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Evidence-Based Oncology

SPECIAL ISSUE: CLINICAL PATHWAYS

Provider Perspective

Cancer Care Pathways: *Hopes, Facts, and Concerns*

BERNARDO HADDOCK LOBO GOULART, MD, MS

WHY USE CANCER CARE PATHWAYS?

The oncology landscape is rapidly changing, in great part due to unprecedented innovations in diagnostic and treatment technologies.[1] Ironically, the same advances in cancer therapeutics that now benefit many patients also dramatically increase the complexity and costs of oncologic care.[2] The latter have forced stakeholders to develop new strategies to provide high-quality, state-of-the-art cancer care while simultaneously bending the cost curve.[3] Among the several new models of cancer care delivery and reimbursement that are currently under evaluation, cancer care pathways (CCPs) are emerging as a strategy to provide evidence-based oncology care at lower costs through reductions in unnecessary treatment variations.[4]

The rationale for adopting CCPs departs from the following assumptions:

1. Cancer care and costs vary substantially across clinics and providers, a concern that many studies have confirmed to be true.[5-8]
2. Low-value treatments account for at least a fraction of the variation, including the use of costly, but marginally effective, drug regimens.[9]
3. Adoption of CCPs can change physician behavior to prioritize the use of high-value evidence-based treatments, thereby improving patient outcomes and reducing the use of costly therapies that are either marginally effective or more toxic.[10]

To the extent that these assumptions hold true, CCPs have great potential to

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Panel Discussion

Are Oncology Clinical Pathways a Value Framework in the Making?

SURABHI DANGI-GARIMELLA, PHD

Clinical pathways remain ambiguous for much of oncology and its stakeholders. Adoption has been slow, and it is fraught with negotiations and push-back from providers. This could be due to a lack of understanding of how a treatment regimen was developed and who participated in the process, or it could be the result of reservations about the recommendations, which may clash with the oncologist's clinical experience or opinion.

To gain an understanding of this gray area, *Evidence-Based Oncology* invited a panel of experts who are experienced in the creation of oncology care pathways, use them in their practice, and have researched the development and implementation of care pathways. The discussion included Robert Dubois, MD, PhD, chief science officer and executive vice president, National Pharmaceutical Council, and Blase N. Polite, MD, MPP, associate professor of medicine, chief quality officer, Section of Hematology/Oncology, University of Chicago. Polite also serves on the American Society of Clinical Oncology's Value Task Force and their Payment Reform Working Group. The panel also included 2 experts from organizations that develop clinical pathways: Michael Fisch, MD, MPH, medical director, Medical Oncology, AIM Specialty Health (a division of Anthem), and Kathy Lokay, president and CEO, Via Oncology.

The discussion began with each panelist providing his or her perspective on what is an oncology care pathway. According to Fisch, pathways are created to provide optimal care choices from among a large pool of evidence-

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Patient Advocacy

Recommendations for the Role of Clinical Pathways in an Era of Personalized Medicine

ALAN J. BALCH, PHD; CHARLES M. BALCH, MD; AL BENSON III, MD; DEBORAH MOROSINI, MD; ROBERT M. RIFKIN, MD; LORETTA A. WILLIAMS, PHD

Clinical care pathways have been used for more than 30 years in hospitals and physician practices as tools to link care decisions with evidence-based practice in ways that reduce variation, improve patient outcomes, and maximize clinical efficiency.[1,2] Healthcare professionals have been the leaders in pathway development for decades, just as they have been in the creation of the clinical guidelines on which they are typically based.

However, some health insurance companies are now developing their own pathways in ways that may limit physician decision making and restrict patients' access to new state-of-the-art treatments for cancer and other chronic diseases. Of special concern to providers and patient advocates are programs that pay physicians a monthly fee to prescribe preselected therapies that are "on-pathway." Coverage is likely to be denied or delayed when the physician opts for an "off-pathway" treatment based on clinical judgment of the patient's unique circumstances, even one that is considered standard-of-care, according to well-established guidelines. Penalizing "off-pathway" prescribing, either directly or indirectly, when supported by evidence, may cause harm to patients and impose unnecessary costs

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Developing an Oncology Clinical Pathway

Following expansion of the UPMC CancerCenter network across several sites, there arose a need to standardize clinical service operations. Peter G. Ellis, MD, deputy director of Clinical Services at UPMC CancerCenter provides an overview of the process, the challenges, and the future of clinical pathways **(SP154)**.

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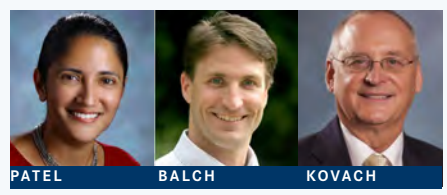
ASCO'S VIEWS ON CLINICAL PATHWAYS

The American Society of Clinical Oncology recently published a policy statement that addresses provider concerns with clinical pathway proliferation in oncology, especially the lack of transparency, administrative burden, and other factors that could affect patient access and care quality. Robin Zon, MD, FACP, FASCO, chair of ASCO's Task Force on Clinical Pathways, provides an overview of the recommendations **(SP162)**.

CONFERENCE COVERAGE: ACCC



The Association of Community Cancer Centers held its 42nd annual meeting in Washington, DC, in March. Cancerscape provided physicians with a taste of all things policy, value, and quality. You can read more about the sessions and panel discussions on **SP166**.

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Standardizing Healthcare Delivery at Low Cost and High Efficiency

Quality care, efficient treatment, improved outcomes, and low costs—these are the cornerstones of medical care. However, variability is expected depending on where care is delivered, who provides the care, and the quality metrics being measured. With the rapid pace of innovation in drug development and the increased number of expensive drugs being churned out into the system, the cost of care is a growing concern for patients, payers, and health systems alike. This, coupled with the fact that providers are free to choose between different guidelines, such as those developed by the National Comprehensive Cancer Network or the American Society of Clinical Oncology (ASCO), could further complicate matters.

To address this issue, oncology care practices and health plans have been working to develop care pathways, also called clinical pathways, to standardize treatment regimens based on clinical evidence for approved drugs per the specified indication. These pathways are either developed in-house by academic cancer centers or by payers who often work with third-party vendors. In this issue, we have gathered perspectives from both.

Peter G. Ellis, MD, a medical oncologist at the UPMC CancerCenter and medical director at Via Oncology, describes how network expansion forced his organization to develop operational standards of care consistent with the expectations of a major National Cancer Institute–designated Comprehensive Cancer Center. Dr Ellis provides an overview of the development process, including integration of pathways into workflow. "The open and democratic pathway development process, the fact that clinical pathways are physician-driven rather than payer-driven, and the ability for each user to contribute to pathway content enhance acceptance of the product," Dr Ellis writes. His company, Via Oncology, was an offshoot of UPMC's efforts and develops clinical care pathways for academic cancer centers that are physician-driven.

Kathy Lokay, president and CEO of Via Oncology, during a panel discussion hosted by *Evidence-Based Oncology,* said that academic cancer centers are the company's primary clients. According to Ms Lokay, the pathway development committee leans toward a more stratified pathway driven by a specific case presentation. For the panel discussion, one of our cover stories of the current issue, Ms Lokay was joined by Robert Dubois, MD, PhD, chief science officer and executive vice president, National Pharmaceutical Council; Blase N. Polite, MD, MPP, associate professor of medicine, chief quality officer, Section of Hematology/Oncology, University of Chicago; and Michael Fisch, MD, MPH, medical director, Medical Oncology, AIM Specialty Health (a division of Anthem).

MIKE HENNESSY, SR

Providers, however, are concerned that clinical pathways could tie their hands and restrict their flexibility with providing patients with evidence-based care. This thought was echoed by Dr Polite during the panel discussion and has been eloquently presented by Robin Zon, MD, FACP, FASCO, in her commentary, ASCO Policy Statement on Clinical Pathways in Oncology: Why Now? Dr Zon, a practicing oncologist at Michiana Hematology-Oncology and chair of ASCO's Task Force on Clinical Pathways, emphasizes the need for standardization of treatment options across payers, as well as more flexibility with off-pathway care and greater emphasis on efficacy and safety.

Bernardo Haddock Lobo Goulart, MD, MS, assistant professor in the Division of Medical Oncology, University of Washington, also wants physicians to be more active in the pathway development process. "Physicians need to have their voices heard in order to feel comfortable with using pathways in their daily routine," he writes. His other concern is the increased administrative burden that pathways could impose on oncology clinics.

How about patients? Are they concerned with the increased implementation of treatment pathways by health plans? From the panel discussion, it seemed that most patients are oblivious that their care regimen is following a predetermined pathway. The commentary, Recommendations for the Role of Clinical Pathways in an Era of Personalized Medicine, coauthored by Alan J. Balch, PhD, CEO, National Patient Advocate Foundation, offers recommendations on increasing transparency standards for pathway development and the steps needed to ensure patients receive the best care in what should be a shared-decision making process. Of course, as Dr Dubois noted during the panel discussion, this is still a fledgling area that will learn, adapt, and grow in the coming years.

Thank you for your readership. Please follow our regular updates on developments in cancer care and healthcare at **www.ajmc.com**.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

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

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- The safety of GRANIX was established in 3 Phase III trials, with 680 patients receiving chemotherapy for either breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL)[2]
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Indication

- GRANIX is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- **Capillary leak syndrome (CLS):** CLS can occur in patients receiving hG-CSFs and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.
- **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

References: 1. This information is an estimate derived from the use of information under license from the following IMS Health Information Service: IMS National Sales Perspective, GRANIX micrograms by non-federal hospital channel September 2015. IMS expressly reserves all rights, including rights of copying, distribution, and republication (micrograms calculated as eaches x strength). **2.** GRANIX® (tbo-filgrastim) Injection Prescribing Information. North Wales, PA: Teva Pharmaceuticals; 2014.

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GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving human granulocyte colony-stimulating factors and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following potential serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [*see Warnings and Precautions (5.1)*]
- Acute Respiratory Distress Syndrome [*see Warnings and Precautions (5.2)*]
- Serious Allergic Reactions [*see Warnings and Precautions (5.3)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Capillary Leak Syndrome *[see Warnings and Precautions (5.5)]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.6)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

6.1 Clinical Trials Experience

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

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^6/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^6/L) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

Additional Adverse Reactions

Other adverse reactions known to occur following administration of human granulocyte colony-stimulating factors include myalgia, headache, vomiting, Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis and thrombocytopenia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of GRANIX in pregnant women. In animal reproduction studies, treatment of pregnant rabbits with tbo-filgrastim resulted in increased spontaneous abortion and fetal malformations at systemic exposures substantially higher than the human exposure. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In an embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

The safety and effectiveness of GRANIX in pediatric patients have not been established.

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.

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This brief summary is based on TBO-004 GRANIX full Prescribing Information.

Clinical Pathways: *A Systems Approach Toward More Patient-Centric Cancer Care Delivery*

JOSEPH ALVARNAS, MD

Cancer care outcomes continue to improve significantly. Based on data from 2005 to 2011, the National Cancer Institute estimates that 66.5% of patients diagnosed with cancer will survival 5 or more years.[1] However, despite the fundamental advances in cancer care technology and care delivery that have made these improvements possible, our delivery system remains quite inefficient and frequently falls short of being truly patient-centered. The Institute of Medicine estimates that 30% of all healthcare dollars are spent on unnecessary tests, procedures, and doctor and hospital visits. The key drivers of higher-cost, less patient-centered care include the use of technologies of dubious clinical value; unnecessary variability in clinical decision making and therapeutic selection; care delivery in higher-cost settings; overuse of imaging, molecular diagnostics, and laboratory studies; and the use of treatments with low cost-to-benefit ratios; ineffective care coordination; and ineffective end-of-life care strategies. These represent systemic failures that both drive up costs and the patient centeredness of care.

Although the quest to improve value delivery is widely touted as an essential goal of healthcare reform, there is little agreement on what this really means and how best to accomplish it. A Google search of the term "cancer care value" yielded 5.9 million results. Payers, pharmacy benefit managers, managed care organizations, state and federal governments, healthcare systems, physicians, and (most importantly) patients have distinct—and sometimes nonoverlapping—ideas of what a system for value-based, patient-centered cancer care should look like. Much of the recent flurry of activity in the cancer value domain has focused on the application of novel value tools and alternative payment systems. The National Comprehensive Cancer Network's Evidence Blocks and the recent American Society of Clinical Oncology's Value Framework are proposed as tools for navigating the effectiveness and value conundrum.[2,3] Similarly, calls by HHS Secretary Sylvia Burwell to shift our payment system from one that rewards volume to one that rewards value delivery is meant to drive transformation of our care delivery system.[4]

Unfortunately, too little of the focus on enhancing value has been on how best to build robust systems for supporting and sustaining a high-functioning, highly effective, cost-efficient cancer care delivery. Systems delivery breakdowns include failing to consistently perform patient risk assessments and establish patient-centered goals of care, failures in intra-team communication and communication between team and patient, technology/goals of care mismatches, scope of care/goals of care mismatches, technology/risk mismatches, and failure to reevaluate patient/goals of care on an iterative basis. Absent a system-based solution for ensuring consistent application of a coherent vision of enhanced value delivery, these piecemeal efforts are unlikely to bring sustainable systemic change.

The ultimate goal of a patient-centered, value-based, cancer care system is to create a deeply integrated healthcare system that brings systemness to care delivery. This includes the regular application of a model of care that can make rigorous clinical risk/appropriate technology assessments, establish clear goals of care, and construct an evidence-based care plan tailored on individualized patient needs. Ideally this would also entail multidisciplinary team engagement centered upon patient care needs, seamless communication between team members, and an "eyes-on-the-prize" care perspective, with care focused on coherent, patient-centered goals rather than on the next intervention.

Clinical pathways are a set of systems-based tools for creating greater cohesion in cancer care. They do so by creating greater transparency around care decision making, therapeutic selection, and care delivery, and also help to improve quality and efficiency by reducing nonvalue-added intra-provider variability in care. Care pathways have the potential to help patients and physicians successfully navigate the tension between personalized medicine and population-based care models. Moreover, they provide systems-based tools that can move us from cost-insensitive to effective, value-based care at the lowest-priced care setting; articulate rationale care escalation schemes; systemize opportunities for increasing efficiency; consistently help to reduce duplicative testing and imaging; and helps to define and avoid the use of nonvalue-added care. Care pathways have the potential to evolve as medical technologies advance so that physicians can practice effective stewardship of healthcare resources, including molecular diagnostic and imaging studies and high-cost pharmaceuticals.

In this issue of *Evidence-Based Oncology,* we explore the potential of clinical pathways as systems-based tools that bring us closer to a model of patient-centered, economically sustainable care. Bernardo Goulart, MD, MPH, reviews the evidence for improved patient outcomes and cost-effectiveness of care through the use of clinical pathways. Peter Ellis, MD, a medical oncologist at UPMC CancerCenter and medical director at Via Oncology, describes the development and application of cancer care pathways at his institution. Finally, our multi-stakeholder expert panel explores the importance of clinical pathways in cancer care delivery and discuss the challenges with their development and implementation.

While we navigate the enormity of creating a more effective and efficient cancer care system that can better and more sustainably address the needs of our patients, cancer care pathways are one of the tools that can help to empower this transformation. As healthcare primes to make the quantum leap from a system that has aligned economic incentives with a transactional model of cancer care to one that focuses on effective longitudinal, sustainable, patient-centered decision making, we can ensure that the system serves our patients and their families in increasingly transformative ways. **EBO**

ABOUT THE EIC

JOSEPH ALVARNAS, MD

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

Care pathways have the potential to help patients and physicians successfully navigate the tension between personalized medicine and population-based care models.

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Developing an Oncology Clinical Pathways Program—*the UPMC Case Study*

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BACKGROUND OF UPMC

UPMC CancerCenter (UPMC) experienced significant expansion between 2000 and 2004, growing to a network of 25 medical oncology sites of service that cover a geographic area extending more than 250 miles in Western Pennsylvania. During this time, an extensive management team was developed to drive operational standards of care consistent with the expectations of a major National Cancer Institute–designated Comprehensive Cancer Center.

THE NEED FOR STANDARDIZATION

Surveys of clinical care patterns completed by practicing physicians at those 25 sites of service during 2004 revealed substantial variation in clinical decision making. Although this variation is to be expected in a geographically diverse network that includes physicians who received training at academic institutions throughout the country, this was not deemed to be in the best interest of the patients served by UPMC. We felt strongly that our entire network should, where possible, standardize care around best evidence for all the patients of UPMC, regardless of location, and that care should be measured and reported. This decision led to the creation of what eventually became Via Pathways.

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DEVELOPING A PATHWAY

In late 2004, UPMC physician staff included academic domain experts and community clinician experts in the various medical oncology subspecialties, such as breast cancer, lung cancer, etc. Using this expertise, we created a methodology to establish a UPMC-wide standard for the best evidence-based care of patients. Disease-specific committees were organized with academic and community co-chairs and membership made up of willing UPMC oncologists. These committees were charged with defining 2 things:

- The various patient clinical presentations of disease
- The best evidence-based care for those presentations

The committees were to reach consensus on a "single best" therapy for each defined presentation. They were also encouraged to outline common comorbidities existing in these patients and to define sub-pathways for patients with those comorbidities as well. When determining the "single best" therapy, committees were asked to consider efficacy first, followed by toxicity; if all else was equal, they were asked to include cost in their deliberations.

Developing clinical pathways was a daunting task, but more vital was the need to keep them current in a rapidly changing oncology environment. This demanded the development of a system where committees were subsequently convened quarterly to review new literature and make appropriate alterations to the content of the pathway. That quarterly committee process continues to be an ongoing standard for Via Pathways today. Conflicts of interest are minimized through disclosure at each meeting along with public disclosures on the Via Oncology (the parent company) website. Pharmaceutical companies are not allowed to participate in the pathways process except to submit published data. Administrative and pharmacy support are provided to each committee to help it complete its task. The decisions of the committee are then converted into a decision support algorithm by a content management team at Via Oncology and sent back to the committees for verification and approval. Currently there are 18 medical oncology disease committees, 12 radiation oncology disease committees, and 6 surgical oncology disease committees (covering well over 90% of all cancers). The chairs of these committees rotate on roughly a 2-year cycle.

IMPLEMENTING PATHWAYS INTO WORKFLOW

Once we had developed pathways for the various disease entities, we turned our focus to their integration into physician work flow (knowing that otherwise, they would gather dust on the shelf). In the early years, a manual process was implemented to identify patients and subsequently append a paper copy of the appropriate pathway to the chart. During the course of a patient visit, the physician was asked to mark his or her therapeutic decision on the paper pathway, based on a decision support algorithm. As the number of pathways expanded, however, this manual process quickly became overwhelming and the need for a Web-based portal to deliver the pathways at the point-of-care became self-evident.

Through many years of multiple iterations and much trial and error within the UPMC network, a simple user interface that integrates with the practice management system was eventually developed to present the appropriate pathway to the physician within his/her daily workflow. This interface (called the Via Portal) pulls patient schedules and demographics from the management system and presents a complete daily schedule to the physician. From that schedule, the physician charts the outcome of that day's interaction with the patient, choosing from options such as:

- Continue plan of care
- Change to a different treatment
- Take off treatment

Under appropriate circumstances, the portal presents the decision support algorithm in real time, for whichever action is taken, to allow the practitioner to initiate the desired therapy. The results of that decision are then communicated back to the practice's electronic health record, if one is in use. All the information about the patient's disease status and treatment are databased into discrete fields within the Via Portal for subsequent reporting and analysis.

Additionally, multiple resources are imbedded into the pathway navigation to facilitate quality care for the patient, including links to full text articles that inform pathway decisions; concise summaries of pathway committee deliberations around appropriate care; 1-page overviews of regimens outlining effectiveness, toxicities, and appropriate dose reductions; patient educational materials; and chemotherapy consents. The system also simplifies the generation of treatment summaries and survivorship plans.

SUPPORTING THE RESEARCH MISSION

It is standard practice to place locally available clinical trials first in the decision algorithm and at the appropriate point in the pathway to facilitate accrual. If the practitioner does not enroll a patient in the trial, he or she must choose, from a drop-down menu, the reason for nonaccrual before

the standard-of-care option is presented to the physician. The data around the number of patients seen by the practice who may be eligible for a given clinical trial, and reasons for nonaccrual, are regularly provided to the research team for analysis. Our research colleagues have found this a useful tool to drive clinical trial accrual.

PATHWAY COMPLIANCE

There are no financial incentives or penalties for compliance with pathway treatments ("on-pathway rates"). It is our philosophy that the pathway is likely to be appropriate for roughly 80% of patient presentations but cannot account for 100% of patient presentations and, therefore, physicians are free to choose "off-pathway" therapies as they deem appropriate. The software requires that the practitioner record the reason for the "off-pathway" decision from a drop-down list and document the actual treatment administered. The system is set up to facilitate the work flow so that "off-pathway" decisions are not more burdensome to document than "on-pathway" decisions.

UPMC does employ financial incentives for all practitioners to use ("chart") the Via Portal. This results in more than 94% of all patient Evaluation and Management (E&M) visits across all sites being reported in the pathway system. In instances where the Via Portal detects a visit in the practice management system that was not charted in the pathway system, a reminder e-mail is sent daily to the practitioner to complete the pathway charting.

Across all diseases and all presentations, the network average "on-pathway" rate is 79.6% (based on all new treatment starts). Reports are presented to all physicians outlining their "on" and "off-pathway" rates each month and list their performance in relation to their peers.

OBTAINING BUY-IN FROM PHYSICIANS

The success of a pathways program ultimately depends on physician acceptance of the content and the delivery tool (the Portal). When polled, very few physicians ask for limitations on their autonomy or to integrate another piece of software into their work flow. As such, obtaining physician buy-in to the value proposition for pathways is paramount. Leadership and transparency around the goals of pathways—to reduce unwarranted variation, drive standardization around evidence-based care, measure performance, and drive clinical trial accrual—are essential. Most physicians today are cognizant of the need for cost containment in oncology care and understand that "if we do not take the lead, someone else will for us, and we will not like the outcome."

The open and democratic pathway development process, the fact that clinical pathways are physician rather than payer-driven, and the ability for each user to contribute to pathway content enhance acceptance of the product. Keeping software design simple and as useful as possible to facilitate clinical care is important, so that practitioners are not burdened. Finally, it is important to always point out to reluctant practitioners that the alternative to a physician-led solution to the cost crisis is a payer- or government-led decision and that status quo is not an option!

PATHWAYS, A DECADE LATER

Throughout the 10 years following the initiation of clinical pathways at UPMC, our "on-pathway" rates have been in the 70%-to-80% range (based on treatment start) and we have consistently captured more than 90% of patient visits to ensure completeness. For the 12 months ended December 31, 2015, we captured over 94% of all E&M visits (n = 241,520) within the pathways database and achieved an on-pathway rate of 81.4% for all treatment decisions (n = 16,484).

Several factors contribute to the high compliance rates. First, physicians are provided a monthly performance feedback compared with UPMC overall and the Via Network overall. Second, the Via disease committees review the pathway compliance reports each quarter to identify poor performing branches and determine a course of action. This action could be:

- A re-review of the data
- An e-mail to all physician users to clarify the rationale for the pathway recommendation
- Delineation of a new alternate patient presentation to address a commonly occurring comorbidity or other factor driving off-pathway use.

With an expansion of Via Oncology's customer base throughout the United States, we have also diversified representation on the disease committees to reflect the views of Via Oncology's many customers. By allowing all Via Network physicians to participate in every meeting and having co-chairs representing the various customers, we have not only created a vehicle for strong physician buy-in, but also improved the quality of our pathway programs.

We have also worked with Via Oncology to expand the concept of pathways beyond drugs. Our clinical care pathways also cover radiation oncology, surgical oncology, and the continuum of care from work-up to symptom management, survivorship, and advanced care planning. Finally, we have the resources and datasets to begin publishing the results of our efforts and are demonstrating the impact of pathways on quality and cost of care by presenting our data at national/international meetings and in manuscripts. We are also supporting our research efforts through prospective trial promotion within the Via Portal as well as retrospective analysis of accrual opportunities by physician, site, and disease. **EBO**

Leadership and transparency around the goals of pathways—to reduce unwarranted variation, drive standardization around evidence-based care, measure performance, and drive clinical trial accrual—are essential.

imbruvica®
(ibrutinib) 140mg capsules

DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

IMBRUVICA® is approved for use in 4 indications

IMBRUVICA® is indicated for the treatment of patients with

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

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

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

ADVERSE REACTIONS

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

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

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

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

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

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

DRUG INTERACTIONS

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

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

SPECIFIC POPULATIONS

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

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

To learn more, visit
www.IMBRUVICA.com

06/15 PRC-01166

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

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

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

**One patient death due to histiocytic sarcoma.*

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

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

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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

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

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

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

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

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

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

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

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

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

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

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

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

IMBRUVICA® (ibrutinib) capsules

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

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

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

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

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

* Based on laboratory measurements.

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

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

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

The Healthcare System's Struggle With Oncology Care Pathways

SURABHI DANGI-GARIMELLA, PHD

As clinical pathways are being actively implemented and tested by health plans, opinions differ on their usefulness and credibility, depending on whom you ask. Pathways evolved as a tool to address the lack of standardization across healthcare. They could even be visualized as a quality tool that would ensure providers strictly follow a predetermined path of care, a move that could potentially avoid waste and restrain costs. Providers disagree, however. We are the best judges of our patient's treatment, they are saying.

Clinical pathways could prove to be an extremely useful tool for oncologists trying to keep up with the barrage of new molecular research on cancer. The complexities associated with cancer have made it quite cumbersome for physicians and other healthcare providers to stay abreast of the constant data flow on disease progression for each cancer type and connect all the dots—from genetic information, to treatments to which the patient may respond, to follow-up care. However, standardization, although preventing confusion and unnecessary care, may also prevent physicians from providing a more personalized approach.

IMPETUS FOR DEVELOPING CLINICAL PATHWAYS

The National Pharmaceutical Council (NPC) conducted a survey and telephone interviews among medical and pharmacy directors from payer organizations, providers from a group practice or hospital, and pathway vendors. The interviews and survey responses supported the review of published literature on electronic databases, gray literature, and websites of care pathway vendors, payers, and major oncology provider networks conducted by NPC.[1] The authors found that care pathway development may be triggered by:

- Disease states associated with a high cost of treatment (most common)
- High prevalence rates (most common)
- Availability of multiple branded therapies
- Heterogeneity in treatment patterns.

More than 50% of survey respondents shared that disease areas were selected based on cost of care (62%) and variation in treatment patterns (57%); only 33% reported selection based on clinical outcomes. With respect to evidence used for developing pathways, more than 80% of those surveyed said they turned to treatment guidelines and randomized clinical trials as their primary data sources. Those who participated in interviews identified the quality of efficacy-reporting studies as the most important consideration for inclusion in care pathway development, followed by data on safety or tolerability and, finally, costs. However, in survey responses, 81%, 71%, and 57% identified medical (nonpharmaceutical) costs, pharmaceutical costs, and healthcare resource use, respectively, as measures that are considered in care pathway development.

There is evidence to document that standardization of care delivered to treat a specific condition can be cost-effective. A study evaluating the use of clinical pathways in the treatment of lung cancer patients in an outpatient community setting was published in the *Journal of Oncology Practice* in 2010.[2] The study included patients with non–small cell lung cancer who were initiated on chemotherapy in practices that were a part of the US Oncology network. The study compared the cost of care and overall survival at 1 year for patients who were on- versus off-pathway, and discovered 35% lower outpatient costs for the on-pathway patients ($18,042 vs $27,737 off-pathway). The trend was mirrored among patients treated in the adjuvant and first-line settings, but not in the second-line setting, the authors reported.

COULD GENERICS AND BIOSIMILARS BEND THE COST CURVE?

If cost control is an important consideration for payers in ensuring adherence to pathways, raising provider and patient awareness on the availability of therapeutically equivalent generic versions of the more expensive brand-name drugs should be given priority. The American College of Physicians recently published the results of a survey that found physician and patient perceptions about the safety and efficacy of lower-cost options significantly influence the use of these medications.[3] A survey among patients across the United States found that although a majority of surveyed patients understand that generic medications are less expensive and believe they can bring more value to healthcare, only 36% said they'd prefer to use the generic version themselves. Their main concerns? Safety and efficacy of the generic products. Physicians, too, were not 100% on board, with 25% of those surveyed expressing similar concerns with the safety and efficacy of generic products.

According to Lee N. Newcomer, MD, MHA, senior vice president, Oncology, Genetics, and Women's Health, UnitedHealthcare, savings from pathways will continue only if they are supported by a reimbursement plan that pays a higher margin for generic drugs or effective, low-cost branded drugs—which will stop physicians from choosing high-cost drugs on their treatment regimen.[4] This parallels the healthcare system's increasing focus on high-value care—ensuring that patient and healthcare dollars are spent on treatment regimens that significantly improve outcomes at reasonable costs. Value frameworks developed by both the American Society of Clinical Oncology and the National Comprehensive Cancer Network hope to serve this purpose: both frameworks consider clinical efficacy, toxicity, and cost to identify the most valuable care for patients.[5]

ARE PATHWAYS RESTRICTING ACCESS?

An important argument being presented, especially by oncologists, is against the one-size-fits-all design of clinical pathways. Increasing evidence suggests that an individual tumor is a heterogeneous mix of cells that makes the disease very difficult to treat and creates a case for a more personalized approach. Via Oncology, a pathway vendor, respects this need and has a more personalized approach to the process, as discussed by the company's CEO, Kathy Lokay (SP176).

In an interview with OncLive, Ray Page, DO, PhD, president of The Center for Cancer and Blood Disorders in Fort Worth, Texas, said, "Today, we have hundreds of drugs out there, and very targeted drugs that only work in certain subsets of tumors. Drugs are very sophisticated, very targeted, have very limited indications, and are very expensive. I can't just go pull a drug off the shelf and say, 'Well, it's got an indication for lung cancer, so let's just give it.' It's not going to work unless you use it in the right population. Given the amount of knowledge you need to maintain an understanding of when to use the drug, we need a pathway system that's evidence-based, that helps guide you in today's society."[6]

Oncologists are pushing back. Page recently co-authored a paper in *JAMA Oncology* that calls on oncologists to take the lead in the development of clinical pathways, rather than health plans. Additionally, the commentary demands that physicians should be allowed to develop one set of pathways that can be applied across health plans, which could reduce the administrative burden associated with using unique pathways for each plan.[7] Whereas these are fledgling years for clinical pathways, with additional data and wider adoption will come a knowledgebase to adapt and improve on their development and clinical application. **EBO**

If cost control is an important consideration for payers in ensuring adherence to pathways, raising provider and patient awareness on the availability of therapeutically equivalent generic versions of the more expensive brand-name drugs should be given priority.

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ASCO Policy Statement on Clinical Pathways in Oncology: *Why Now?*

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In addition to healthcare providers, commercial organizations, and other health systems, an estimated 60 individual health insurance plans in the United States currently implement oncology pathways programs.

Today's healthcare system offers significant challenges, as well as opportunities that are shaping the practice of cancer care. On the one hand, oncology providers and patients are fortunate to witness the benefits from advancing science and precision medicine, including new drugs and biologic therapies. Additionally, our clinics are filled with increasing numbers of cancer survivors—more than 14 million in 2014.[1] On the other hand, the demand for cancer services is increasing as the American population ages and expands. These realities have resulted in tremendous tension on our healthcare system, as evidenced by soaring cancer care costs, attributable to increases in utilization and rising drug prices which result in particular financial toxicity to patients.[2]

In response to mounting pressures to improve the value of cancer care, payers and other stakeholders, including the American Society of Clinical Oncology (ASCO), are pursuing new payment and care delivery models that enhance quality while lowering spending.[3] Moreover, in exchange for the US Congress Sustainable Growth Rate formula repeal in April 2015, the Medicare Access and CHIP Reauthorization Act of 2015, also known as, MACRA, was codified to encourage physicians to participate in new payment models in exchange for increased accountability in delivering high-quality care. This has resulted in a paradigm shift away from remunerating quantity of care toward rewarding quality and value. Clinical pathways are one of the tools being adopted to meet the aims of better managing utilization by reducing unnecessary and costly treatment variation, while meeting the stated goals of enhancing quality and value.

As the leading professional organization representing physicians who care for people with cancer, ASCO has been a leader in assisting oncology providers in providing the highest quality care to all patients with cancer. ASCO's clinical practice guidelines provide critical guidance to practicing oncologists and represent ASCO's efforts to ensure that evidence-based medicine is the gold standard in oncology.

ASCO's Quality Oncology Practice Initiative (QOPI) offers a way to provide assessment, achieve program recognition, assess and improve safety, and engage clinical staff in an ongoing culture of quality improvement. Additionally, ASCO's QOPI Certification program provides a mechanism to formally certify those practices that achieve the highest standards of oncology care delivery to their patients. Our community's embrace of quality is reflected in the high rate of participation and certification in QOPI.

Clinical pathways represent another important tool for promoting high-quality, high-value cancer care. Currently used by healthcare providers, commercial organizations, and other health systems, pathways are also increasingly being adopted by insurance plans in the United States, with an estimated 60 individual health insurance plans in the United States currently implementing oncology pathways programs.[4] More than 170 million individuals covered by those insurance plans are potentially being treated under a health plan-sponsored pathways program—many under active treatment for cancer.[4] Furthermore, approximately 15% of oncology "lives" were treated according to clinical pathways in 2010; a percentage expected to rise significantly over the coming years.[5]

TASK FORCE ON CLINICAL PATHWAYS

Under ideal circumstances, clinical pathways are detailed, evidence-based treatment protocols for delivering quality cancer care for patients with specific disease types and stages. So, why is ASCO providing comment and guidance *now*? ASCO members have articulated concerns regarding the current proliferation of pathways in oncology, including lack of transparency, administrative burden, and other factors that could affect patient access and care quality. In response, ASCO established an ad hoc Task Force on Clinical Pathways last year to examine this issue. In January 2016, the Task Force issued a policy statement on clinical pathways in oncology to guide the future development and implementation of these treatment management tools.[6]

From the outset, it's important to note that clinical pathways in oncology are viewed by many in the field as a way to improve, not hinder, care. Indeed, cancer specialists, themselves, are often leading the development of pathways as a means for promoting evidence-based care and shared decision making with patients. That said, the responsible use of pathways means that not all patients should be treated "on pathway" due to the presence of comorbidities or other patient-specific factors.

Additionally, the Task Force recognizes that there is a wide variation in the quality and utility of existing pathways, with some pathways placing priority on cost control, inserting hurdles for treating patients "off-pathways," and being opaque about how a pathways program was designed, is updated, and even how decisions are made about what treatments are put on or off a pathways program. ASCO's policy statement serves to convey a cautionary note, that we must be thoughtful and deliberate in the development and implementation of pathways to ensure that our patients receive the best and most appropriate evidence-based cancer care possible, as well as have access to well-designed clinical trials.

In releasing the *ASCO Policy Statement on Clinical Pathways in Oncology*, the Society has 3 primary objectives:

- To increase awareness about the growing use of clinical pathways in oncology, and concerns that exist about the manner in which they are being deployed
- To ensure quality, transparency, and consistency in the design and implementation of these treatment management tools
- To ensure that pathways are used in the way they are intended to ensure quality care and reduce costs.

CONCERNS ABOUT CLINICAL PATHWAYS

The ASCO Task Force's review of clinical pathways in oncology identified a range of concerns, including tremendous variation with regard to pathways that do not consistently offer an appeals process when denying off-pathways treatment; pathways that often have a cumbersome approval and appeals process and provide no reimbursement when off-pathways treatment is denied; pathways that do not cover rare cancers and those patients treated in the inpatient setting (eg, acute leukemias); pathways that do not disclose methodology used in development nor report all potential conflicts of interest by the pathway developers; and pathways that focus on cost savings, with efficacy and safety as secondary considerations.[4]

ASCO's examination also found that the number of regimens offered for specific cancers varies widely from pathway to pathway, and treatment options within the same pathway can be different in different demographic regions.

Additionally, we discovered that the proliferation of oncology pathways has created major administrative burdens on oncology practices, some of which report having to adhere to multiple different pathways by differing payers for the same type and stage of cancer.[7] Practices are increasingly forced to sift through the requirements of each payer's pathway program on a patient-by-patient basis, diverting time away from direct patient contact and potentially eroding the doctor-patient relationship.

NEED FOR MORE DATA

At this juncture, the focus should be on learning, revising, and improving the process of pathway utilization through prospective research on current implemented pathways. Although some studies have shown that pathways can reduce costs while improving, or at least maintaining quality of cancer care, data are not complete.[8] ASCO's clinical pathways policy statement calls for additional research to understand the impact of pathways on care and outcomes.

ASCO RECOMMENDATIONS

ASCO envisions a collaborative effort for strengthening clinical pathways by involving all stakeholders, including physicians, patients, payers, clinical researchers, pathways developers, healthcare administrators, and policy makers—a specific recommendation articulated in its policy statement. Transparency, consistency, and the full promise of clinical pathways will not be fully realized until all concerns and perspectives are considered and thoughtfully addressed.

We believe that the ASCO policy statement will serve to engage all stakeholders in clinical pathways in oncology and facilitate a constructive dialogue for moving forward. The ASCO policy statement sets forth the following 9 recommendations that can provide the structure for this much-needed dialogue:

1. Pursue a collaborative, national approach to reduce the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways. This would include eliminating preauthorization requirements if the patient meets the criteria for a selected pathway, and allow physicians to select one, deemed pathway accepted by all payers.
2. Adopt a process for development of oncology pathways that is consistent and transparent to all stakeholders with public disclosure of methodologies for the pathway development and conflict of interest disclosures.
3. Ensure that pathways address the full spectrum of cancer care, from diagnostic evaluation through medical, surgical and radiation treatments, and include imaging, laboratory testing, survivorship and end-of-life care in order to maximize opportunities for value-based medical outcomes.
4. Update pathways continuously to reflect new scientific knowledge, as well as insights gained from clinical experience and patient outcomes, to promote the best possible evidence-based care. The emergence of big data and rapid learning systems further accentuate the need for rapid pathway refinements and more granular pathways to best serve the needs of distinct populations.
5. Recognize patient variability and autonomy, and allow for physicians to easily diverge from pathways when evidence and patient needs dictate. Appropriate variation considering varied patient comorbidities and therapeutic goals should be supported without significant administrative burdens.
6. Implement oncology pathways in ways that promote administrative efficiencies for both oncology providers and payers. In addition to removal of preauthorization when providers provide health services consistent with clinical pathways, the additional costs in complying with pathway adherence, which are not currently included in the codes for evaluation and management or care management, should be factored into payment for oncology services.
7. Promote education, research, and access to clinical trials in oncology clinical pathways. Furthermore, robust oncology pathways may help with collection of data outside of small trials and help advance understanding of therapy toxicities, patient comorbidities, and survival.
8. Develop robust criteria to support certification of oncology pathway programs; pathway programs should be required to qualify based on these criteria, and payers should accept all oncology pathway programs that achieve certification through such a process.
9. Support research to understand the impact of pathways on care and outcomes focusing on pathway development, dissemination and implementation, cancer care delivery, patient experiences, and impact on clinical outcomes and value.

THE FUTURE VISION FOR PATHWAYS IN PAYMENT REFORM

Oncology clinical pathways are likely here to stay, at least for the near future. Value-based pathways are considered by many an essential component of a comprehensive oncology payment reform initiative. This includes the ASCO model, which suggests payment adjustments based on quality, pathway adherence, and resource utilization, as well as alternative payment models such as the Oncology Medical Home. The future could also include the potential integration of rapid learning system data in optimizing the pathway evidence base, and therefore, improving the quality of patient care. Additionally, as pathways are used to measure outcomes, value-based pricing may also be realized, further promoting cost containment. The ASCO Value Framework, which assesses the relative value of cancer treatments by examining effectiveness, toxicity, and cost of regimens in a comparative manner, may also assist pathway development.[9]

The business model for incorporating pathways needs to be more fully examined and understood to assure sustainability of the care model for payers, providers, and patients. This includes mitigating administrative burden through oncology certification and acceptance of a deemed pathway by all payers.

The business model for incorporating pathways needs to be more fully examined and understood to assure sustainability of the care model for payers, providers, and patients. This includes mitigating administrative burden through oncology certification and acceptance of a deemed pathway by all payers.

CONCLUSION

- ASCO believes there need to be uniform standards for the development and implementation of clinical pathways that are transparent to oncology stakeholders including physicians, patients, and payers.
- Pathways should address the full spectrum of cancer care, and be updated in a timely manner to reflect new scientific knowledge, as well as insights gained from clinical experience and patient outcomes.
- Clinical trial access should be considered an on-pathway option.
- Pathways should recognize patient variability and autonomy, and off-pathway options when this is in the best interests of the patient.
- Finally, pathways must be implemented in ways that promote administrative efficiencies rather than burdens for oncology patients, providers, and payers with strong consideration for certification and deeming of pathways.

Recognizing the critical importance of this issue for physicians, patients, and payers throughout the United States, ASCO's Task Force on Clinical Pathways will continue its efforts to ensure that pathways are developed in such a way that ensures quality, consistency, transparency, and administra-

tive efficiency to all stakeholders. Our recommendations will form the basis of this work, which will involve consulting with payers, vendors, providers, and others to develop a collaborative approach to ensure that clinical pathways promote—and don't hinder—high-quality patient care. **EBO**

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ONCOLOGY MEDICAL HOME

The Oncology Medical Home—*Beyond Clinical Pathways*

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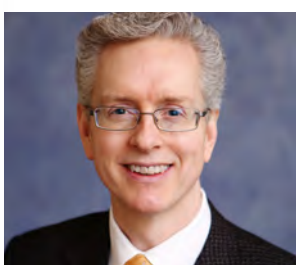

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INTRODUCTION

With the skyrocketing costs of oncology care, it is imperative that the cancer care community develop a strategy to control costs, while providing high-quality, comprehensive care to patients diagnosed with cancer. Clinical pathways have been emphasized as a means to deliver efficient, quality care and to ensure better outcomes at lower costs. The Oncology Medical Home (OMH) takes this to the next, more comprehensive, step of quantifying and improving quality and value in cancer care while lowering overall costs. Patients, providers, policy makers, payers, and employers all agree that we must work together to curb the rising costs of cancer care while maintaining and promoting higher quality. This focus should encompass all aspects of the cancer care journey for patients and their family.

The OMH accreditation model being implemented by the American College of Surgeons' Commission on Cancer (CoC) was designed to help cancer care teams transition their focus, energy, and processes to ensure the delivery of quality and value in cancer care. The model is centered around 5 core areas including:

- Patient engagement
- Expanded access
- Evidence-based medicine
- Team-based care
- Quality improvement

Achieving OMH certification includes specific guidelines for these areas that cover well-defined policies and efficient procedures, and emphasizes compliance with or results from applying the guidelines. Evidence is to be provided through reporting and trending of compliance with the required policies and procedures, and proof of improved quality and value, as demonstrated in the 18 OMH measures.[1] These measures are the result of a collaboration among an 18-member team of insurance payers, cancer care providers, practice administrators, and patients or patient advocacy organizations.

The CoC has been associated with recognizing and promoting quality cancer care. Founded in 1922, the CoC has been instrumental in improving cancer care in hospital-based cancer programs. In addition, the CoC has developed and maintained the National Cancer Data Base, which stores information on approximately 70% of newly diagnosed cancer patients in the United States. The CoC improves care by setting mandatory standards for cancer programs and using the data submitted by cancer programs to compare their compliance with mandatory quality measures.

Likewise, the OMH model has been developed as a mechanism to hold oncology practices accountable for meeting the standards that ensure quality, comprehensive care, and decreased variation. This is achieved through constant monitoring and measuring of compliance with the accepted standards and quality metrics—measuring compliance, and comparing it against peers, helps raise the bar in quality and will set the foundation for payment or delivery system reform. Examples of compliance measures include:

- Policies and procedures to minimize unnecessary emergency department (ED) visits and inpatient hospitalizations
- Proof of effectiveness of these policies and procedures to avoid ED visits and hospitalizations
- Improving patient satisfaction: each practice must administer a patient satisfaction survey and monitor results. The goal is to ensure that care is truly patient-centered and meets the needs of patients and their families or caregivers.

IT TAKES A TEAM: DISTINCT PERSPECTIVES ON QUALITY AND VALUE

OMH accreditation standardizes measurement and assesses performance against a set of uniform standards and requirements that may improve quality, outcomes, efficacy, and efficiency. Of course, oncologic outcomes cannot simply be defined by survival rates—they include demonstrated compliance and improvement of evidence-based standards, improvement in quality measures, patient and family engagement, and a variety of patient-centered services.

There are 3 central perspectives to be considered when measuring the quality and value of the OMH model: patients, providers, and payers.

All cancer patients expect a positive outcome following their treatment, along with an individualized survivorship care plan for the best quality of life. Patients also merit education on diagnosis, treatment, and financial implications, so that they may make informed care decisions, and have confidence that their input and preferences are taken seriously by their trusted clinicians.

Oncology clinicians are being asked to provide evidence and rationale for their clinical decisions with proof in the form of measurable quality and value. Under the OMH model, this includes adherence to proven treatment plans, appropriate and timely communication with patients and their families, minimizing unnecessary visits to hospital EDs, and survivorship care. In return, clinicians are seeking better reimbursement rates along with higher patient satisfaction of the care delivered.

For the payer, cost-efficient care is a priority. Insurance companies are urging hospitals and private clinics to help reduce the rising costs of cancer care by promoting and providing evidence-based care that minimizes unnecessary expenditures. Clinical pathways and performance measures are 2 strategies that can help achieve this. If all these interests are to be met successfully, it is vital that clinicians, patients, and payers continue to work together to define the measures of what high-quality, high-value oncology care is.

ACCREDITATION OF THE ONCOLOGY MEDICAL HOME

An ideal cancer care team is focused on providing the *right* care at the *right* time, and, at the *right* place. At the core of the OMH are measures of quality, including patient satisfaction and value. These measures cover the full range of the cancer care journey, from diagnosis to the initial visit, through treatment and to survivorship or advanced care planning. They are intended to help improve clinical outcomes and increase cost efficiency of cancer care.

The OMH program covers all aspects of care delivery in a cancer clinic seeking accreditation. It is an oncology-specific version of the general patient-centered medical home model that takes into account the unique services and issues managed by cancer practices. Cancer clinics achieving accreditation are publicly recognized as, "Oncology Medical Homes." According to standardized criteria, payers may find this accreditation helpful when evaluating whether payment reform initiatives are being implemented.

IMPLEMENTING THE ONCOLOGY MEDICAL HOME

This transition to evidence-based cancer care, in all aspects of the team model, begins with commitment. Each care team needs at least one champion who will educate, coach, and encourage the practice to take on this new accountability of their service. Historically, having a practice champion has proven to be the hardest step for any healthcare transformation.

For at least the last 50 years, healthcare has been structured to incentivize volume over value, with the system rewarding consumption or utilization. The concept of having healthcare services be evidence-based, validated, and recognized, in a quantifiable way, is relatively new. But it is an important step; so, having a champion rally the team may need to be repeated several times before a plan can truly be successfully implemented.

Those involved in developing an OMH often hear of how overwhelming and expensive the journey could be. The goal of the CoC-OMH team and allied supporters, who have helped lay the foundation for today, is to minimize the administrative and financial tasks that may be encountered. This sets the OMH program apart from other programs.

The OMH model does not prescribe how to accomplish a certain goal; instead, it simply emphasizes the goal that needs to be met. The cancer care team has the flexibility to determine the most efficient path towards achieving the goal and the target, and measurable outcomes will be proof that they are a leader among their peers.

For those considering the OMH, implementation of the patient survey is probably the easiest step to grease the wheels of change. Deployment is extremely easy and the feedback paints the picture of how specific areas might be benchmarked, discussed, and addressed. The bonus, for adopting the model, are patient surveys that reflect the patient's view of how well a practice is performing with achieving high standards.

CONCLUSIONS

Healthcare has come a long way in the last 5 years, and it seems cancer care has been on the forefront of that change. What was a specialty emphasizing clinical pathways *only* is now pursing evidence in all aspects of the field—from comprehensive and timely communications with patients and their families, to efficient and effective care, to appropriate survivor and end-of-life care. Most importantly, evidence is central to the entire care delivery model.

The CoC accreditation program for OMH provides an organized and comprehensive plan to guide any cancer care team that is ready to distinguish itself as leader in this era of healthcare reform and accountability. **EBO**

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How Can We Identify the Value of Personalized Medicine in Cancer?

SURABHI DANGI-GARIMELLA, PHD

Kavita Patel, MD, MS

At Cancerscape, the Association of Community Cancer Center's 42nd annual meeting on policy, value, and quality, held March 2-4, 2016, in Washington, DC, Kavita Patel, MD, MS, senior fellow at the Brookings Institution, spoke about the clinical imperatives of personalized medicine, with considerations for curbing healthcare costs and simultaneously demonstrating value to all stakeholders.

Patel posed the question: Can Value and Personalized Medicine in Cancer Care Co-Exist? "As a clinician, I always thought I was providing personalized medicine. So what has changed?"

Overall, Patel said, oncologists and physicians must start thinking about where they will position themselves in the new value-based payment models and value-based care. "Where can you insert value-based practices in your clinic?" she asked.

Drawing a simile with Tesla—a luxury vehicle that offers the promise of a reduced carbon footprint—Patel said that Tesla received tremendous subsidies from the federal government because of the value proposition the company presented for its expensive vehicle. "We need to come up with our own models and metrics, rather than have the government tell us what to do with respect to value," Patel told the audience.

She said that as physicians try to prepare patients for the onslaught of costs coming from the therapies that are being developed, "we need alignment between what we are telling the various stakeholders, including physicians, payers, and patients."

A few of the strategies that Patel proposed include:

- Targeting mechanisms that lead to cancer progression to improve outcomes
- These mechanisms are individual or personalized
- The goal should be to identify the mechanism of progression so we can specifically target it.

> "We need to come up with our own models and metrics, rather than have the government tell us what to do with respect to value."
>
> —KAVITA PATEL, MD, MS

"Precision medicine boils down to taking each patient, identifying the best clinical evidence, identifying the molecular mechanisms, and then selecting the best algorithm that considers the longevity of treatment, screening, and follow-up," Patel added. In her opinion, the ideal solution to improve outcomes with targeted therapies is to test the algorithm used [to develop the clinical trial] rather than the drug being used in the treatment.

How is value being defined today? Patel emphasized the utter lack of clarity around the term "value." The definition often seems far removed from reality. "You cannot be held responsible for measures that do not make sense for the population you take care of!" Patel remarked.

"Patients trust us, we are their point person, and we are accountable for their health, not the hospital. This needs to be considered in these value-based models," she stressed. **EBO**

The Tightrope Act of Personalized Value in Cancer Care

SURABHI DANGI-GARIMELLA, PHD

Alan Balch, PhD

George Kovach, MD

Most of us, who are familiar with the oncology value models proposed by organizations like the American Society of Clinical Oncology,[1] the National Comprehensive Cancer Network,[2] and others, realize the myriad practical questions that these models create for those on the frontlines of cancer care delivery. Unless these frameworks are implemented in the clinic, questions regarding their utility will remain. However, implementing these tools may require educating not just the providers, but also patients and payers.

To discuss these and other challenges with transitioning to value-based care, the Association of Community Cancer Centers (ACCC) invited a panel of experts during its 42nd annual meeting on policy, value, and quality, in Washington, DC. The panel, moderated by Christian Downs, JD, MHA, executive director of ACCC, included Alan Balch, PhD, chief executive officer, Patient Advocate Foundation (PAF); Thomas A. Gallo, MS, executive director, Virginia Cancer Institute, Inc; and George Kovach, MD, Iowa Cancer Specialists.

Balch explained how their foundation functions. PAF, he said, provides patient support and guidance on patient access issues as well as financial problems that patients face pertaining their care. The National Patient Advocate Fund, he explained, is their policy and advocacy wing.

Circling back to the topic at hand, Balch said, "There's need to standardize the frameworks to improve system efficacy." There are 2 ways to approach this, he explained. "Decide the patient's faith beforehand or discuss the options with them and personalize their journey through the disease." Balch believes that an ideal provider–patient conversation should discuss goals of concordant care. "Over-standardization runs the risk of losing out on goal concordance and what is valuable for the patient," he said. However, Balch feels that discussions around cost of care and affordability, which are so important for the patient, are the most difficult to handle. "I am not sure when the right time is to introduce that conversation, because it can stress the patient, but it needs to be done in a way that is meaningful to the patient."

Gallo provided an operational perspective on this move to value-based care. "Physicians usually stay out of the conversation on finances because they are not comfortable with it. A lot of different frameworks and programs make it difficult operationally," Gallo said. "We are still experimenting with the various options and trying to place programs in place to bring value. The burden is huge on the clinics because it takes time away from focusing on the patient."

Balch added that the patient is faced with a lot of information all at once when it comes to a cancer diagnosis. They are overwhelmed since they are expected to understand and make decisions on a lot of clinical issues. Discussions on the financial aspects of care just add to the burden, Balch said, adding that "it should be a precision conversation."

"Insurance has changed and out-of-pocket costs have risen significantly," continued Gallo. "Further, the lack of oral parity creates additional burden. It's bad enough that patients are worried about their diagnosis, and then over and above that they are required to have the conversation on financial matters." He said that they have a very good team of financial counselors at the Virginia Cancer Institute that provides their patients the best information and guidance to navigate the journey.

Kovach, however, raised the issue of 'insured but not covered.' "A problem we have missed discussing is that many of these patients have insurance, but they are not necessarily covered for their required treatments." Balch noted that not all patients would necessarily be interested or keen on understanding or discussing the cost of care. "The pace and scale at which they would want that information is what could be operationally difficult," he said.

Kovach added that, as a physician, he tries his best to do everything on his end to insulate patients as much as he can around issues of cost and access. "I believe that physicians really need to be involved in this," Kovach added. Gallo raised concerns with the rising administrative burden that oncologists face. "Most are already overburdened in the clinic. The fact that some of these frameworks have an information deficit just makes it that much harder," he said. "If we can have a global approach for harmonizing the process, it'd definitely help," Gallo continued. "Something like a common patient assistance form would ease matters so much more for us operationally. Standardizing would be a big help." **EBO**

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Expert Advises Physicians on What to Expect From Medicare in 2016

SURABHI DANGI-GARIMELLA, PHD

Speaking at the 42nd annual meeting of the Association of Community Cancer Centers, Cancerscape, held in Washington, DC, Lindsay Conway, MSEd, managing director, Advisory Board Company, brought the oncologists in the audience up to speed on Medicare's reimbursement strategies for the coming year.

"Our team takes up strategic and operational issues that our members view as problematic and seek our advice on," said Conway, adding that the issues could range from reimbursement to financing.

The following is an outline of the tips Conway provided:

- Drug payment will hold at average sales price (ASP) + 6% for 2016. However, this may not hold true for prescription drugs covered under the Medicare Part B program. CMS has announced plans to test a model with a lower add-on payment for Part B drugs, which is expected to roll out for testing by the end of the year.[1]
- Biosimilars could potentially lower cost of care for Medicare, and the margin of payment would stay the same for providers, Conway said.
    - Reimbursement would be ASP of biosimilar + 6% add-on of reference product.

"Oncologists need to be aware that nearly 700 cancer-related biosimilars could hit the market in the near future," Conway said, and there's no escaping this new therapeutic option. She did agree that the current barrier seems to be physician awareness about a biosimilar product and their confidence with replacing the reference molecule with the biosimilar.

- While reimbursement is fixed for radiation therapy, overall, the more complex radiation therapy modalities are seeing a modest increase, while the less complex are seeing slight cuts in payments.

Lindsay Conway, MSEd

- Reimbursement for lung cancer screening has begun in 2016. This follows the release of coding and billing instructions by CMS in November 2015. "This means hospitals and clinics can find it financially sustainable to offer lung cancer screening," Conway said.
- Hospital outpatient departments will be the testing grounds for new oncology-specific measures, Conway told the audience. This would fall under the umbrella of physician quality reporting system.
- Come 2017, patient surveys would be widespread. While CMS is yet to finalize its decision on which survey would be used, Consumer Assessment of Healthcare Providers and Systems or CAHPS survey is being considered in the cancer realm. The CAHPS survey is an 85-question tool that includes 5 main domains: effective communication, shared decision making, patient self-management, access, and technical communication.
- Medicare Access and CHIP Reauthorization Act (MACRA) and physician payment stability. Following repeal of the sustainable growth rate (SGR) patchwork formula, a 0.5% annual increase in physician payment is expected through 2019. MACRA, the SGR replacement, helps hardwire risk-based payments for providers via 2 tracks:
    - Merit-based incentive model system
    - Advanced alternate payment models (APM)

> **"Oncologists need to be aware that nearly 700 cancer-related biosimilars could hit the market in the near future."**
>
> —LINDSAY CONWAY, MSED

"CMS still has to iron out the details, such as performance categories, provider payment, interchange between the 2 tracks, APM participant qualification criteria, etc." added Conway.

She ended her review on a high note, speaking to CMS' decision to reimburse providers for the time they spend on advance-care planning (ACP) discussions with their patients. "CMS has said that all primary care physicians and advanced practitioners should be eligible for ACP conversations with their patients," Conway said. **EBO**

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Legislators Urge HHS and NIH to Intervene With the Price of Enzalutamide

SURABHI DANGI-GARIMELLA, PHD

Twelve members of the US Congress, including Democratic presidential candidate Bernie Sanders (I-VT) and Representative Elijah Cummings (D-MD), have signed a letter addressing HHS Secretary Sylvia Matthews Burwell, and director of the National Institutes of Health (NIH), Francis Collins, MD, PhD, calling on them to intervene with the current high price of the prostate cancer drug enzalutamide (Xtandi).[1]

Pointing out that high drug prices are access barriers, the letter states, "When Americans pay for research that results in a safe and effective drug, an unreasonably high cost should not limit their access to it." On this premise, the Congressmen are demanding a public hearing, citing the Bayh-Dole Act of 1980, which, the letter states, gives federal agencies like the NIH the authority to license a patent when the "action is necessary to alleviate health or safety needs which are not reasonably satisfied", or if the invention is not "available to the public on reasonable terms."

Enzalutamide was developed by Medivation, in collaboration with the Japanese company, Astellas Pharma. Initially approved in August 2012 by the FDA, for the treatment of patients with metastatic castration-resistant prostate cancer who have progressed on docetaxel, the drug subsequently received expanded approval for use in the pre-chemotherapy setting. Priced at $129,000 for the entire course in the United States, the drug is priced at almost one-third that cost in Japan and Sweden ($39,000) and at less than one-fourth the cost in Canada ($30,000).

In their letter, the lawmakers recommend that the government bodies hold a public hearing to openly discuss whether NIH and HHS can invoke their march-in rights to address excessive drug prices. According to Cornell University Law School, march-in rights allow the Federal agency that has funded a project, that resulted in an invention, to gain a nonexclusive, partially exclusive, or exclusive license for various reasons, including "To alleviate health or safety needs which are not reasonably satisfied." The drug, developed and patented by the University of California, Los Angeles (UCLA), was licensed to Medivation, in 2005. It was recently reported that UCLA will receive $1.14 billion in royalty rights to the drug.[2]

In a response to the letter, a spokesperson for Astellas told the Business Insider, "Xtandi is a standard of care for advanced prostate cancer in the United States and widely available as is evidenced by the 20,000 patients who received it in 2015. During 2015, 81% of privately insured patients paid $25 or less out of pocket per month for Xtandi, and 79% of Medicare patients paid nothing out of pocket per month for Xtandi. For eligible patients who do not have insurance or are underinsured, and have an annual adjusted household income of $100,000 or less, Astellas provides Xtandi, for free, under the Astellas Access Program; in 2015, over 2,000 men fighting advanced prostate cancer received Xtandi for free."[3] **EBO**

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NICE Reverses Stand on Abiraterone After Janssen Submits Additional Data

SURABHI DANGI-GARIMELLA, PHD

Based on the review of some additional data submitted by Janssen, the manufacturer of abiraterone (Zytiga), an appraisal committee from the National Institute for Health and Care Excellence (NICE) has finalized a guidance that recommends the drug for use in a subset of patients with prostate cancer, prior to chemotherapy.

Back in 2014, NICE refused the use of the drug at the early stage—following hormone deprivation therapy and prior to chemotherapy—citing insufficient evidence to prove value.[1] "We know how important it is for patients to have the option to delay chemotherapy and its associated side effects, so we are disappointed not to be able to recommend abiraterone for use in this way," Andrew Dillon, chief executive of NICE, had said in a statement, adding that data submitted by Janssen failed to prove abiraterone's cost effectiveness when administered to patients at that stage.

Subsequently, Janssen submitted supplementary evidence from a large group of patients treated with abiraterone in the United States, which showed that 14% of the patients were still taking abiraterone after 4.4 years. According to the press release by NICE, following a review of the new evidence, the appraisal committee agreed that it supported the case for some patients taking abiraterone for long periods of time, and justified the cost of £2300 for 120 tablets of the medication.[2]

Carole Longson, PhD, who heads the Centre for Heath Technology Evaluation at NICE, said in a statement, "I am very pleased that the new evidence submitted has meant we are able to recommend abiraterone. There are few treatments available for patients at this stage of prostate cancer, so this is very good news."

The final guidance recommends abiraterone as an option for treating hormone-relapsed prostate cancer in patients with mild to no symptoms, who have relapsed after androgen deprivation, and prior to initiating chemotherapy.[3] This provided Janssen grants a rebate on the cost of the drug after the 11th month (for patients who stay on treatment for more than 10 months) and till the end of treatment. The following are some of the features of the recommendation:

- Janssen is expected to reduce the list price of the drug from £2930 to £2300 for 120 tablets, in addition to agreeing on a complex patient access scheme with the Department of Health.
- The committee believes abiraterone trumps placebo in extending the time to progression and survival in this patient population.
- The committee agreed that £28,600 and £32,800 would be the ideal range for incremental cost effectiveness ratio per quality-adjusted life year, for abiraterone compared to the best supportive care.
- The committee recognized the value of delaying chemotherapy (and the associated side effects) in these patients, and a cost-effective use of the National Health Service's resources. **EBO**

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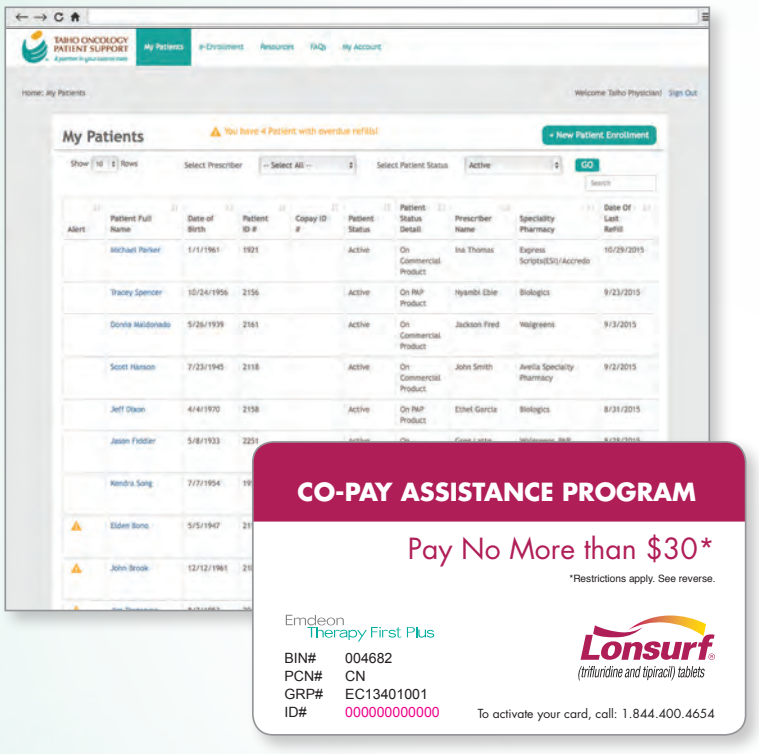

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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.

Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild type, an anti-EGFR therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see brief summary of Prescribing Information on the following pages.

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

Brief Summary of Prescribing Information
For complete Prescribing Information, consult official package insert.

1 INDICATIONS AND USAGE

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery resume LONSURF at a reduced dose. *[see Dosage and Administration (2.2) in the full Prescribing Information]*

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
Gastrointestinal disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders and administration site conditions				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)
† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treatment patients (2%) compared to no patients on placebo.

Additional Clinical Experience

Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

7 DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

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.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifuridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. *[*see *Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. *[*see *Nonclinical Toxicology (13.1) in the full Prescribing Information]*

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m^2 per day.

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[*see *Warnings and Precautions (5.1)]*

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[*see *Adverse Reactions (6.1)]*

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. *[*see *Dosage and Administration (2.1) in the full Prescribing Information]*

Advise the patient that anyone else who handles their medication should wear gloves. *[*see *References (15) in the full Prescribing Information]*

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[*see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3)]*

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. *[*see *Use in Specific Populations (8.2)]*

TAIHO ONCOLOGY, INC.

Hospital Stay Did Not Improve Survival Among Terminal Cancer Patients in Japan

SURABHI DANGI-GARIMELLA, PHD

Hospital stay, hospice, or home—does the choice of site for patients, at the end stage of their cancer, significantly affect survival and quality of life? According to a new study conducted in Japan, patients who chose to die at home had similar or even longer survival than those who chose to remain in a hospital.[1]

More than 2000 Japanese patients were included in this prospective study, conducted between September 2012 and April 2014, among Japanese cancer patients receiving palliative care in the hospital (n = 1582) or at home (n = 487). The primary outcome to be evaluated was the difference in survival between the 2 cohorts. While 1607 patients died in a hospital, 462 died at home. Importantly, survival among those who died at home was significantly longer than the survival of patients who died in the hospital, the authors report.

Among patients who had a survival prognosis of a few days, the estimated median survival for those who died at home was 13 days (95% CI, 10.3-15.7 days) while for those who died in the hospital, was 9 days (95% CI, 8.0-10.0 days; $P = .006$). In the group with a prognosis in weeks, those who died at home had a median survival of 36 days (95% CI, 29.9-42.1 days), significantly longer than 29 days for those who died in the hospital (95% CI, 26.5-31.5 days; $P = .007$). However, the difference plateaued out in the group that had an estimated survival in months.

"The cancer patient and family tend to be concerned that the quality of medical treatment provided at home will be inferior to that given in a hospital and that survival might be shortened," according to the study's lead author Jun Hamano, MD, from the Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba. He said in a news release that their findings should help ease the concerns of patients and their families, in terms of choosing the site of death for the patient. "Patients, families, and clinicians should be reassured that good home hospice care does not shorten patient life, and even may achieve longer survival," Hamano added.

Cost is also an important consideration in this discussion. The intensity of treatment provided to patients at the end of life can significantly increase healthcare costs. But this is improving, at least according to a recent study published in *JAMA*.[2] The study, comparing the utilization of healthcare services and end-of-life costs among developed countries, found that the United States has the lowest proportion of deaths in the hospital and the lowest number of days in the hospital in the last 6 months of life among 7 developed countries, including Belgium, Canada, England, Germany, the Netherlands, and Norway. This is a significant improvement compared with about 20 years back when more than one-fourth of Medicare's budget was devoted to the care of patients with terminal illness who died in the hospital. **EBO**

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Oncotype DX Test for Breast Cancer Finds Clinical Acceptance, but Disparity Exists

SURABHI DANGI-GARIMELLA, PHD

The 21-gene Recurrence Score assay, also known as the Oncotype DX Breast Cancer Assay, has been developed to predict disease recurrence and response to chemotherapy in estrogen receptor–positive, lymph node–negative early stage breast cancer (EBC). A retrospective research study has identified disparity in the use of this test, primarily driven by race, insurance status, and the type of facility where treatment was administered.

Researchers at the University of Colorado Cancer Center analyzed 143,032 records in the National Cancer Data Base of patients diagnosed with EBC between 2004 and 2012. "We meant this study as a kind of state of the union for the use of this test. What we found were some pretty stark disparities along socioeconomic and racial lines," said Jagar Jasem, MD, MPH, investigator at the CU Cancer Center and the study's lead author, in a statement.

According to the company website, this assay predicts chemotherapy benefit and the likelihood of distant breast cancer recurrence in those who have been diagnosed with an invasive form of the disease. It can also predict the risk of local recurrence in those who have the more common non-invasive form of breast cancer, ductal carcinoma in-situ or DCIS. A glimpse into the molecular make-up of the patient's tumor using this 21-gene assay has changed treatment decisions, according to Genomic Health, the test developer—a low Recurrence Score resulted in 33% of a study population to switch from hormonal therapy plus chemotherapy to hormonal therapy alone. This test can therefore protect those with low grade disease from the unnecessary adverse effects of chemotherapy, but can also ensure more aggressive treatment for those who really need it.

In the present study, the authors found that the assay was ordered in 54% of the study population, and it presented a very strong association with the recommendation for chemotherapy. Further, test use was strongly associated with younger age, white race, academic centers, private insurance, and pT2/pN0(i+) grade 2 to 3 disease. African American patients (adjusted odds ratio [AOR], 1.31; 95% CI, 1.20-1.43) and those treated at community facilities (AOR, 1.49; 95% CI, 1.35-1.63) were more likely to be treated outside of the National Comprehensive Cancer Network guidelines, the authors write. Further, younger African American patients were more likely to receive chemotherapy (AOR, 1.33; 95% CI, 1.16-1.54) despite a low Recurrence Score.

This shows that younger African American patients were, in fact, over-treated, and the African American patients, overall, were under-tested. "We show that doctors are absolutely using this test to decide who gets chemotherapy along with their treatment. In fact, of all the variables we explored, this test was most strongly associated with the chance that a patient goes on to receive chemotherapy. But, what we show is that the treatment of minority and low socioeconomic patients is more likely to be disconnected from these test results," explained Jasem. **EBO**

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Cancer Care Pathways: Hopes, Facts, and Concerns

(CONTINUED FROM COVER)

ABOUT THE AUTHOR

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succeed as a model for the delivery of high-value cancer care. But do they hold true?

As an increasing number of cancer care clinics are adopting CCPs, either voluntarily or as required by payers, an early look at pathways' performance becomes necessary to inform stakeholders whether the investments in CCPs have resulted in the expected returns and what efforts need to take place to optimize pathway development, if any.

Our goal here is to discuss the impact of adoption of CCPs on treatment variation, patient outcomes, and cancer care costs, based on published literature. This review focuses on commercially available CCPs (ie, computer-based treatment decision programs offered by vendors as part of oncology management programs) because most of the available literature pertains to this particular type of pathway. Several academic cancer centers have developed their own CCPs for internal use, including the University of Washington, Dana-Farber Cancer Institute, and University of Tennessee, to name a few.[11-13] A review of these programs is beyond the scope of this article, as very little published literature is available to inform their performance. Although this review is by no means comprehensive or exhaustive, it provides some insights about the promises and concerns regarding adoption of CCPs.

THE PROCESS OF DEVELOPING CANCER CARE PATHWAYS

To ensure an informed discussion of how CCPs impact outcomes, a brief explanation is in order to define CCPs and clarify the process by which pathways are developed. Pathways consist of complex electronic treatment decision support tools that provide evidence-based treatment recommendations to physicians at the point-of-care for individual patients. These tools are often integrated with electronic health records (EHRs) in a manner that allows managers to evaluate whether the treatments actually delivered were concordant or discordant with pathway recommendations. This information is relevant for monitoring pathway adherence. Pathways, in general, cover several cancers at all stages. With a primary focus on drug regimens, some CCP programs have also developed content for supportive care and radiation therapy.[10,14]

CCP programs typically apply a hierarchical order of criteria to select the treatments to be included in the pathways. The first criterion is treatment efficacy, wherein regimens of superior efficacy receive top priority for pathway inclusion. As a side note, the available literature does not clearly specify the disease endpoints used to measure efficacy (eg, overall vs progression-free survival, response rates, etc.). Toxicity is the next selection criterion applied to regimens of similar efficacy; those with lower toxicity and similar efficacy receive priority. Drug cost is the third and last selection criterion; pathways prioritize regimens of lower cost when efficacy and toxicity are similar.

Most [cancer care pathways] emanate from collaborative efforts involving physician network groups, healthcare payers, and oncology management–program consulting firms.

Most CCPs emanate from collaborative efforts involving physician network groups, healthcare payers, and oncology management–program consulting firms. Physicians elect disease-specific committees that appraise the current evidence and select the treatments for pathway inclusion. Leaders of several CCP programs have publically declared that the committees offer an opportunity to all physicians using the pathways to comment on the contents and participate in the process of pathway treatment selection.[10,14,15] The committees are also in charge of continuously updating pathway contents—as evidence becomes available—to support the use of novel therapies.

Once physician committees decide on the contents of a pathway, the oncology management programs integrate the treatments into the electronic supporting tools and offer technical assistance to network physicians using the pathways in daily practice. Oncology management programs also assist clinics in reporting pathway adherence to healthcare payers, and help monitor patient outcomes and costs. Payers offer financial incentives to maximize pathway adherence, usually in the form of higher fees for on-pathway drugs and by increasing the reimbursement for evaluation and management charges for adherent physicians.

CANCER CARE PATHWAYS AND TREATMENT VARIATION

The central hypothesis for CCP use is that adherence to pathways reduces costs and maintains quality of care by curtailing the use of unnecessary and costly oncologic treatments. Surprisingly, there is very scant published evidence to support or reject this hypothesis. After a short PubMed literature search, I could only retrieve 1 article reporting on the impact of the Cardinal Health Specialty Solutions (formerly, P4 Healthcare) pathway on treatment variations. The study compared the number of chemotherapy regimens used for breast, lung, and colorectal cancers in the year preceding and the year following pathway implementation, in several practices located in Michigan.[10]

Physicians used 168 and 136 distinct regimens in the years pre- and post-pathways implementation, respectively, which represents an 8% absolute reduction in treatment variation (**TABLE**). Interestingly, 10% of the study population accounted for 81% of the reduction in the number of drug regimens used, suggesting that a minority of patients drive most of the treatment variation, perhaps because of higher disease complexity. Although this single report does not provide any firm conclusions about the effects of pathways on treatment variation, the reduction in the number of chemotherapy regimens used was quite modest. An important point to note is that the report does not provide any information on the cost of the chemotherapy regimens avoided to establish a causal relationship between reductions in treatment variation and costs.

CANCER CARE PATHWAYS AND PATIENT OUTCOMES

At least 1 report indicates that adherence to CCPs reduces the number of emergency department (ED) visits and hospital admissions for treatment-related complications (**TABLE**). Kreys et al evaluated the effect of adherence to the Cardinal Health Specialty Solutions supportive care pathways on ED visits and hospitalizations for neutropenia, anemia, and chemotherapy-induced nausea and vomiting in patients with breast, lung, and colorectal cancers. Compared with patients who received off-pathway supportive care, pathway adherence was associated with a 15% absolute reduction in ED visits and hospitalizations for neutropenia (adjusted odds-ratio, 0.42; 95% CI, 0.30-0.58).[16] The study demonstrated no clinically or statistically significant differences in admissions for anemia or chemotherapy-induced nausea and vomiting. Pathway adherence was associated with lower expenditures for hospitalizations to manage neutropenia and anemia, and with lower expenditures related to the use of granulocyte colony–stimulating factors and antiemetics.

Current evidence suggests that adherence to CCPs results in either a neutral or favorable effect on survival outcomes, depending on the disease and treatment setting (adjuvant vs metastatic) (**TABLE**). Using EHR and pathway reporting data, Neubauer et al conducted a cost-effectiveness analysis of adherence to Level I Pathways among 1409 patients with non-small cell lung cancer (NSCLC) treated at several US Oncology network clinics. After adjusting for patient characteristics and line of therapy, the study showed no statistically significant difference in 1-year overall survival (OS) (HR, 0.95; 95% CI, 0.77-1.16) between patients treated on- versus off-pathway.[17] Hoverman et al also utilized EHR and claims data to compare disease-free survival (DFS) and OS in patients treated on versus off Level I Pathways with adjuvant and palliative chemotherapy for stage III and IV colorectal cancer, respectively.[15] Pathway adherence was associated with a

substantial increase in DFS (HR, 4.98; 95% CI, 2.11-11.74 for non-adherence) in the adjuvant setting and prolongation of OS (HR, 1.57; 95% CI, 1.04-2.39 for non-adherence) in the metastatic setting, respectively.

CANCER CARE PATHWAYS AND DIRECT MEDICAL COSTS

Cost is perhaps the outcome measure for which the evidence is most robust to support the use of CCPs. At least 3 economic evaluations suggest that adherence to CCPs reduces direct medical costs (**TABLE**). The cost-effectiveness analysis of adherence to Level I Pathways for NSCLC found that total mean direct medical costs were 35% lower in patients treated on- versus off-pathway ($18,042 vs $27,737 per patient), suggesting that pathway adherence saves costs in this disease setting.[17] The study by Hoverman et al showed mean reductions in total direct medical costs of $52,641 and $60,163 associated with adherence to Level I Pathways for adjuvant and metastatic treatment of colorectal cancer, respectively.[15] Chemotherapy costs accounted for most of the cost reductions in this study.

In a time series study that compared 57 practices that participated in the Cardinal Health Specialty Solutions pathway with 43 non-participant practices, pathway participation was associated with an aggregate $8.5 million in cost savings 1 year after pathway implementation, the majority of the savings being related to drug expenditures.[18] In a study of the same pathway implemented in different hospitals, drug expenditures did not differ before and after pathway implementation, although mean hospitalization costs were reduced by $1400 per patient.[19]

Collectively, these studies provide preliminary evidence that high adherence to CCPs can improve patient outcomes and reduce costs. The effect of pathways on treatment variation remains unclear, however. The results seem to vary considerably across hospital, disease, and treatment settings. Although the analyses show a consistent favorable impact of CCP adherence on total costs, the evaluations provide conflicting data as to the components of care responsible for the cost savings (ie, chemotherapy use, hospitalization, or supportive care).

TABLE. Examples of Cancer Care Pathway Programs and Their Impact on Practice and Outcomes

PATHWAY PROGRAM	DESCRIPTION	IMPACT ON PRACTICE OR OUTCOMES
Cardinal Health Specialty Solutions (formerly, P4 Healthcare)	Physician-led set of systemic therapy and supportive care recommendations for breast, lung, and colon cancers. Available via a Web portal for use at the point of care.	• 8% absolute reduction in the number of chemotherapy regimens used.[10] • 15% absolute reduction in the number of ED/hospitalizations for neutropenia associated with pathway adherence.[16] • Aggregate cost savings of $8.5 million for the first year in 57 practices.[18]
Level I Pathways	Physician-led set of recommendations of chemotherapy regimens, radiation, and supportive care for multiple cancers; integrated to iKnowMed EHR; managed by McKesson Specialty Care Solutions.	• 35% absolute reduction in 1-year direct medical costs in patients treated on vs off-pathway for NSCLC; no differences in OS.[17] • Longer DFS and OS for patients with CRC treated on- vs off-pathway in the adjuvant and metastatic settings, respectively.[15,a] • $52,600 and $60,200 reductions in mean total direct medical costs for patients with CRC treated on- vs off-pathway in the adjuvant and metastatic settings, respectively.[15]
Via Pathways	Interactive software tool integrated to EHRs that provides treatment recommendations based on disease stage and state; covers 90% of oncologic presentations; initially developed at UPMC and now managed by Via Oncology.	• Pathway adherence rates of 70% to 86% for 5 common cancers.[14,b]

CRC indicates colorectal cancer; DFS, disease-free survival; ED, emergency department; EHR, electronic health record; NSCLC, non-small cell lung cancer; OS, overall survival; UPMC, University of Pittsburg Medical Center.
[a]Median DFS of 26.9 months versus not reached (P <.05) for patients treated off- vs on-pathway in the adjuvant setting, respectively. Median OS of 20.1 versus 26.9 months (P = .03) for patients treated off- vs on-pathway, respectively.
[b]Breast, non-small cell lung, colorectal, lymphoma, and prostate cancers.

AREAS OF UNCERTAINTY AND CONCERNS

These published studies contain several limitations that preclude an accurate estimate of the impact of CCPs on patient outcomes and costs. All study designs are observational and subject to selection bias—patients treated off-pathway may systematically differ from patients treated on-pathway with respect to characteristics that affect outcomes. Pre- and post-type of study designs do not account for changes in practice that occur over time, particularly the introduction of new expensive drugs in the market. This limitation may lead to an underestimate of any cost savings generated by adherence to CCPs. Ascertainment bias may also prevent accurate comparisons, as the availability of clinical data may differ between patients treated on- and off-pathways, respectively. Virtually no data inform about pathway adherence and its impact on patient outcomes for less common malignancies, although some programs intend to gradually cover additional cancers.[14] Finally, no studies have evaluated how CCPs affect other important patient-reported outcomes (PROs), such as quality of life, symptoms, and satisfaction with care.

The oncology community has also voiced concerns about potential detrimental effects of pathway adoption on patient care and clinic workflow. The American Society of Clinical Oncology recently released a statement that outlines some of these concerns.[20] Many oncology clinics are experiencing an excessive administrative burden imposed by payers that require frequent reporting of pathway adherence. This burden is particularly disruptive for clinics that have to report adherence to multiple pathways for the same disease because each payer requires the use of its own preferred pathway. Some oncologists and patient advocates worry that the process of pathway development is not as transparent as the leadership of CCPs claim it to be. Other concerns include a possible negative impact of pathway adoption on the patient–physician relationship if adherence forces physicians to significantly narrow treatment options, as well as a detrimental effect on the outcomes of patients treated off-pathways if pre-authorizations or other excessive administrative hurdles prevent timely initiation of therapy.

FUTURE DIRECTIONS

Physician adherence is critical for the successful implementation of CCPs, which implies that efforts to develop CCPs should include all physicians affected by them. Physicians need to have their voices heard in order to feel comfortable with using pathways in their daily routine.

Ideally, randomized controlled trials would provide more robust evidence on the effectiveness and economic impact of CCPs. In reality, such trials are difficult to conduct and unlikely to ever materialize because many clinics could not agree with randomization to either the intervention (pathway) or control (no pathway) arms. The oncology community will likely have to rely on the synthesis of the evidence generated by observational studies to develop a better understanding of how pathways affect variation in care, costs, and outcomes. Future investigations should focus on risk-adjusted comparisons between practices that participate in pathways versus practices that decide not to do so. Although still imperfect, this type of comparison is probably less subject to selection bias than studies that measure pathway effectiveness based on adherence.

If CCPs are to become a sustainable model of care delivery, the administrative burden of managing them has to be minimal. Payers cannot realistically expect that oncology clinics will be able to report adherence to multiple pathways for the same cancer, and even less so for different cancers, only because payers elect to use a particular pathway of their choice.

If [cancer care pathways] are to become a sustainable model of care delivery, the administrative burden of managing them has to be minimal.

A much more rational approach is to leave the choice of pathway to the oncology clinics and let the clinics manage 1 pathway for each cancer type.

Finally, the development of CCPs should include more than recommendations for drug regimens, in order to maximize the benefits of pathway use. Pathway recommendations need to cover the entire spectrum of cancer management—from early detection to end-of-life care. In doing so, pathway programs will have to face the challenge of incorporating the applications of precision oncology, including the many recommendations for biomarker-guided use of target therapies.

Although survival and hospitalizations are important metrics, PROs should become an additional outcome measure of pathway effectiveness.

In summary, preliminary evidence indicates that adherence to CCPs favorably impacts some patient outcomes and direct medical costs. The oncology community has a great opportunity to improve value in cancer care by engaging all stakeholders in transparent processes of pathway development. In order to ensure that pathways become a sustainable model of delivery of high-value cancer care, the administrative burden to oncology clinics needs to be minimal. **EBO**

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PANEL DISCUSSION

Are Oncology Clinical Pathways a Value Framework in the Making?

(CONTINUED FROM COVER)

based choices that oncologists are faced with on a daily basis, although he said they may not be as comprehensive as the guidelines developed by the National Comprehensive Cancer Network. "I think our focus, at least with the pathways that we're doing with AIM Specialty Health and Anthem, is on drug regimen treatment choices," said Fisch, where the emphasis is on efficacy and safety, with cost considered only when the first 2 features overlap for the treatments being compared.

Via Oncology takes a slightly different approach, according to Lokay, but that's only because of their customer base, she pointed out: cancer centers that are open to a more specific, case-by-case method. According to Lokay, the pathway development committee leans toward a more stratified pathway driven by a specific case presentation. In her opinion, care pathways extend beyond medical oncology and can be mirrored in all aspects of cancer care, including radiation oncology and symptom management, as long as the highest standards of evidence are used.

"If you want to be a purist, in my way of thinking about it, the element that's unique about pathways is a longitudinal characteristic," said Dubois, unlike guidelines that work off of a single node. The practicing oncologist in the group, Polite considers pathways a clinical decision tool that ensures care providers avoid unnecessary variability in care while also being armed with necessary flexibility. "This is a way to ensure some consistency in how we see patients, such that if a patient comes into my office or comes into one of my satellite's offices with the same diagnosis, they're not being treated in several different ways," he said. "It's not whose door [patients] choose to open on that day and what appointment they get, but much more a consensus-driven opinion by experts using evidence-based medicine."

AIM Specialty Health and Via Oncology have somewhat distinct approaches to their pathway development process, in terms of the evidence used. AIM uses published clinical data, updated in a quarterly fashion, which is then implemented based on the specific cancer type, and the outcome being evaluated (progression-free survival, overall survival, response rate, etc) may vary, according to Fisch. He added that safety and quality-of-life outcomes are also curated in the pathway development process, along with costs.

Via Oncology, on the other hand, defragments individual

case presentations to identify the subpopulations of patients for which a specific treatment can be defined. Then, this is corroborated with published literature and included as a pathway recommendation, Lokay said. Their committee also considers alternate scenarios for patients that might warrant a different approach, although she agreed with Fisch in that efficacy, toxicity, and cost are considered, in that order, when comparing treatments. "So for us, really if we look across all the end branches, the primary end branches of our medical oncology pathways at least, the cost decision really only comes into account about 5% of the time."

Dubois referenced a recent analysis that was published by the National Pharmaceutical Council (NPC) in *The American Journal of Managed Care* that stemmed out of a survey conducted by NPC among the various stakeholders—developers to end users.[1] "What we found was extremely variable approaches to both the development and the implementation of the pathway," said Dubois. As of yet, there are no stringent guidelines for developing these pathways, he added, saying that the variability is multifactorial and may lend itself in the form of evidence used, outcomes evaluated, or whether expert assessment versus consensus is used. Dubois believes there needs to be more consideration for heterogeneity of patient response, and the granularity of guidance should be driven by the extent of compliance that is expected.

Polite responded, saying that from a policy standpoint, clinical pathways—whether used to ensure quality or for preauthorization—"should have some sort of deeming process where we essentially bless pathways and say if you're using a blessed pathway, then that pathway should be considered by all payers." This process would also blend with healthcare's movement to value-based pricing. Polite, however, does not believe that clinical pathways have matured enough to be a useful tool for a shared decision-making process. Fisch and Lokay agreed that pathways are a general guide and that the final decision should be made by the physician in discussions with the patient.

When queried on the increased administrative burden of pathways, Polite said, "Well, there's no question it can be a very clunky process as you start a pathway." However, some pathways, like the ones used by practices within the US Oncology network, have been around long enough that they are a part of the clinic's regular workflow. When used as a standalone, pathways can add to the administrative burden, Polite said, but he expects this will improve with time.

"If we're facing a situation where I have to use a different pathway based on whether my patient is a Blue Cross patient or an Aetna patient or Medicare Advantage patient, and each one of those has a different order set and different priority, that is going to create significant frustration and blowback from the oncology community," said Polite, adding that the field is moving in the direction of a consensus for which payers, the pharmaceutical industry, and providers all need to lend an equal voice.

ENCOURAGING OFF-PATHWAY REGIMENS

Doctors are concerned that they would be penalized for wavering from the recommended treatment regimen, based on patient response or if they want to include a new and innovative treatment. Lokay explained that 100% pathway adherence is never the goal. "Really what you're doing is you're saying 'Can we really develop pathways to address about 80% of the patients within a given disease?' There's always the ability to go off-pathway."

According to Lokay, the pathway program developed by Via Oncology offers physicians the option to explain why they chose to go off-pathway and to document the alternative treatment being used. Lokay said that newer therapies are included in the bucket of therapies that can be used if a physician decides to go off-pathway. Depending on the impact of the new treatment, the decision committee could either meet immediately or discusses the inclusion of the new treatment at its quarterly meeting. "Ultimately, everything comes back to that shared decision making between the physician and the patient," added Lokay. "The pathway should never drive an inappropriate decision."

Fisch agreed with Lokay on the need for flexibility in pathways, especially in the scenario that a uniform set of pathways could be used across health plans to allow nimbleness to the process as new evidence builds. He said that clinical pathways will never be exhaustive because they are built "to make adjustments in real time."

CREATING A LEARNING HEALTHCARE SYSTEM

Can the standardized, evidence-based regimens proposed by care pathways provide assurance of high-value care? According to Polite, the definition of the term "value" is muddled at best. Technically, value is a ratio of efficacy and cost, and he believes pathways prevent oncologists from being penalized for offering the optimal treatment to their patients. Citing biomarker-driven treatment as an example, Polite said that if oncologists use anaplastic lymphoma kinase (ALK) expression or programmed cell death protein 1 (PD-1) expression to decide that their patient should be treated with an ALK inhibitor or a PD-1 inhibitor, respectively, being on- or off-pathway becomes a moot point.

On the other hand, pathways stop physicians from repeatedly administering expensive treatments that are less efficacious, he said. "There may be one or two patients that you decide that's appropriate for, but if that becomes your pattern of care, that's not going to be acceptable."

Dubois agreed, but emphasized that clinical trial data—the evidence most commonly used to develop pathways—are a snapshot in time, which contradicts the longitudinal nature of pathways. Collecting evidence to support the continual impact of following a pathway to treat a patient would require quality measures that out healthcare system currently lacks, according to Dubois.

Lokay argued that clinical pathways are embedded with quality checks—from the tests to be ordered to the drugs to be used based on mutational analysis. She believes that empirical evidence is built into the pathways. When Dubois argued that these are actually process measures and do not provide a window into patient performance and effectiveness of a treatment, Fisch responded that there is opportunity to gather evidence over time. He reasoned that one can collect patient performance data over time from clinical trials and by following clinical guidelines as well as Choosing Wisely recommendations. Additionally, hospitalization data, other outcomes data, cost of care data that assimilate over time can be fed back to modify the pathways, resulting in a learning healthcare system, Fisch said. Polite pointed out that it is often missed that pathways provide granularity to data collection that would otherwise be impossible to assemble with claims data, such as the pathological detail, performance status, or biomarker expression.

CHALLENGES WITH ADOPTION

Is it harder to implement pathways in a small community center versus in a bigger place, like an academic cancer center? According to Polite, who works in an academic hospital setting, a bigger cancer center might witness more resistance from physicians. "The struggle that you have at an academic medical center is that the people who are treating these cancers are all justifiably experts in their field," said Polite, and they can have strong clinical opinions, making it difficult to drive consensus. So the approach devised by several cancer centers is to be flexible and to involve the experts at the institute in pathway creation, in tandem with the pathway vendor, he explained. "I think it's about having a process, like at Via Oncology, where people can be at the table and express their opinions on why they think things should be done differently."

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> **"This is a way to ensure some consistency in how we see patients, such that if a patient comes into my office or comes into one of my satellite's offices with the same diagnosis, they're not being treated in several different ways."**
>
> —BLASE N. POLITE, MD, MPP

Fisch would like to see academic centers break their mold and focus on ways to distinguish themselves beyond having the most renowned experts on the roster. He said they need to highlight their unique research environment, which creates a melting pot of diverse medical experts such as in surgery and pathology. These centers would gain from emphasizing the extent of communication and patient-centered care that they provide and the various resources that are coalesced to improve patient outcomes, Fisch said.

PATIENT AWARENESS ON CLINICAL PATHWAYS

Dubois highlighted another important and interesting finding from their survey, which was the level of transparency for the patients being treated on pathways.[1] The survey found that patients are not necessarily aware that doctors are making treatment recommendations based on pathways. "I think what is probably the least transparent are the financial incentives to pathway compliance and whether the patients are aware of that," Dubois noted. He believes that patients should be told if their treatment follows a predetermined pathway, and they should also be made aware of financial incentives that may be associated with adherence to pathways.

Polite, however, did not agree. He said that he does not share this information with his patients and has not thought of doing so in his clinic. "If you want to start [sharing this information], then it comes down to [us] telling our patients about our compensation packages, our productivity packages, how much money we get for enrolling patients in clinical trials," Polite said.

Fisch pointed out the minimal understanding and concern that patients and physicians often have with the cost of cancer care. He cited the example of clinical fellows making treatment choices without any knowledge on how much the regimen costs. "There are dozens of choices that are evidence-based, and the fellow makes a recommendation and I ask—that's perfectly acceptable—'How much do you think 12 weeks of that therapy costs? The fellow has not even a point estimate." Physicians are also quite unaware of their patients' insurance plan and their liability.

Fisch doesn't believe transparency is a problem with clinical pathways. "AIM or Anthem pathways are completely transparent—what they are, what the nature of the program is—and we encourage doctors to talk to patients about it and for patients and families to understand it," he said. Fisch believes it is important to educate patients and their families on which pathway choices can be optimal based on efficacy, safety, and cost.

When asked to comment on the incorporation of palliative care in pathways, Fisch said that the pathways approach can extend beyond just drug regimens to other realms as well. With widespread acknowledgement of the benefits of palliative care to patient outcomes, he thinks principles of palliative care will soon be included on pathways to promote value and quality care.

"I don't think there's any one right answer," said Lokay. "We've tried a number of things, using the software decision support tool, to ask physicians to document the treatment intent and whether it was discussed with the patient as a proxy for encouraging those discussions," she said. Via Oncology, Lokay said, has struggled to figure out the right pieces to incorporate in pathways that would make an impact on palliative care in oncology.

Polite believes that although the oncology community has lagged in providing better options to patients for palliative care, pathways could force a more formal process for "thinking through some of the issues that perhaps either we don't think about or maybe sometimes don't want to think about." He believes that pathways will have a very important role to play as healthcare increasingly moves toward alternate payment models. Polite is personally against the bundled payment models. He argues that oncologists are not responsible for the launch price of drugs and should not be penalized for using these high-priced drugs if they are using them appropriately. "I think [pathways] have a lot of ability to help us in new payment worlds," he said.

Agreeing with Polite, Lokay said that helping individuals understand that they do not necessarily have to take risks with the way they use drugs and treatments is important. "Maybe pathways are a better way to control utilization, and they don't really put the physician and the patient in the middle when costs go up."

Fisch emphasized that pathways are a value framework, in a sense, because they summarize clinical evidence while weighing in costs and outcomes. He added that despite the differences in specific choices, there is enough concordance between pathways created by different pathway developers, considering that the pool of clinical evidence is the same. While pathways will continue to evolve with the accumulation of longitudinal data, "there's widespread acceptance of the specific choices that are involved in the pathways because they're familiar and evidence-based," Fisch said.

Dubois believes clinical pathways is a relatively young field that requires improvements in multiple aspects. In addition to gathering more long-term data, outcome measures that ensure patient performance are necessary, he said. "As we progress [in this field], we need to compare different sites that are using pathways or not, patients that are on the pathways or not. Making certain that patient outcomes are the way they need to be. If they're not, then we revise the pathways and move forward accordingly." **EBO**

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> **"AIM or Anthem pathways are completely transparent—what they are, what the nature of the program is—and we encourage doctors to talk to patients about it and for patients and families to understand it."**
>
> —MICHAEL FISCH, MD, MPH

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Recommendations for the Role of Clinical Pathways in an Era of Personalized Medicine

(CONTINUED FROM COVER)

on the health system. Compounding the problem, the process, by which some clinical pathways are developed, is not transparent—providers and patients may not know why certain treatments are covered, what evidence was considered when creating pathway protocols, and whether their physician has a financial incentive to prescribe specific drugs.

We offer recommendations, in the following areas, in an effort to establish a set of normative criteria for the development and design of pathways that creates trust and transparency: the fundamental elements of a clinical pathway, the necessary transparency standards for their development, and the steps needed to ensure patients receive the best care in a shared decision-making context that reflects their physician's clinical judgment.

WHAT ARE THE COMMON CHARACTERISTICS OF A PATHWAY?

Ideally, clinical pathways should consist of a structured, multidisciplinary plan that details essential steps to improve continuity and coordination in the care of specific patients, and should span areas like diagnostics, surgery, nutrition, medications, and discharge planning.[3] However, pathway programs in medical oncology often place a greater emphasis or focus on drug selection.

In 2010, a team of Cochrane Review authors identified at least 5 characteristics (**TABLE**) that define a clinical pathway from the literature that has subsequently been recognized as "a standardized, internationally accepted definition of a clinical pathway."[3] Clinical pathways are often developed and defined at the local or institutional level by the providers who are expected to implement them.[4] This approach takes into account variations in the ways providers practice medicine within their local ecosystem to ensure that the needs of their patients are met.[4] Some clinical pathways, however, are intended to standardize treatment protocols at a national, state, or regional scale to further reduce variations in the delivery of evidence-based care across sites, particularly in the absence of scientific merit for local variability in treatment regimens.[5]

NOT ALL PATHWAYS ARE CREATED EQUAL

The healthcare community's reaction to pathways has been mixed, particularly on the part of medical oncologists.[4] Some resist it as a "cookie-cutter" approach that can interfere with personalizing a care plan to the individual.[4] Others support it as an important tool for reducing errors and costs while increasing efficiency based on the best available evidence.[6]

A pathway program that is meant to drive coverage decisions for an individual patient treatment will operate differently from one that seeks to create quality at an aggregate level while maintaining flexibility and clinical judgment at the individual treatment level. The methods, by which the pathway is developed, and the preferred concepts on which it is based, are likely to differ when the program is driven by a group of providers as opposed to a payer.

Payers have a financial interest to place greater emphasis on cost control and pathway compliance in lieu of clinical judgment, than typically found in provider-sponsored pathways and guidelines. There exists a concerted and growing effort on the part of some health plans to either standardize pathways or create their own.[7,8]

Pathways can be designed as a comprehensive decision support tool that enables treating physicians to navigate their patients through various healthcare decisions—including clinical trials—based on different safety and effectiveness profiles, as well as cost considerations.[2,6,9,10] On the other hand, a clinical pathway may serve to limit the need for clinical judgment and customization through rigid standardization based on the "average" patient. Some pathways, for example, consist solely of a pre-determined "checklist" of drug regimens from which the prescribing physician is financially incentivized to select for nearly all patients.[8] Such a limited approach to a pathway more closely resembles common utilization management techniques like step therapy or "fail first" requirements that payers apply to regulate patient access to medications in an effort to control cost. Cost containment should not be the central organizing principle for clinical pathways.

PATIENT ACCESS AND TRANSPARENCY

Some healthcare providers have expressed concern with the potential dilemma that might arise when the pressure to follow a payer's limited set of predetermined pathway options conflicts with the provider's clinical judgment about the best treatment option based on the individual's unique circumstances.[11] When providers elect to administer therapies that diverge from a payer's clinical pathway, the latter is likely to deny coverage or require prior authorization and take time to review the provider's chosen course of treatment regimen. Not only can such delays in physician-recommended treatment threaten patient health and impose unnecessary costs on the system, they also waste providers' time, effort, and resources.

Patients place a sense of trust and mutual respect with their physician. This relationship must be protected from attempts to influence the physician's treatment recommendations in the form of kickback arrangements to the practice by those who stand to benefit financially from the decision. Thus, there exists a growing concern among some physicians and patient advocacy groups regarding the use of payer-designed clinical pathways designed that include payments to physicians to induce the use of a narrow list of "on-pathway" therapies preselected by the payer.[11] Such pay-to-prescribe incentives might short circuit the shared decision-making process and limit patient access to viable treatment options that are "off-pathway."

We recommend that, at the very least, patients should have the right to know when their physician is participating in such a program. Patients need to be aware, not just of how options on pathways were chosen, but also of what other alternatives are viable, according to guidelines, that may not be listed in the pathway. Patients can then have an honest consultation with their physician about the various risks, benefits, and costs associated with each viable option. If reasonable clinical evidence exists to support one drug treatment regimen over others, based on what is going to provide the best approach for the patient, then healthcare professionals should be trusted to follow the evidence without an extra financial inducement to do so.

PROVIDERS SHOULD BE PATHWAY LEADERS

Pathway development should be owned and led by physician scientists and other members of the care team and/or the professional societies that represent them with specific expertise in the clinical area covered by the pathway. Clear mechanisms should exist for involving patient advocates throughout the pathway development process.

Pathways should be evaluated against their ability to meet transparency standards such as those contained in the **TABLE**, that are consistent with those used by groups like the National Comprehensive Cancer Network, when developing clinical guidelines.

The providers who must live by the pathways are in the best position to determine how to translate guidelines into their institutional structures.[12] Local design and control also helps prevent pressure to have multiple pathways from different

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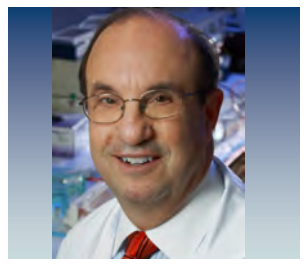

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TABLE. Guidelines for Clinical Pathway Design and Development

Fundamental elements of a clinical pathway from Cochrane Review	1. Delineates a structured and multidisciplinary plan of care that spans multiple categories of care. 2. Translates guidelines or evidence into local structures. 3. Details the steps in a course of care or treatment in a plan, pathway, algorithm, guideline, protocol or other inventory of actions. 4. Includes time frames of criteria-based progression. 5. Standardizes care in a specific population for a specific clinical subject for a specific clinical problem, procedure, or episode of care.
Transparency standards for clinical pathways development	1. Process used to develop pathways is disclosed and replicable, including the criteria applied for evidence selection. 2. Participants involved in the pathway development process are disclosed. 3. The development and review process involves representatives for all relevant stakeholders with experience in the clinical area covered by the pathway, including patients. 4. Adherence to an established conflict of interest policy. 5. Pathway content, and the evidence on which it is based, should be reviewed and updated on a continuing basis.
General clinical pathway recommendations	1. Pathways should support shared decision making and be process-driven to allow patients to express their preferences for how to individualize their care, leading to a personalized treatment plan that accounts for differences in the clinical and biological characteristics of individual disease processes. 2. Include discussion and consideration of clinical trial options as a required pathway element. 3. Pathways should be developed by physician scientists and/or the professional societies that represent them, with expertise in the clinical area covered by the pathway, and have clear mechanisms for involving patient advocates throughout the pathway development process. 4. Pathways should focus on improving patient health outcomes and quality, and should provide feedback and measurement components to ensure that they are improving quality of care. 5. Efficacy and safety should be the main considerations in the design of clinical pathways. This can be achieved by focusing on clinical effectiveness and toxicity data, as the primary variables, while incorporating relevant personalized/precision determinants of effectiveness. 6. Pathways should not use cost as a factor to limit the initial set of choices in the pathway, but instead should enable patients and their providers to consider cost information when selecting the best available option based on clinical evidence.

sources deployed in the same provider ecosystem. Competing pathways within the same practice could lead to variability and inconsistency in the patient care experience, which are exactly the types of issues pathways are intended to reduce. For example, if multiple payers were to create different clinical pathways, then different patients with the same disease in the same hospital system might receive different care experiences based on their payer's pathway.[12]

CONCLUSION

Pathway protocols should support shared decision making and patient preferences that lead to a personalized treatment plan that accounts for differences in the clinical and biological characteristics of individual disease processes. Discussion and consideration of clinical trial options should be a required pathway element. Efficacy and safety should be the main considerations in pathway design, while incorporating relevant personalized/precision determinants. The pathway process can navigate patients and providers through a cost discussion when selecting from among viable treatment options, and pathway programs should be measured against their ability to improve patient health outcomes and quality. Ultimately, clinical pathways should be a tool for optimizing treatment protocols by personalizing them for each patient in accordance with their physician's clinical judgment. Isn't that, after all, what medicine is all about? **EBO**

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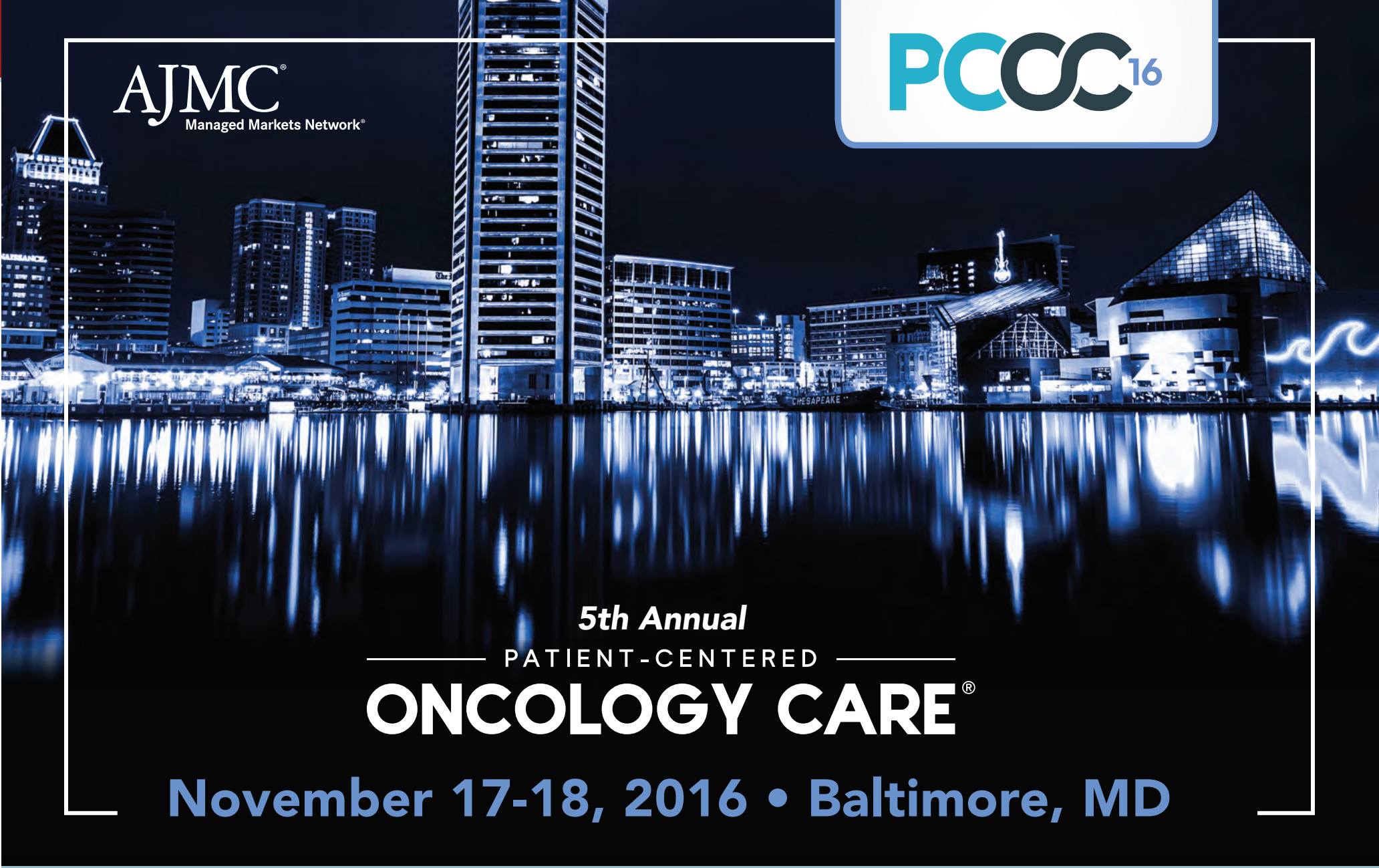

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