newer technologies such as next-generation sequencing (NGS), both public and private payers have established processes and criteria to aid in making coverage decisions. Establishing the clinical utility, namely, changes in clinical decision making and outcomes based on the information obtained by the test, has been a significant hurdle faced by industry stakeholders when introducing new diagnostics into the market.

Under Medicare, one requirement for determining that a diagnostic test is medically reasonable and necessary is that the results of the test will change the management of a beneficiary's condition. This could be shown by changing treatment pathways or determining eligibility for a unique drug or drugs based on the test's results. While there have been several Medicare Evidence Development & Coverage Advisory Committee meetings on molecular diagnostics, coverage determinations have largely been developed at the local level. In 2011, Palmetto GBA (Palmetto), the Part A/B MAC for Jurisdiction 11 (North Carolina, South Carolina, Virginia, and West Virginia), launched the MolDX Program, which was designed to produce evidence-based coverage policies for molecular diagnostic tests. As part of the new program, all manufacturers and laboratories seeking coverage for their tests must provide Palmetto with robust clinical evidence demonstrating not only the analytic validity but also the clinical validity and utility of their test. To date, Palmetto has issued 18 local coverage determinations (LCDs) detailing limitations and indications for coverage of certain molecular tests, although they have also made de facto coverage decisions for a large number of analyte-specific molecular tests outside of the LCD process.[9] While the Palmetto MolDX Program is only active in certain MAC jurisdictions at present, it could grow to the national level in the future, particularly with the new authority delegated to the secretary of HHS under PAMA. However, CMS has not yet indicated that it will move to a consolidated coverage process for laboratory tests.

*As payers demand robust evidence demonstrating the clinical utility of diagnostic testing, it is critical that manufacturers provide adequate evidence on how changes in clinical action based on test results lead to an improvement in patient outcomes.*

Private payers are also active today in determining whether molecular testing used in the clinic is experimental, investigational, or medically necessary. While most large private payers have internal health technology assessment committees, the levels of focus and expertise in the technical aspects of complex testing methodologies vary. While Medicare policies are relied on as a basis for determining private payer coverage policies for certain tests, such as in oncology for companion diagnostics, many tests are more appropriate for populations outside of the Medicare population, or are excluded by statute from the Medicare program (eg, susceptibility or screening tests).[10] This means that payers will need to evaluate coverage and payment on their own terms for a wide range of new tests. Payers generate coverage policies based on peer-reviewed literature, external technology assessments, and evidence-based guidelines produced by medical specialty societies or other groups such as the National Comprehensive Cancer Network.

As payers demand robust evidence demonstrating the clinical utility of diagnostic testing, it is critical that manufacturers provide adequate evidence on how changes in clinical action based on test results lead to an improvement in patient outcomes.

### WHAT DOES THE FUTURE HOLD FOR LABORATORY TEST REIMBURSEMENT?

The number of clinical laboratory tests—in particular molecular diagnostics—on the market will continue to rise, and that growth will impact various players in the healthcare industry in several ways. Payers will likely see a continued steady increase in the volume of claims entering their systems as well as the sustained need for medical review of novel diagnostics. Due to increased payer scrutiny and efforts to control costs, as well as greater market competition, manufacturers and laboratories will need to be prepared with higher levels of evidence, in particular strong clinical utility. Manufacturers and clinical laboratories should invest in establishing this higher bar of evidence during test development and prepare for pricing and reimbursement pressures to continue, especially in the time leading up to and after the changes in Medicare payment rates, outlined in PAMA, take effect in 2017.

As private payer rates will drive future Medicare reimbursement, contracting and price negotiation will form an increasingly important piece of the puzzle for both laboratory providers and payers. If pricing pressures are too great to bear for some smaller laboratories, we could see further consolidation or narrow laboratory networks come into play even more than today. In addition, we will see a greater payer focus on managing laboratory testing benefits through shifts in cost-sharing or benefit management services, such as UnitedHealthcare's use of Beacon Laboratory Benefit Solutions, Inc (Beacon LBS) for commercial members in Florida.[11] It is uncertain if the program will be expanded geographically or if other payers will look to manage laboratory benefits through a third party—as many do today for prescription drugs through pharmacy benefit managers—but the potential exists.

Laboratory testing is often a gatekeeper to, or influencer of, other healthcare services. As we await regulations around the Medicare payment changes under PAMA, and as laboratory testing continues to rise as an area of focus for payers and providers, the next 2 years will prove crucial for testing. All stakeholders should monitor the ongoing changes to Medicare payment and coverage for clinical laboratory testing, as the impact will be felt throughout the healthcare industry. **EBO**




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# Myriad's New CEO Discusses Promises, Challenges of Changing Times in Genetic Testing

Mary K. Caffrey

When the words "precision medicine" make it into a State of the Union address, one could argue it's the best of times for anyone in the genetic testing business.[1] And in some ways, it is.

But 2 years have passed since the US Supreme Court found that a naturally occurring DNA segment is not patent eligible.[2] That ruling changed the landscape for Myriad Genetics, which since its founding in 1991 has cemented its place as the provider of tests for BRCA1 and BRCA2 mutations, alerting women to their risk of breast or ovarian cancer.

Today, Myriad competes in its core business with other test makers; these include both conventional laboratories and companies that sell genetic tests directly to the public. These "direct to consumer" tests are sold without insurance coverage at very low prices—Color Genomics' test costs $249,[3] compared with Myriad's reported pricing of $2700 to $4000, depending on whether the test screens for BRCA mutations only or for multiple hereditary cancers (prices reported by the company).

It's not clear whether the FDA will let direct-to-consumer sales continue. While the prospect of regulation looms for molecular diagnostic testing, it's not there yet. The industry lacks the level of certainty seen in drug development, where a regulator's seal of approval can be hard won but typically means payment will follow.

In genetic testing, challenges abound with reimbursement, with different payers seeking different levels of evidence. Recently, Myriad has been able to consolidate its reimbursement processes with a single Medicare Administrative Contractor, the Molecular Diagnostics Services (MolDX) Program of Palmetto GBA. But change in the industry is coming, thanks to legislation passed in 2014 that will eventually call for CMS to move to a market-driven reimbursement system.[4]

Among private payers, disparities in decision making persist. For example, Cigna, which has been a leader in requiring genetic counseling along with genetic testing, will only cover testing that is determined to be "valid and reliable," and that "meets the requirements for medical necessity," spokesman Mark Slitt told *Evidence-Based Oncology* in an e-mail. This may include requirements for genetic counseling, precertification, and other indicators of risk, according to Slitt.

The past year has been both challenging and eventful for Myriad Genetics. It received a local coverage determination from Palmetto GBA for its Prolaris prostate cancer test, although Medicare reimbursement is taking longer than anticipated.[5] The company is transitioning its business from the historic reliance on BRCA testing to broader hereditary cancer screening, as well as new areas that include mental health and its 2014 acquisition of Crescendo Bioscience, which makes a test that guides treatment of rheumatoid arthritis.[6] Companion diagnostics is another growth area, and in December 2014 the company reached a high water mark when FDA approved BRACAnalysis CDx as the companion diagnostic for Lynparza (olaparib) in patients with ovarian cancer.[7] Some press accounts have been rough, and Wall Street reviews have been mixed; other reports say the company's customer service record and arsenal of data should allow it to weather a period of transition.[8,9]

And as of June, Myriad Genetics has its first new president and CEO since its founding. Mark C. Capone joined the company in 2002 and had served as president of Myriad Genetic Laboratories since March 2010. As he took the helm as CEO, *Evidence-Based Oncology* spoke with Mr Capone about the challenges and opportunities in molecular diagnostics, and what's ahead at Myriad Genetics. Below are edited excerpts from the interview.

**Q: WHAT ARE YOUR THOUGHTS ON THE OBAMA ADMINISTRATION'S PRECISION MEDICINE INITIATIVE?**

**A:** We were delighted to hear President Obama talk about the promise of personalized medicine. We have shared that perspective for over 2 decades, and we believe that these technologies not only have the opportunity to transform the lives of our patients, but also to fundamentally change the trajectory of healthcare costs in this country.

**Q: ACCESS TO PERSONALIZED MEDICINE CAN COME DOWN TO WHETHER INSURERS WILL PAY FOR TESTING. MUCH HAS BEEN WRITTEN ABOUT THE CHALLENGES WITH REIMBURSEMENT, PARTICULARLY WITH CMS. HOW IS THE PROCESS GOING THESE DAYS?**

**A:** It's fair to say that reimbursement in personalized medicine is still in its infancy, and there are still some shifting sands around the criteria required for reimbursement. We have seen progress from the CMS perspective with all of the decisions around coverage being consolidated with [Palmetto GBA's] MolDX program.

Having a single contractor with a consistent process by which medical diagnostic products are evaluated is useful for those of us that develop these products. We need some forward visibility as to how they will be evaluated so that we can put together our clinical development programs.

The MolDX program has been open to feedback from industry about different ways to approach reimbursement. We have been quite active in providing feedback, and in working with MolDX to identify appropriate ways to provide clinical data for their technical assessment programs.

MolDX has also put in place consultation services for companies that are developing products prior to those clinical development programs being initiated, to provide further insight into what types of programs would be useful.

**Q: IS THERE AN EMERGING SET OF BEST PRACTICES TO OBTAIN APPROVAL FOR REIMBURSEMENT? ARE WE GETTING CLOSER TO A DEFINED PROCESS, SIMILAR TO WHAT EXISTS AT FDA?**

**A:** It's emerging slowly. There are some guidelines that have been published by MolDX on levels of evidence that would be required to obtain reimbursement.

You also have some other technical assessment committees that are beginning to establish evidence-sharing levels as well. I think we're slowly beginning to see those emerge, but I would say that at this point the process is not nearly as defined as you might have at an agency like the FDA.

There are still some uncertainties, and the best way to deal with that uncertainty is to have very early conversations with payers about what level of evidence they will require for a specific test.

**Q: WHAT ABOUT COMMERCIAL PAYERS? IS THERE CONSISTENCY FROM PAYER TO PAYER?**

**A:** I would still characterize it as significant inconsistency between payers. In Medicare, with all of that decision making now consolidated within the MolDX program, at least you don't have an inconsistency between Medicare contractors; so I think that's a positive step forward. Among the private payers, there is still quite a wide disparity as to levels of evidence that may be required.

**Q: ARE THESE DISPARITIES BETWEEN PAYERS GETTING WIDER OR NARROWER?**

**A:** Because the education levels are increasing among payers in general, I do see some progress toward consistency, but I think that pace is relatively slow at this point.

**Q: HOW ARE PROVIDERS DOING WITH MOLECULAR DIAGNOSTIC TESTING? ARE TESTS BEING USED CORRECTLY?**

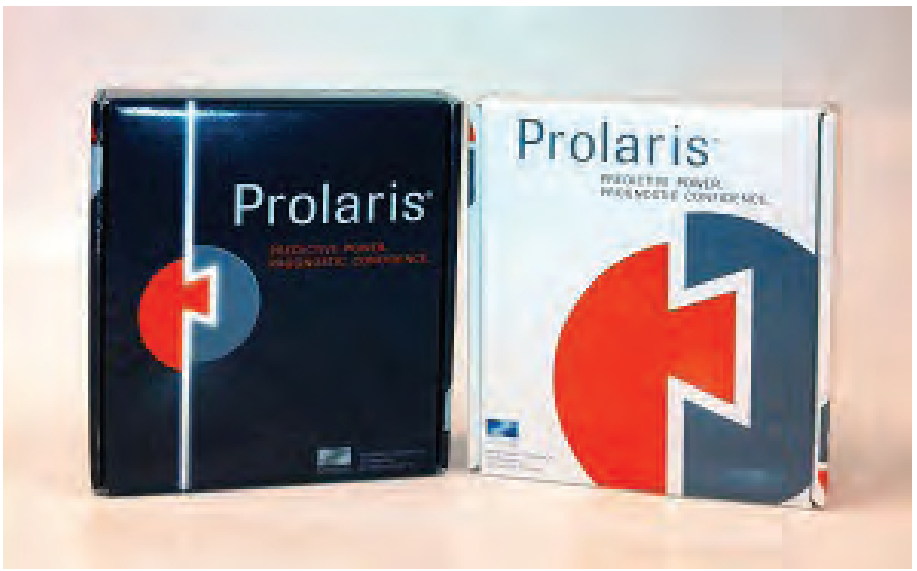
**A:** It's imperative for a laboratory to

**ABOUT THE EXPERT**

MARK C. CAPONE

**Mr Capone** is president and CEO of Myriad Genetics, Inc.

> *"It's imperative for a laboratory to [provide] extensive education to healthcare providers about the appropriate patients to test, how to interpret tests, and how to modify medical management after the patient receives the results."*
>
> —MARC C. CAPONE




SOURCE: Myriad Genetics, Inc.

[provide] extensive education to healthcare providers about the appropriate patients to test, how to interpret tests, and how to modify medical management after the patient receives the results.

We have seen examples where that type of education by Myriad, which invests very heavily in education, makes a big difference with providers. By way of example, we had a poster published that showed for hereditary cancer testing over 93% of the tests we received were for patients who met [National Comprehensive Cancer Network or NCCN] criteria, and another 6% of the patients had an underlying cancer consistent with the general criteria for that particular hereditary cancer. That leaves only 1% of the patients [receiving the test] that didn't seem to have any ties to the NCCN guidelines.[10]

By comparison, another lab that published similar data found that 30% of the tests were being ordered inappropriately. That's a lab that has little educational efforts with providers. I think it's a very clear distinction between laboratories that invest in education and those that don't.

When physicians are properly educated, when you have quality control procedures in your lab like we do at Myriad, you can be sure the tests that are being run are consistent with guidelines.

**Q: WHAT ABOUT DIRECT-TO-CONSUMER TESTS THAT ARE SOLD WITHOUT INVOLVEMENT OF INSURANCE COVERAGE? HOW DOES MYRIAD RESPOND TO THESE TESTS?**

**A:** I think it's a critical part of the education process that physicians understand the difference between the various tests that are available. There are a number of companies that are characterized as [offering] "recreational genomics," and there are companies like Myriad that are very focused on the highest quality clinical tests in order to ensure the appropriate decision making by both the patient and the physician. We try to ensure that our education efforts allow the patient and the physician to understand those differences.

For example, we invest very heavily in the quality of sequencing we provide. We employ a number of different technologies to ensure that the sequence is accurate. Second, we also invest an enormous amount to ensure the *interpretation* of that sequence is accurate as well. There's evidence that public databases that were designed for research purposes are fraught with errors, and if you were to use those databases to interpret test results, you run the risk of getting a false result to patients.

> *"What's important to a payer is that the implications of a false test result are very significant. Either one of those false test results can cost a payer hundreds of thousands of dollars, so it's worth it to make sure the most accurate test is being used up front to avoid that patient impact and cost implication downstream."*
>
> —MARC C. CAPONE

Third, we provide an appropriate level of service, so that a patient and a physician know when testing is appropriate and know how to use that test for medical management. When you look at what it takes to ensure that quality of end-to-end service…it really requires a pretty significant cost structure to ensure that kind of accuracy.

What's important to a payer is that the implications of a false test result are very significant. A false positive means that a patient is potentially going to pursue prophylactic surgery and unnecessarily remove healthy organs. A false negative means the patient is not going to undergo the surveillance required to ultimately prevent cancer. Either one of those false test results can cost a payer hundreds of thousands of dollars, so it's worth it to make sure the most accurate test is being used up front to avoid that patient impact and cost implication downstream.

**Q: HAVE PAYERS REFUSED TO COVER A SURGICAL PROCEDURE BASED ON A RESULT FROM A DIRECT-TO-CONSUMER TEST?**

**A:** I would not know if there are specific examples because we don't see that information. However, providers are beginning to appreciate that these tests are not regulated by the FDA. So, claims that are being made by these tests have not undergone rigorous review by an agency such as the FDA.

You are aware of the extensive conversations surrounding regulation of laboratory-developed tests; but at this point they remain outside FDA regulation. Both payers and providers are aware some of these claims may not be substantiated by significant additional data.

**Q: WILL THE RISE OF DIRECT-TO-CONSUMER TESTS MAKE REGULATION HAPPEN MORE QUICKLY?**

**A:** I do know the FDA has stated before that when it comes to *BRCA* or hereditary cancer tests, in which the patient is making very significant medical management decisions—those are the examples of the tests they are most concerned about. Those are the ones they would classify as high risk. To the extent that high-risk tests proliferate in the marketplace without having those claims reviewed by the agency, I think it does increase the urgency with which the FDA will pursue regulation.

**Q: WHEN ANGELINA JOLIE HAD HER FIRST SURGERY—AND ANNOUNCED IT IN *THE NEW YORK TIMES*—THE EFFECT ON MYRIAD WAS SO SIGNIFICANT THAT YOU REFERENCED IT IN YOUR QUARTERLY EARNINGS REPORT. WHEN MS JOLIE ANNOUNCED HER SECOND SURGERY TO REMOVE HER OVARIES RECENTLY, WE HEARD REPORTS THAT SOME PAYERS DID NOT WANT TO COVER TESTING. DID YOU FIND THIS TO BE TRUE?**

**A:** We haven't seen any difference, but again, we have extensive quality control procedures in place to screen upfront testing, to ensure that testing meets the criteria for each of our payers. If tests met the criteria prior to the celebrity publicity, they were being covered; if they met criteria after the publicity, they were covered as well.

If there are labs without those quality control procedures, then payers have concerns that inappropriate tests will be run.

**Q: IT'S BEEN 2 YEARS SINCE THE SUPREME COURT DECISION ON THE DNA PATENT. WHAT HAS HAPPENED IN THE MARKET THAT HAS SURPRISED YOU? WHAT HAS HAPPENED THAT HAS NOT SURPRISED YOU?**

**A:** The magnitude of the decisions being made will not only affect the patient but generations of family members that will follow this patient. As a result we were not surprised that what we've seen in the market, patients and providers continue to be willing to use what they consider the absolute highest quality test upon which they can base these very important decisions. We continue to see that after the Supreme Court decision, and that's why we continue to be the market leader in providing these test results to patients. [*The Wall Street Journal* reported in May that *BRCA* testing still accounts for 80% of Myriad's sales.[7]]

The one thing that has been surprising, and important for the United States as a country, is that we continue to see the erosion of intellectual property rights, particularly in the life sciences industry. We now stand out of step with all of the other developed countries in our willingness to protect intellectual property in the life sciences.

From our perspective and many others, if we are going to get back to a footing equal to other countries, we are going to need to look at our approach to intellectual property in the life sciences.

**Q: WHERE DO YOU FEEL THERE IS A PROBLEM? IS IT WITH CONGRESS? THE REGULATORS? THE COURTS?**

**A:** The decisions that have been made have been largely in the courts. It will either take additional cases to be litigated through the court system to provide clarity in those areas that remain uncertain, or legislative action to ensure Congress' intent around intellectual property are made clear to the courts. Either one of those avenues are a possibility. For those of us who invest enormously in research in the life sciences industries, having comparable intellectual property protection with the rest of the developing world is really essential.

**Q: TO THAT END, WHAT IS HAPPENING IN SCIENCE THAT IS EXCITING—AND MIGHT BE WORTH PROTECTING?**

**A:** If you went to ASCO [American Society of Clinical Oncology], it's really

remarkable if you look at the evolution of cancer treatment from 5 years ago to where we are today—and I think what will happen over the next 5 years. We truly are getting to the point where we are understanding the genetics of the disease for a specific individual and tailoring the drug selections to that genetic understanding. While that has always been the promise of molecular diagnostics in cancer, I think we really are starting to see that promise become a reality, and you will see that more so over the next 5 years.

For Myriad, we now have a number of companion diagnostics—everything from BRACAnalysis CDx, to Tumor BRACAnalysis CDx, to myChoice HRD—all of which provide increasing sensitivity in identifying patients that are most likely to respond to DNA-damaging agents. We think over the next 5 years you will see a groundswell of opportunities to identify those patients and allow them to respond to drugs in a much more effective way than we would have otherwise seen.

The other areas for us that are most interesting are outside cancer. You've seen a lot of investment in molecular diagnostics in cancer, but we have really just scratched the surface in diseases outside cancer—things like autoimmune disorders; things like preventive care such as cardiovascular disease, diabetes, neuroscience—we are doing some exciting work in helping to do differential diagnoses in bipolar disease, or in drug selection in the neuroscience field. You're going to see an expansion in other diseases, which in reality constitute an even larger share of our healthcare spend than cancer. **EBO**

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# Equalize Payment Across Site of Service

Barry Brooks, MD

Improving Medicare quality and efficiency, in order to keep the program solvent for the nearly 10,000 new beneficiaries who turn 65 years old each day,[1] has been an ongoing priority for Congress and policy makers. Efforts to improve patient safety and outcomes, while tying payments to quality instead of quantity, have resulted in a seismic shift in the delivery of healthcare.

Yet amid these major changes and cost-cutting improvements, we still see examples of questionable and costly policies that undercut the progress being made elsewhere.

A striking example, with which cancer care providers are all too familiar, is the ongoing payment disparity between cancer care provided in community settings and that same care provided in hospital outpatient departments (HOPDs). Medicare policy today still allows for significantly higher reimbursements for essential healthcare services provided by HOPDs than for the same service or treatment administered in a physician's office.

When the specific service is not dependent on the hospital facility's associated technologies, and in the absence of any evidence-based rationale, paying more for a service in the hospital is wasteful, costly, and endangers patient access and choice.

A decade ago, nearly 90% of Americans being treated for cancer had many options for care in the community setting, but changes in reimbursement methodologies have made the previous landscape almost unrecognizable. Today, fewer than 65% of patients receive care in these centers, while HOPDs have seen a 150% increase in patient volume in just 6 years.[2] This transition has allowed hospitals to more than triple their income for these services (from $90 million to $300 million from 2005 to 2011) while many freestanding cancer centers nationwide have been forced to close their doors for financial reasons. Indeed, a survey of oncology practices found 544 practices have been acquired by hospital systems and 149 have merged with other practices, in addition to 313 community oncology treatment clinics that have closed since 2008.[2]

For many US community cancer centers, keeping the doors open has often meant making the difficult decision to consolidate with hospitals and large hospital systems. Although this gambit allows an individual practice to survive, these consolidations largely due to payment disparities increase total Medicare costs and ultimately increasing patients' out-of-pocket expenses and limiting patient choice. A recent study of the medical records of 4.5 million patients published in *JAMA* concluded that expenditures per patient were 10.3% higher for physician groups owned by hospitals than for independent practices, and expenditures were 19.8% higher for physician groups owned by multihospital systems.[3]

A 2015 study by the IMS Institute also concluded that Americans are paying higher prices for cancer treatments because of these acquisitions. According to the report, reimbursement levels for drug administration costs in hospital outpatient facilities average 189% higher than physician office reimbursement costs for commercially insured patients under the age of 65 years. In 2014, Medicare paid HOPDs twice as much as a physician's offices for the same drug administration service.[4] The pain in the pocketbook doesn't end there: a report by the Milliman research group concluded that Medicare beneficiaries pay $650 more in out-of-pocket co-payments when cancer care is delivered in the hospital setting as opposed to a physician's office.[5]

The US healthcare system today is unquestionably complex, with a great many variables affecting the cost of care. However, some problems are easier to fix than others, and this one has a common sense solution: policy makers should neutralize payments across sites of service and pay the same fee for the same service regardless of where it is performed.

Site-neutral payment reform is not only common sense—it is also already widely supported.

In his 2016 budget proposal, President Obama outlined an estimated savings of $29.5 billion over 10 years, achievable by improving incentives for providing ambulatory care in the most appropriate clinical setting. The proposal would effectively lower payment for services provided by off-campus HOPDs under the Outpatient Prospective Payment System, to either the Medicare Physician Fee Schedule–based rate or the rate for surgical procedures covered under the Ambulatory Surgical Center payment system.[6] Likewise, the Medicare Payment Advisory Commission (MedPAC) has repeatedly advocated that "site-neutral payments that base the payment rate on the less costly sector can save money for Medicare, reduce cost sharing for beneficiaries, and reduce the incentive to provide services in the higher paid sector, without compromising beneficiary access to care or health outcomes."

Consumer groups agree. The AARP supports equalizing Medicare payments for physician services between hospital outpatient and office settings, believing that this will save billions in taxpayer dollars.

In June, Representatives Mike Pompeo (R-KS) and Don Beyer (D-VA) introduced the Medicare Patient Access to Treatment Act (H.R. 2895), legislation to level the playing field by creating a more adequate reimbursement structure for cancer care delivered in the community setting. This needed legislation would equalize payments for oncology care across sites of service to help ensure patient access to high-quality cancer care in the community-based setting.

Improving and safeguarding Medicare is undeniably a difficult process, but one that our elected officials have committed themselves to undertaking. Site neutrality is a critical step in the journey toward better healthcare for all Americans and a healthy future for Medicare. **EBO**


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*For many US community cancer centers, keeping the doors open has often meant making the difficult decision to consolidate with hospitals and large hospital systems. Although this gambit allows an individual practice to survive, these consolidations increase total Medicare costs and ultimately increasing patients' out-of-pocket expenses.*

# No Solution in Sight Yet With the Federal 340B Program, Say Stakeholders

Surabhi Dangi-Garimella, PhD


Experts believe that while the 340B Drug Pricing Program is vital for safety net hospitals, policies that can regulate its growth are needed.

The federal 340B Drug Pricing Program, initiated in 1992, requires pharmaceutical manufacturers participating in the Medicaid Drug Rebate Program to negotiate a drug pricing agreement with HHS—the manufacturer will provide specified discounts on "covered outpatient drugs" to government-supported facilities. The program enables covered entities to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services. Per the Health Resources and Services Administration (HRSA) website, eligible healthcare organizations or covered entities are defined in statute and include HRSA-supported health centers and lookalikes such as the Ryan White clinics and state AIDS Drug Assistance Programs, Medicare/Medicaid Disproportionate Share Hospitals, children's hospitals, and other safety net providers.[1]

Although this preferential pricing policy typically involves providers who work with vulnerable patient populations such as the uninsured or underinsured, there may be some misuse, with unintended repercussions on patients, payers, and physicians. At a summit hosted by the Alliance for Integrity and Reform of 340B last year, participants discussed the need for increased transparency requirements for hospital-based 340B-covered entities.[2] Participants questioned whether the program had metrics in place to clearly identify hospitals that provide charitable care and highlighted the negative impact of this program on both community-based oncology practices and patients. A study by IMS Health found that shifting cancer care from a community clinic to a hospital increases treatment cost by a staggering 189%.[3] This increased cost, when borne by patients through increased out-of-pocket spending, can result in adherence issues.

A panel of healthcare experts invited by *The American Journal of Managed Care* participated in the Oncology Stakeholders Summit, Spring 2015 Peer Exchange, to discuss 340B and other issues in oncology care. The discussion, moderated by Bruce Feinberg, DO, vice president and chief medical officer of Cardinal Health Specialty Solutions, saw participation by Scott Gottlieb, MD, resident fellow at the American Enterprise Institute; Brian Kiss, MD, vice president of Healthcare Transformation at Blue Cross Blue Shield of Florida; Michael Kolodziej, MD, national medical director for Oncology Strategy at Aetna; and Ted Okon, MBA, executive director of Community Oncology Alliance.

Feinberg started the discussion by asking the panelists to comment on whether and how 340B has changed the dynamic of the healthcare industry. According to Gottlieb, while several reasons factor into the consolidation across provider segments, he believes 340B is the biggest driver of the process. "This is a classic example of a government program born of good intentions gone awry," he said. Gottlieb said that the program, originally conceived for hospitals that serve disadvantaged patients, was initiated in 90 hospitals and has now been adopted by over 1700.

Hospitals, he said, are manipulating the program by securing a discounted rate from manufacturers while billing payers at a full rate. This practice, according to Gottlieb, is driving patients to the hospital to receive oncology care when it may not be the best place for them to receive care. In his opinion, the patient no longer gets priority in the system, and there might even be a step down in the quality of care rendered. The end result, in his opinion, is a higher cost to payers and to the entire healthcare system.

Gottlieb went on to add that the premise of the 340B program was very sound, but that the hospitals that are gaming the system have a completely different mission, distinct from the original purpose of the program. "I'd be worried about preserving this for the hospitals that really need it and be worried about the hospitals that are exploiting it," he said, adding that it might result in lack of access to hospitals that really are in need of the program's privileges.

*Okon said that 340B is a critical access program, not just historically, but even today clinics such as the Ryan White clinics, hemophilia clinics, and community health centers hugely benefit from it. The problem, he pointed out, is the disproportionate share hospitals that have increasingly enrolled in the program.*

Okon, a big proponent of retaining the integrity of the 340B program to save community oncology practices, said that the program gives anywhere from upwards of 50% discounts to 340B participants, which would mean 100% margins for the participating hospital. Okon added that 340B is a critical access program, not just historically, but even today clinics such as the Ryan White clinics, hemophilia clinics, and community health centers hugely benefit from it. The problem, he pointed out, is the disproportionate share hospitals that have increasingly enrolled in the program, a majority following the passage of the Medicare Modernization Act in 2003.

Okon drew attention to the fact that both cancer patients and smaller practices come out on the losing end of the bargain. He explained that when a clinic consolidates with a hospital because they can no longer foot the bills and have to decide between closing shop and joining a bigger health system, the patient who is midtreatment continues to receive care at the same site and from the same group of providers. But suddenly the patient's bills are significantly higher. And the patients, he said, are thinking, "'Wait a minute, why did my bill go up?' in some cases by 50%. They're not getting the benefit of that drug." Rather, he said, it's the facility that retains the profits and the patients end up actually paying more.

Okon then elucidated some of the tactics used by covered entities to maximize on profits. Citing an example of a multiple myeloma patient on the R-CHOP regimen who needed to be ad-

## GAO: Congress Must End Incentives to Prescribe More Expensive Drugs Through 340B Program

MARY K. CAFFREY

A report from the Government Accountability Office (GAO) has found that a program for hospitals serving poor and uninsured patients has created perverse incentives to prescribe more drugs and more expensive drugs, particularly in the area of cancer care.

Congress must curb these incentives, the GAO recommended on July 6, 2015, not only to hold down Medicare spending but also to benefit patients, who face larger co-payments under the current setup.[1]

The report examined practices in the 340B Drug Pricing Program and compared spending in 2008 and 2012. The program lets participating hospitals gain access to discounts for outpatient drugs, including expensive oncology therapies. According to GAO, 40% of all US hospitals take part in the program, and most discounted 340B drugs are sold to hospitals. Among the findings:

- Medicare Part B spending per beneficiary in 340B hospitals is more than twice that of other hospitals. For 2012, per beneficiary spending was $144 in 340B hospitals, compared with approximately $60 in other hospitals.
- Higher spending was not due to different hospital characteristics or patients' health status. Both HHS and the 340B health program questioned this, but the GAO report outlines how it controlled for these factors.
- While the 340B program was created to assist hospitals with higher rates of uncompensated and charity care, the GAO found that it has evolved. Most hospitals in the program have high rates of these services, but 12% of the 340B participants had small amounts of charity care, and 14% had low amounts of uncompensated care.
- Overall, Medicare Part B spending in hospitals has exploded since 2008, with costs per beneficiary more than doubling between 2008 and 2012. However, in every comparison the GAO reported, 340B participants outspent their non-340B counterparts. Of note, the per-beneficiary Part B cost in major teaching hospitals that do not take part in 340B was $105; that amount was *less* than the $107 per-beneficiary cost for *nonteaching* hospitals enrolled in 340B.
- While it is not unlawful for hospitals to benefit financially from the drug discount program, the report said, such practices are "not consistent with the legislative intent of the 340B program." Both taxpayers generally and patients individually suffer harm, since Medicare Part B beneficiaries are responsible for 20% co-payment. The report also asks whether all healthcare provided in 340B hospitals is appropriate, and states, "Absent a change in financial incentives, potentially inappropriate spending on drugs may continue."

In response, HHS said that while the report compares spending by hospital type, it does not compare patient outcomes or quality of care. It is possible, HHS said, that prescribing more drugs has produced better clinical outcomes. GAO responded that it did not attempt to measure patient outcomes, but added, "We have no evidence" that hospitals outside the 340B program had incentives to provide fewer drugs to achieve good outcomes. **EBO**

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ministered a cocktail of brand-name and generic medications, he said a facility that was not 340B covered wanted a patient to split the treatment—to get the generic drugs at the clinic and then drive to the hospital, which was 340B covered and would make $6300 per dose of the brand-name drug being administered. "It's crazy patient care and when it blows up, who's going to get hurt? Patients." Okon added that while clinics will always need to partner with hospitals, they need to identify the right hospitals—the ones that are following the principles that make up 340B.

Gottlieb believes that policies that will constrain the burgeoning growth rate of the program will soon be rolled out and will prevent the program from dialing back to its current state.

Feinberg then turned to the payers at the table and asked their opinions on the program and its influence on healthcare costs. He was curious whether payers thought consolidation would hand them better control, albeit at an increased cost.

Kiss responded that payers are acutely aware of the tremendous costs associated with consolidation, adding that this is not restricted to oncology care. The overheads with physicians working in a hospital are 20% to 25% higher than an independent physician's, whether he's at a patient-centered medical home, is a primary care doctor, or is an oncologist.

> *"I think if some folks who are deciding policy had their druthers, they'd try to recreate Kaiser Permanente or the Mayo Clinic in every market and even squeeze out health insurers and just have the consolidated institutions take over the provision of health insurance as well."*
>
> —SCOTT GOTTLIEB, MD

Feinberg pointed out that while hints of this happening were obvious a decade ago, payers did not act to improve private practice physician reimbursement, which could have prevented physician migration. The situation became worse after the Medicare Modernization Act, he said.

Agreeing that Medicare largely controls physician reimbursement, Gottlieb said policy makers are partial to consolidation and believe it is the ideal model of healthcare delivery. "I think if some folks who are deciding policy had their druthers, they'd try to recreate Kaiser Permanente or the Mayo Clinic in every market and even squeeze out health insurers and just have the consolidated institutions take over the provision of health insurance as well."

Okon agreed with Gottlieb that while several in the Obama administration are partial to a single-payer system, it contradicts what the Affordable Care Act purports to achieve. He said that instead of reducing the cost of healthcare, consolidation is actually increasing costs.

"They're creating local healthcare monopolies and we're getting into a bigger issue now, and that's going to ultimately drive up cost," said Gottlieb. He thinks that while integrated delivery systems like Geisinger, Mayo Clinic, and Intermountain Healthcare have been successful, they may not translate equally well in every single market. "Healthcare is local. Markets are very local," and local markets will have different dynamics and specific needs that need to be recognized. Gottlieb predicts that a lot of healthcare institutions being created may not sustain for long. "If I was going to choose a business to be in right now, it would be in the business of helping distressed and bankrupt hospitals because I think that's going to be a growth industry going forward."

New models are emerging according to Kiss, where community oncologists may be working for regional hospitals on a contractual basis. This has resulted in novel referral networks, he said, which could drive up costs because hospitals are getting increasing referrals. The result is a clinically integrated network model. **EBO**

AJMC PEER EXCHANGE

To watch the discussion online, visit
**http://bit.ly/1CSWzlw**

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# CHAARTED Study: Conceptual Shift in Early Prostate Cancer Treatment

Surabhi Dangi-Garimella, PhD

Analysis of results from the ECOG E3805 CHAARTED trial, published in the *New England Journal of Medicine*,[1] has found that 6 cycles of chemotherapy (docetaxel) before androgen-deprivation therapy (ADT) early in the treatment of metastatic prostate cancer significantly improved overall survival than treatment with ADT alone.

The lead author on the study, Christopher Sweeney, MBBS, from the Dana-Farber Cancer Institute, had provided a trial update in an interview with *The American Journal of Managed Care* last year,[2] where he said that positive results from the CHAARTED study had led to additional agents being explored in prostate cancer treatment, such as enzalutamide and abiraterone, in combination with chemotherapy.

The trial assigned men with metastatic, hormone-sensitive prostate cancer to receive either ADT plus docetaxel (at a dose of 75 mg per square meter of body-surface area every 3 weeks for 6 cycles) or ADT alone. The primary outcome of the study, designed in 2005 by the Eastern Cooperative Oncology Group, was overall survival. The trial enrolled 790 patients (median age 63 years) who were followed for a median duration of 28.9 months. Treatment with the combination of ADT and docetaxel improved overall survival by 13.6 months (median) compared with ADT alone (57.6 months versus 44.0 months, respectively). The hazard ratio (HR) for death with chemohormonal therapy was 0.61 (95% CI, 0.47 to 0.80; *P*<.001). The time to progression was 20.2 months for the group treated with chemohormonal therapy and 11.7 months for the group treated with ADT alone (HR, 0.61; 95% CI, 0.51 to 0.72; *P*<.001). The rate of a prostate-specific antigen (PSA) level of less than 0.2 ng/ml at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group.

Based on these results the authors conclude that docetaxel, given at the time ADT was initiated for hormone-sensitive disease, resulted in better cancer control than that with ADT alone. The combination resulted in a longer time to the development of castration resistance, a higher rate of decrease of the PSA level to less than 0.2 ng/ml at 12 months, a lower number of prostate cancer deaths, and substantially longer overall survival. This was achieved despite the fact that patients administered ADT alone did receive docetaxel when their disease progressed to being castration resistant.

The results of the CHAARTED study make it imperative that doctors speak to their newly diagnosed prostate cancer patients about using chemotherapy upfront. **EBO**

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# Chemoprevention With Oral Contraceptives Could Be a Reality

Surabhi Dangi-Garimella, PhD

Evidence provided by a study published in *The Lancet Oncology*[1] affirms that oral contraceptives provide long-term protection against endometrial cancer. The authors estimate that about 400,000 cases of endometrial cancer in women 75 years or younger may have been prevented in developed nations—as a result of oral contraception—during the period between 1965 and 2014, with 50% of these cases being prevented just in the last decade.

The incidence of endometrial cancer is rare in women younger than 45 years of age and the risk of disease increases in women 55 years and older. The American Cancer Society estimates that more than 10,000 women will die of uterine cancers in the United States in 2015.[2]

The researchers of the *Lancet* study combined data on 27,276 women with endometrial cancer from 36 epidemiological studies from North America, Europe, Asia, Australia, and South Africa. The median age of the women in the study was 63 years and the median year of diagnosis was 2001. While 35% of the 27,276 cases reported using oral contraception for a median of 3 years, 39% of the more than 115,500 controls had used oral contraceptives for a median duration of 4.4 years.

The analysis revealed that every 5 years of oral contraceptive use was associated with a risk ratio of 0.76 (95% CI, 0.73-0.78; *P*<.0001), and the reduction of risk persisted for more than 30 years after the women had stopped using the contraceptive agent. In high-income countries, 10 years of oral contraceptive use reduced the risk of developing endometrial cancer before age 75 years from 2.3 to 1.3 cases per 100 users, the authors found. However, the risk reduction varied by tumor type—it was stronger for carcinomas than sarcomas.

Considering that estrogen levels in pills in the early decades were double the levels in contraceptive pills manufactured today, the reduction in risk was comparable, which suggests that the amount of hormones in the lower-dose pills is still sufficient to reduce the incidence of endometrial cancer, according to the authors. The proportional risk reduction did not vary substantially by women's reproductive history, adiposity (amount of body fat), alcohol use, tobacco use, or ethnicity.

"The strong protective effect of oral contraceptives against endometrial cancer—which persists for decades after stopping the pill—means that women who use it when they are in their 20s or even younger continue to benefit into their 50s and older, when cancer becomes more common," explained study author professor Valerie Beral, MD, from the University of Oxford.[3] She added "Previous research has shown that the pill also protects against ovarian cancer. People used to worry that the pill might cause cancer, but in the long term the pill reduces the risk of getting cancer."

So what do the results of this retrospective study mean?

In an accompanying commentary in the journal,[4] Nicolas Wentzensen and Amy Berrington de Gonzalez from the Division of Cancer Epidemiology and Genetics at the National Institutes of Health in the United States discuss other ongoing studies examining the use of oral contraceptives as chemoprevention in women carrying *BRCA1* and *BRCA2* mutations and against Lynch syndrome. "Even if the biological mechanisms remain elusive and the existing evidence falls short of wider recommendations for chemoprevention, women need to be more aware of the unintended benefits and the risks of oral contraceptives, so that they can make informed decisions," they write. **EBO**

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Medical World News®
FDA UPDATES

# Gefitinib Approved as Frontline in EGFR-Positive NSCLC

Surabhi Dangi-Garimella, PhD

Lung cancer leads the charts in cancer-related mortality among both men and women in the United States. According to the American Lung Association, lung cancer causes more deaths than colorectal, breast, and prostate cancers combined; an estimated 158,040 people will die from lung cancer in the United States this year—27% of all cancer-related deaths. Non-small cell lung cancer (NSCLC) is the most common subtype of the disease, with *EGFR* mutations observed in 10% of NSCLC tumors.

Now, the FDA has approved gefitinib (Iressa) as first-line treatment for pa-

tients with metastatic NSCLC with exon 19 deletions or exon 21 L858R substitution in epidermal growth factor receptor (*EGFR*), with *therascreen* EGFR RGQ PCR kit as a companion diagnostic to appropriately identify patients who harbor the said mutation(s) and would be candidates to receive Iressa as first-line treatment. The approval follows a multicenter, single-arm, safety and efficacy study of Iressa in 106 treatment-naïve patients with *EGFR*-mutated NSCLC. The primary end point of the trial was ORR or the percentage of patients who presented with complete and partial shrinkage of tumor following treatment. The results showed that 50% of trial participants had tumor shrinkage that lasted an average of 6 months.

Another trial, a retrospective analysis conducted in a subgroup of 186 patients with *EGFR* mutation-positive metastatic NSCLC, had a comparator arm of 6 cycles of carboplatin/paclitaxel. The trial supported evidence from the prospective trial described above in that Iressa-treated patients had improved progression-free survival (PFS) compared with the comparator arm.

An independent panel determined that gefitinib reduced the risk of disease progression by 46%, with a median PFS of 10.9 months versus 7.4 months with carbopla-

tin/paclitaxel. The objective response rate for the gefitinib arm was 67% compared with 41% with chemotherapy, and the duration of response was 9.6 months versus 5.5 months, respectively.

Diarrhea and skin reactions were the most common side effects of treatment with Iressa.

Iressa, developed by AstraZeneca Pharmaceutical, was originally approved in 2003 for the treatment of patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel. Iressa was voluntarily withdrawn from the market after subsequent confirmatory trials failed to verify clinical benefit. The current approval is for a different patient population than the 2003 approval.

AstraZeneca is also examining combination regimens with gefitinib in lung cancer, including a study evaluating the EGFR inhibitor with the anti–PD-L1 agent durvalumab. **EBO**

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Medical World News®

FDA UPDATES

# Sonidegib Approved for Basal Cell Carcinoma

Surabhi Dangi-Garimella, PhD

An oral agent developed by Novartis Pharmaceuticals Corporation has been approved for the treatment of refractory patients with locally advanced basal cell carcinoma (laBCC). Patients who have undergone unsuccessful surgery or radiation treatment, or those who are not eligible for either, can initiate treatment with the sonic hedgehog inhibitor sonidegib (Odomzo). The FDA approval followed results of a randomized, double-blind, multi-center, 2-arm study in patients with laBCC or metastatic BCC. The approval was contingent on a durable objective response rate (ORR).

**ZYTIGA® (abiraterone acetate) Tablets**
Brief Summary of Prescribing Information.

**INDICATIONS AND USAGE**
ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

**CONTRAINDICATIONS**
**Pregnancy:** ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

**WARNINGS AND PRECAUTIONS**
**Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess:** ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

**Adrenocortical Insufficiency:** Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

**Hepatotoxicity:** In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

**ADVERSE REACTIONS**
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.

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**Clinical Trial Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

**Study 1: Metastatic CRPC Following Chemotherapy:** Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

**Table 1: Adverse Reactions due to ZYTIGA in Study 1**

| | ZYTIGA with Prednisone (N=791) | | Placebo with Prednisone (N=394) | |
|---|---|---|---|---|
| **System/Organ Class** | All Grades[1] | Grade 3-4 | All Grades | Grade 3-4 |
| Adverse reaction | % | % | % | % |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Joint swelling/ discomfort[2] | 29.5 | 4.2 | 23.4 | 4.1 |
| Muscle discomfort[3] | 26.2 | 3.0 | 23.1 | 2.3 |
| **General disorders** | | | | |
| Edema[4] | 26.7 | 1.9 | 18.3 | 0.8 |
| **Vascular disorders** | | | | |
| Hot flush | 19.0 | 0.3 | 16.8 | 0.3 |
| Hypertension | 8.5 | 1.3 | 6.9 | 0.3 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 17.6 | 0.6 | 13.5 | 1.3 |
| Dyspepsia | 6.1 | 0 | 3.3 | 0 |
| **Infections and infestations** | | | | |
| Urinary tract infection | 11.5 | 2.1 | 7.1 | 0.5 |
| Upper respiratory tract infection | 5.4 | 0 | 2.5 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 10.6 | 0 | 7.6 | 0 |
| **Renal and urinary disorders** | | | | |
| Urinary frequency | 7.2 | 0.3 | 5.1 | 0.3 |
| Nocturia | 6.2 | 0 | 4.1 | 0 |
| **Injury, poisoning and procedural complications** | | | | |
| Fractures[5] | 5.9 | 1.4 | 2.3 | 0 |
| **Cardiac disorders** | | | | |
| Arrhythmia[6] | 7.2 | 1.1 | 4.6 | 1.0 |
| Chest pain or chest discomfort[7] | 3.8 | 0.5 | 2.8 | 0 |
| Cardiac failure[8] | 2.3 | 1.9 | 1.0 | 0.3 |

The phase 2 BOLT trial enrolled 230 patients randomized to receive 800 mg or 200 mg of sonidegib until progression or unacceptable toxicity was observed. Eighty-four percent of trial enrollees had locally advanced disease. Most patients (76%) had received prior therapy for treatment of BCC, and approximately half of these patients (56%) had aggressive histology. The trial results showed a durable ORR of 58% (95% CI, 0.45-0.70) in 66 patients randomized to receive the 200 mg dose of sonidegib, with 3 complete responses and 35 partial responses. While the disease progressed in 7 of the 38 responders, response in 4 of the 7 patients lasted at least 6 months. Patients (128) on the 800-mg arm had an ORR of 44% (95% CI, 0.35-0.53).

The most serious risks of sonidegib are rhabdomyolysis and embryofetal toxicity. **EBO**

Reference

**1.** Sonidegib. FDA website. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm455865.htm. Accessed July 27, 2015.

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[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

**Table 2: Laboratory Abnormalities of Interest in Study 1**

| | Abiraterone (N=791) | | Placebo (N=394) | |
|---|---|---|---|---|
| Laboratory Abnormality | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| Hypertriglyceridemia | 62.5 | 0.4 | 53.0 | 0 |
| High AST | 30.6 | 2.1 | 36.3 | 1.5 |
| Hypokalemia | 28.3 | 5.3 | 19.8 | 1.0 |
| Hypophosphatemia | 23.8 | 7.2 | 15.7 | 5.8 |
| High ALT | 11.1 | 1.4 | 10.4 | 0.8 |
| High Total Bilirubin | 6.6 | 0.1 | 4.6 | 0 |

**Study 2: Metastatic CRPC Prior to Chemotherapy:** Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

**Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2**

| | ZYTIGA with Prednisone (N=542) | | Placebo with Prednisone (N=540) | |
|---|---|---|---|---|
| **System/Organ Class** | All Grades[1] | Grade 3-4 | All Grades | Grade 3-4 |
| Adverse reaction | % | % | % | % |
| **General disorders** | | | | |
| Fatigue | 39.1 | 2.2 | 34.3 | 1.7 |
| Edema[2] | 25.1 | 0.4 | 20.7 | 1.1 |
| Pyrexia | 8.7 | 0.6 | 5.9 | 0.2 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Joint swelling/ discomfort[3] | 30.3 | 2.0 | 25.2 | 2.0 |
| Groin pain | 6.6 | 0.4 | 4.1 | 0.7 |
| **Gastrointestinal disorders** | | | | |
| Constipation | 23.1 | 0.4 | 19.1 | 0.6 |
| Diarrhea | 21.6 | 0.9 | 17.8 | 0.9 |
| Dyspepsia | 11.1 | 0.0 | 5.0 | 0.2 |
| **Vascular disorders** | | | | |
| Hot flush | 22.3 | 0.2 | 18.1 | 0.0 |
| Hypertension | 21.6 | 3.9 | 13.1 | 3.0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 17.3 | 0.0 | 13.5 | 0.2 |
| Dyspnea | 11.8 | 2.4 | 9.6 | 0.9 |
| **Psychiatric disorders** | | | | |
| Insomnia | 13.5 | 0.2 | 11.3 | 0.0 |
| **Injury, poisoning and procedural complications** | | | | |
| Contusion | 13.3 | 0.0 | 9.1 | 0.0 |
| Falls | 5.9 | 0.0 | 3.3 | 0.0 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 12.7 | 0.0 | 8.0 | 0.0 |
| Nasopharyngitis | 10.7 | 0.0 | 8.1 | 0.0 |

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**Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2 (continued)**

| | ZYTIGA with Prednisone (N=542) | | Placebo with Prednisone (N=540) | |
|---|---|---|---|---|
| **System/Organ Class** | All Grades[1] | Grade 3-4 | All Grades | Grade 3-4 |
| Adverse reaction | % | % | % | % |
| **Renal and urinary disorders** | | | | |
| Hematuria | 10.3 | 1.3 | 5.6 | 0.6 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash | 8.1 | 0.0 | 3.7 | 0.0 |

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

**Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2**

| | Abiraterone (N=542) | | Placebo (N=540) | |
|---|---|---|---|---|
| Laboratory Abnormality | Grade 1-4 % | Grade 3-4 % | Grade 1-4 % | Grade 3-4 % |
| Hematology | | | | |
| Lymphopenia | 38.2 | 8.7 | 31.7 | 7.4 |
| Chemistry | | | | |
| Hyperglycemia[1] | 56.6 | 6.5 | 50.9 | 5.2 |
| High ALT | 41.9 | 6.1 | 29.1 | 0.7 |
| High AST | 37.3 | 3.1 | 28.7 | 1.1 |
| Hypernatremia | 32.8 | 0.4 | 25.0 | 0.2 |
| Hypokalemia | 17.2 | 2.8 | 10.2 | 1.7 |

[1]Based on non-fasting blood draws

**Cardiovascular Adverse Reactions:** In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

**Post Marketing Experience**

The following additional adverse reactions have been identified during post approval use of ZYTIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Respiratory, Thoracic and Mediastinal Disorders:* non-infectious pneumonitis.

*Musculoskeletal and Connective Tissue Disorders:* myopathy, including rhabdomyolysis.

**DRUG INTERACTIONS**

**Drugs that Inhibit or Induce CYP3A4 Enzymes:** Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

**Effects of Abiraterone on Drug Metabolizing Enzymes:** ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In

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# Need for Palliative Care for Improved Performance at the End of Life

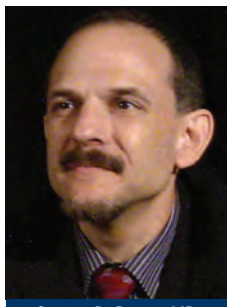
Surabhi Dangi-Garimella, PhD

While increased attention is being paid to quality of life for patients with advanced stage disease, discrepancies exist that may harm the patient. CMS recently announced that hospices have been selected to participate in the Medicare Care Choices Model so dually eligible beneficiaries can receive supportive care services provided by a hospice while undergoing curative treatment.[1] Now, an article published in *JAMA Oncology*[2] underscores the need for these efforts to improve quality of life (QOL), especially for cancer patients. The study found that chemotherapy for pa-

tients with end-stage cancer was associated with worse quality of life near death (QOD) while they still retained their ability to perform many life functions.


Erik K. Fromme, MD

In examining 661 patients with end-stage cancer across multiple institutions, researchers employed the Eastern Cooperative Oncology Group Status (ECOG) to determine the patients' performance status at the time of study entry and at their passing. Patient performance at passing was estimated based on interviews with the caregivers most closely involved with the patient's care, a median of 2.4 weeks after death, to understand physiological and physical distress and overall QOL. Among their results, the authors found that QOD did not improve for patients with moderate or poor ECOG scores following chemotherapy in the last week of life, and worsened for those with good ECOG scores. In a related commentary,[3] Charles D. Blanke, MD, and Erik K. Fromme, MD, of the Oregon Health & Science University, Portland, write: "These data from Prigerson and associates suggest that equating treatment with hope is inappropriate. Even when oncologists communicate clearly about prognosis and are honest about the limitations of treatment, many patients feel immense pressure to continue treatment.…At this time, it would not be fitting to suggest guidelines must be changed to prohibit chemotherapy for all patients near death without irrefutable data defining who might actually benefit, but if an oncologist suspects the death of a patient in the next 6 months, the default should be no active treatment."


Charles D. Blanke, MD

*Evidence-Based Oncology* recently published an entire issue on palliative care in April 2015, inviting payers, health policy experts, and providers of palliative care to address the topic. Authors agreed that clear communication with patients and their family in palliative care decision making is of utmost importance. **EBO**

**References**

**1.** CMS announces Medicare Care Choices Model awards [press release]. http://www.hhs.gov/news/press/2015pres/07/20150720a.html. Washington, DC: HHS; July 20, 2015.

**2.** Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy use, performance status, and quality of life at the end of life [published online July 23, 2015]. *JAMA Oncol.* doi:10.1001/jamaoncol.2015.2378.

**3.** Blanke CD, and Fromme EK. Chemotherapy near the end of life: first–and third and fourth (line)–do no harm [published online July 23, 2015]. *JAMA Oncol.* doi:10.1001/jamaoncol.2015.2379.

# Massive Consolidation Among Healthcare Payers

Mary K. Caffrey and Laura Joszt

The month of July saw a major rumble in the payer world. First, Aetna announced a $37 billion agreement to acquire Humana at the beginning of July—a deal that had been anticipated for weeks and moved forward after the US Supreme Court left intact a key piece of the Affordable Care Act (ACA). In less than a month following the Aetna-Humana merger, Anthem announced the purchase of Cigna for $54.2 billion after a month of rocky negotiations.

Both deals continue the trend of consolidation that has swept the healthcare industry since passage of the ACA and would shrink the US health insurance market from 5 big insurers to just 3. Some fear that ongoing consolidation will thwart competition and drive up prices for consumers, undermining a key goal of the law.

Reports of the Aetna-Humana deal had been floated since the spring, but both sides awaited the outcome of *King v Burwell*; on June 25, the Supreme Court ruled 6 to 3 that consumers in states without healthcare exchanges could still obtain financial assistance to buy coverage.

Aetna has benefited from the ACA and looks to keep up that trend in its acquisition of Humana, which is the nation's second-largest provider of private Medicare coverage. New rules proposed by CMS will call for increased movement to payment reform in both Medicare and Medicaid, and for more seamless transitions for consumers who move between Medicaid and coverage on the exchanges that are purchased with tax subsidies. Thus, having strong footholds in all sectors of public coverage will prove beneficial, analysts have said.

While Aetna is currently the larger company by revenue, its number of Medicare enrollees is smaller at 1.26 million, compared with Humana's 3.2 million. Value of this sector is expected to increase as the baby boomer population ages.

Joseph R. Swedish, Anthem's chief executive officer, will serve as chairman of the board and chief executive of the new combined company from the Anthem-Cigna merger—the combined revenue is estimated at $115 billion. David Cordani, chief executive of Cigna, will be president and chief operating officer, and once the deal closes the Anthem board of directors will be expanded to 14 members with Cordani and 4 other members of Cigna's current board joining.

The purchase of Cigna will give Anthem more negotiation power with hospitals and doctors. Two-thirds of the combined entity's new membership will be in self-insured plans, 15% in traditional commercial insurance, 11% in Medicaid, and 4% in Medicare.

"Our companies share proud histories and an even brighter future," Cordani said. "Going forward our new company will deliver an acceleration of innovative and affordable health and protection benefits solutions that help address our health system's challenges and provide supplemental insurance protection, and health care security to consumers, their families, and the communities we share with them."

On June 20, Anthem proposed to acquire Cigna for $184 per share, which valued the company at $53.8 billion; however, Cigna's board of directors deemed the proposal inadequate, and expressed concern that Swedish would assume 4 roles: chairman of the board, chief executive officer, president, and head of integration.

At this time only UnitedHealth Group, the current largest American insurer, has sat out of the merger frenzy. Once Cigna and Anthem combine, the new company will have 53 million members, which is more than UnitedHealth.

The Anthem-Cigna purchase and the Aetna-Humana purchase are both still subject to regulatory review. **EBO**

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National Medical Director, Oncology Strategy
Aetna

**Ted Okon, MBA**
Executive Director
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**ABOUT THE AUTHOR**

We want you healthy. Crystal Run Healthcare

GNANAMBA VARUNI KONDAGUNTA, MD

**Dr Kondagunta** is a medical oncologist with Crystal Run Healthcare.

*Balancing the appropriate use of diagnostic testing and treatment and ensuring that opportunities for improved survival and quality of life are not missed is the goal of value-based oncology. Elimination of duplicative and unnecessary care by adherence to evidence-based clinical pathways can result in cost savings that can then be invested in the appropriate use of innovative tests or treatments.*

sive progress toward treating and improving patient outcomes, costs have risen exponentially over the past 3 decades.[1] The cost of healthcare has become an important topic in the United States. During his keynote address at ASCO's annual meeting, Michael Porter, PhD, MBA, a world-renowned expert in economics and competitiveness who has written extensively about healthcare, emphasized the importance of considering cost of care in cancer treatment. During his presentation, Value-Based Health Care Delivery, Porter implored the cancer community to give serious thought to how the value of care can be maximized.

These ideas are being considered in the community at large, as 361 presentations at the meeting included the word *cost* in the title. Porter's presentation looked for ways to maximize value of care. As a first step, testing and treatment regimens ("pathways") need to be evaluated to minimize cost while maintaining or improving quality of care for patients, he said. This is especially important when considering newer molecular testing and targeted therapies, which may be more expensive compared with older tests and treatments. In my practice, we have implemented significant measures to deal with some of these cost issues while maintaining quality care in line with clinical, evidence-based guidelines.[2]

In June 2015, ASCO released a framework for assessing the value of newer cancer therapies and treatments. The hope is to establish a tool that physicians and patients can use, to determine the benefits and costs of various treatments, which can help establish the value of newer, costlier treatments as compared with standard treatments.[3]

The Center for Medicare and Medicaid Innovation (CMMI) has also instituted a process by which oncology specialty physician practices can apply to participate in a new payment model, which allows the practice to be reimbursed in an innovative way—arrangements that include accountability for episodes of care surrounding chemotherapy administration for cancer patients. This new Oncology Care Model (OCM) aims to provide higher quality coordinated oncology care. A pioneer program established by CMMI for a medical subspecialty, OCM ascertains that the cost of oncology services is being reevaluated.[4]

These examples clearly indicate that "value" has developed into an important aspect of clinical decision making for physicians and patients alike.

## A PROVIDER'S PERSPECTIVE ON DIAGNOSTIC TESTING

I am one of 5 practicing medical oncologists at Crystal Run Healthcare, a physician-owned, multispecialty practice of over 300 physicians at multiple sites in New York. Crystal Run Healthcare has been a leader in value-based care for the past 10 years, being one of the first 27 accountable care organizations (ACOs) in Medicare Shared Savings Program and one of the first 6 ACOs to be accredited as part of the National Committee for Quality Assurance. We have also recently established our own healthcare plan, which also mirrors our philosophy of being a value-based organization. The oncology division was among the first 16 community cancer care practices nationwide to be certified by ASCO through their Quality Oncology Practice Initiative. In the oncology division, we have worked on variation reduction programs and established that pathways in oncology patient management result in high-quality, cost-effective care.

We have implemented a similar value-based approach to molecular diagnostic testing and treatments in my community setting.

Molecular diagnostic testing provides new information that can broaden treatment options, but in some cases these tests are not needed. Historically, pathology reports included information that described histologic findings and immunohistochemical stain profile. As targets such as Her2-neu (breast), epidermal growth factor (EGFR) (lung), KRAS (colon), and BRAF (melanoma) emerged, these became part of the routine testing done for each type of cancer. Newer methods to identify these targets include next generation sequencing (NGS), which allows for sequencing of tumor tissue or patient serum for somatic and germline mutations in a very short period of time. The advances in the chemistry behind these techniques have allowed for rapid sequencing but also a significant decrease in cost per base tested. Some of these tests may not be very expensive (eg, fluorescence in situ hybridization or FISH testing) but may be performed on a large number of patients (eg, all breast cancer patients), which can lead to multiplicative increase in cost for a population. More expensive molecular diagnostic tests (eg, NGS) are typically prescribed for select patients. Historically, physicians have not considered cost in determining treatment.

### *Multiplicative Cost of Less Expensive Tests*

To illustrate an example of the multiplicative cost of a relatively inexpensive test in a large population, we will look at 2 patients with invasive breast cancer. The expression of Her2-neu can be evaluated with immunohistochemistry (IHC) assays as well as with more expensive, but more precise, FISH techniques. Her2/neu testing in invasive breast cancer is an important prognostic and predictive factor. Trastuzumab in the adjuvant and metastatic setting, and several other drugs, including lapatinib and pertuzumab in the metastatic setting, are important therapeutic options available to patients based on positive Her2-neu testing. The National Comprehensive Cancer Network (NCCN) Guidelines indicate that FISH testing should be pursued specifically when IHC testing is equivocal at 2+. When IHC is negative, 1+ (negative), or 3+ (positive), then FISH can be deferred—IHC being more definitive. Since discordance between IHC and FISH testing is observed in less than 2% of patients, appropriate use of FISH can avoid the excess cost.[5]

## CASE STUDIES

At our community hospital Tumor Board, we discussed a 43-year-old woman who had a 2.5-cm invasive breast cancer that was estrogen receptor- and progesterone receptor-positive, and whose IHC was 3+ for Her2-neu. FISH testing, performed as part of the hospital's routine protocol, was also positive. At the same tumor board, a 69-year-old woman had a 0.8-cm invasive estrogen receptor– and progesterone receptor–positive breast cancer, with Her2-neu 1+ by IHC (negative). FISH testing, performed as part of our routine protocol, was negative as well.[6]

The cost of IHC is approximately $125 per specimen, and the cost of FISH is approximately $450 per specimen. Given that 300 breast cancer cases are treated at our regional medical center, at least $100,000 in extraneous FISH tests could be avoided. Performance of FISH testing on every specimen is redundant, wasteful, and a clear deviation from national standards. Oncology has always been, and has increasingly become, a multidisciplinary field. Pathologists, surgeons, radiologists, and medical subspecialists—including pulmonologists, gastroenterologists, and others—are all an important part of the team of physicians needed for the optimal treatment of cancer patients. One of my roles during Cancer Committee meetings and Tumor Boards at our local hospitals has been educating others involved in the care of oncology patients to incorporate value-based practices. At a recent meeting, following initial resistance to the change in practice on IHC and FISH testing in breast cancer patients, I discussed the NCCN and ASCO guidelines, and we approved a programmatic change to reflect adherence to national guidelines. In addition, as we at Crystal Run Healthcare have expanded our clinical services, we have pursued internal reviews of breast biopsy and pathology services within the practice through the use of our own Ambulatory Care Center

(continued on **SP428**)

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- Visit **www.youandisupport.com** and click the “Enroll Here” button
- Call 1-877-877-3536, Monday through Friday, 8 am - 8 pm ET; or
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Once enrolled, patients being treated with IMBRUVICA® will be provided with:

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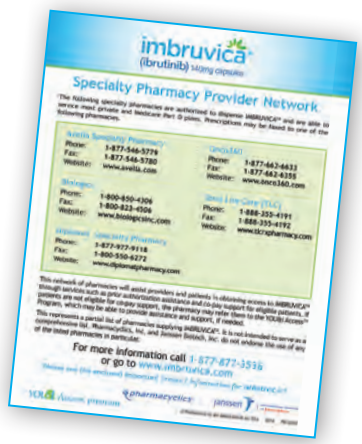
- Information about the prior authorization process
- Information about the insurance appeals process

To help connect patients to a specialty pharmacy, download a current list of specialty pharmacies that are authorized to dispense IMBRUVICA® and are able to service most private and Medicare Part D plans.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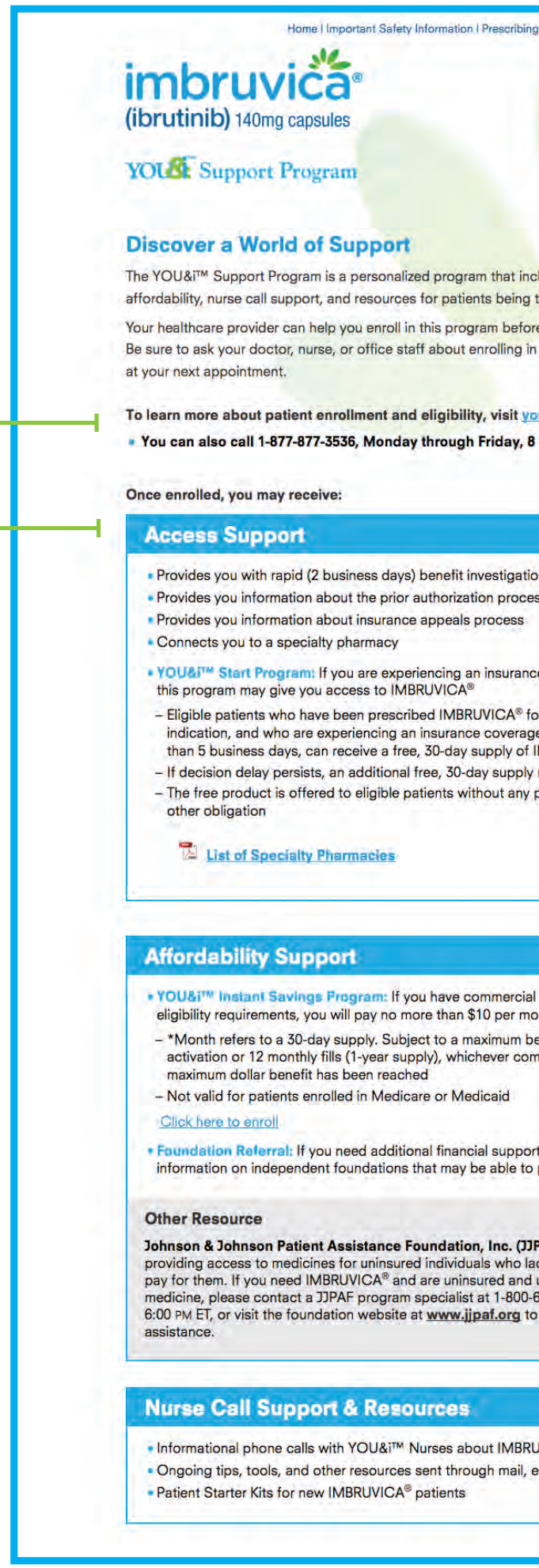
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YOU&i™ Support Program

**Discover a World of Support**

The YOU&i™ Support Program is a personalized program that inc
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Your healthcare provider can help you enroll in this program before
Be sure to ask your doctor, nurse, or office staff about enrolling in
at your next appointment.

**To learn more about patient enrollment and eligibility, visit yo**

- **You can also call 1-877-877-3536, Monday through Friday, 8**

**Once enrolled, you may receive:**

**Access Support**

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- Provides you information about the prior authorization proces
- Provides you information about insurance appeals process
- Connects you to a specialty pharmacy
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other obligation

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  - Not valid for patients enrolled in Medicare or Medicaid

Click here to enroll

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information on independent foundations that may be able to

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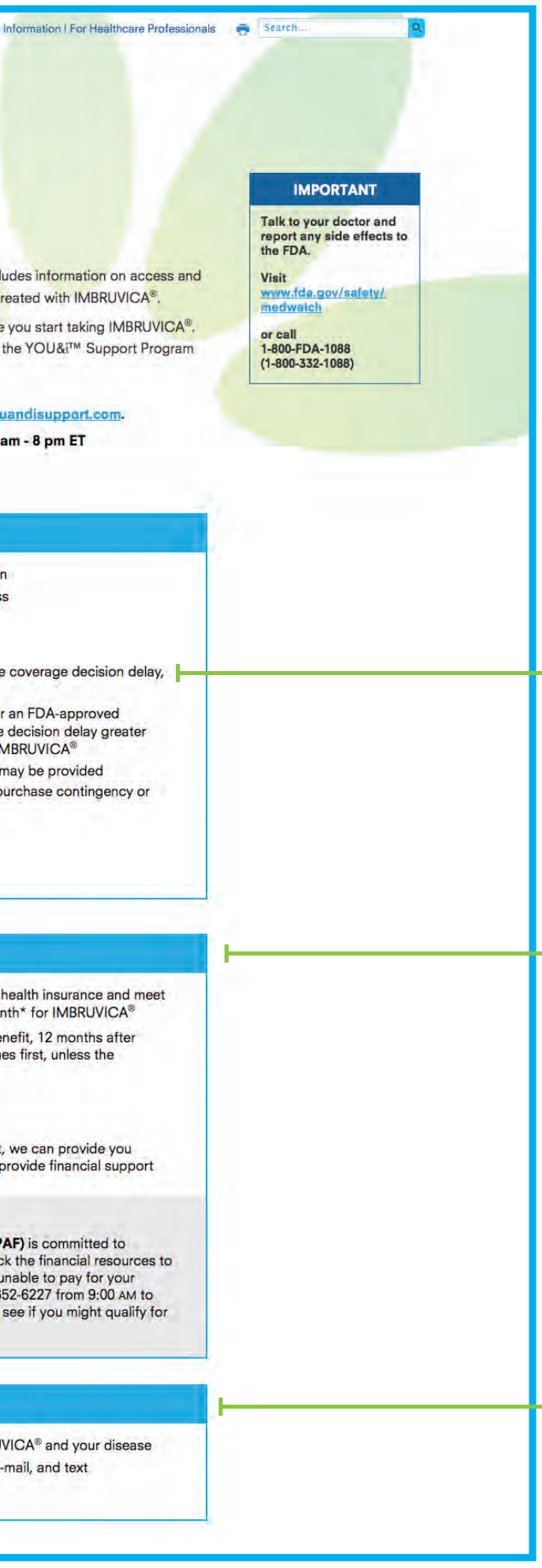


## YOU&i™ Start Program

Learn about providing eligible new patients with access to IMBRUVICA® during an insurance coverage decision delay.

## Affordability Support

Discover the benefits of the YOU&i™ Instant Savings Program, and help enroll patients in the program. Eligible patients will receive instant savings on private insurance co-pays, deductibles, and co-insurance for IMBRUVICA®. Not valid for federal and state healthcare program beneficiaries.


## Nurse Call Support & Resources

The YOU&i™ Support Program also offers nurse call support services to provide information and respond to patients' questions about their disease and IMBRUVICA®.

Ongoing tips, tools, and other resources about IMBRUVICA® are sent through mail, e-mail, and text. Patient Starter Kits for new IMBRUVICA® patients are also available.

Please see full Prescribing Information for IMBRUVICA® at **www.imbruvica.com**.


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(continued from **SP425**)

**TABLE.** PEG-filgrastim in Breast Cancer: Costs Before and After Implementation of Cancer Care Pathways

| | COST PER PATIENT BEFORE PATHWAY | COST PER PATIENT AFTER PATHWAY | TOTAL DIFFERENCE PER PATIENT |
|---|---|---|---|
| Physician A | $12,324 | $7176 | $5148 |
| Physician B | $11,856 | $6676 | $5180 |
| Physician C | $10,296 | $9494 | $812 |
| Physician D | $9672 | $7488 | $2184 |
| **Average** | $11,037 | $7706 | $3331 |

and our own pathologists, where we are assured of a value-based approach.

NGS is also an important tool that can be used to select patients for newer targeted therapies and to enrich the clinical trial patient cohorts to include best responders to newer agents. While the appropriate use of molecular testing is important, unnecessary testing can lead to a significant escalation of expenses since each NGS test can cost from $1500 to $5000, depending on the type of sequencing conducted.

Recently a 78-year-old man, an active smoker, with a new diagnosis of non–small cell lung cancer, was referred to me by a primary care physician (PCP) in the community. The patient had advanced disease, and the pathology report indicated that he had a poorly differentiated adenocarcinoma, with ALK-negative and EGFR-negative status. The patient's PCP, at the request of the patient's son, had asked the pathology department to send the NGS test. It was clear to me when I saw the patient that he was not a candidate for a clinical trial based on his performance status, nor would he be able to tolerate standard chemotherapy. Molecular testing in this patient was unnecessary. It is reasonable to limit NGS to those patients who are eligible for clinical trials where the information may be useful. It may also be helpful in patients with a good performance status who have already received standard therapies, and where the extended testing could help identify beneficial alternate treatment strategies. This type of testing should also be generally ordered by oncologists who have determined the clinical utility of the test.

## OPTIMIZING CLINICAL PATHWAYS

In our practice, treatment protocols are currently chosen at the discretion of the treating physician. We are committed to treating patients using clinical pathways based on data we obtained from a pilot project in our practice last year. We created our own breast cancer clinical pathway based on NCCN guidelines and used standard ranking criteria to choose optimal pathways.

- Protocols were first selected based on the best clinical outcome.
- Among equivalent regimens, the next selection was based on least toxicity.
- Finally, among regimens that were considered most effective and least toxic, regimen selection was based on lowest cost.

Data around costs associated with PEG-filgrastim and PET scan use (a costly but important part of treatment and surveillance programs) were collected on patients treated between March 2012 and September 2012 (*before* implementation of pathway) and compared with patients treated between March 2013 and September 2013 (*after* implementation of pathway) (**TABLE**). The average cost per patient for PEG-filgrastim use dropped by $3331 per patient during the measured interval, for a total cost savings of $227,000. There was no associated increase in febrile neutropenia or hospitalization. The calculated cost savings for PET scan use were $143,000.

*As clinical targets in more common malignancies including breast, lung, and colon cancers emerge, testing and treatment options will increase. Balancing these choices with the high costs associated with the new technology will be the challenge in order to determine value in oncology care.*

With increasing awareness of NCCN guidelines among our oncologists, the reduction in growth factor and PET scan utilization was also seen in other cancers that were not on pathways. This experience has led us to actively embrace the use of clinical pathways, which can heighten an oncologist's awareness of cost and appropriate use of diagnostic testing. For example, in the patient discussed earlier, NGS would not have been ordered since he was not a candidate for active therapy.

Reconciling the rapid advances, the exciting world of new targeted therapies, and the need to pursue value-based care is integral to the future of oncology patient care. Balancing the appropriate use of diagnostic testing and treatment and ensuring that opportunities for improved survival and quality of life are not missed is the goal of value-based oncology. There certainly are difficult decisions that need to be made when defining, as a medical community, what makes a test or treatment "worth" the cost (either toxicity or monetary). With medical progress, the value-based aspect of using new drugs, testing, and techniques needs evaluation. Elimination of duplicative and unnecessary care by adherence to evidence-based clinical pathways can result in cost savings that can then be invested in the appropriate use of innovative tests or treatments. **EBO**


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*The Need to Eliminate Barriers to Personalized Medicine*
(CONTINUED FROM COVER)

**ABOUT THE AUTHOR**

NPAF National Patient Advocate Foundation
The Patient's Voice | since 1996

ALAN BALCH, PHD

**Dr Balch** is CEO of the Patient Advocacy Foundation and its advocacy affiliate, the National Patient Advocate Foundation.

*If we can match patients to a personalized treatment regimen most likely to succeed based on the unique characteristics of their disease, then we can simultaneously put many on the most direct track to good health, preempt costs associated with less effective or unnecessary treatments, and prevent future health problems.*

for his new cancer treatment.

But for every Tom, there are countless Americans for whom clinically advanced genetic testing and precision treatments are simply not an option. Tom himself does not fit into the patient category for whom good healthcare should be out of reach. His family has a comfortable income, and he has full healthcare coverage.

The advantages of personalized medicine are still unattainable for many Americans—even those who are well insured and financially stable. From a patient advocacy perspective, this situation is concerning.

Precision medicine will perhaps establish some of the most important biomedical innovations of our generation. We at National Patient Advocate Foundation (NPAF), the advocacy arm of PAF, fully support wide-ranging investment in innovative, personalized medicines—especially in oncology. However, for that future to become a reality, we have to create an access and reimbursement environment that is conducive to precision care.

## IMPACT OF PERSONALIZED MEDICINE

We believe, and research has shown, that personalized diagnostics and medical treatments can improve outcomes by offering individually tailored treatment plans to patients based on certain genetic or other defining characteristics. Especially when it comes to cancer, the appropriate use of genetic testing and counseling will better align cancer treatment from the get-go.

Further, we know that research and healthcare will only progress when patients have access to, and participate at much higher rates in, clinical trials. Tom Hall had 5 options that might have worked for him. While he was already too weak from previous failed treatments to travel to participate in some of the trials, patients and their physicians should be well informed of all treatment options, including clinical trials.

Insurers have questioned whether some of the genetic tests being used have been validated. They request more research, and evidence that the overall concept works. We must support positive collaborations among providers, insurers, patients, drug companies, and diagnostic labs to document the success of comprehensive genomic profiling in linking patients to appropriate treatments as early as possible and without administrative hoops and excessive coinsurance. We believe such individually tailored plans can produce dramatic clinical responses in some cases, particularly in areas that have traditionally had few options, including melanoma, lung cancer, and pancreatic cancer. In doing so, personalized medicine can help achieve an incredible goal for patients: the slowing or reversal of diseases that once seemed unstoppable.

It is important to keep in mind that cures should not be considered the only success story in healthcare. As Tom Hall's family understands well, more time and better quality of life can be incredible gifts to patients and their loved ones. Our optimism grows as we hear more stories of scientific and clinical success, such as individualized cancer vaccines that induce the immune system into action or screening methods that increase the accuracy of ovarian cancer prognosis and diagnosis.

Fortunately, our lawmakers have taken notice and are responding with action. Congressional leaders are championing bipartisan proposals like 21st Century Cures to improve medical innovation, including precision medicine.[1] The federal government has now assembled a team of medical and science experts to build President Obama's Precision Medicine Initiative, which he first introduced in this year's State of the Union address.[2]

The big challenge increasingly facing patients is their ability to access and afford these new and innovative therapies. In order for precision medicine to truly succeed, we need to ensure ready access to appropriate diagnostic and genetic tests, coupled with easy access to optimal personalized treatment regimens. With unwavering determination, advocates throughout the country must champion clinical decision and payment models that support precision medicine.

## SURMOUNTING EXISTING BARRIERS

We have identified at least 2 significant issues that need to be addressed in order for personalized medicine to be a reality for most Americans: specialty tiers and clinical pathways.

Medicare and other payers have placed many advanced medications, including personalized treatments already on the market, on a "specialty tier," which requires payments beyond traditional co-pay amounts. In these instances, patients, regardless of income, must pay a *percentage* of the drug cost, often in the range of 20% to 40% or more. These costs often stretch into the thousands for a single treatment, rendering the treatment inaccessible for some. Patients should not have to decide between potentially life-altering treatment and debilitating medical debt. In order to protect patients, we must manage patient exposure to exorbitant coinsurance costs. Thus, NPAF supports Congressional bills such as HR 1600, the Patients' Access to Treatments Act of 2015,[3] along with state legislation that limits specialty tier pricing in an attempt to keep costs reasonable for patients.

In addition to specialty tiers, patients must be aware of certain clinical pathway programs in which payers are incentivizing doctors to prescribe treatments based on a small pre-determined list that is not likely to include one of the many options suggested by a genomic profile. Many insurers already utilize a fail-first approach to certain treatment regimens, which require lower-cost medications to be prescribed and to fail before more expensive medicines are made available to patients, even when the latter are included in nationally recognized clinical guidelines.

There must be a better way. If we can match patients to a personalized treatment regimen most likely to succeed based on the unique characteristics of their disease, then we can simultaneously put many on the most direct track to good health, preempt costs associated with less effective or unnecessary treatments, and prevent future health problems. Basket trials are one such innovation that hold great promise for science and for patients and allow rapid testing and approval of novel therapies. These trials are designed to assess positive responses to a targeted therapy among a small number of patients and, in the process, validate a clinical target linked to a molecular marker, independent of tumor site.[4]

Clinical pathways, trials, and reimbursement models must be structured in a way that accommodates precision medicine by allowing physicians to pursue treatment options that hold the greatest promise for personalized treatments from the very start of a patient's deeply personal care journey. We like to think of it as precision access or reimbursement.

As we continue to make bold scientific advances, we must keep the powerful stories of individuals like Tom Hall with us. For in the years to come, personalized medicines should be judged by the years of life they add for patients, not by the years it took for people to gain affordable access to them. **EBO**

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*Alternative Payment Models: Paving the Way or Building a Wall for Personalized Medicine?*
(CONTINUED FROM COVER)

thorization Act of 2015[2] has generated urgency among healthcare stakeholders to embrace a transition toward a more value-based payment system.

The most prominent move toward value has been the development of alternative payment models (APMs), which have grown exponentially in variety and scale in the past few years. If executed well, these new paradigms could represent a new set of incentives that build on personalized medicine's progress, improving care coordination and outcomes while controlling costs. However, if structured inappropriately and without the safeguards necessary to ensure high-quality care, APMs could have unintended consequences that limit patient access to vital services and medications. These consequences could derail the advancements in personalized medicine that have transformed cancer care in recent years.

To understand how the most prominent APMs might impact personalized medicine, the Personalized Medicine Coalition (PMC) published a white paper titled Paying for Personalized Medicine: How Alternative Payment Models Could Help or Hinder the Field.[3] Brief descriptions and analyses of each of the 3 models covered in the paper, as well as an exploration of how clinical pathways and transparency trends are impacting them, are presented below. The most prominent APMs include:

- Accountable care organizations (ACOs), which utilize shared savings incentives for an attributed population;
- Episode-based payments (also known as "bundled payments"), which pay for a set of services for a specific condition or procedure; and
- Medical homes, which focus on care coordination, usually via a primary care practice.

## ACCOUNTABLE CARE ORGANIZATIONS

ACOs allow for shared governance from a variety of stakeholders who work together to manage and coordinate care for a specified group of patients. In ACO models, providers can form legal entities with other providers; each is then held accountable for the cost and quality of a defined population of Medicare beneficiaries. ACOs that enter into 2-sided risk arrangements are given a target spending benchmark based on the historical cost of their attributed Medicare population and can earn "shared savings" based on the amount of Medicare spending below the benchmark in a given year. Alternatively, if an ACO cannot contain costs beneath their target amount, they may be required to pay back the Medicare program.

Unfortunately, while policy makers have lauded the potential to reduce Medicare spending, there is still an open question as to whether the ACO model improves quality. An initial evaluation of the Medicare ACO model showed that while 49 ACOs (22%) qualified for shared savings payments by successfully reducing total spending, 29 (59%) performed below the Medicare Shared Savings Program national average on quality. As the ACO program continues to evolve, it will be essential to emphasize that delivery system reforms take into account, quality-improving goals as the central focus of patient-centered reforms.

## "BUNDLED PAYMENTS"

Bundled payments have been designed as a way to encourage coordination across different providers and to promote more efficient care. However, they have historically failed to recognize the importance of personalized medicine. Although variations of bundled payment have existed for decades, the emergence of personalized medicine has occurred largely outside their evolution. Since passage of the ACA, bundled payments have seen a resurgence in both public and private healthcare programs.

A bundled payment is a single payment to providers or healthcare facilities (or jointly to both) for all services to treat a given condition or provide a given treatment. This could include a procedure in a hospital, acute care following discharge, and services during a window of time afterward. The payment can be divided among providers across the care spectrum. Bundled payments are usually limited to 1 episode of care for an individual patient, usually for up to 90 days.

Evidence indicates that the programs might reap cost savings in unexpected ways. For example, in 2009 the largest commercial insurer in the country, UnitedHealthcare (United), launched a pilot program with the primary goal of reducing the overall cost of cancer care. The premise for the pilot was that by removing the economic incentive for oncologists to prescribe high-cost chemotherapy drugs, overall spending would be reduced. Oncology providers in the pilot program were responsible for choosing the treatment regimen they wished to use (eg, a certain drug at a certain dose, additional drugs for side effects) for 19 specific cancer scenarios. The physicians then committed to at least 85% compliance with the chosen therapy.

Three years later, United announced that the pilot had reduced cancer care costs by 34%—or approximately $40,000—per chemotherapy patient. The pilot participants achieved those cost savings despite spending 179% more on chemotherapy drugs through savings in case management services, following evidence-based protocols that reduced complications and hospital admissions, and the use of innovative patient engagement tools.[4] Arguably, the program put into question the causal link between drug utilization and overall health costs.

Based on this recent experience, bundled payments seem much more useful in targeting waste and improving care coordination for procedures and conditions where there are fewer new tools and therapeutic strategies that could dramatically change the treatment paradigm.

## MEDICAL HOMES

Also known as the patient-centered medical home (PCMH), the medical home model is designed around an individual patient's needs and aims to improve access to care (eg, through extended office hours and remote access to medical records), increase care coordination, and enhance overall quality, while simultaneously reducing costs. According to the Agency for Healthcare Research and Quality (AHRQ), the model is defined by 5 criteria[5]:

1. *Comprehensive Care*

PCMH is accountable for meeting the large majority of each patient's physical and mental healthcare needs, including prevention and wellness, acute care, and chronic care requiring a team of providers.

2. *Patient-Centered*

PCMH actively supports patients in learning to manage and organize their own care at the level the patient chooses.

3. *Coordinated Care*

PCMH coordinates care across all elements of the broader healthcare system, including specialty care, hospitals, home-based care, and community services, and supports transitions between different care settings.

4. *Accessible Services*

PCMH delivers services to patients quickly through both in-office and remote mechanisms, including 24/7 access to a member of the care team and alternative methods of communication such as telehealth.

5. *Quality and Safety*

PCMH demonstrates a commitment to quality by ongoing engagement in best practices, performance measurement and improvement, and responding to patient experiences and patient satisfaction.

Although medical homes are much more focused on case management and access to primary care, they are also likely to have an impact on personalized medicine, especially when considering the role of diagnostics and the primary care physician as gatekeeper under many health plans.

## FACTORS INFLUENCING APMS: CLINICAL PATHWAYS AND TRANSPARENCY

Whether independent or as embedded tools in an APM, clinical pathways are becoming more common. For drugs and diagnostics, pathways may incentivize physicians to choose one therapy over another based solely on its availability on a particular pathway that is instituted by a patient's insurance plan. The fundamental issue remains the choice of certain pathways and specific guidelines used in their development. Furthermore, it is important to understand what incentives and data a payer uses

(continued on **SP432**)


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(continued from **SP430**)

to choose one pathway over another. Typically, preference for a particular pathway is based on evidence-based research. Ideally, that evidence is regularly updated to keep pace with advances in clinical research.

Transparency is another essential element of APMs. Although transparency is often a necessary and laudable goal, transparency without recognizing critical data gaps could be damaging in a personalized medicine context. For example, reporting specific genetic information could illuminate the reasons why a particular therapy is the most appropriate treatment. Including information on life decisions could also help add specificity to transparency data and help mitigate the risk of unfairly characterizing spending and utilization where, for much of the population, a course of treatment would not be appropriate.

Indeed, in creating new systems and processes, personalized medicine does not often correspond to how we currently define and measure quality using today's concept of value. The very nature of targeted therapies requires completely different mechanisms to empower clinicians with the tools they need to provide the highest quality care possible and facilitate engagement with healthcare stakeholders.

To adequately assess quality of care, organizations that span payers, providers, academics, and government have committed significant resources to develop appropriate quality measures. In the context of APMs, quality measures serve as important benchmarks to gauge the quality of care that patients receive, along with presenting goals for providers, and are often categorized by process, outcome, or efficiency measures.

- *Process measures:* Determine whether a specific healthcare service was provided to a patient in a manner consistent with evidence-based guidelines.
- *Outcome measures:* Assess the health status of a patient after receiving healthcare services.
- *Efficiency measures:* Evaluate the relationship between the cost of the care that has been provided and the quality of that care.

And yet until recently, there have been few efforts to promote quality measurement that captures the value gained from interventions that improve a patient's quality of life and/or functional status, arguably an essential step toward truly patient-centered reforms. Coupled with robust outcome measurement and appropriate weighting in determining payment, quality measurement plays a vital part in determining what behavior change(s) are likely to occur within APMs. In other words, for APMs to be ultimately successful, quality measurement must be comprehensive and accurate enough to insure that every patient receives the highest quality of care, while also being appropriately valued as part of a payment mechanism so that providers are incentivized in a truly patient-centered manner.

## CONCLUSION

Although APMs are growing in number, their true impact on quality and costs is still evolving. Questions remain: What will be the impact of APMs on how research and development resources are allocated for therapies that yield potentially life-altering treatments for sometimes significantly smaller subsets of the population? Will APMs allow enough flexibility for providers to take advantage of clinical innovations like those in personalized medicine?

As APMs continue to evolve and as plans consider how to potentially expand cost-reducing initiatives, the effect that changing incentives and payment systems will have on the decision to invest in personalized medicine must be carefully considered. In short, if new incentives begin to hamper access to personalized medicines in a meaningful way, the ability to invest in research and development of highly personalized therapies and diagnostics will likely shift to align with the inflexible payment systems. Such a shift would threaten the pace of innovation in personalized medicine, which represents one of the most useful cancer care options currently available.

Knowing what treatments will work for whom will prevent patient exposure to ineffective treatments. That knowledge, which in the future has the power to improve patient care at systemically lower costs, must be protected. **EBO**


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- What policy solutions are likely to improve access to critical therapies for individuals with chronic or rare diseases?

## Eligibility

The PAN Challenge is open to individuals and teams of up to 4 individuals who are 18 years of age or older at the time of entry. **Entrants must be residents of the United States and sponsored by (a) a university or college or (b) a health system**. Entrants may submit 1 paper that addresses the questions above for 1 of the following patient populations:

a) Medicare population, including individuals covered by original Medicare and by Medicare Advantage.

b) Insured population, including individuals with employer-sponsored insurance (ESI) or coverage by a Qualified Health Plan (QHP) offered on an Exchange or Marketplace.

## How to Enter

- **Entrants are required to read the rules and judging criteria upon registering for the Challenge.**
- Entrants can **register** and submit abstracts from June 1 to October 30, 2015.
- Selected semifinalists will be asked to submit papers (2500 to 5000 words) between November 13 and December 31, 2015.
- Two winning entries (1 entrant per population category) and 2 runners-up (1 entrant per population category) will be chosen from the semifinalists on January 15, 2016.

## Prizes

- Winners' sponsor organizations (1 from the Medicare population category and 1 from the insured population category) will each receive $10,000. Second-place winners' sponsor organizations (1 from the Medicare population category and 1 from the insured population category) will each receive $5000.
- First-place winners will be given an opportunity to attend and present (1 member per winning entrant; expenses paid) at the Cost-Sharing Roundtable to be held in Washington, DC, in mid-February 2016 (date to be determined).
- Papers of first-place winners will be published in a future print and online supplemental edition of *The American Journal of Managed Care*.

For more information, contact Arny Niles at **challenge@panfoundation.org** or **(202) 661-8073** or visit **http://www.panfoundation.org/challenge**.

AJMC® 20th ANNIVERSARY
Managed Markets Network®

# PATIENT-CENTERED ONCOLOGY CARE®

NOVEMBER 19-20, 2015 • BALTIMORE, MD

## Patient-Centered Oncology Care 2015

*The American Journal of Managed Care*® will host its *4th Annual* **Patient-Centered Oncology Care®** meeting on November 19-20, 2015, in Baltimore, MD. The event will offer unique perspectives on emerging topics in oncology care from today's leading health experts. Go to **ajmc.com/meetings/PCOC15** for important updates, to access the agenda for the meeting, or to make a reservation to attend.

## STEERING COMMITTEE:

**Bruce Feinberg, DO**
Vice President and Chief Medical Officer
Cardinal Health Specialty Solutions, Clinical Pathways

**John L. Fox, MD, MHA**
Associate Vice President of Medical Affairs
Priority Health

**Richard W. Joseph, MD**
Assistant Professor
Division of Medical Oncology
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**Ira Klein, MD, MBA, FACP**
National Medical Director
Clinical Thought Leadership
Aetna

**Michael A. Kolodziej, MD**
National Medical Director, Oncology Strategy
Office of the Chief Medical Officer
Aetna

**Debra Patt, MD, MPH**
Physician
Texas Oncology

**Burton F. VanderLaan, MD, FACP**
Medical Director, Network Effectiveness
Priority Health

## LOCATION:

**Baltimore Marriott Waterfront**
700 Aliceanna Street
Baltimore, MD, 21202
(410) 385-3000

## Topics

### Session 1: Genomics in Oncology

- Next-Generation Genetic Sequencing (Genomics 101) for Payers
- Outcomes from Mandatory Genetic Testing and Counseling Programs
- ***Panel:*** The Impact of FDA Regulation on Diagnostics in Oncology

### Session 2: Genomics in Oncology, Part 2 - Precision Medicine

- How the President's Precision Medicine Initiative Will Learn From Oncology Practice
- The Patient Lens on Precision Medicine
- ***Panel:*** Reimbursement Challenges for Oncology Innovations: Who Pays?

### Session 3: The Future of Immuno-oncology

- Are We Close to the Big "C": Cure?
- Evaluation of Options and Outcomes in a "Me Too" Market
- ***Panel:*** The Role of PBMs in Managing High-Cost Treatment Options

### Session 4: Innovations for Patient-Centered Care

- Updates in Big Data for Oncology: What Are We Learning?
- Payment Models in Oncology Care at the Patient Level
- ***Panel:*** Navigating the Conflict of Personalized Medicine vs Population Management

### Session 5: Accountable Care in Oncology

- ***Panel:*** Evolution of the ACO Model to Meet the Needs of Oncology Patients and Payers

THE AMERICAN JOURNAL OF MANAGED CARE®

**subject to change*