SPECIAL ISSUE: REIMBURSEMENT MODELS

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PATIENT-CENTERED CARE

Oncology Practice Transformation Helps Deliver Patient-Centered Cancer Care in a Community Oncology Practice

Kashyap Patel, MD; Maharshi Patel, MBA; Asutosh Gor, MD; Sashi Naidu, MD; Niyati Nathwani, MD; Radhee Kothadia, BS; Saheli Parekh; and Eric Singhi, MD

Introduction

THE US HEALTHCARE system is in a state of crisis. Compared with other economically developed countries, the United States has been shown to be drastically overspending on healthcare while outcomes remain inferior. A 2013 report by the Institute of Medicine (IOM)—now The National Academies of Sciences, Engineering, and Medicine—described the US healthcare system as one that leads to "shorter lives, poorer outcomes."[1] While the United States leads in innovation for cancer therapies, the IOM report pointed out that the nation's "increasingly chaotic and costly" cancer care system is in crisis and fails to deliver consistent care that is patient-centered, evidence-based, and coordinated.

Cancer care is among the fastest-growing segments of the US healthcare system, outpacing many other subspecialties. In the United States, total spending on cancer care has increased from $27 billion in 1990 to $124 billion in 2010, with spending projected to reach about $157 billion by 2020.[2,3] Total costs of cancer care for the US population are predicted to increase across all phases of care: Cost drivers include technological innovation, rising costs of hospitalization, and a population-level increasing susceptibility to malignancy due to an aging demographic and increasing life span.[4] Global spending on oncology and supportive care drugs reached $100 billion in 2014, with targeted therapy expenditures accounting for almost 50% of this amount.[5] In the United States, oncology drug expenditures, excluding supportive care agents, increased by 18.0% from 2014 to 2015.[5]

Along with payers, employers, and the government, patients, caregivers, and family members shoulder an increasing share of these rising costs due to changes in benefit design, which now combine higher out-of-pocket costs with rising premiums and deductibles.[3] Cancer treatment can have a substantial financial impact on patients and their families; in fact, financial toxicity has been cited as a contributing factor to adverse outcomes in patients with cancer.[6-9]

One possible way to reduce overall cost, improve patient experience, and improve outcomes is to shift the focus of healthcare delivery away from volume and toward value. Patient-centered cancer care (PCCC) holds the promise of addressing these issues. The Oncology Care Model (OCM), developed by CMS' Center for Medicare & Medicaid Innovation (CMMI), is a leading pilot that has been in place for over a year and seeks to test the efficacy of PCCC for Medicare beneficiaries over the next 5 years.[10,11]

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PAYING FOR THERAPY

Value-Based Contracting: Creating the Terms of Engagement Around High-Cost Cancer Therapies

Susan Dentzer

THERE IS GOOD NEWS and bad news ahead for patients with cancer, oncology care, and the US healthcare system. The good news is that a phenomenal array of breakthrough cancer treatments, and possibly cures, are now on the market or in the development pipeline; many of those under development will be approved and launched on the market within a few years. The bad news is that these treatments will be very expensive. As a nation, we have no strategy, or even a minimal notional framework, of how we will pay for or afford them.

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CLINICIAN PERSPECTIVE

The Risk Conundrum in Healthcare

Peter Aran, MD

RISK. THIS 4-LETTER word is problematic, but not for the usual reasons. In healthcare, the term, and more importantly the concept, is immensely important. Risk has very different meanings depending on whether one views it from a clinical or financial perspective. Clinicians deal with clinical risk analysis multiple times each day as we care for our sickest patients. But so too do healthcare policy experts and healthcare financial leaders, although how they use this terminology and view the concepts behind it is very different from how clinician providers do so. Herein lies a problem, and although it is not a new problem, it has been brought into focus recently: Policy makers are trying to engage clinicians in the transformation of the Merit-based Incentive Payment System (MIPS) into an advanced alternative payment model (APM) under the Quality Payment Program (QPP), which was formerly known as the Medicare Access and CHIP Reauthorization Act (MACRA).[1]

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CLINICIAN PERSPECTIVE
SP151

In healthcare, the term "risk" can mean different things, depending on whether one views it from a clinical or financial perspective.

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In January, the FDA approved denosumab for the prevention of skeletal-related events in patients with multiple myeloma.

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FROM THE CHAIRMAN

Transitioning to APMs in Cancer Care—A Bridge to Something Better

THREE YEARS AGO, the American Medical Group Association (AMGA) surveyed key decision-makers in healthcare, who said they believed that 50% of all commercial payers would be using value-based mechanisms by 2018.

Fast forward, and the share of payers using value-based structures is far short of those projections—but at 24%, the Healthcare Financial Management Association (HFMA) reports it's still twice what it was when the original survey was taken in 2015.1 Many reasons are given why the pace of reform is so slow, from challenges with interoperability to simple fear of the unknown.

Whatever the reason for the slow pace, most healthcare experts believe that fee-for-service (FFS) reimbursement is on the way out. Timing that transition is challenging because no one quite knows when healthcare will reach the tipping point—when it will no longer make financial sense to stick with FFS, even for some part of the business.

And so today, we find ourselves with one foot in the world of alternative payment models (APMs) and one still in FFS. This is perhaps best seen with the Oncology Care Model (OCM), created by the Center for Medicare & Medicaid Innovation and embraced by 17 commercial plans. The core features of the OCM are 6-month episodes of care and $160 per-patient per-month payments, along with care coordination and care management requirements. Critics say the approach doesn't eliminate FFS, and the 6-month time frame for episodes creates improper incentives that override a doctor's good judgment. The American Society of Clinical Oncology has petitioned for its own APM to be approved for reimbursement.

But the arrival of OCM starts conversations about rewarding care coordination, nurse navigation and taking on risk, all of which were long absent within the context of Medicare. As we see in this issue, groups like Carolina Blood and Cancers Center are making the OCM work for patients. The model is being adapted for younger patient populations with a focus on the nursing component and the use of technology in New Jersey, where Regional Cancer Care Associates and Horizon Blue Cross and Blue Shield are running a pilot program.

We still have much to do to advance the value discussion. But 3 years from now, we should be able to measure our progress. ◆

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Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

FROM THE EDITOR-IN-CHIEF


ALVARNAS

A Game of Risk

WE ARE NOW in the longest, most dramatic period of cancer care innovation that we have ever seen. In the early days of cancer research, the victories came slowly, painfully, and at a pace that left far too many patients and their families seeking answers that would never come in time. The initial dramatic victories achieved through the development of combination chemotherapy, increasingly precise radiation therapy, and more effective surgical strategies also came with the realization that even these marvelous technologies could not cure every patient. Over the past decade, however, we have seen the traditional anticancer armamentarium grow in extraordinary ways, with new technologies that were targeted with increased precision against the molecular and protein biology at the core of cancer. With the advent of highly effective therapeutics like the tyrosine kinase inhibitors, monoclonal anticancer antibodies, checkpoint inhibitors, and the rapidly growing myriad of gene-mutant targeted agents, patients' hopes for more effective treatments and a greater chance for cure (or long-term containment) of their cancer are increasingly realized.

Yet, what is it about this extraordinary period in cancer care innovation that is so disquieting? While the promise of increasingly effective cancer care brings a sense of hope, the spiraling cost of delivering this care provokes anxiety about whether these therapies can be delivered in a sustainable, equitable way. Many, including authors in *Evidence-Based Oncology*™ (*EBO*™), have written about the growing level of healthcare expenditures in the United States (which CMS listed at $3.3 trillion in 2016) and the extraordinary costs of new targeted anticancer drugs (in 2014, the average monthly cost for a new anticancer oral agent was $11,325). These factors, coupled with the rise in patient-borne costs of cancer care and the resulting "financial toxicity" crisis, beg the question: can we restore order, equitability, access, and financial sustainability to our care delivery system?

No single "magical" fix to the healthcare system can make these issues go away. Moreover, the current level of political rhetoric surrounding the question of "fixing" our healthcare ills is more likely to provoke gastrointestinal distress than real, meaningful systemic change. The hope of getting this right lies in the ability of key healthcare stakeholders to more effectively align patient risk, therapeutic strategy, and reimbursement in a way that more effectively rewards better, more effective care, while ensuring that those healthcare systems/providers who provide appropriate care for high-risk/high-cost patients are not penalized financially for doing so. In their seminal article, "The Strategy That Will Fix Health Care," Porter and Lee review a series of systemic realignments in care delivery that could help to address the issue of financial sustainability while allowing for better transparency (and financial rewards) for delivering excellent care. This clinical/quality/financial realignment is one in which those providing care accept financial risk in the process, but do so in a way that is financially sustainable and provides an effective reward system for doing it well.

While we understand the right sensibilities in creating a sustainable care delivery, we have not yet created the ideal model for delivering this consistently, at scale, across a nation of more than 325 million individuals. We do, however, have evidence of progress in this pursuit through the development of advanced alternative payment systems (AAPM). The Medicare Access and CHIP Reauthorization Act (MACRA) has helped push physicians and care systems into greater numbers of 2-sided risk–bearing payment models in the hopes of better aligning reimbursement with effective care delivery. While the number of initial AAPM choices for oncologists under MACRA were quite limited, we are beginning to see growing numbers of new, innovative models gaining acceptance by the Physician Focused Payment Model Technical Advisory Committee. What some of the emerging models have in common include rigorous financial risk-grouping of patients around both diagnosis and clinical risk, alignment of financial risks around costs that physicians can actually control, and more meaningful outcome measures than those used in the current Physician Quality Reporting System. Inasmuch as innovations in care technology promise patients greater hope when faced by a life-threatening cancer, innovation in the care delivery and payment systems may help create new strategies for delivering this care sustainably. Although the idea of a chimeric antigen receptor (CAR) T-cell therapeutic costing more than $400,000 is a new reality, a fundamental realignment of our care and payment system around the patients' needs can help ground us in ensuring that those patients who need and will benefit from these technologies can receive the best care possible. ◆

For an expanded version of Dr Alvarnas' letter, see ajmc.com.

Joseph Alvarnas, MD
EDITOR-IN-CHIEF

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.

Oncology Nurse Navigators: Putting the Value in Value-Based Payment Models

Lani M. Alison, BSN, MS-HCQ, PCMH CCE

ALISON

Lani M. Alison, BSN, MS-HCQ, PCMH, CCE, is vice president of clinical affairs for Regional Cancer Care Associates.

THE US HEALTHCARE SYSTEM is in a transition from traditional fee-for-service reimbursement to value-based contracts in cancer care delivery through oncology medical homes (OMHs), fostered by both CMS' Oncology Care Model (OCM) and by commercial payers, such as Cigna and Horizon Blue Cross and Blue Shield of New Jersey (BCBSNJ). OMH models are designed to address all 3 parts of the triple aim: decrease the total cost of care while keeping quality and patient experience high. These initiatives have resulted in many innovative ideas to make practice transformation as smooth as possible.

Implementing these constructs requires the engagement of *people*, the creation or revision of *processes*, and the deployment of reliable *technology*, to make disruption[1] as minimal as possible to patients and physicians, keeping routines as normal as possible, and to achieve the payers' requirements. Disruption requires people in roles that can accelerate the changes or practice transformation,[2] thereby providing the value in the new value-based payment world. The most recognizable accelerators in this transition are oncology nurse navigators (ONNs).

The role of the ONN was developed in the early 1990s by Harold Freeman, MD, who sought to diagnose cancer at earlier stages among underserved patients in the neighborhood of Harlem in New York, New York. Through a controlled experiment, Freeman showed that patients guided by a navigator after a suspicious cancer screening were more likely to follow through with biopsies—and in less time—than those who did not receive help.[3] Over the next 2 decades, the nurse navigator's role within the care team rose in importance[4] even if fee-for-service payment models did not always recognize it.[5]

ONNs provide the "constant" in what seem to be undulating waves of changes to workflows, the adoption of new technology, the near-weekly onslaught of new drugs, and the need to ensure every nuance of documentation is entered in discrete fields in electronic health records (EHRs) so the practice meets reporting requirements. A practice could have 1 ONN or a team of nurses who work with other clinicians and support staff to transform practices into OMHs. The ONN keeps the care team, including the oncologist, in rhythm, making sure the office is operating as smoothly as possible in the eyes of the patients and their families. The ONN can be dedicated to performing 1 or all the following functions, depending on the number of oncologists and patient volume in a practice:

- Ensuring safe and reliable care is provided in the treatment and infusion rooms, by periodic reviews of policies and procedures and by visual checks utilizing Quality Oncology Practice Initiative safety standards,[6] which ensure safe delivery of chemotherapy
- Anticipating patient and family needs for new patients
- Triaging and managing patients on the phone and making assessments and decisions using a technology-driven decision support of clinical pathways: for instance, whether to bring the patient in to avoid an emergency department (ED) visit or hospital admission, or to instruct the patient to take medications for adverse effects, with a computer notation to call back in 2 hours to make sure the patient will not go to the ED
- Providing regular updates to referring physicians, such as primary care physicians (PCPs), on their patient's prognosis, chemotherapy, and goals of treatment

The ONN must be a compassionate person, armed with clinical skills that nurses, of all healthcare professionals, have best developed: ONNs can "float" from uplifting conversations with patients and families about survivorship and community linkages, to staying solid as a rock when initiating end-of-life conversations. The ONN must explain the concept of Medical Orders for Life-Sustaining Treatment, and must become an advocate to ensure that the patient's wishes are honored throughout and at the end of the cancer journey. The ONN must also track which patients are due to come to the practice each day and which ones are eligible for clinical trials.

Care coordination, according to the Agency for Healthcare Research and Quality, is the deliberate organization of patient care activities among providers, and among provider visits, to ensure care is provided at the right place, at the right time, the first time and all the time.[7] Sometimes it is called "managing the white spaces," referring to the spaces between sites of care. Value-based reimbursement means 24/7 access to providers: not just ensuring that patients are adherent to oral therapy, but, to name a few examples, providing chemotherapy instructions to new patients who are of child-bearing age, serving patients whose cancer has progressed, holding the hand of a patient having another bone marrow aspiration, and calling back the spouse of a patient who needs to be told that "vomiting is expected and will pass." It means hugging a mother who has just been told her child has cancer. This is cancer care delivery in a patient-centered OMH led by an ONN or a team of nurse navigators working in conjunction with oncologists.

At Regional Cancer Care Associates (RCCA), this is how we practice nursing, enabled by partnerships with commercial payers such as Horizon BCBSNJ and Cigna, as well as by participating in OCM. These payment models are still relatively new and may evolve. But nursing, despite challenges of shortage, burnout, and aging, is here to stay: for our patients, their families, and the communities we serve.

A recently announced pilot program between RCCA and Horizon BCBSNJ will provide ONN services from the time the patient is identified as participating in this program through survivorship care planning or palliative care services.[8] The goal of the pilot program is to reduce care gaps by having nurses reach out to patients between treatments and identify issues that could lead to a trip to the ED. Horizon will pay a monthly management fee for the nurse navigators to manage each patient.[9]

The pilot will be powered by Cota, an analytics platform based on real-world data that helps payers and providers optimize outcomes of individual patients while holding down costs.[10] Once RCCA receives the lists of qualified patients from Cota, the RCCA practices are notified about these patients. The navigators then

HEALTHCARE Analytics News

Cota CMO Details Collaboration With IBM Watson Health: **ajmc.com/link/2886.**

review the patients' medical records and identify any gaps in care before the patient comes to the office. If the triage system shows that the patient has called in about any symptom, the patient is immediately contacted by the ONNs and either managed over the phone or brought to the office to be seen by the oncologist. The ONNs will utilize data from the EHR or analytic platforms to address any further gaps in care. The ONNs may access Jersey Health Connect,[11] a nonprofit health information exchange, to find out if the patient has been admitted to the hospital, or access Health Sphere, a platform developed by Horizon to create a comprehensive care plan for the patient.[12]

When the patient comes to the office, the ONN spends time with the patient, sometimes even during treatment, to further assess the patient's needs. This includes educating the patient and family members about the crucial process of calling the ONN about any issues the patient may be going through *before* they think of going to the ED. If the patient has any comorbid conditions, the ONN will also contact the PCP or specialist who is co-managing the patient to create full care coordination.

If the patient's journey is moving toward palliative care, through markers such as stage, ECOG scores, pain scales, and frailty scores, the ONN will work with the oncologist and, where appropriate, the clinical social worker, to meet with the family and discuss the patient's wishes. The ONN will help providing information regarding power of attorney, physician or medical orders for life-sustaining treatment, and a durable do not resuscitate order, if desired; the ONN will also help the family with the decision about placing the patient on hospice, when the time comes.

Through the pilot, Horizon will track many measures about the patients, including time to treatment, medications used, unplanned readmissions within 30 days, number of ED visits, and number of inpatient admissions. By serving about 2000 patients through this pilot over 3 years, RCCA will help Horizon develop valuable best practices that will advance cancer care for patients across New Jersey.[8] ◆

AUTHOR INFORMATION

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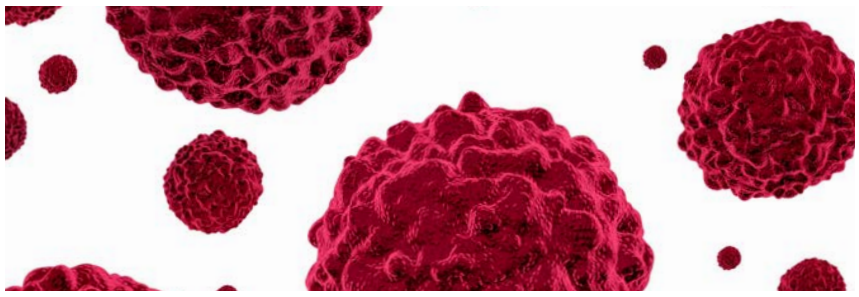

Cancer cells

Medicaid Expansion Led to Earlier Stage at Diagnosis of Testicular Cancer

Jaime Rosenberg

WHEN MEDICAID EXPANSION began in 2014, under the Affordable Care Act (ACA), there started to be fewer uninsured patients and a shift to earlier-stage cancer at the time of diagnosis for patients with testicular cancer in states that adopted the expansion, according to findings presented February 9, 2018, at the American Society of Clinical Oncology Genitourinary Cancers Symposium, which was held in San Francisco, California.

SHEN

"We all know insurance status is a key determinant of cancer outcomes," said Xinglei Shen, MD, radiation oncologist, University of Kansas Medical Center. "People who don't have insurance do poorly, and the ACA sought to improve outcomes by improving access to insurance."

Shen and his co-author hypothesized that Medicaid expansion would lead to earlier diagnoses and more guideline-concordant treatment for patients with testicular cancer. They looked at the Surveillance, Epidemiology, and End Results (SEER) data from 2010 to 2014, which provides information on cancer statistics, and identified 12,731 cases of testicular cancer during the time period. The time frame of 2010 to 2013 was used as the pre-expansion group.

The expansion states included in the analysis were California, Connecticut, Hawaii, Iowa, Kentucky, Michigan, New Jersey, New Mexico, and Washington. Nonexpansion states included Arkansas, Georgia, Louisiana, and Utah.

Looking at Medicaid enrollment numbers for the SEER states that did not expand coverage, there was a modest increase in the amount of people on Medicaid versus a robust increase in those enrolled in expansion states, said Shen. The biggest change was seen in New Mexico, which had a 50.3% increase.

For insurance status at time of diagnosis, Shen et al found that in expansion states, there was a significant drop in patients who were uninsured at the time of diagnosis: from 8.7% to 4.3%, and a corresponding increase in the proportion of people enrolled in Medicaid: from 14.8% to 19.4%.

In nonexpansion states, there were no significant changes, according to Shen.

There was also an effect on the stage at diagnosis. In states that expanded Medicaid, 20.2% of patients had stage III cancer at the time of diagnosis, down from 27.1% before expansion. There was also a corresponding increase in the proportion of patients diagnosed at stage I, according to Shen. For states that did not expand coverage, 29.2% of patients had stage III cancer at the time of diagnosis, up from 23.2% before 2014.

Lastly, they look to see if there was an effect on quality of care, but the results did not indicate a significant difference. Shen concluded by indicating that longer-term follow-up is needed to study how Medicaid expansion would affect cancer outcomes and survival. ◆

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Combining Radiation and Immunotherapy in Patients With Bladder Cancer

Jaime Rosenberg

"I THINK THIS is an exciting time in the treatment of bladder cancer and really oncology in general, because we're learning to harness the body's immune system against malignancies," said Abhishek Solanki, MD, MS, assistant professor, Radiation Oncology, Loyola University of Chicago, during a February 9, 2018, session at the American Society of Clinical Oncology Genitourinary Cancers Symposium. The meeting took place in San Francisco, California.

While discussing the role of immunotherapy in patients undergoing radiation therapy for bladder cancer, Solanki emphasized that it's also an exciting time because there's a lot of preclinical data that have led to us evaluating this approach. Radiation is a local therapy, delivered for local purposes, like treating a primary tumor and in a bladder preservation case, he said. It's also known that immune invasion is a critical hallmark of cancer and the main mechanisms by which tumors grow, progress, and metastasize.

According to Solanki, there's emerging evidence that suggests that one of the reasons radiation is effective is because it is immune driven. Cytotoxicity related to radiation releases tumor antigens, which leads to activation of antigen-presenting cells and migration to the lymph nodes and, in turn, priming of T cells. There's also a release of cytokines that lead to T-cell trafficking back to the tumor and an increased expression of major histocompatibility complex, class I, known as MHC1, within tumor cells. All of these things together lead to cell-mediated death, said Solanki.

However, radiation itself rarely leads to long-term immune memory and the ability to prevent late recurrences. Additionally, there's emerging data that suggest that radiation can lead to upregulation of programmed cell death-1/programmed death ligand-1 (PD-L1) and regulatory T-cell infiltration into the tumor cell, suggesting that there may be some immunosuppressant effect of radiation.

"This brings us to the hypothesis that we can combine radiation immunotherapy to improve local control through radiosensitization by bypassing those resistance mechanisms," said Solanki. "Potentially, by combining these modalities, we can improve systemic response and have long-lasting immune memory when we combine these agents"

SOLANKI

Solanki cited what he said is one of the only studies of bladder cancer specifically looking at the question of the combination of radiation immunotherapy. Investigators implanted bladder cancer tumors in mice and then separated them into 2 groups: one treated with radiation alone and the other treated with radiation and an anti–PD-L1 antibody. With radiation, there was a decrease in the size of the tumor, but it started growing again shortly after. In the combination group, there was more durable and more significant tumor control.

"This leaves us with 2 clinical questions," said Solanki. "The first is with our traditional paradigms of bladder preservation and definitive chemoradiation therapy. Can we use immunotherapy to improve the outcomes? On the flipside, for patients who have metastatic disease who are being treated with checkpoint inhibitors and for palliation, can we use local radiation to augment that effect and give them more mileage with the available therapies?" Although there is not a lot of data available for bladder cancer, Soalnki said that we can turn to some non–small cell lung cancer (NSCLC) studies that can provide leads on benefits observed.

In the PACIFIC trial, patients with stage III NSCLC receiving definitive chemoradiation with cisplatinum-based chemotherapy were randomized to be administered either placebo or up to 12 months of durvalumab.

Investigators found a clear difference in progression-free survival (PFS) that favored the durvalumab group. Also, in the metastatic setting, in the KEYNOTE-001 study, UCLA investigators assessed their NSCLC cohort and found that radiation prior to pembrolizumab was associated with PFS and overall survival.

"Bringing things back to bladder cancer, one of the reasons why it's hypothesized that immunotherapy's so successful in NSCLC is because of the high somatic tumor mutation burden, and bladder cancer is right up there," said Solanki. "And we already have a track record of success with immunotherapy in bladder cancer with [Bacillus Calmette-Guérin] for nonmuscle invasive disease and checkpoint inhibitors for metastatic disease. So I'd argue that bladder cancer is the ideal setting [in which] to investigate the combination of radiation immunotherapy."

Solanki explained that while there is a lot of clinical and preclinical rationale to combining immunotherapy and radiation for bladder cancer, there's a lot we don't know, and the unknown at this time is bigger than the known.

He concluded: "I think it's up to us, as a community, to find out exactly how best to combine radiation with immunotherapy to augment the effects of both modalities."

Docetaxel Plus Hormone Therapy Improved Quality of Life, Cost-Effectiveness in Prostate Cancer

Jaime Rosenberg

THE ADDITION OF docetaxel to first-line long-term hormone therapy in patients with prostate cancer is associated with improved quality of life (QoL) and cost-effectiveness, according to study results presented February 8, 2018, at the American Society of Clinical Oncology Genitourinary Cancers Symposium in San Francisco, California.

Nicholas James, MBBS, PhD, Queen Elizabeth Hospital, presented results from the STAMPEDE trial, which looked at patients with M0 and M1 disease. The primary outcome of the trial was overall survival, and secondary endpoints included failure-free survival (FFS), progression-free survival (PFS), metastatic PFS, skeletal-related events (SREs), toxicity, cost-effectiveness, and QoL.

"Docetaxel produced a very consistent improvement in FFS across the whole trial," said James. "The other thing that was very consistent across the whole trial was a 40% reduction in symptomatic skeletal events."

JAMES

The researchers used a standard model-based approach, explained James. All patients started hormone sensitive and progressed to M0 castration-resistant prostate cancer (CRPC) or M1 lymph node disease, CRPC with bone metastases, CRPC with bone metastases with a SRE, or CRPC visceral. The STAMPEDE trial data were used to determine how much time each patient spent in each category and what were the QoL implications. The researchers also assessed cost-effectiveness.

Because patients with M0 disease have a 40% delay in the time to relapse, the patients getting docetaxel up front spend more time hormone sensitive than patients in the control arm, said James. Thus, the onset of CRPC M0 or M1 lymph-node only disease is delayed, and patients live fewer months with these conditions or with bone metastases, with or without an SRE. This correlates to a longer period of relatively good QoL and less time with poor QoL. For the metastatic setting, the same effects were observed. Patients spend more time in the hormone-sensitive state, which means less time with the factors that harm your QoL and increase your costs, said James.

"For metastatic patients where there's a survival advantage, not surprisingly you see a quality-adjusted life years [QALYs] gain as well," said James. "In other words, the benefits of not relapsing, not having SREs, wipes out the quality-of-life penalty that you incur from your up-front chemotherapy."

The same effect was seen in patients with M0 disease. Although there wasn't a robust survival advantage in this setting, there is still a QALY gain.

Over the course of the trial, treatment with docetaxel didn't change end-of-life costs substantially. But docetaxel costs increased, management costs generally went up, and the costs of other life prolonging therapies went up. However, there's been big changes over the duration of the trial with the emergence of androgen receptor–targeted therapies, said James.

The researchers remodeled the data using patients who had enrolled later in the trial and who were getting abiraterone/enzalutamide for M1 CRPC. When they did that, there were still increases in docetaxel and management costs and little effect on end-of-life care. However, there was a significant reduction in the use of other life-prolonging therapies compared with the control arm. When looking at net total costs, there was a reduction in overall lifetime care costs in M0 disease from the up-front addition of docetaxel. And although there was a net increase for the metastatic setting, the total cost was approximately £3000 over the lifetime of the patient.

"Up-front docetaxel results in robust gain in quality-adjusted life years in all subgroups," concluded James. "It supports existing healthcare policy in metastatic patients, but it also supports the use of docetaxel in high-risk nonmetastatic patients." ◆

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Use of Biomarkers to Identify Patients, Therapies for Neoadjuvant Chemotherapy

Jaime Rosenberg

DURING THE 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium, Peter Black, MD, professor, Department of Urologic Sciences, University of British Columbia, discussed 3 clinical biomarkers that have potential use to select patients and therapies for neoadjuvant chemotherapy (NAC).

Black began the discussion by explaining that there are multiple prospective randomized trials and meta-analyses that demonstrate a survival advantage from NAC. The 2 main limitations with NAC are: Only about 40% of patients seem to be benefiting from the treatment, with the other 60% are potentially suffering from adverse effects from chemotherapy and unnecessary delay in definitive radical cystectomy, and NAC has not been widely adopted in North America or in Europe.

"I think one of the ways forward, to overcome both of these limitations, is with biomarkers," said Black. "If we have a biomarker that would tell us which patients are likely to respond or not to respond, we can avoid using NAC in the likely nonresponders, and if we had better patient selection, we'd also probably have better buy in for adoption of NAC. "Black identified 3 clinical biomarkers that are in development and close to potential clinical implementation.

Molecular Subtypes

Several research groups have identified a molecular taxonomy for bladder cancer based on RNA expression. The key classifications are basal and luminal cell lines; with basal tumors having a gene expression profile that resembles the basal layer of the urothelium; it's more stem-like and less differentiated. The luminal tumors, on the other hand, have a gene expression »


BLACK

profile that resembles more differentiated luminal cells, Black explained.

According to Black, these subtyping systems have a limitation in that a patient cohort is needed to create a cluster so that an individual patient can be classified in one of the subtypes, which is not practical in clinical practice. So, Black's team developed a single-patient classifier called a genomic sequencing classifier, or GSC. It includes 4 cohorts: luminal, luminal-infiltrated, basal, and claudin-low. They next gathered a multicentric cohort of 305 patients, all of whom were receiving NAC, which included 269 patients who received cisplatin-based chemotherapy who were used for all survival analyses. The control population of almost 500 patients who did not receive NAC was based on publicly available data and literature.

"The bottom line with this classifier was, and if you look at the non-NAC patient population, you can see that the luminal patients clearly do better than everyone else," said Black. "The other 3 cohorts are relatively closer together. In the NAC data set, you can see they jump up the most; they get the most benefit from NAC with respect to survival."

Coxen Model

A research team at the University of Virginia developed the Coxen model, which is currently being evaluated in a clinical trial. The model was initially based on the National Cancer Institute 60 cell line (NCI-60) panel of cancer cell lines, none of which were bladder cancer; however, it's a comprehensive database of gene expression and IC50 values for over 100,000 compounds, said Black. The team was able to integrate bladder cancer data, gene expression data and a panel of bladder cancer cell lines, and through bioinformatics techniques, was able to come up with a predictive model for any given drug based on gene expression.

Genomic Alterations, Mutations, and Copy Number Changes

A research team led by Eliezer Van Allen, MD, from Dana-Farber Cancer Institute, and Jonathan Rosenberg, MD, from Memorial Sloan Kettering Cancer Center, examined *EERC2* mutations in a cohort of 50 patients. The team compared 25 patients who received cisplatin-based chemotherapy and had a complete response with 25 who had residual muscle-invasive disease. According to Black, the *ERCC2* gene was predominant in the responders, while nonresponders did not carry *ERCC2* mutations.

Combining Subtypes and Mutations

Black concluded by demonstrating what would happen if the subtyping and mutation biomarkers were put together. "One-third of patients are basal, and if you add in the patients who have the DNA repair gene mutations, you end up with about 50% of patients who we would predict would respond well to cisplatin-based chemotherapy based on a combination of mutations and subtyping," said Black. ◆

Experts Emphasize the Value of Cancer Care Integration at ACCC Meeting

Surabhi Dangi-Garimella, PhD

CARE COORDINATION AND integration of multiple care teams are vital to a seamless experience for a patient being treated for cancer. It can help break down silos and allow for a continuum of care, which can, in turn translate into improved outcomes.

At the Association of Community Cancer Centers' (ACCC) 44th Annual Meeting & Cancer Center Business Summit, March 14-16, 2018, in Washington, DC, panelists discussed the most powerful forces that are reshaping cancer care to be more multidisciplinary.

Thomas Asfeldt, MBA, RN, director, Outpatient Cancer Services, Sanford Cancer Center, joined Robin Hearne, RN, MS, director, Cancer Services, The Outer Banks Hospital; Kavita Patel, MD, MS, FACP, nonresident senior fellow, Brookings Institution; and outgoing president of ACCC Mark S. Soberman, MD, MBA, FACS, Monocacy Health Partners, on this panel.

"Cancer care continues to get complex," Soberman said. He said that cancer care was already at a point where patients and primary care physicians (PCPs) needed help to deliver the care, and "care teams keep getting complicated." However, he noted that care coordination is typically not reimbursed, neither are psychosocial care or social work services. "How do we develop platforms that can do all this while ensuring that the patient remains at the center?" Soberman asked.

In his opinion, community-based providers need to collaborate among themselves, as well as with health systems, to better coordinate their patient's care and provide them with options. An important consideration, in Soberman's opinion, is "How do we assign responsibility for survivorship care? Does it require training the PCPs?"

Asfeldt has helped build Sanford Cancer Center's cancer program from the ground up. He informed the audience on the struggles, the changes, and the outcomes that he has witnessed along the way. He particularly highlighted their cancer extenders program, which stemmed out of a grant from ACCC and the BMS Foundation.


ASFELDT

"We are currently testing the Oncology Care Collaborative Model at 7 sites," Asfeldt said. "The program was developed from an assessment tool for optimal care coordination. Oncology care includes a team of researchers, radiation oncologists, medical oncologists, pharmacists, nurse practitioners," along with others. "Therefore, integrating [the services of these providers] is important."

At Sanford, champions and commitment among team members are important to help ensure care integration, Asfeldt said. The champion does not necessarily need to be a physician, he emphasized—it can be a nurse navigator, a clinical pathologist, a social worker, or a dietitian. "If someone is not a natural champion, you can try to nurture them, because without a champion, such programs cannot fly," he added.

Providing a contrast perspective for a smaller, more rural practice, Hearne presented a case study of a program to advocate a prospective peer review for radiation oncology treatments, "Which is difficult for rural [health] systems like ours."

"Our radiation oncologist championed a project for prospective peer review across our region and he brought in experts from the various centers to develop a standard framework for care," she said. The peer review group emphasized the importance of evidence-based guidelines, and developed metrics to measure the impact of implementing the process over time. "This was then turned into a scoring tool. We achieved 100% prospective peer review over a period of 1 year and documented a reduction in treatment variability, and better outcomes," Hearne said.

How do you find the resources for this? Patel asked.

"We can bucket resources," Soberman said, "such as for people (navigators, coordinators, information technology, etc), technology resources (platforms needed to communicate, data, etc), or site of care." Additionally, if there are prospects for collaborations or affiliations with other practices or health systems, it presents opportunities for outside resources, he added.

Motivation can be a big driver, Asfeldt said, adding that the scaling up is not a big concern for an integrated cancer care team. There also needs to be clarity around the depth of services that a cancer care team can provide in-house and which services would require either collaboration with another practice or a referral.

Resource allocation decisions require evidence-based guidance on what adds value to the care and services. "We need to make sure our upper management understand the appropriate value of the cancer service line," Asfeldt said, which will assist with informed decisions.

He also highlighted the importance of philanthropy as an important funding resource. "Philanthropy should be an active part of your revenue stream. One of our other goals is to get 25% of our revenue from areas that are not taking care of sick people, which includes offering weight management programs, licensing on innovation, and commercial real estate." Sanford Health System's CEO has been emphasizing this avenue as a resource stream across their health system. ◆

The Price of Innovation When Improving Cancer Care Delivery

Surabhi Dangi-Garimella, PhD

IMPROVING PATIENT OUTCOMES, ensuring the cost of care remains in check, and not losing site of the patient at the center of it all—healthcare can be tough. And this transition to value-based care requires innovative approaches to care delivery by all involved.

At the Association of Community Cancer Center's 44th Annual Meeting & Cancer Center Business Summit, March 14-16, 2018, in Washington, DC, payer and physician representatives shared the stage with the president of a cancer foundation that is striving to break the barriers that prevent easy healthcare information exchange and access to cancer care. Participants included Roy A. Beveridge, MD, chief medical officer, Humana; Barbara McAneny, MD, FASCO, MACP, president, American Medical Association (AMA); Anand Shah, MD, MPH, chief medical officer, Center for Medicare and Medicaid Innovation (CMMI); and Greg Simon, JD, president, Biden Cancer Initiative. Harlan Levine, MD, City of Hope moderated the discussion.

Levine asked the panelists to provide context to the audience, asking them, "Why are you on this panel?" on innovation in cancer care delivery.

McAneny said that AMA is working to create tools that would make things easier for physicians. "We are designing the workflow that physicians use to be the center piece. There's a tremendous influx of data and we do not want to drown in it, but use it smartly," McAneny said. She added that interoperability is a buzz word, but doctors want all the information on wherever their patients have been treated. "AMA has taken this up by setting a consortium to sort and transfer patient information within sites of care," she added.

McAneny then moved on to discuss the influence of social determinants of health (SDH) on patient outcomes and cost of healthcare. There has been growing realization, not just among health policy researchers who have been studying this for a while, but also among providers that environmental factors and where we stay have a big influence on our treatment outcomes.

"SDH is also high on our agenda. We are not measured based on a patient's zip code," McAneny said, but efforts are underway to develop measures, and a code, that account for SDH. "We need to level the playing field, to accounting for disparities," McAneny added.

Payers recognize the influence of interoperability on efficiency, according to Beveridge. "The inability to exchange data is profound…we have been working with CMS to figure out ways to break data exclusivity and improve sharing [among stakeholders]," he said. He agreed with McAneny on the influence of SDH on not just outcomes, but also the cost of care. "In patients with malignancies, cost of care ranges about 2-6 times higher [among patients who face social challenges]," Beveridge said.

For Simon and his team at the Biden Cancer Initiative, interoperability is incredibly important. "We need to develop data-sharing models, launch virtual clinical trials, and we should conduct trials where people are," Simon emphasized. He also underscored the importance of cross-pollinating innovative care models between health systems and community-based practices. "How can we let big cities know what's happening in the community? We need to work toward creating standardized systems, and connectivity is key," Simon said.

"CMMI is constantly trying to test new models and services, which can potentially reduce burden, because they require scale and the burden could potentially lead to consolidation. My role [at CMMI] is to make the system more accessible, affordable, and multi-stakeholder–driven for care providers," Shah said. ◆

Changing Trends in Oncology Practice: Value-Based Care and an Empowered Patient

Surabhi Dangi-Garimella, PhD

WHAT ARE THE BIGGEST drivers of change in oncology care and what needs most attention? This was the crux of the discussion during an early panel at the Association of Community Cancer Centers' (ACCC) 44th Annual Meeting & Cancer Center Business Summit, held March 14-16, 2018, in Washington, DC.

Deirdre Saulet, PhD, practice manager, Advisory Board, led the discussion by introducing findings from the 2017 Trending Now in Cancer Care Survey, which was developed through a partnership among ACCC, the Oncology Roundtable, and the Advisory Board. Saulet was joined on the panel by Jo Duszkiewicz, MSA, vice president and administrator, Renown Health Institute for Cancer; and Mark Liu, director of strategic initiatives, Mount Sinai Health System.

There were several key takeaways from the survey, which had a majority of respondents from nonteaching community hospitals, followed by teaching hospitals and academic medical centers:

- The cost of drugs or new treatment modalities (68%), as well as physician alignment around services and program goals (47%), were top threats to the growth of future cancer program growth.
- Respondents felt that clinical standardization (63%) and drugs (62%) presented a significant opportunity for cost savings.
- Market consolidation was a common theme among survey respondents, with 75% reporting that their group had partnered with an existing hospital or health system and 36% had merged with a private oncology practice.
- Regarding information technology, data abstraction and interoperability of electronic health records were listed as significant challenges.
- Just over half (51%) agreed that prior authorization had significantly increased in the 12 months prior to the survey.
- There exist staff shortages, especially for oncology nurses, medical oncologists, and advanced practitioners.

Saulet then invited Duszkiewicz to share how Renown Health Institute for Cancer has adapted to the changes.

Renown's health system is a combination of acute care, transitional care, network services, and insurance services, Duszkiewicz said.

"Understanding where patients are, where they got their treatment, drawing out specifics of treatment into EPIC, and then ensuring we have all the information is difficult," she explained. It is further complicated by the fact that Renown works with many rural community practices, which may be 200 to 300 miles away.

"We do practice oncology telemedicine for a few of our communities, in parallel with medical oncologists conducting site visits," Duszkiewicz said. "We also link with primary care in those areas. However, we found out that primary care physicians were struggling with diagnosis and the tests that were needed." Consequently, these struggles resulted in an extended time to diagnosis.

To unscramble this situation, Renown developed a solution: the intake oncology coordinator (IOC) process, which included conducting a phone triage first, then a chart review, and finally, bringing the patient in for a clinic visit.

"On evaluating the data, we see that 31% of patients get phone advice, and 25% do a chart review, but 44% of patients who are referred come to see the advance practice nurse," Duszkiewicz said, adding that IOC has resulted in a very successful clinic.

Duszkiewicz then presented trends within the fee-for-service reimbursement model from 2013 to 2022, which show that productivity adjustments have been increasing, from $4 billion to $94 billion, she said. The shift now is toward value-based contracts, such as the Oncology Care Model (OCM), alternate payment models, and others. »

However, Duszkiewicz asked, are shared savings feasible in oncology? She shared data from the Miami Cancer Institute on the results of adopting a value-based approach to care:

- First-year savings were modest: $354 per patient per year (PPPY)
- Second year: $2235 PPPY
- Third year: $9095 PPPY
- Fourth year: $4917 PPPY

She explained that clinical pathway adherence had a significant impact on the savings seen over the first to the third year. However, the diminishing returns of savings in year 4 have triggered more cost savings initiatives within the institute that are focused specifically on the inpatient population.

Next, Liu spoke of Mount Sinai's practice changes. To be able to provide high-value care and broaden patient access, the hospital has developed several projects and programs, including creating disease management teams (DMTs), building clinical pathways programs, establishing a chemo council, and using Epic Beacon to monitor the clinical pathways being used.

DMTs, Liu said, are focused on quality metrics, value-based care, care pathways, tumor boards, and clinical trials. They are also tasked with narrowing down the quality metrics to avoid overlap and integrating OCM quality metrics with disease-specific metrics for tracking and decision making.

Saulet then spoke about the changing dynamic between the patient and the provider. "Cancer patients are acting independently and asking questions," she said. "Patients are taking more responsibility for their healthcare costs. Patients have information available at hand on sites of care as well as drugs and treatment. Plus, the patient–provider relation is changing—there are rising expectations on service, with patients feeling more empowered and being skeptical about the care they receive."

Saulet said that patients with cancer are doing their research: 25% of patients who were surveyed said that they are spending an hour on average reviewing oncologists and 41% said they had researched their treatment options.

Precision medicine is also evolving rapidly, Saulet said, with 92% conducting predictive tests, 92% conducting single-gene tests, 72% conducting small panel tests, and 31% conducting whole-genome sequencing. ◆

FROM OUR CONTRIBUTORS

Oncologists Are Crucial to Advancing Precision Medicine

Aradhana Ghosh, MD

GHOSH

Aradhana Ghosh, MD, is vice president of oncology at Syapse.

CANCER CARE IS IN the midst of a dramatic shift toward precision medicine. Our country's leading health systems are embracing this new form of care, and patients are seeing better outcomes.

Two forces are converging to enable this shift: We now have an unprecedented amount of data on individual patients, and we have an abundance of smarter, more effective cancer therapies that are tailored to patients' unique genetic makeup. But realizing the full power of precision medicine and bringing it to more patients hinges on us—the entire healthcare ecosystem, from health system leadership to pharmaceutical and technology companies—making the oncologist a central part of our strategy.

Before precision medicine came along, oncologists already were overworked. The United States is facing a massive oncologist shortage, leading to packed schedules.[1] Those who work full time see many patients every day of their workweek, all while trying to keep up with the latest treatment information. I am aware of this because I was a practicing community medical oncologist.

Now, with the advent of next-generation sequencing, oncologists often have access to a treasure trove of extremely detailed genetic and molecular data for patients who have been tested. The challenge is to make sense of this vast amount of information and put it to use, all while maintaining an extremely busy schedule. And it is not just vast but also new information: Most oncologists today were not trained to interpret complex genetic and molecular data. Simply put, it's overwhelming for oncologists.

Technology, and software in particular, can help bridge this gap, but it must be built with the oncologist in mind. One oft-cited criticism of the previous healthcare technological upheaval—electronic health records—is that they created more administrative work for physicians while offering little clinical benefit. In precision medicine, technology's role should be to supply oncologists with the data they need when they need it and in a format they can understand, so they can make the most informed treatment decisions.

Oncologists frequently seek help in cutting through the noise of all the new data and treatments at their fingertips. Technology should not show every piece of data and every possible treatment but only those data that really matter to help inform treatment decisions.

Another area where oncologists see untapped potential is real-world evidence. Most decisions made by oncologists today are the result of published literature, which is largely informed by clinical trials. However, just 3% of US patients diagnosed with cancer participate in clinical trials,[2] which means that there are millions of patients whose data, including molecular profiling results and treatment outcomes, are not being considered when oncologists make treatment decisions. Software can compile and bring these insights to the surface, arming physicians with the most relevant information possible.

Precision medicine is rapidly becoming the new standard of care in oncology. Soon, the vast majority of cancer patients will have their tumors genetically sequenced. We will have even more targeted therapies and more detailed individual patient data than we do today. As the various parts of the healthcare ecosystem move precision medicine forward, it's our responsibility to keep oncologists at the forefront. ◆

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The Fallacy of Estimating OCM Target Prices

Darcie Hurteau, MBA, and Alyssa Dahl

THE ONCOLOGY CARE MODEL (OCM), a 5-year alternative payment model (APM) for oncology practices and independent practitioners, began on July 1, 2016. Participants, whose episode cycles run for 6 months, received their fourth performance data feed from CMS in December 2017.[1]

Because CMS views oncology care as life encompassing, OCM differs greatly from traditional bundled payment models like Bundled Payments for Care Improvement and the Comprehensive Care for Joint Replacement. Providers manage not just the cancer but also a complex set of factors affecting the patient, so each patient essentially has a unique target. This is based on their personal risk factors and specific events that occurred within the episode time period.

In an ideal world, OCM participants would know these targets early in the patient's care journey, allowing them to refine their OCM strategy. However, knowing a patient's episode target price with any kind of acceptable margin of error is impossible.

The desire to estimate an episode's target price is understandable—how else can one plan budgets and forecast spending? However, because of the many unknowns and variables in healthcare, those estimates can result in wildly inaccurate numbers. Here are 3 reasons you should not waste time and effort estimating individual episode target prices:

1. Performance period episodes need to be approximated. Because oncology patients usually are given several opinions upon diagnosis, it's likely that they'll receive care at multiple practices throughout their treatment. This makes it difficult to identify which practice was ultimately most responsible for the patient's care and should "own" the episode. CMS' solution to this challenge is an attribution method based on visit frequency—something that can't be immediately determined at the forefront of an episode.

Attribution is unknown until the reconciliation process begins about a year after the performance period ends. This affects any totals, since there could be overlap between practices in the same system and the calibration of when the episode actually started. Practices also will have to estimate beneficiary eligibility, as some patients likely will drop out due to changes in Medicare coverage or may not initiate care until a later date. Another consideration: Actual expenditures may be underestimated, leading to incomplete knowledge about what was actually spent on each patient when making a target price comparison.

Episode construction has to happen no matter what before making any sort of cost comparison to a target price. However, while using the claims data in CMS' feedback report, OCM participants would need to make some big assumptions even before they have an idea of when to define their episodes.

2. Covariates—even some of the ones that are known—may change, and others can only be abstracted. While some covariates, such as the patient's age, sex, hospital referral region, and dual eligibility status, are known at the time a potential episode is initiated, others, such as episode length, could change based on the date identified to trigger the episode. Even the patient's cancer type could change because it is based on coding plurality rules during the 6-month episode period.

When it comes to estimable covariates that can be abstracted from the claims data, practices can't yet know all the factors needed at the start of an episode to complete the regression model calculation and generate the target price. These covariates require the presence of complete claims information during an episode to be determined with certainty and include:

- Cancer-related surgery
- Radiation therapy
- Bone marrow transplant
- Clinical trial participation
- Part D enrollment

Other covariates are complete unknowns in the performance period data. Without adequate patient history and gaps in the feedback report claims data, it's impossible to know when the patient last had chemotherapy prior to episode initiation, as well as the patient's hierarchical condition categories and institutionalization status (which cannot be determined from claims data). Some of these factors significantly influence the magnitude of an episode's target price.

3. There are other unknowns. If all that isn't enough, additional unknowns impact the ability to estimate target prices:

Until the performance period ends, there is no way to estimate the trend factor between baseline and performance period data.

Practice-specific novel therapy adjustment factors do not exist yet. In the absence of reconciliation, it is difficult to estimate the amount of impact on the target price, following adjustment.

For claim-dependent factors, practices will need to rely on claims from the CMS feedback reports until the actual reconciliation data for attributed episodes are released. This is tricky because, for the purposes of estimating target prices, some attributed beneficiaries will not be present in a feedback report population. The only known factors for these patients will be cancer type, age, and sex. Additionally, some attributed beneficiaries will have dropped in and out of feedback report populations, so their claims would be unavailable to practices, leading some claim-dependent factors being missed.

It's understandable that OCM participants will want to look at target pricing, but OCM is such a complex bundled payment model that any estimate made today might cause practices to make inaccurate assumptions on financial targets anyway.

It is, however, possible to simulate an episode with the information currently at hand, understanding that it will definitely be inexact and the magnitude of inaccuracy will vary across episodes. Another tack to take is to wait until attribution happens for the period before trying to calculate a target price. The result will be more precise regarding the timing of when the episode and claims run out, but it will be less time sensitive because it can't be done until about a year after the performance period ends. By then, CMS will be providing the real target price in about 2 months, so the exercise is likely not worth the time and effort.

So many factors impact care for cancer patients that attempting to estimate flawed target prices simply isn't worth the effort. Applying that time instead to quality-focused care management tactics based on observed utilization and patient outcomes may prove more valuable and help reduce unnecessary spending. ◆

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ASCO Review Finds Clinical Pathway Programs Adhere to Guidelines

Samantha DiGrande

ON FEBRUARY 7, 2018, the American Society of Clinical Oncology (ASCO) published[1] its review of the leading oncology pathway vendors in the United States in the *Journal of Oncology Practice*. The report showed that overall, the prominent commercial pathway programs in the United States are aligned with ASCO's evaluation criteria.

The report examined clinical pathways offered by 6 commercial vendors using the organization's set of 15 interrelated criteria.[2] "ASCO conducted this assessment to provide more complete information about how current pathway programs are developed, implemented, and analyzed by specific pathway vendors. Equipped with this information, the oncology community will be better able to evaluate and use these pathways in practice," ASCO President Bruce E. Johnson, MD, FACP, FASCO, said in a statement.[3]

Although ASCO's Task Force on Clinical Pathways found some differences among the oncology clinical pathways and decision support tools that were evaluated, largely due to unique vendor business models and different customers, it also discovered that all vendors met key ASCO criteria for being expert driven, patient focused, up-to-date, and comprehensive. Vendors also offered integrated decision support and provided outcomes-driven results.

"By and large, prominent pathway programs are adhering to ASCO's criteria for high-quality clinical pathways."

– Robin Zon, MD, FACP, FASCO

However, the ASCO review found that as a group, oncology clinical pathways met fewer aspects of the criteria in terms of having clear and achievable expected outcomes and public reporting of performance metrics. This shows that as pathway programs enter the healthcare delivery system, more information should be provided about the specific cancer type the pathway is intended to cover as well as what indicates on-pathway versus off-pathway treatment. Additionally, the review found that there is a need to ensure that pathway programs offer more in-depth reporting that reflects when the provider has gone off pathway.

ASCO's task force also evaluated the vendors' products against the criteria for high-quality clinical pathways based on publicly available information and in collaboration with the vendors. Some vendors actually modified their processes during the review, potentially based on the ASCO criteria or as a result of interactions with task force members.

"We are encouraged to see that, by and large, prominent pathway programs are adhering to ASCO's criteria for high-quality clinical pathways. We hope our assessment of the pathways landscape will help these programs make further refinements, with the ultimate goal of improving the care of our patients," said the chair of ASCOs task force, Robin Zon, MD, FACP, FASCO.[3] ◆

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Roche Acquires Flatiron Health for $1.9 Billion

Mary Caffrey

ON FEBRUARY 15, 2018, Roche acquired Flatiron Health, a leader in oncology-focused electronic health decision-making software and data storage. Flatiron, which taps a network of community oncology practices and research centers across the country, possesses tools[1] that practices need to pursue the value-based care models that Medicare and commercial payers believe are essential to rein in the escalating cost of healthcare as the population ages.

This is especially true in cancer care, and a statement[2] on Roche's acquisition touts Flatiron's leadership as a data curator as it pursues a personalized healthcare strategy, while vowing that Flatiron will maintain its independence.

"We believe that regulatory grade real-world evidence is a key ingredient to accelerate the development of, and access to, new cancer treatments," Daniel O'Day, CEO of Roche Pharmaceuticals, said in the statment.[2] "Flatiron Health is best positioned to provide the technology and data analytics infrastructure needed not only for Roche, but for oncology research and development efforts across the entire industry."

The statement stated that Flatiron "has worked with industry leaders and regulators to develop new standards for how real-world evidence is used in regulatory decisions," including the creation of novel endpoints. "A key principle of this is to preserve Flatiron's autonomy and their ability to continue providing their services to all existing and future partners," O'Day said.

Roche made a similar move in the diabetes sector in 2017 when it acquired mySugr,[3] a diabetes app with 1 million users that had earned a loyal following among those who track personal data to manage their condition.

In an interview last year with *The American Journal of Managed Care®*, Flatiron co-founder and CEO Nat Turner discussed the barriers to providing oncology care that the company seeks to dismantle, leading to democratization of care.[4]

"For access, it's really hard, as a community practice, to attract great clinical trials. You can if you have a local affiliation with a hospital, but if you're just a small independent practice, access to clinical research can be rough," Turner said. Flatiron's technology can also help independent practices stay that way, even in an era of shrinking margins and payer pressure, he said.

While Flatiron helps the smallest players, Roche touts its size as the world's largest biotech company, with a footprint in oncology, immunology, infectious disease, ophthalmology, diabetes management, diagnostics, and central nervous system disease.

Roche already had a stake in Flatiron, and today, Turner said, "Roche has been a tremendous partner to us over the past 2 years and shares our vision for building a learning healthcare platform in oncology, ultimately designed to improve the lives of cancer patients. This important milestone will allow us to increase our investments in our provider-facing technology and our services platform, as well as our evidence-generation platform, which will remain available to the entire healthcare industry."

Flatiron expects to keep its current business model in the deal, maintaining the segregation of patient protected health information and provider-facing life science initiatives. ◆

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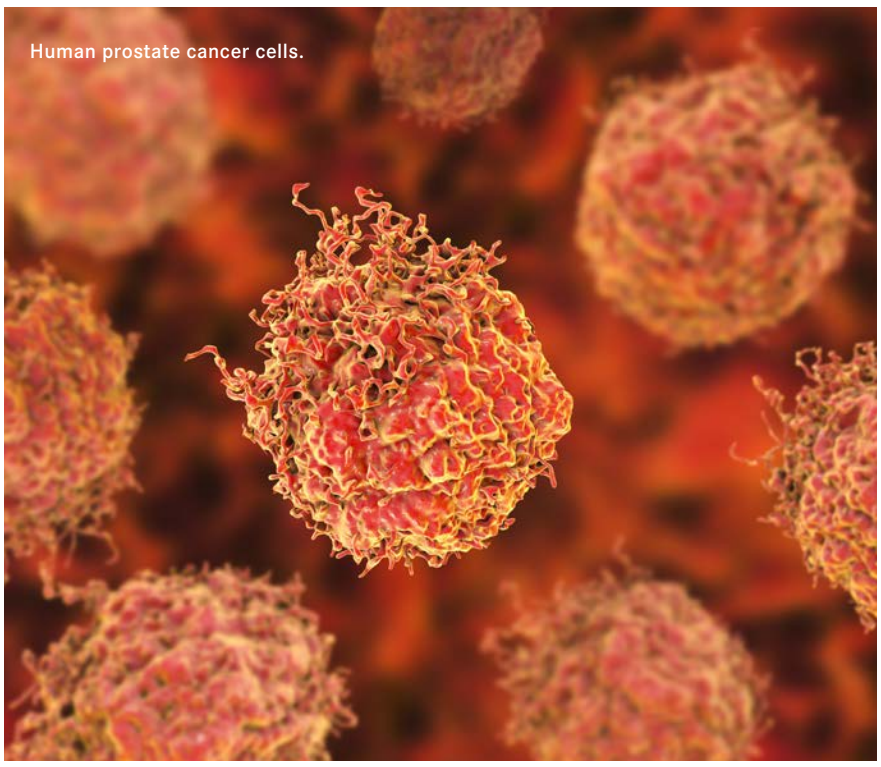

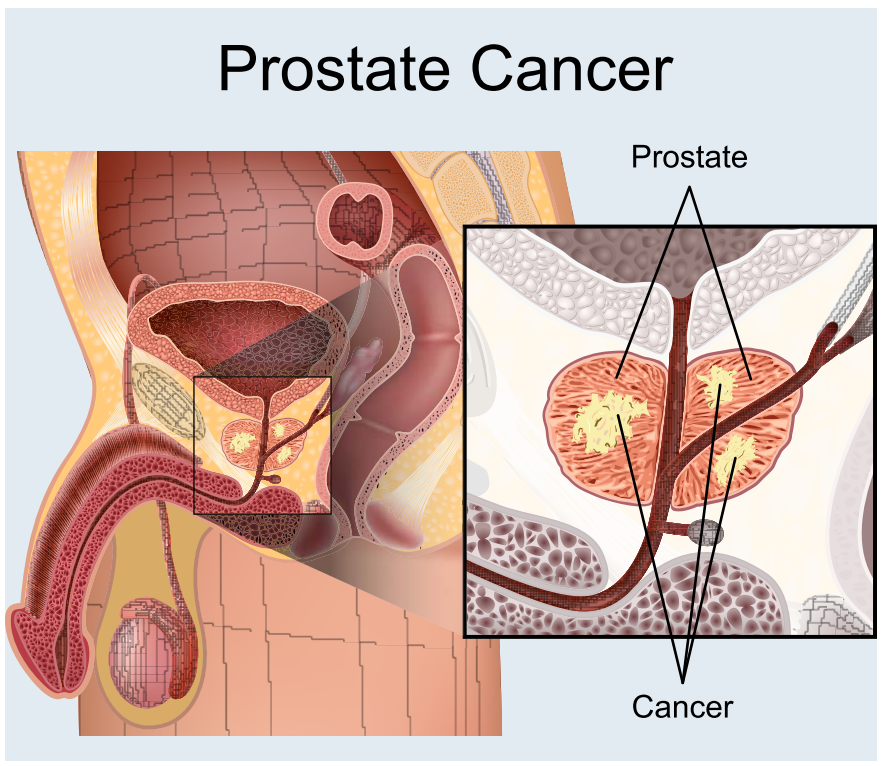

FDA Approves Apalutamide, First Treatment for Nonmetastatic Castration-Resistant Prostate Cancer

Jaime Rosenberg

APALUTAMIDE, WHICH HAS BEEN shown to improve median metastasis-free survival by more than 2 years, has been approved by the FDA to treat patients with nonmetastatic castration-resistant prostate cancer (CRPC). Prostate cancer is the second most common form of cancer in American men, and approximately 10% to 20% of these cases are castration resistant, according to the National Cancer Institute at the National Institutes of Health.[1]

The drug, which will be sold as Erleada by the Janssen Pharmaceutical Companies of Johnson & Johnson, is an investigational next-generation androgen receptor inhibitor. The drug blocks the effect of androgen, a hormone that can promote tumor growth. It is the first FDA-approved treatment for this indication. The approval was based on findings of the phase 3 SPARTAN trial, which also found that apalutamide reduced the risk of metastasis or death by 72%.

"These compelling results are the first to show that metastases can be delayed in these patients."

– Eric Small, MD, FASCO

"This approval is the first to use the endpoint of metastasis-free survival, measuring the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment," Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said in a statement.[1] "In the trial supporting approval, Erleada had a robust effect on this endpoint. This demonstrates the agency's commitment to using novel endpoints to expedite important therapies to the American public."

The results of the SPARTAN trial were presented[2] at the American Society of Clinical Oncology 2018 Genitourinary Cancers Symposium in San Francisco, California, and simultaneously published in *The New England Journal of Medicine*.[3]

The randomized, double-blind, placebo-controlled, multicenter study enrolled 1207 patients, who were randomized 2:1 to receive apalutamide in combination with androgen deprivation therapy or placebo.

"While there have been advances in the treatment of prostate cancer over the years, metastatic castration-resistant prostate cancer is still a lethal disease. These compelling results are the first to show that metastases can be delayed in these patients," Eric Small, MD, FASCO, professor of medicine; chief of the Division of Hematology and Oncology at the University of California, San Francisco; and lead SPARTAN study investigator, said in a statement. "These data suggest that apalutamide could potentially be a new standard of care for patients with nonmetastatic castration-resistant prostate cancer."[4] ◆

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#1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS[2]

*Based on market share data from IMS from November 2016 to April 2017.
†Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including 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 and patients should be monitored for signs of bleeding.

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 (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent 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, hypertension, 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. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®.

Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

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® and for 1 month after cessation

pharmacyclics® An AbbVie Company

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

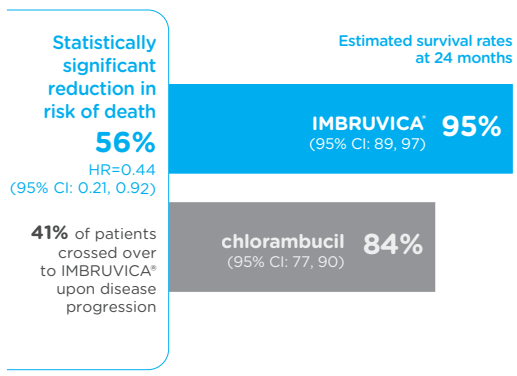
RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3] Patients with 17p deletion were excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS
IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

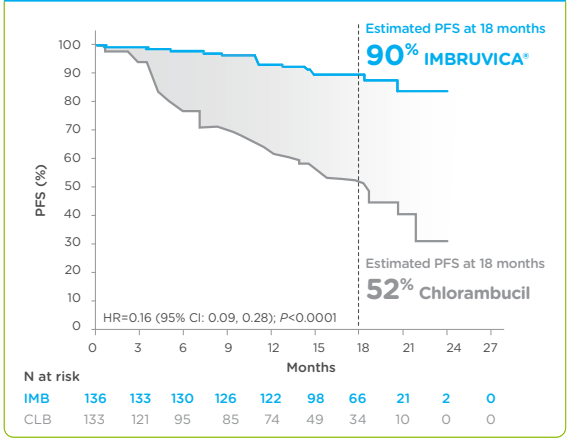


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS
IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

of therapy. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%), neutropenia (61%), diarrhea (43%), anemia (41%), musculoskeletal pain (30%), rash (30%), bruising (30%), nausea (29%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

DRUG INTERACTIONS

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria)**:** Avoid use of IMBRUVICA® in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

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To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

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 adult 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 and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information]*.

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

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

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5) 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 (intracranial hemorrhage [including 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 and patients should be monitored for signs of bleeding.

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 (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent 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, hypertension, 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. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. 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]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: 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.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) 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)

Body System	Adverse Reaction	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 administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
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* Hematologic Laboratory Abnormalities 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/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

RESONATE: 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 RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	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				
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 body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	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

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

The most commonly occurring adverse reactions in Studies 1118 and 1121 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 1118: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63)

Body System	Adverse Reaction	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
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (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

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea Nausea Dyspepsia Stomatitis* Abdominal pain Constipation Abdominal pain Upper Vomiting	43 25 19 17 16 14 13 11	5 0 0 2 2 0 0 2
General disorders and administrative site conditions	Fatigue Peripheral edema Pyrexia	44 24 17	6 2 2
Skin and subcutaneous tissue disorders	Bruising * Rash* Pruritus	41 29 14	0 5 0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain* Arthralgia Muscle spasms	40 24 19	3 2 3
Infections and infestations	Upper respiratory tract infection Sinusitis* Bronchitis Pneumonia*	21 19 11 11	0 0 0 10
Metabolism and nutrition disorders	Decreased appetite Hyperuricemia Hypoalbuminemia Hypokalemia	16 16 14 13	2 0 0 0
Vascular Disorders	Hemorrhage* Hypertension*	30 14	0 5
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	22 21	2 2
Nervous system disorders	Dizziness Headache	19 13	0 0
Psychiatric disorders	Anxiety	16	2

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

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue Pyrexia Edema peripheral	57 17 12	12 5 0
Skin and subcutaneous tissue disorders	Bruising* Rash*	40 12	0 0
Gastrointestinal disorders	Diarrhea Stomatitis* Nausea Constipation	36 29 26 12	10 2 0 0
Musculoskeletal and connective tissue disorders	Muscle spasms Musculoskeletal pain*	29 14	2 5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia* Upper respiratory tract infection Sepsis*	21 19 10	10 0 10

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Table 13: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4(%)
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	14 12	0 2
Metabolism and nutrition disorders	Hypokalemia	12	7

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

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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.

- Hepatobiliary disorders: hepatic failure
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Patients with B-cell Malignancies: *Posaconazole:* Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease: *Moderate CYP3A Inhibitor:* Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors: Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Animal Data)*. 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.

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All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at 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 resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL 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 rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

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

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for adverse reactions of IMBRUVICA and follow dose modification guidance as needed. *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA.

Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, 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].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[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 to 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 during treatment and for 1 month after the last dose of IMBRUVICA *[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 (2.6) 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 *[see Adverse Reactions].*

Active ingredient made in China.

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PRC-03045

Denosumab Effectively Prevented Skeletal-Related Events in Multiple Myeloma

Laura Joszt

MONOCLONAL PARAPROTEIN PRODUCTION and osteolytic lesions resulting from multiple myeloma often lead to skeletal-related issues, such as spinal cord compression or pathologic fracture. New research published in *The Lancet Oncology* found that denosumab (Xgeva) was noninferior to zoledronic acid for time to skeletal-related events (SREs) in patients with newly diagnosed multiple myeloma.[1] The FDA approved denosumab for the prevention of SREs in patients with multiple myeloma in January.[2]

The international, double-blind, double-dummy, randomized, active-controlled phase 3 study included 1718 patients in 259 centers in 29 countries. The patients were randomly assigned 1:1 to receive either subcutaneous denosumab 120 mg plus intravenous placebo every 4 weeks or intravenous zoledronic acid 4 mg plus subcutaneous placebo every 4 weeks.

"Until recently, treatment options for the prevention of skeletal-related events in multiple myeloma were limited to bisphosphonates, which are cleared through the kidneys and can be associated with increased renal impairment," lead study author Noopur Raje, MD, director of the Center for Multiple Myeloma at Massachusetts General Hospital Cancer Center, said in a press release. "Denosumab, which is not cleared through the kidneys, provides a new treatment option for the prevention of skeletal-related events in patients with multiple myeloma."

"Until recently, treatment options for the prevention of skeletal-related events in multiple myeloma were limited to biphosphonates, which...can be associated with increased renal impairment. Denosumab...provides a new treatment option for the prevention of skeletal-related events..."

– Noopur Raje, MD

In the trial, the median time to first SRE was 22.8 months for patients on denosumab compared with 24 months for patients receiving zoledronic acid. The most common grade 3 or worse adverse events, occurring at similar rates, for both treatments were neutropenia, thrombocytopenia, anemia, febrile neutropenia, and pneumonia.

There were fewer reported incidents of renal toxicity reported in the denosumab group (10%) compared with the zoldronic acid group (17%), but more hypocalcaemia adverse events (17% vs 12%).

"The results from this study suggest denosumab could be an additional option for the standard of care for patients with multiple myeloma with bone disease," the authors concluded. ◆

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Family History Associated With Breast Cancer Risk for Women 65 and Older

Jaime Rosenberg

FIRST-DEGREE FAMILY HISTORY is associated with an increased risk of invasive breast cancer in all subgroups of older women irrespective of a relative's age at diagnosis, according to study results published in *JAMA Internal Medicine*.[1]

"Evidence of the association between first-degree family history and the risk of invasive breast cancer among women 65 years and older is limited," wrote the authors of the study. "Although family history is a strong risk factor for breast cancer among younger women, controversy exists about the magnitude of the association between family history and breast cancer among older women."

"Crucially, family history needs to be taken into account when considering the potential benefit versus harms of continued mammography in this population."

– Study authors

According to the authors, it has yet to be determined if the association of first-degree family history with breast cancer among older women varies by age and breast density. Using data from 7 registries from the population-based US Breast Cancer Surveillance Consortium prospective cohort study, the authors extracted information about the population of women presenting for screening mammography.

A total of 472,220 mammograms from 403,268 women 65 and older who had at least 1 mammogram with self-reported information about first-degree family history between 1996 and 2012 were included in the study. Risk factor information was collected from the self-reports and included age, family history in a first-degree relative, race/ethnicity, weight, and height.

During the mean follow-up of 6.3 years, 10,929 invasive breast cancers were diagnosed. Results showed that the 5-year cumulative invasive breast cancer rates per 1000 persons increased with first-degree family history and age among women with heterogeneously or extremely dense breasts. For women aged 65 to 74 with a family history, there were 27 cases for every 1000 persons versus 20 for women without a family history; for women 75 and older with a family history, there were 28 for every 1000 persons, versus 18 for women without a family history.

Results also showed that the estimate per 1000 persons for women aged 65 to 74 with a first-degree relative's diagnosis at an age younger than 50 was 28 (95% CI, 23-25) versus 24 (95% CI, 20-28) for women with relatives diagnosed at 50 or older. The estimate per 1000 for women 75 or older with a first-degree relative's diagnosis age younger than 50 years was 26 (95% CI, 18-32) versus 27 (95% CI, 23-33) for women with relatives who received a breast cancer diagnosis at age 50 or older.

For women aged 65 to 74, the risk associated with first-degree family history was highest among those with fatty breasts (HR, 1.67; 95% CI, 1.27-2.21), while for women 75 and older, the risk was highest among those with dense breasts (HR, 1.55; 95% CI, 1.29-1.87).

"Based on this pattern of findings, clinicians should continue to ask older women about family history of breast cancer to personalize mammography screening strategies," concluded the authors. "Crucially, family history needs to be taken into account when considering the potential benefits versus harms of continued mammography in this population." ◆

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Produced by Laura Joszt and Jaime Rosenberg

Nat Turner on the Main Barriers for Flatiron Health in Providing Care in Oncology

Nat Turner, co-founder and CEO of Flatiron Health, says that clinical research accessibility is one of the biggest barriers in oncology care that Flatiron Health is working to remove.

What are the main barriers to providing care in oncology that Flatiron Health is trying to remove?

I would say, in no particular order, clinical research accessibility. For access, it's very hard, as a community practice, to attract great clinical trials. You can if you have a local affiliation with a hospital, but if you're just a small independent practice, access to clinical research can be tough. Second, you have to be very efficient as a practice these days. [There are] a lot of shrinking margins, payer pressure, value-based care, and hospital pressure that make it hard to be a practice. So, through [our] software and services, we help those practices remain independent even in a low-margin environment. Also, I'd say, access to information: OncoEMR [a Flatiron Health platform] has a lot of content built in; it helps you diagnose [disease in] patients easier; it helps you make treatment decisions more effectively with integrated content from nonprofit institutions. So, it basically provides medical oncologists with at-their-fingertips information because they're seeing maybe 20 different types of cancer in 1 day in their patient population.

Are there future areas where Flatiron isn't currently involved that you see as the next opportunity to help community oncologists?

For sure. I think the biggest areas would be certainly clinical trials. We're just starting there. We have a relatively nascent product on co-trials that have a long way to go that we're really excited about. We also need to bring our own clinical trials through sponsors to the table [and] revenue cycle management. Practices need to, in this low-margin world, be much better at collecting insurance for their patients for their services provided, and our revenue cycle offering is just coming off the shelf. We have only 3 or 4 clients, so we're really excited to see that develop over time. Practice management software, both developed by Flatiron but also interfacing with third parties, that's becoming very critical.

How are oncologists using data to help them meet the requirements in new payment models?

There are some simple things and some complicated things. The simplest ones—our software has the care plan built in, so the IOM [Institute of Medicine] care plan physician doesn't have to think about it. It autopopulates an OncoEMR, you can print it right there, the patient can be in the room and done. A lot of analytics—getting a little more complicated but very important—are around how many patients do I have that are potentially eligible for the episode? Which of my physicians are appropriately completing the care plan for the appropriate patients?

Getting a little more sophisticated: quality measures. These are very complicated measures; some of them are easy and some are pretty hard. It takes a lot of manual work if you are going to do it on your own, to be compliant and provide the data. Some of them you have to track and some Medicare tracks for you. We help you in both.

So, the software is basically automating the quality measure process and moving it to the more sophisticated realm, with more analytics around: What is your cost of care? What are the opportunities to implement programs that could reduce cost? For example, in hospital admissions or [emergency department] visits—more deeper analytics to help you transform your practice.

Editor's Note: On February 15, 2018, Flatiron Health was acquired by Roche; see story ***SP136.***

Dr Adam Brufsky: Choosing a Therapy for Patients With Breast Cancer

There are a number of treatment choices available to treat patients with breast cancer, and diagnostic tests can assist in the decision making, according to Adam M. Brufsky, MD, PhD, co-director of the Comprehensive Breast Cancer Center at the University of Pittsburgh.

How do you decide between chemotherapy, endocrine therapy, or targeted therapy for your patients? What role do diagnostic tests play in your treatment decisions?

The way I decide between chemotherapy and endocrine therapy, really, in early-stage breast cancer is [first], using the estrogen receptor, and [second], I really think that a lot of use of multiparametric genomic tests, such as MammaPrint, Oncotype, EndoPredict, that sort of thing, to help us make clinical decisions as to whether someone should get chemotherapy or not based on their risk.

In late-stage breast cancer, it also is estrogen receptor positivity. It's HER2 positivity. And I think that even as people get further along in their clinical course and have gone through multiple therapies, a lot of us are really starting to incorporate sematic DNA testing [in] these patients to try to find ESR [erythrocyte sedimentation rate], estrogen receptor status, mutations. Potentially, HER2 tyrosine kinase mutations to help us figure out how to best treat these patients. Although those things are kind of experimental at this point, I think generally what I tend to use is estrogen receptor [status], HER2, how much disease the patient has, for example, to decide between hormone therapy, receptor base, or HER2 base therapy in chemotherapy.

Robin Shah Outlines the Biggest Challenges Facing Community Oncologists

The changing payment and competition landscape in healthcare are the 2 biggest challenges facing community oncologists today, explained Robin Shah, vice president of provider marketing and strategy at Flatiron Health.

What are the biggest challenges facing community oncologists that Flatiron Health is trying to help with?

I would say 2 of the biggest challenges community oncologists face today are there's a changing landscape from a payer perspective. So right now, practices get paid 1-way and they've built their businesses to get paid in that way. These are large businesses, and there's a shift in payment for these massive businesses, which don't have the support system, infrastructure, and technology to help them operate in that new era of payment. So, the shift has been tectonic, where it'll sort of buzz and then come »

back because the practices can't handle it. A real shift hasn't come yet, it's sort of been piecemeal, but we do think that it'll come sooner than later and the smaller practices won't be able to survive in this new market because they won't have the infrastructure to operate. So that's No. 1.

No. 2 is competition. As you have this shift, those that can handle that type of change become bigger, stronger, better, and those that can't will continue to falter. As the larger groups, the ones that actually have the infrastructure are successful. They then become an engine to compete against the other groups. Right now, the systems that are capable of doing this are hospitals, specifically because the government has built a number of incentive programs for the hospitals to be sustainable. So, that is a complicated and difficult arena for community oncology providers unless there's a shift in the government regulation that favors hospitals. That may or may not happen. Right now, a lot of it is focused on payment, but how does an organization actually build the infrastructure around the new business models that are being created?

Aaron Lyss Highlights Early Lessons of the Oncology Care Model

Aaron Lyss, director of value-based care for Tennessee Oncology, discusses the lessons learned after the cancer care specialist's experiences with the Oncology Care Model.

What are some early lessons from the Oncology Care Model (OCM)?

I think there are some early lessons from the OCM that aren't new things that we didn't know before, but things that we've been able to see in our experience in the model that have confirmed that a lot of our thinking on our strategy for being successful with [the] OCM is on the right track.

One is the importance of palliative care, in terms of managing patients with the highest symptom management complexity—how we manage the most complex care requirements that our patient population has—that's going to be an important aspect of our success in the model. Also, managing the psychosocial factors that patients face outside of the circumstances of their cancer treatment. You can't decouple those things. The environment the patient goes home to when they leave the clinic needs to be as much a concern for us as how they present when they're in the office.

I think those 2 factors, I'm not going to say that we didn't anticipate that they would be important, but I think it's one of the things that we've been able to confirm is going to be critical to our success in value-based payment programs.

Dr Ron Kline on Best Practices for the OCM

Sharing data and a collaborative relationship are 2 best practices from commercial payers participating in the Oncology Care Model (OCM), according to Ron Kline, MD, FAAP, of the Center for Medicare and Medicaid Innovation.

What is the emerging experience with OCM for commercial payers?

We have 14 commercial payers that are a part of OCM. They follow basic guidelines, which is a care management fee and a value-based payment system. I think they are learning in their interactions with practices. [People say] that making it more of a collaborative relationship rather than a conflict relationship is better. I think that practices have discovered, the commercial payers have discovered, that sharing data with our practices is very important, because if you don't have information you can't improve your practice. I think that is what's occurring, and I think their experience with OCM or OCM-like programs have been positive.

Dr Oliver Dorigo Discusses PARP Inhibitors in Gynecologic Cancers

Oliver Dorigo, MD, PhD, associate professor, obstetrics and gynecology, Stanford University Medical Center, discusses the use of poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapy in gynecologic cancers.

How have innovative new therapies changed the treatment landscape for gynecologic cancers?

I think that the new therapies that we now have approved, over the last 4 years in particular, have made a very valuable impact on patients. In particular, PARP inhibitors that are very effective in patients that have certain genomic mutations. Those patients are particularly patients with *BRCA1* and *BRCA2* mutations, or patients that have certain genomic changes in the tumor that makes the tumor particularly sensitive to PARP inhibition. PARP inhibitors are oral drugs; we do like to give them after completion of chemotherapy for recurrent ovarian cancer, and we do now have several drugs approved.

We use this a fair amount in our clinical practice. These drugs are fairly new, so we still have to learn who the patients are that most benefit from these type of drugs, learn how to deal with the side effects, and how to use them most effectively. A lot of these drugs have not quite entered the first line treatment, but there are clinical trials going on that actually might show us that they are effective early on in the treatment process.

We've also used a fair amount of immunotherapy. Immunotherapy is a very young field, in particular gynecologic oncology, but in general we still need to understand who the patients are that benefit the most from immunotherapy. A number of immune checkpoint inhibitors have been approved for other solid tumors. We do need biomarkers to select those patients that can receive immunotherapy for gynecologic malignancies, but we do use immunotherapy, I would think quite a bit, in those patients that have no other treatment options. Immunotherapy is not without side effects, so I would say we need to be careful about what patients to treat, and again, who are the patients that benefit the most from these approaches.

Dr Scott Page Explains the Importance of Different Patient Experiences in Healthcare

Having healthcare professionals with different sets of experiences or different training can help create better solutions and improve patient outcomes, explains Scott Page, PhD, the Leonid Hurwicz Collegiate Professor of Complex Systems, Political Science, and Economics at the University of Michigan.

How can diversity be leveraged in healthcare to improve patient outcomes?

If the question is how does diversity give better health outcomes, I think you have to make a distinction between experiential diversity, training diversity, identify diversity, there's lots of different types of diversity. What happens is when people have had a different set of experiences or filtered the world differently or have been trained differently and then a patient comes in and they're resenting in a particular way that's complex, then diversity turns out being really useful in terms of coming up with better solutions.

For example, the Vermont Oxford Network, which is a group of people who work in neonatal medicine. They get together and share ideas like what did we learn here, what did we learn there. So, I think this is an interesting combination of being trained in different ways, having different patient experiences, and having different personal experiences where you maybe look at the world through different lenses that allows you to sort of see a particular presentation in greater granularity, different dimensionality, which I think leads to better outcomes.

Oncology Practice Transformation Helps Deliver Patient-Centered Cancer Care in a Community Oncology Practice

Kashyap Patel, MD; Maharshi Patel, MBA; Asutosh Gor, MD; Sashi Naidu, MD; Niyati Nathwani, MD; Radhee Kothadia, BS; Saheli Parekh; and Eric Singhi, MD

CONTINUED FROM COVER

METHODS AND RESULTS

At Carolina Blood and Cancer Care Associates (CBCCA), we began exploring our practice's journey from volume to value in 2013 by understanding the concept of patient-centered care and taking the steps necessary to acquire accreditation as a patient-centered specialty practice (PCSP) through the National Center for Quality Assurance (NCQA). Our path for NCQA accreditation primed us for the transition, as NCQA has many common denominators with OCM. Under the practice transformation requirements of expanded access leading to PCSP accreditation (a corresponding OCM requirement), we realized that expanded access would lower expenses, improve patient experience, and likely improve outcomes. We found that expanded access, including same-day appointments and weekend access, prevented unnecessary emergency department (ED) visits and hospitalizations.

As a part of the transition to PCSP, CBCCA started providing patients the convenience of same-day appointments and walk-in access. Our 2 clinic locations each have 2 slots per day reserved for walk-in patients. In addition to recruiting staff to accommodate additional patients, we created a triage process and pathways, and we trained both clinical and nonclinical staff to learn the relevance of these process changes. This initial investment is paying off in multiple ways. We have documented a significant increase in office visits resulting from phone triage (**Figure 1**). Initially, this seemed burdensome, as it required the allocation of additional resources. However, upon analysis of overall trends, we noticed a more-than-50% increase in overall revenue from additional office visits over the 3-year period from 2014 to 2016 (**Figure 2**). For patients, same-day access and expanded access reduced the number of hours waiting in the ED, leading to both improved outcomes and quality of life (**Figure 3**), along with a reduced likelihood of after-hours ED visits and hospitalizations (**Figures 4-6**). Additionally, patients were able to spend more time at home with their loved ones. Overall, patients and their caregivers received better quality of care. Patient satisfaction is being measured and data will be released later this year.

For payers, the increased quality of life for beneficiaries was coupled with a reduction in spending and a reduced likelihood of healthcare-associated conditions, as well as hospitalizations and visits to the emergency department.

DISCUSSION

OCM is the first major initiative by CMMI to pilot the transition from fee-for-service (FFS) toward value-based care. CMMI has been relatively flexible and accommodating of changes made to the program in response to stakeholder input. While OCM encourages oncologists to assume 2-sided risk, in which the practice is exposed to the possibility of both receiving shared savings and experiencing shared losses, the significant disparity between negative risk and upward reward is a barrier that has discouraged participating oncology practices from considering 2-sided risk. Additionally, fulfilling the data registry requirements in terms of data entry is both arduous and labor-intensive, and a high degree of technical expertise is required to do so.

Nevertheless, OCM is a first positive shift away from volume-based care to the value-driven path. Indeed, this transition into patient-centered care delivery will inevitably lead us down the path to fulfill the triple aim of better care, lower expenses, and improved patient experience. While Part B drug utilization is somewhat hard to regulate due to multiple factors, improving access to care—particularly, offering same-day access as well as slots to walk-ins—is low-hanging fruit, relatively easy to reach to help achieve the triple aim of healthcare reform.

CONCLUSIONS

Patient-centered care offers a definite option to address some of the challenges posed by ever-rising healthcare costs and deteriorating quality of care (**Figure 7**). »

FIGURE 1. Incremental Follow-up Visits With Expanded Access

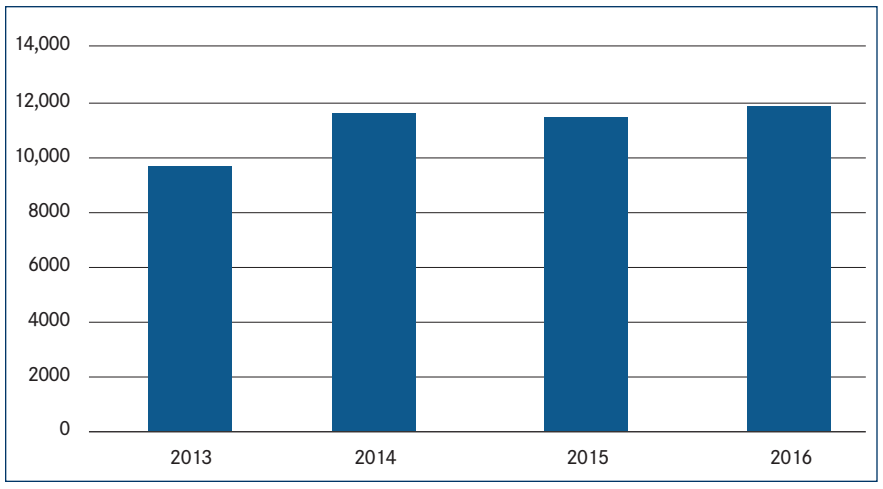


FIGURE 2. Increase in Revenue Since Expanded Access

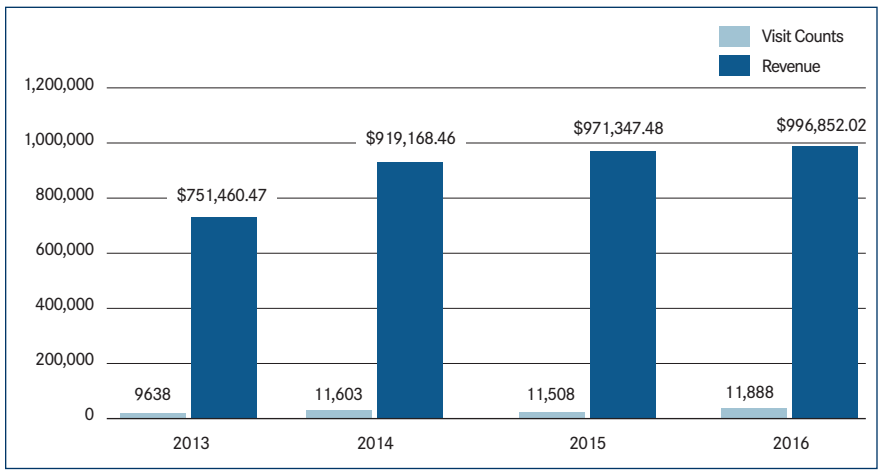
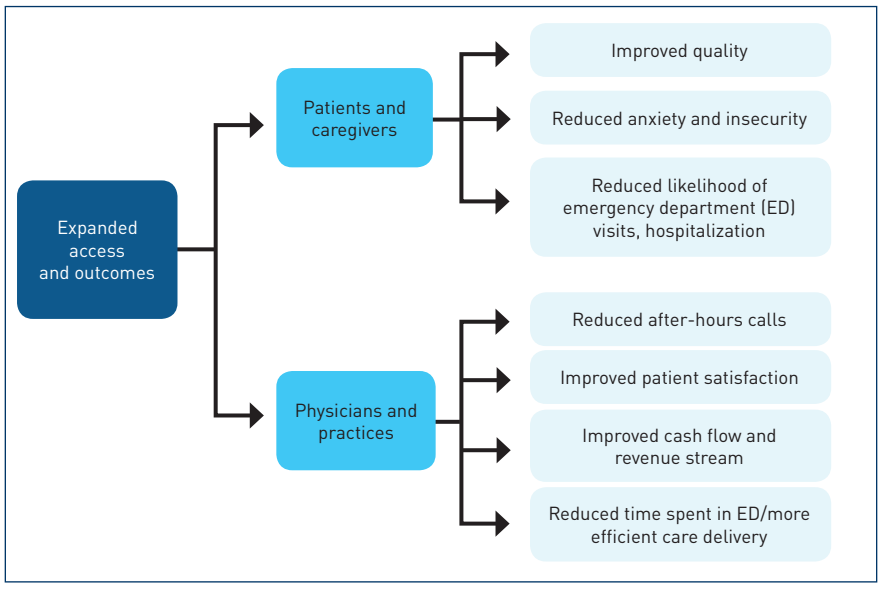


FIGURE 3. Outcomes of Expanded Access for Patients and Physicians



The goal of value-based care in oncology is to improve the quality of care, while containing costs. Advanced APMs, such as the Medicare Shared Savings Program, 2-sided risk models, and OCM are examples of a shift away from the traditional volume-based FFS model. For the OCM, this objective targets Medicare beneficiaries through an episode-based payment model that financially incentivizes high-quality, coordinated care. In moving toward a value-based specialized care system, payers recognize and reward providers who proactively seek to improve the patient experience and health outcomes. ◆

AUTHOR INFORMATION

Kashyap Patel, MD, is president at Carolina Blood and Cancer Care Associates, based in Rock Hill, South Carolina. He is secretary of the Community Oncology Alliance and a trustee of the Association of Community Cancer Centers. Dr Patel is the past president of the South Carolina Oncology Society and the former chief of staff of Springs Memorial Hospital. Maharshi Patel, MBA, is practice administrator, Carolina Blood and Cancer Care Associates. Asutosh Gor, MD, is board-certified in hematology, oncology, and internal medicine. and has been with Carolina Blood and Cancer Care since 2004. Sashi Naidu, MD, is board-certified in hematology, oncology, and internal medicine and has been with Carolina Blood and Cancer Care since 2005. Niyati Nathwani, MD, is board certified in internal medicine, hematology and medical oncology and has been with Carolina Blood and Cancer Care since August 2007. Radhee Kothadia, BS, is a student at Brody School of Medicine at Eastern Carolina University, North Carolina. Saheli Parekh is a student at North Carolina State University, Class of 2020. Eric Singhi, MD, is a second-year resident at Vanderbilt University School of Medicine who received his medical degree from the Medical College of South Carolina.

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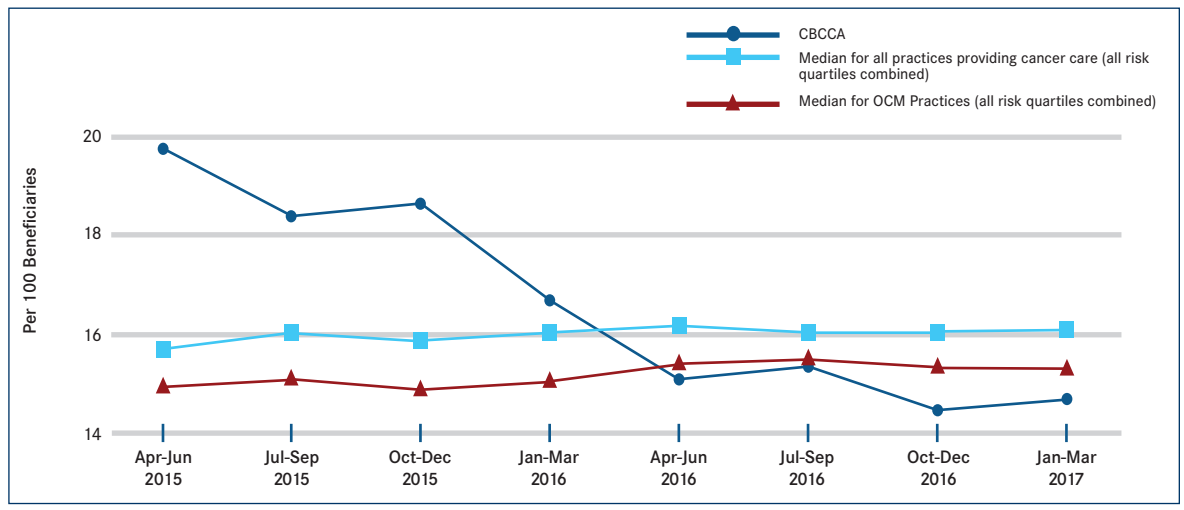
FIGURE 4. Data From CMMI for Reduced ED Visits Following Patient-Centered Care Transition at CBCCA



CBCCA indicates Carolina Blood and Cancer Care Associates; CMMI, Center for Medicare & Medicaid Innovation; ED, emergency department; and OCM, Oncology Care Model.

FIGURE 5. Patient-Centered Care, Expanded Access, and Payers

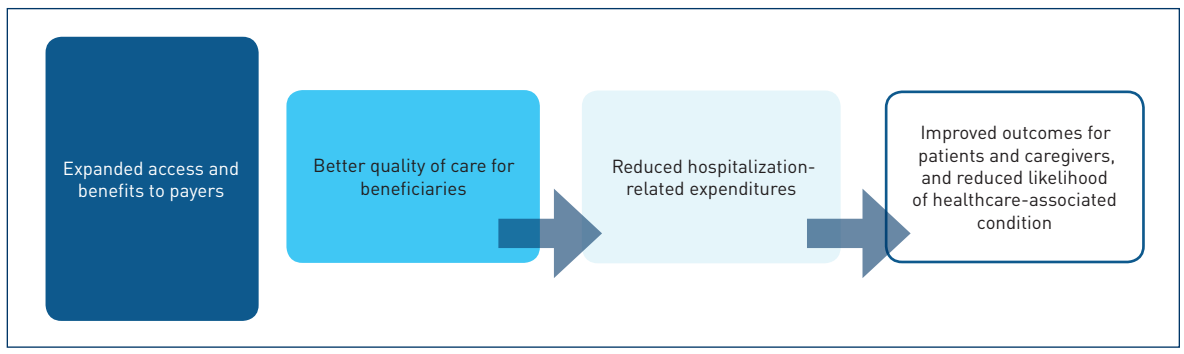
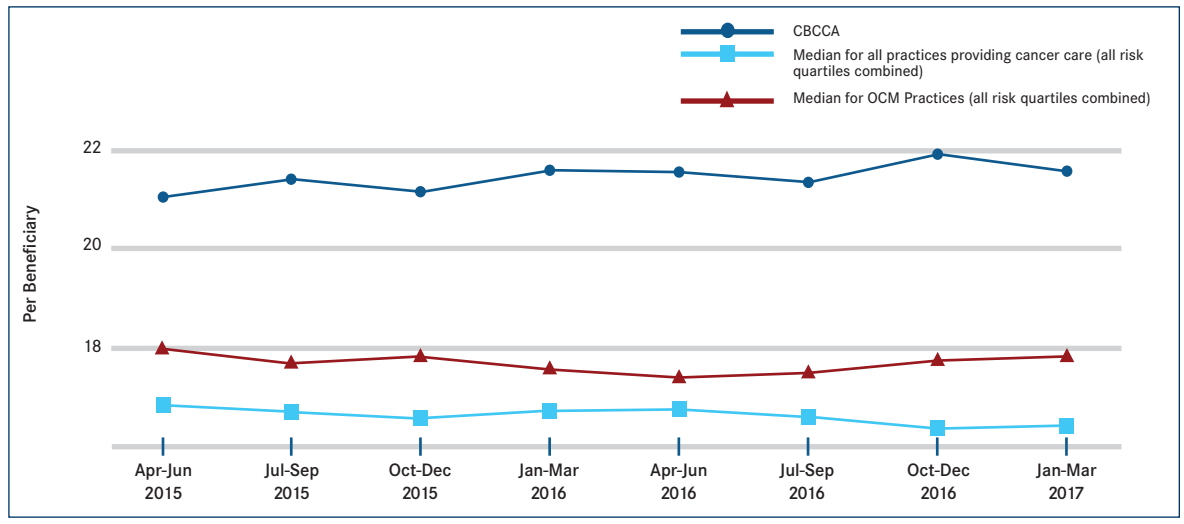


FIGURE 6. Increased Office Visits Resulting From Patient-Centered Care Transition



OCM indicates Oncology Care Model.
[a]Not risk-adjusted 4-quarter averages.
Based on our report and feedback from the CMMI so far, we project savings of about a million dollars for our first year of reconciliation.

FIGURE 7. Projected Savings to CMS Following Transition to OCM

Service	Average cost at hospital per patient	Average cost at POV per patient	Total savings per patient	Total annual savings (300 patients)
In-house radiology	$2772	$1416	$1356	$406,800
ED visits	$1136	$543	$593	$177,900
Hospitalizations	$17,108	$13,489	$3619	$373,300
End-of-life care and choosing wisely (3 months)	$13,083	$4665	$8418	$126,270
Total annual savings (Medicare) = $1,084,270				

Note: Estimated savings for 2016. Final savings to be confirmed by CMS' Center for Medicare & Medicaid Innovation.
ED indicates emergency department; OCM, Oncology Care Model; and POV, physician office visit.

Value-Based Contracting: Creating the Terms of Engagement Around High-Cost Cancer Therapies

Susan Dentzer

CONTINUED FROM COVER

These cancer drugs and other treatments—many of them "targeted" therapies tailored to the specific genetics and molecular pathways of different types of cancer—have already garnered plenty of headlines in the popular news media. Drugs already on the market, such as the chimeric antigen receptor T-cell therapy Kymriah (tisagenlecleucel) and the programmed cell death-1 inhibitor Keytruda (pembrolizumab), have demonstrated very successful outcomes for some patients and cancer types. For example, they can produce added months of survival without any progression of disease or total remission for some patients with previously untreatable or relapsed cancers. Other new cancer drugs have proved less effective. One recent study for the American Society of Clinical Oncology (ASCO) showed that fewer than 1 in 5 recently approved cancer drugs met ASCO's goals for producing "clinically meaningful survival outcomes" in patients.[1]

Many news stories about targeted cancer therapies have featured the drugs' lofty list prices, and legitimate questions have been raised about just how high these prices should be. But there is little doubt that these "ultrapersonalized" therapies constitute a new category of treatments that take years of complex research and testing to develop, are often painstaking to produce and administer, and are likely to be suitable for relatively small numbers of patients. Wherever the prices end up after negotiations among payers, manufacturers, and the healthcare providers that administer them, they will still be high.

A related, and possibly even more important, question: What will be these treatments' *value*—to patients, to families, and to society? Many of these drugs are likely to be reviewed and approved by the FDA under expedited pathways for drugs that address unmet medical needs in treating serious or other, life-threatening conditions. For example, the FDA approved Idhifa (enasidenib), a targeted treatment for a type of acute myeloid leukemia, after phase 2 trials alone were completed.[2] Such expedited approvals mean that at least some proportion of new therapies will not even have been tested in a broader phase 3 trial against standard therapies.

What's more, many of these drugs will appear on the market quickly, long before health insurers have been able to factor the costs into their budgets or premiums for policyholders. For months, if not years, there will almost certainly be lingering uncertainties regarding which patients will be benefit from these drugs, let alone what the adverse effects and long-term consequences will be.

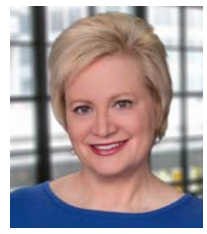
In the largest sense, it is important to establish broadly agreed-on and accepted frameworks for thinking about the value of such drugs so that we as a society can weigh the choices in front of us. Although groups such as ASCO and the Institute for Clinical Effectiveness Review have done important research and thinking to create frameworks for gauging the value of therapies, no framework to date has gained universal acceptance among all stakeholders.[3] Because money isn't unlimited, we will face trade-offs: investing more in lower-cost preventive agents such as vaccines, for example, versus high-cost cancer therapies. But even within a narrower context—deciding what drugs to pay for patients with cancer—we as stakeholders, and as a society, need some way of agreeing on the terms of engagement around their use. We need to devise frameworks for deciding which patients will receive these therapies, what expectations we should have of therapeutic performance, what we will attempt to learn about these therapies as we observe outcomes over time, and what we will pay.

In the absence of such broadly accepted frameworks, an alternative approach that has arisen is value-based contracting—a strategy in which payers and biopharmaceutical manufacturers agree to specific terms that tie payment to results.[4,5] Also known as outcomes-based contracting, there are multiple varieties of these contracts, but the overall objective is to hold manufacturers more accountable for value than the typical drug sales arrangements that tie net prices to the volume of drugs purchased. Value-based contracts compensate manufacturers based on whether they obtain improved outcomes for patients from the use of drugs or better financial outcomes overall (for example, from lower rates of hospitalization because patients are healthier). In many instances, these contracts also involve shared financial risks between the parties: For instance, drug manufacturers may have to pay more if drugs don't work as well as demonstrated in clinical trials.

As many as several dozen of these contracts have been reached between manufacturers and payers in recent years, and there is great appetite among manufacturers for negotiating more. These emerging strategies are not themselves a solution to the challenge of paying for high-cost oncology therapies or other medications, nor do they yet add up to a cohesive framework around value. But they do start the parties down the road to agreeing on the terms of engagement around value as they pertain to particular drugs. And in the absence of overarching frameworks for having discussions about value of high-cost therapies—especially in as fragmented a system of healthcare payment and delivery as that of the United States—they may be the best available option.

As important as these value-based contracts may be in setting the terms of engagement, however, they also pose innumerable challenges that must be overcome if they are to become a standard feature of the healthcare landscape. My organization, the Network for Excellence in Health Innovation, described these challenges and issued a number of recommendations to address them in a recent white paper.[5] To encapsulate the difficulty of some of these challenges, consider the example of Kymriah, the Novartis therapy approved by the FDA for use in patients up to 25 years old who have acute lymphoblastic leukemia that is either relapsing or refractory (ie, the cancer did not go into remission with other leukemia treatments).

The FDA approved the treatment in August 2017, after a phase 2 trial in which 63 patients showed an *83*% remission rate within 3 months of infusion.[6] To produce the therapy, a patient's white blood cells are extracted through a special process in qualified hospitals, frozen, shipped to a special manufacturing facility where they are genetically reprogrammed, shipped back to the hospital, and reinfused into the patient after the patient »



DENTZER

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undergoes low-dose chemotherapy to prevent the reengineered cells from being rejected.

At the time of approval, Novartis said that Kymriah would cost $475,000 for the onetime treatment for pediatric and young-adult patients.[7] Some of the roughly 40 treatment centers that have been certified to offer the treatment have told payers that their "all-in" costs of treating a patient, including the cost of Kymriah, will top $1 million.[8]

At the same time as the FDA issued its approval of Kymriah, Novartis also announced an agreement with CMS,[9] presumably around the use of the therapy for patients on Medicaid. Under the agreement, Novartis offered the assurance that if a patient treated with Kymriah for this indication does not respond in the first month, there will be no charge for the drug to patients, and to payers, including Medicaid. CMS heralded the agreement and the approval of Kymriah as "reinforc[ing] our belief that current healthcare payment systems need to be modernized in order to ensure access to new high-cost therapies." It promised to issue future guidance to explain how pharmaceutical manufacturers can engage in these and other innovative payment arrangements.

Enormous operational challenges will also accompany value-based contracting, chiefly around the collection, analysis, and use of data. Predicating a contract on patient outcomes means there must be a means of tracking them, not just in the immediate aftermath of the treatment but possibly for years.

The parties said little else about the contours of the agreement, but reading the tea leaves, observers guessed that some commitments had been made about navigating around an important obstacle to value-based contracting: Government Best Price and Price Reporting requirements, the stringent rules that drug manufacturers must comply with as a condition of participating in federal healthcare programs such as Medicare and Medicaid. Complex calculations carried out under these federal requirements are designed to ensure that federal health programs—Medicaid, the 340B Drug Discount Program, and Medicare Part B Drug Reimbursement—benefit from discounts provided in the broad commercial healthcare market. These requirements stipulate a minimum discount for Medicaid of 23.1% off the so-called Average Manufacturer Price—the average price paid by wholesalers to manufacturers for drugs distributed to retail pharmacy, minus discounts—and locks in a similar discount for hospitals, health centers, and various safety-net providers under the 340B program.[10]

For Novartis to have agreed to "no charge" for patients who did not respond within a month of treatment—without the "price" then becoming zero and triggering the same improbable price, or a deeply discounted one, for all of Medicaid, 340B, and Medicare Part B—it appears that CMS simply agreed that in such circumstances, no sale would be deemed to have taken place. But CMS has said nothing publicly since to confirm this interpretation, nor has it yet issued any of the promised guidance about how other innovative payment arrangements could legally be struck in the face of other federal regulations that pose similar obstacles, such as the Anti-Kickback Statute.

Aside from regulatory barriers to value-based contracts, there are other obstacles. Biopharmaceuticals and manufacturers alike would like the FDA to issue clear guidance about what will be permissible in the realm of communications from manufacturers about therapies that have not been approved and about uses of a given therapy that may not have been spelled out on the therapy's label but are consistent with it (eg, data from patient-reported outcomes collected in the course of the drug's FDA-approved clinical trial).

Enormous operational challenges will also accompany value-based contracting, chiefly around the collection, analysis, and use of data. Predicating a contract on patient outcomes means there must be a means of tracking them, not just in the immediate aftermath of the treatment but possibly for years. At no level, anywhere in healthcare, are current data tracking systems sufficient to accomplish this task. As the Blue Ribbon report of the Cancer Moonshot called for in 2016,[11] we need to build the national cancer data ecosystem that is equal in dimension to the disease burden cancer imposes on society and the resources that we plow into cancer care.

Multiple steps are needed to build such a data ecosystem, including greater standardization and sharing of routinely collected cancer data, albeit within appropriate privacy safeguards. In a disease state as vast as cancer, it is also almost beyond comprehension why a core set of patient-centered and patient-reported cancer outcomes measures has neither been proposed, agreed on, or put into effect. Stakeholders should make adopting such a core measure set a priority. In addition to various quality-of-life metrics, given the costs of new cancer drugs, it will be critical to gather information on financial toxicity, or the problems that patients with cancer have that are related to their costs of treatment.

Given the complexities of value-based contracting, the barriers that stand in the way of it, and the operational difficulties that will accompany it, it would be easy to dismiss this approach as impractical and infeasible. But what other serious alternatives exist? These therapies will come onto the market; they will be useful and life-extending for many patients; and even if costs are heavily discounted from initial list prices, they will still be expensive. We need to hold these therapies up to the careful scrutiny that value-based contracting makes possible and then hold ourselves collectively accountable for spending resources wisely—to get appropriate treatments to the right patients, to understand the consequences, and to continue our research and development efforts to treat and cure cancer. ◆

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CLINICIAN PERSPECTIVE

The Risk Conundrum in Healthcare

Peter Aran, MD

CONTINUED FROM COVER

This article has 2 learning objectives:

1. To offer clinically and financially oriented readers a better understanding of how clinicians and healthcare policy/finance experts distinctly, and differently, define the concept of risk.
2. To highlight how issues related to the responsibility of controlling healthcare costs might also serve as an impediment to finding common ground on care-for-value programs.

The advent of MACRA has forced policymakers to require that physicians accept contracts that carry 2-sided financial risk in order to qualify as an advanced APM. Many physicians have been reluctant to enter into these agreements. Part of that reluctance may be related to physicians' lack of understanding of the nuances of financial risk. But a more important problem may be whether physicians should be held responsible for the total cost of care.

Clinically, the concepts of risk and risk stratification are very important factors in how we triage and care for our patients. The same terminology is used quite differently when thought of in financial terms, however. As long as those 2 worlds or universes don't overlap there is no real problem. But as mentioned earlier, more and more value-based care agreements include financial risk terminology. When financial documents speak of risk, and these documents are read by clinicians, who are trained to understand clinical risk, they generally do not clearly differentiate the meaning of risk in this nonclinical usage. Because cost of care is then linked to financial risk, the misunderstanding of both issues leads to reluctance by physicians to collaborate. It is important to point out that this reluctance is not due to any lack of agreement related to the importance of value-related care but rather to confusion around the terminology and concepts underpinning risk and cost of care.

Therefore, in this article, we will describe risk from both a clinical and financial point of view. You, the reader, are likely to be tasked with being the liaison between clinical leaders and financial leaders as they craft agreements that support transformation of care based on the quadruple aim, which builds on the strength and success of the triple aim by involving physicians in the design, development, and rollout of care improvement initiatives.[2] This continued involvement of the frontline physicians and nurses increases the likelihood that a given quality improvement initiative will be successful once deployed. Some readers may think of the quadruple aim as a measure intended to lessen burnout. I think that occurs secondary to physicians and nurses feeling valued—feeling that they have been included in the design of a care improvement initiative that relies on their input and expertise and offers real clinical value for their patients.

ARAN

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Risk Scores

This article does not try to serve as a primer on risk scores. To better understand the differences, I will provide examples of both clinical and financial risk systems. **Table 1** lists some commonly used clinical risk scoring systems. All physicians, nurses, pharmacists, care managers, residents, and students use these daily in both the inpatient and outpatient settings. It is unlikely that nonclinical healthcare leaders are familiar with most of these. **Table 2** describes 2 risk scores frequently used by health policy leaders:

- Hierarchical Condition Categories (HCCs), developed by CMS, are used with Medicare Advantage programs and CMS initiatives like the Comprehensive Primary Care Plus (CPC+) initiative.[3] They attempt to classify patients according to disease severity.
- Chronic Conditions Hierarchical Groups (CCHGs) is another disease severity model, developed by Milliman.

Both the HCC and CCHG models use information from claims data in a retrospective analysis, while the clinical risk scoring systems use patient history, physical exam, laboratory, radiologic, »

TABLE 1. Clinical Risk Models in Healthcare

Commonly Used Model Abbreviation	Model Name	Comments
ASA	American Society of Anesthesiologists	Classification used to assess severity of illness to patients prior to surgery
APACHE	Acute Physiology and Chronic Health Examination	Clinical data used to assess disease severity in an intensive care unit (ICU) patient in order to predict likelihood of dying
SOFA	Sequential Organ Failure Assessment	ICU data used to predict likelihood that a patient will develop sepsis
qSOFA	Quick Sequential Organ Failure Assessment	Likelihood that a patient in a non-ICU setting will develop sepsis. Replaces Sequential Organ Failure Assessment
MELD	Model (for) End-Stage Liver Disease score	Used to assess severity of illness for patients prior to liver transplantation
GCS	Glasgow Coma Scale	Severity score for patients with coma or neurologic events
APGAR	Score named after Virginia Apgar, MD	Used to assess clinical status of newborns 1 and 5 minutes post delivery
ASCVD	Atherosclerotic Cardiovascular Disease estimator	Severity model to predict 10-year risk forecast of different cardiac interventions
NYHA CHF Classification	New York Heart Association Congestive Heart Failure classification	Quantifies disease severity of CHF in terms of functional limitations
Ranson's criteria	To assess acute pancreatitis	Classification developed to assess severity and prognosis of acute pancreatitis; pioneered by John Ranson, MD

TABLE 2. Financial Risk Models in Healthcare

Commonly Used Model Abbreviation	Model Name	Comments
HCC	Hierarchical Condition Categories	CMS severity of illness model. Used for Medicare Advantage program patients and for CPC+ program. Claims-based data. Retrospective
CCHC	Chronic Conditions Hierarchical Groups	Milliman patient severity of illness model. Claims-based data. Retrospective

[a]Not included in this category would be the financial risk models used in investing, money management, or credit rating that deal with financial events.

TABLE 3. CMS/Center for Medicare & Medicaid Innovation Transformation of Care Initiatives

Commonly Used Model Abbreviation	Model Name	Comments
CPC+	Comprehensive Primary Care Plus	Primary care transformation of care initiative involving 2982 practices in 18 areas of the United States. The 5-year program is a sequel to the Comprehensive Primary Care initiative involving 484 practices in 7 US regions. Includes cost and utilization management measures. Includes emphasis on social determinants of health. Based on care principle of the Patient-Centered Medical Home initiative. Multipayer initiative with 61 payers. Emphasis on behavioral health integration.[1]
OCM	Oncology Care Model	Cancer care transformation project. 187 US oncology practices; 5-year program with 14 payers collaborating. Based on the oncology medical home care principles. Cost and utilization measures included. Emphasis on improved planning for end-of-life care.
AHC	Accountable Health Communities	5-year program with 32 participants nationally linking community and healthcare organizations/practices. Emphasizes first the identification of social determinants of health, and second, practical approaches to deal with these barriers to care.[2]

intensive care unit and surgery monitoring data as real-time clinical measures. I encourage you to acquaint yourself with these various methodologies in order to understand the differences between clinical and financial risk models.

Both systems of risk measures are very important, yet they serve very different functions. The clinical models in Table 1 help the caregiver identify patients "at risk" for certain clinical problems and provide the caregiver the knowledge and flexibility to tailor the care plan, in real time, to minimize those occurrences. The systems in Table 2 offer a patient snapshot at one point in time, usually from a retrospective point of view, that helps the administrative leadership predict the need and intensity of future care.

In my opinion, approaching the issue of risk based on patient care principles, and not issues solely related to cost or savings, could yield some common ground and would be more meaningful for caregivers.

Determinants of Risk

Clinical risk analysis helps a caregiver stratify patients based on disease severity to better design each patient's individual care plan, which increases the likelihood of their responding to various clinical interventions. Clinicians understand the problems of financial waste and duplicative testing and the benefits of evidence-based guidelines as we develop and improve our patients' care plans. We understand how those factors impact costs for patients and their families. And what nonclinicians may not realize is that caregivers also understand that the high cost of care alone, or as deductibles or co-pays, often preclude the successful enactment of carefully designed personal plans of care because the patient cannot afford the medicine, the test, the surgery, or whatever therapeutic intervention is suggested. Over the past 8 years an initiative adopted by many physicians that incorporates concerns related to waste and inappropriate utilization of healthcare resources is the Choosing Wisely campaign.[4] This initiative started out as a collaboration of a dozen physician healthcare organizations and has now grown to hundreds that share guidelines and best practices in an effort to improve patient care.

Certain ongoing care transformation programs from CMS—including CPC+ and the Oncology Care Model—incorporate cost into their clinical models. Unfortunately, those 2 programs presently involve only a small number of primary care and oncologic practices in the United States. However, as those programs continue and expected gains ensue, we will be able to share their processes of care and successful outcomes with other physicians.

Other care improvement initiatives are currently under way to benefit our patients and their families by improving clinical outcomes of care, including the CMS-initiated Accountable Health Communities (AHC) program[5,6] (**Table 3**). Under AHC, 32 sites in the country will be working to operationalize concepts of care based on social determinants of health (SDH). This is germane to our present discussion because while physicians and nurses have long known of the importance of SDH, they did not take responsibility for including those challenges in their care plans because no processes existed that would allow for them to be improved. The frustrating reality, repeated over and over, was that we could improve our patients' conditions while they were in our hospitals but upon returning to where they lived, their conditions often worsened, which resulted in their being seen again in our offices or in emergency departments or hospitals. Or, even more sadly, they would succumb to their underlying conditions for reasons that most of us would describe as nonmedical. Now, more and more providers understand that SDH might fall into the care plans as well. So we are, in effect, asking those 32 sites in the AHC grant to demonstrate to the rest of us how best to overcome these healthcare barriers. And so too it may be with issues of cost.[7] Most physicians and nurses, outside the above-mentioned programs, do not consider cost and utilization aspects of care as fundamental issues that they are able to control. But this could change. Just like SDH are now being viewed as part of the patient's care plan, so too might costs of care and utilization. This could happen if we are able to provide physicians and nurses with tools that would help them incorporate these aspects of healthcare into their patients' plans of care.[8] Once that occurs, then collaboratively designing APMs that include 2-sided financial risk models may be more likely to succeed.

Changing the Terminology

Most clinicians do not understand the broad concept of "1- sided" versus "2-sided risk": that terminology is very different from concepts in the "clinical risk" realm. One option might be that healthcare policy/finance experts move away from the use of the terms 1- sided and 2-sided risk altogether and adopt other terminology to describe where cost and utilization fit into value-based care agreements. If we truly want to catalyze the movement of practices from a MIPS model to that of advanced APMs, we must accept that concepts and terminologies may be hindering our efforts.

But beyond clinicians and financial leaders not being on the same page on concepts of "risk," a potentially greater problem is identifying who is ultimately responsible for the problem of the rising cost of care in our country.

One school of thought suggests that doctors should be more willing to accept the responsibility for that high cost of care. A phrase sometimes used by these proponents is, "Only God can make a tree and only doctors can order a test." This overly simplistic idea may have some merit when viewing physicians as some type of global group; however, it holds little real-life value when thinking in terms of individual physicians or practices. According to this school of thought, physicians should accept the responsibility for the high cost of healthcare. One way to have a positive impact on the cost crisis would be for physicians to enter into financial agreements where they are asked to assume "financial risk" for the total cost of care; terminology such as "2-sided risk" or "upside/downside risk" are often used in these agreements. It should not be surprising, though, that physicians are reluctant to partner in these agreements because physicians:

1. May not agree that they are able to control the costs attributed to them
2. Do not understand the meaning of risk in these settings

Where Do We Go from Here?

1. Reserve the use of the term "risk" to clinical care only.
2. Include caregivers early in the design phase of care improvement initiatives and provider-payer programs. In other words, design programs using the "Quadruple Aim" approach.
3. Convene providers, payers, patients, families, pharmaceutical companies, and information technology companies in the design of care improvement projects, following the lead of the CMS multi-payer care transformation models. One of the tasks of this group would be that of discussing the many aspects related to healthcare costs and how best to lower those costs.

The answer to the question "Who is responsible for the high cost of care in this country?" may surprisingly be an easy one. You are. I am. We are. The responsibility, or blame, does not reside with any single component of our healthcare industry, and if we each act as representative only of one component it will be difficult to change the trending direction of the cost curve. However, we can take our cue from what providers are trying to do in the clinical sector—expand the concept of team-based care to better care for patients and families wherever they are, whether in the hospital, in our offices, in nursing homes, at the workplace, or (the most important "long- term care facility") their homes.

We should expand our concept of team in terms of healthcare policy. That expanded collective might be able to metaphorically get their arms around the multiple reasons why healthcare costs are so high. The blame does not rest *only* with the physicians, the hospitals, the pharmaceutical industry, the device makers, the payers, the patients or their families: The blame rests on *all* of the above.

In summary, we need to expand our concept of the healthcare policy team. That group should collaborate on the design of clinical care improvement initiatives that incorporate issues of clinical risk and ways to blunt the rising healthcare cost curve. We should avoid the use of the term "risk" in the agreements unless we are speaking to issues of clinical risk. We should be able to hold caregivers responsible for the appropriate use of healthcare resources as a part of patients' care plans, but it is unfair to hold them responsible for total cost of care. That responsibility resides with the above-mentioned healthcare policy collaborative. Agreements that are part of the MACRA/QPP or other provider-payer agreements should reflect that shared responsibility. ◆

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