Bridging the gap among payer, provider, and patient perspectives

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Evidence-Based Oncology

SPECIAL ISSUE: QUALITY METRICS

Health IT Platform

CancerLinQ—ASCO's Rapid Learning System to Improve Quality and Personalize Insights

ROBERT S. MILLER, MD, FACP, FASCO

The promotion of the highest quality cancer care has long been foundational to the mission of the American Society of Clinical Oncology (ASCO). To make this vision a reality, ASCO has been building a big data, health information technology (HIT) platform called CancerLinQ (**C**ancer **L**earning **I**ntelligence **N**etwork for **Q**uality), based on principles articulated by the Institute of Medicine (IOM) and others. (The division of the National Academies of Sciences, Engineering, and Medicine that focuses on health and medicine was renamed the Health and Medicine Division, from the Institute of Medicine, in 2016).

CancerLinQ extracts data from electronic health records (EHRs) and other sources, and using transformational data analytics, generates knowledge that can be accessed by oncologists, researchers, and patients. CancerLinQ's primary objectives are to provide real-time quality feedback to oncologists to enable them to measure the care they render against clinical guidelines and that of their peers, to deliver personalized insights at the point of care, and to accelerate the generation of new research hypotheses by uncovering patterns in patient and tumor characteristics, therapies, and outcomes that require massive data sets and real-world evidence.

(continued on **SP308**)

Measuring PROs

Partnering With Patients to Rapidly Develop a Quality-of-Life Measure in Mycosis Fungoides/Sézary Syndrome Type Cutaneous T-cell Lymphoma

PAUL WICKS, PHD; MARJAN SEPASSI, PHARMD; GAURAV SHARMA, PHARMD; AND MARGOT CARLSON DELOGNE

INTRODUCTION

Mycosis fungoides and its leukemic variant Sézary syndrome (MF/SS) are the most common forms of cutaneous T-cell lymphoma (CTCL), a class of non-Hodgkin's lymphoma.[1] Approximately 3000 new cases of this rare disease are reported in the United States every year.[1] Although CTCL typically affects older adults (median age at diagnosis: 55 to 60 years[2]) around 7% of cases are diagnosed before age 30.[3] CTCL also affects more males than females (male to female ratio is approximately 1.6:1) and is more prevalent within the black population (black-to-white ratio is approximately 1.3:1) although both these trends have been stabilizing relative to historic norms.[4]

Measuring the impact of MF/SS CTCL experience for research purposes, or even clinical management with a healthcare provider, is made more challenging by the absence of disease-specific validated measures.[5] Clinicians currently use patient-reported outcome (PRO) tools such as the Itchy-QOL,[6] DLQI,[7] Skindex-29,[8] VAS itch, or cancer PROs such as the EORTC family of tools[9] or the FACT-G.[10] In order to capture quality-of-life (QoL) informa-

(continued on **SP310**)

Physician Perspective

So Many Metrics, Yet So Little Known About Quality and Value in Cancer Care

JOSEPH ALVARNAS, MD

We are in the midst of a volatile period of time in which healthcare processes, patterns of utilization, cost, care delivery, and outcomes are increasingly metricized. This headlong rush toward greater metrification of care delivery, including cancer care, accelerated following passage of the Affordable Care Act (ACA) in 2010. An important strategic goal of the ACA was that of linking payment to measures of performance and effectiveness, rather than making payments based simply upon volume.[1] In 2015, HHS Secretary Sylvia Burwell wrote in the *New England Journal of Medicine* that an important goal of CMS was that, "85% of Medicare fee-for-service payments should be tied to quality or value by 2016."[2]

Beyond CMS, many cancer care stakeholders are heavily invested in the goal of more effectively aligning payment with care quality and value delivery. Although quality metrics are viewed as important tools for ensuring greater care efficiency and improving the financial sustainability of our care systems, they are also seen as an objective and transparent means for ensuring that patients receive better, more effective, and more patient-centered care.[3] Toward this end, numerous organizations have proposed, endorsed, and reported performance based upon defined quality measures. These metrics stewards include the National Quality Forum,[4] the Commission on Cancer,[5] the American Society of Clinical Oncology (ASCO) through its Quality Oncology Practice Initiative or QOPI,[6] and

(continued on **SP312**)

MEASURING PRO-PMS

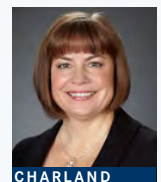
GOLDWATER JOHNSON SILVERMAN ROILAND

Read about the Measure Incubator, a platform for the development of patient-reported outcome performance measures in palliative cancer care, the product of the Measure Applications Partnership convened by the National Quality Forum (**SP282**).

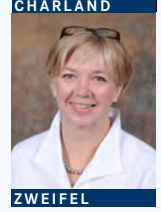
NATIONAL QUALITY FORUM

Also in This Issue...

PREPARING FOR OCM PARTICIPATION



CHARLAND



ZWEIFEL

The Oncology Care Model by CMS aims for higher quality and more coordinated care for patients receiving treatment at participating sites. Kim Charland, BA, RHIT, CCS; and Robin Zweifel, BS, MT (ASCP), of Panacea Healthcare Solutions, provide an overview of the model and guidelines to help meet the quality and performance measures required for participation (**SP293**).

PANEL DISCUSSION

Linda Bosserman, MD, City of Hope; Jason C. Goldwater, MA, MPA, National Quality Forum; and Jennifer Malin, MD, Anthem, participate in a conversation on identifying the most valuable quality metrics and the importance of making these metrics relevant for use in the clinic (**SP295**).

BOSSERMAN GOLDWATER MALIN

AJMC® Managed Markets Network®

The Institute for Value-Based Medicine®

For patients with 3rd-line+ multiple myeloma (MM) after a PI and an immunomodulatory agent,

DISCOVER THE POSSIBILITIES OF SINGLE AGENT EFFICACY

DARZALEX® is a first-in-class fully human monoclonal antibody that binds to CD38[1]

Indication

DARZALEX® (daratumumab) is indicated for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX® can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy for life-threatening (Grade 4) reactions.

For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients the first and second day after all infusions. Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders.

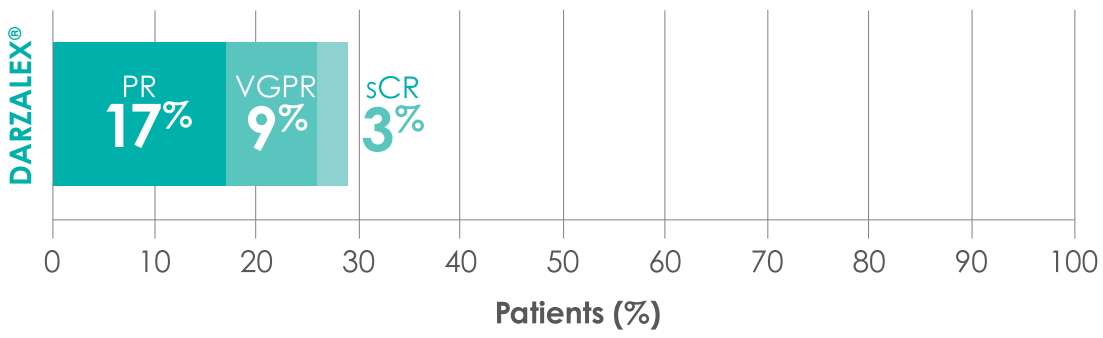
Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

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

DARZALEX® responses were demonstrated in patients with a median of 5 prior therapies[1]*

Overall response rate (ORR)[1†]



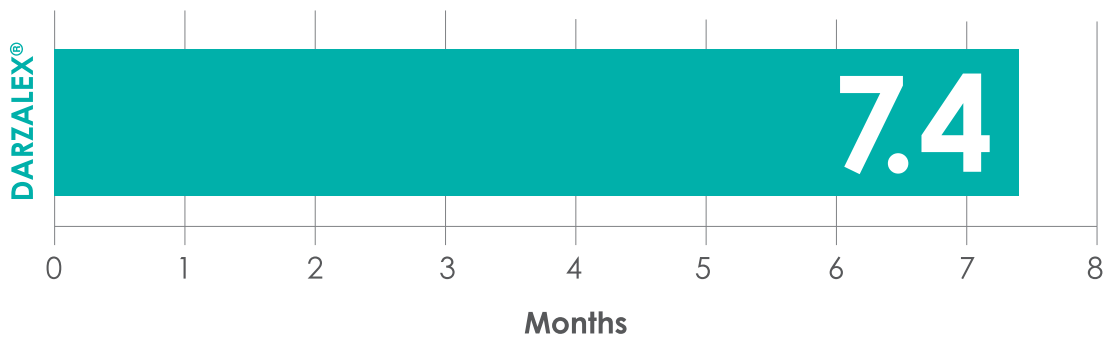
29%

overall response rate[1]

(95% CI: 20.8, 38.9)

- DARZALEX® achieved sCR + VGPR in 12% of patients[1]

Median duration of response[1]



PR=partial response; VGPR=very good partial response; sCR=stringent complete response.

*For this open-label single-arm phase 2 trial of 106 relapsed/refractory patients who were administered pre- and post-infusion medications and treated with 16 mg/kg DARZALEX® until unacceptable toxicity or disease progression, efficacy results were based on ORR as determined by an Independent Review Committee assessment using International Myeloma Working Group (IMWG) criteria.[1,2]

†In the trial, sCR was defined as complete response (CR) plus a normal serum free light chain (FLC) ratio and the absence of clonal plasma cells in the bone marrow by immunohistochemistry or immunofluorescence or 2- to 4-color flow cytometry.[3]

- Duration of response range: 1.2 to 13.1+ months[1]
- The most frequently reported adverse reactions (≥20%) were infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%)[1‡]
  - Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%)[1]
- 4% of patients discontinued treatment due to adverse reactions (ARs); ARs resulted in treatment delay for 24 patients (15%), most frequently for infections[1]

‡Safety data were pooled from 3 open-label clinical studies of relapsed/refractory patients treated with 16 mg/kg DARZALEX® (N=156).[1]

Important Safety Information

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Adverse Reactions

The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%).

Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

DRUG INTERACTIONS

No drug interaction studies have been performed.

048504-160304

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Trial Design. Janssen Biotech, Inc. **3.** Data on file. sCR. Janssen Biotech, Inc.

For more information, visit **www.darzalex.com**

Janssen Oncology

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARE TO DREAM

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills *[see Adverse Reactions]*.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients the first and second day after all infusions. Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum[1] *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions]*.

Adverse Reactions in Clinical Trials

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 safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.4 months).

Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 1. Table 2 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 1: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

System Organ Class	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0

Table 1: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg (continued)

System Organ Class	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia

Table 2: Treatment Emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

The incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 5% with the second infusion, and 4% with subsequent infusions. None of the reactions with second or subsequent infusions were Grade 3 or higher.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 9.3 hours). The incidence of infusion interruptions due to reactions was 37%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.6 and 3.4 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, hypoxia, and hypertension (<2% each). Common any grade adverse infusion reactions (≥5%) were nasal congestion, cough, chills, rhinitis allergic, throat irritation, dyspnea, and nausea.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. Systemic anti-viral medications were used in 73% of patients. Herpes zoster was reported in 3% of patients.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In an open-label, clinical trial of patients with relapsed or refractory multiple myeloma treated with DARZALEX, 111 patients were evaluated for anti-therapeutic antibody (ATA) responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment using an electrochemiluminescence-based immunoassay. Following the start of DARZALEX treatment, none of the patients tested positive for anti-daratumumab antibodies. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

No drug interaction studies have been performed.

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding[1] *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use

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

Geriatric Use

Of the 156 patients on the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information]*.

Renal Impairment

Based on a population pharmacokinetic (PK) analysis no dosage adjustment is necessary for patients with pre-existing renal impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Hepatic Impairment

Based on a population PK analysis, no dosage adjustments are necessary for patients with mild hepatic impairment (Total Bilirubin [TB] 1.0× to 1.5× upper limit of normal [ULN] or aspartate aminotransferase [AST] >ULN). Daratumumab has not been studied in patients with moderate to severe hepatic impairment (TB >1.5× ULN and any AST) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

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

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions* and *Adverse Reactions]*.

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response.

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Phases of PRO Tool Development on the Open Research Exchange (ORE)

Concept Elicitation	Feedback	Test/Re-test	Follow-up
• Obtain input from patients using open-ended questions • Examine patient experience on a large scale • Start item generation process	• Evaluate clarity, relevance, and adequacy of response options for each item (equivalent to cognitive debriefing) • Review items based on patient feedback • Gather patient feedback via questions displayed below each evalutated item	• Psychometric evalutation of the new instrument (validity and reliability) • Flexible study design • Ongoing patient input available through item-level and post-survey feedback	• Evaluate the ability to detect change

← Qualitative → ← Quantitative/psychometric →

SP310 *PatientsLikeMe and Actelion Pharmaceuticals have developed a patient-reported outcomes measurement tool for patients with a particular form of cutaneous T-cell lymphoma. Read about the collaboration and the platform used by the 2 organizations to develop the tool on* **SP310**.

SP280 FROM THE CHAIRMAN
What Are We Lacking in Oncology Quality Metrics?

SP281 FROM THE EDITOR IN CHIEF
Surmounting the Quality Chasm in Healthcare

SP304 Aligning Reimbursement With Quality: *Are We There Yet?*

SP305 Industry Insight on the Challenges With Developing and Adopting Biosimilars

FEATURE ARTICLES

NQF MEASURE INCUBATOR

SP282 Using the NQF Measure Incubator to Develop Patient-Reported Outcome Performance Measures in Palliative Cancer Care
JASON GOLDWATER, MA, MPA; NICOLE SILVERMAN, MBA; KAREN JOHNSON, MS; AND RACHEL ROILAND, PHD

UTILIZATION MANAGEMENT

SP284 Integrative Oncology Program Improves Efficiency and Outcomes in Oncology Care
AMIT GUPTA, MD

ONCOLOGY CARE MODEL

SP293 Quality Metrics for Oncology in a Value-Based Reimbursement World
KIM CHARLAND, BA, RHIT, CCS, ANDg ROBIN ZWEIFEL, BS, MT (ASCP)

PANEL DISCUSSION

SP295 A Discussion on Oncology Quality Tools: *Filling in the Gaps*
SURABHI DANGI-GARIMELLA, PHD

CONFERENCE COVERAGE

COA

SURABHI DANGI-GARIMELLA, PHD

SP298 Oncology Payment Reform: *Payers and Providers Discuss APM and Beyond*

SP303 An Update on the Oncology Medical Home Model at the COA Conference

Medical World News®

POLICY UPDATES

SURABHI DANGI-GARIMELLA, PHD

SP306 ASCO Releases an Updated Value Framework

SP306 MSK Survey Indicates Misbelief Responsible for Dismal Cancer Trial Participation

FROM THE COVER

HEALTH IT PLATFORM

SP308 CancerLinQ—ASCO's Rapid Learning System to Improve Quality and Personalize Insights
ROBERT S. MILLER, MD, FACP, FASCO

MEASURING PROs

SP310 Partnering With Patients to Rapidly Develop a Quality-of-Life Measure in Mycosis Fungoides/Sézary Syndrome Type Cutaneous T-cell Lymphoma
PAUL WICKS, PHD; MARJAN SEPASSI, PHARMD; GAURAV SHARMA, PHARMD; AND MARGOT CARLSON DELOGNE

PROVIDER PERSPECTIVE

SP312 So Many Metrics, Yet So Little Known About Quality and Value in Cancer Care
JOSEPH ALVARNAS, MD

What Are We Lacking in Oncology Quality Metrics?

How much is too much when it comes to measuring quality in healthcare? Do hundreds of quality metrics ensure that a clinic in a hospital or a small group practice are providing the patient access to the highest quality of care? Or is the message getting lost in all of the boxes that providers are required to check?

In this June issue of *Evidence-Based Oncology*, we hope to address some of these questions on the quality of care in oncology. The opinions and views presented are quite diverse, as they should be.

In its article, experts from the National Quality Forum (NQF), an organization that facilitates the evaluation of, and endorses, quality measures, presents a measure that is being developed for patient reported outcomes (PROs) in palliative care, called the Measure Incubator. The objective of this performance measure is to understand the functional status and well-being of a cancer patient.

A similar PRO tool, which measures the quality of life in patients with a particular type of cutaneous T-cell lymphoma, is the product of a collaboration between PatientsLikeMe and Actelion. The tool helps patients describe their experience and can also guide treatment decisions. Experts from both organizations who were involved with developing this online platform describe the nuances of the process.

Linking clinical, cost, and patient data is the ultimate goal of healthcare today. One such platform is provided by HealthHelp: the company's Integrative Oncology program facilitates cross-specialty collaboration and supports the treatment decision-making process, with considerations of cost of care. The American Society of Clinical Oncology also has a huge project underway called CancerLinQ, which will integrate clinical outcomes data from electronic health records, both within and between practices, with the objective of quality benchmarking and hypothesis generation. Dr Robert Miller, vice president, Quality and Guidelines, and medical director, CancerLinQ, provides insight on how the platform captures clinical information from various data systems and the potential of this data to complement traditional evidence.


MIKE HENNESSY, SR

Finally, we invited 3 experts to put all this information into the right perspective for our audience. Linda Bosserman, MD, assistant clinical professor and staff physician, City of Hope; Jason C. Goldwater, MA, MPA, senior director, NQF; and Jennifer Malin, MD, staff vice president, Clinical Strategy, Anthem, engaged in a conversation on developing processes that can help identify the most valuable metrics and the importance of making these metrics relevant for use in the clinic.

As always, thank you for your readership, and please visit the Oncology Compendium on our website, www.ajmc.com, for the latest clinical and managed care updates.

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.

Surmounting the Quality Chasm in Healthcare

In its 2001 report, Crossing the Quality Chasm: A New Health System for the 21st Century, the Institute of Medicine described 6 essential attributes of care that needed to be systematically applied in order to fundamentally transform healthcare for the better. These attributes included care that was safe, effective, efficient, equitable, patient-centered, and timely.[1] Passage of the Affordable Care Act in March 2010 not only embedded these priorities into law, but also began the complex process of realigning economic incentives toward making this healthcare vision a reality.[2] In this process, quality metrics have been stewarded by multiple healthcare stakeholders to ensure a transparent link between quality improvements in healthcare and resulting payment for performance enhancement.[3,4]

Despite the breadth of metrics, there seems to be a significant disconnect between the relatively prosaic, process-based measures that largely dominate our quality portfolio and the high-level, aspiration-driven demands of delivering increasingly complex care to patients in need of precision medicine and personalized cancer care solutions.[5] This disconnect is no more acute than in the domain of cancer care, where advances in the state of the art of care far outpace our palate of quality measures and where our very limited capacity to abstract adequate clinical data from electronic health records (EHRs) has undermined the ambition, utility, importance, and effectiveness of our cancer care measures. This disconnect is further magnified by a paucity of patient-reported outcomes measures—meaningful outcomes measures like survival and time to recovery of patient function—and metrics that seek to discern and reward the development of better systems of care rather than reward effective care transactions.[6]

In this edition of *Evidence Based Oncology*, the challenges and opportunities for developing and deploying better cancer care quality measures are explored. More importantly, we also explore the question of how these measures coupled with innovative payment systems can lead to better systems of care. Jason Goldwater from the National Quality Forum (NQF) describes the NQF's Measure Incubator, which is a platform for the development of better patient-reported outcome performance measures for palliative cancer care. Kim Charland and Robin Zweifel from Panacea Healthcare Solutions describe CMS' Oncology Care Model, or OCM. The goal of this model is to better align economic incentives with physician practice quality initiatives in a longitudinal care model that seeks to improve financial and performance accountability for cancer patients. Dr Amit Gupta from HealthHelp describes a multidisciplinary, multidimensional model for improving decision support, enhancing cross-specialty care collaboration, and reducing care-related costs. Dr Robert Miller from the American Society of Clinical Oncology (ASCO) describes CancerLinQ. This is a proprietary ASCO big data platform for aggregating clinical data from EHRs for quality benchmarking, hypothesis generation, and empowering the development of more robust clinical metrics. Finally, we have a multi-stakeholder panel discussion regarding the challenges of developing better cancer care measurement and quality assessment tools.

The words "quality" and "value" are perhaps 2 of the most overused words when discussing the future evolution of cancer care. At times, they become clichés and catchphrases rather than tools for delivering more effective cancer care or creating better care delivery systems. By looking at quality metrics and cancer care value delivery more critically, we can make genuine steps toward realizing care systems and quality metrics that are worthy of the patients that we serve. **EBO**

ABOUT THE EIC

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REFERENCE

1. Across the chasm: six aims for changing the health care system. Institute for Healthcare Improvement website. http://www.ihi.org/resources/pages/improvementstories/acrossthechasmsixaimsforchangingthehealthcaresystem.aspx. Accessed June 1, 2016.
2. Burwell SM. Setting value-based payment goals—HHS efforts to improve US health care. *N Engl J Med.* 2015;372(10):897-899. doi:10.1056/NEJMp1500445.
3. National Quality Forum website. http://www.qualityforum.org/Home.aspx. Accessed June 1, 2016.
4. Measures overview. ASCO Institute for Quality website. http://www.instituteforquality.org/qopi/measures. Accessed June 1, 2016.
5. Geiger AM. Quality and precision medicine. Healthcare Delivery Research Program/National Cancer Institute website. http://healthcaredelivery.cancer.gov/blog/node/22. Accessed June 1, 2016.
6. Porter ME. What is value in health care? *N Engl J Med.* 2010;363(26):2477-2481. doi:10.1056/NEJMp1011024.

Using the NQF Measure Incubator to Develop Patient-Reported Outcome Performance Measures in Palliative Cancer Care

JASON GOLDWATER, MA, MPA; NICOLE SILVERMAN, MBA; KAREN JOHNSON, MS; AND RACHEL ROILAND, PHD

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INTRODUCTION

Cancer is currently the second leading cause of death in the United States, with 17 million new cases predicted to be diagnosed in 2016.[1] The lifetime risk of developing cancer among US men is 50% and among US women, 38%. It is estimated that approximately 622,690 individuals across the United States will die from various forms of cancer in 2016. Despite the statistics, treatments for various forms of cancer have improved; for example, we now have better protocols for the early detection of cancer, as well as more effective therapies for treatment. Moreover, since the late 1970s, 5-year survival rates have increased from 50% to almost 70% in 2011.[2]

Regardless of the advances in medications and positive trends in survival rates, however, the general consensus among cancer professionals is that the quality of cancer care is suboptimal.[3] These problems are inherent, largely attributable to a fragmented system that lacks coordination of care, does not ensure access to care, and is inefficient in its use of resources. As a result, some patients fail to receive effective treatments, receive treatments that compound their risk and lower their chance for survival, or have significant side effects and do not improve their chances for survival.[4] These quality deficiencies are pervasive and found throughout the various phases of cancer care, including diagnosis, initial treatment, survivorship, and palliative care.

To improve the overall quality of cancer care, valid and reliable measures of practice, performance, and patient outcomes must be developed and implemented.[5] Cancer organizations—such as the American Society of Clinical Oncology (ASCO), the Alliance of Dedicated Cancer Centers, and the American Society for Radiation Oncology, among others—have maintained portfolios and registries of healthcare performance measures that focus on individual cancers, assess specific providers, and address specific processes of care, particularly initial management strategies. Despite the development of approximately 150 cancer-related measures, numerous noticeable gaps in the current measurement environment persist, as several aspects of cancer care remain unaddressed. Some of these include:

- Patient assessment and supportive care
- Patient experience of care
- Use of palliative care
- Interdisciplinary and multidisciplinary coordinated care
- Assessment and support of patients and caregivers at the end of life (EOL).[6]

Many professional organizations and specialty societies, that lead rigorous measure development activities on numerous cancer-related topics, recognize the relatively narrow focus of existing cancer quality measures, and the increasing demand for measures from patients, payers, and other organizations to address the shortcomings of the current system.

The dearth of reliable and valid measures is most evident in the area of providing palliative care to cancer patients. Large-scale, post-death surveys demonstrate that a considerable portion of families feels the needs of the patient were not attended to adequately. For example, 18% of hospitalized patients did not consider their pain adequately controlled, and 42% of cancer patients did not receive appropriate levels of analgesia.[7] While pharmacologic interventions are often the first level of treatment for cancer pain, non pharmacologic techniques have also proven effective in addressing pain. These may include physical modalities such as exercise, acupuncture, and massage, and psychosocial modalities such as relaxation techniques, support groups, and family counseling. Studies have demonstrated that the consistent use of an interdisciplinary approach that combines pharmacologic agents with other forms of treatment may alleviate the need for invasive interventions, such as intrathecal opioids, and facilitate a safe discharge to the community.[8]

Organizations, such as ASCO, have postulated that the development and validation of cross-cutting, patient-reported outcome–based performance measures (PRO-PMs), to assess the quality of care for cancer patients in palliative care, is essential. However, a number of persistent problems has hampered the development of such measures:

- Lack of available data to provide sufficient detail for a broad-based assessment of cancer care in palliative settings
- Understanding how to create appropriate symptom and functional status assessments
- Implementation of the measures to ensure that the appropriate information is captured and used to report on the measure
- The time it would take to develop and test these measures.

Additionally, current cancer patients in palliative care are often viewed as too ill to fill in an assessment tool due to cognitive impairment or may not understand what is required of them.[9] The validity and reliability of the tool, and the complexity of the PRO-PM to provide a meaningful and useful metric, are also barriers for staff employed at palliative care facilities.[10]

Adequately developed PRO-PMs in palliative care can be helpful in identifying a patient's response to a particular treatment modality, particularly, in terminal cases, when the difference in survival among each of the options is small or nonexistent.[11] Leveraging a psychometrically validated instrument that is inclusive of patient input across a number of significant domains would be beneficial for providers to understand the needs of their cancer patients. These may include:

- Individual wishes for medical care
- Issues in palliative care that trouble patients
- Priorities for treatment.

Understanding the most important and significant of these needs is crucial for both the development and implementation of patient-reported outcome measures.[12] There are a number of valid instruments that have been developed that measure the quality of life (QoL) in palliative cancer care, such as the European Organization for Research and Treatment of Cancer, or EORTC, the Functional Assessment of Cancer Treatment, or FACT, and the Palliative Care Quality of Life Instru-

ment or PQLI. Each of these encompasses a short questionnaire that provides patients an ability to voice their opinions and concerns regarding EOL care, and has shown to be a limited burden on patients.[13,14]

THE NATIONAL QUALITY FORUM AND THE MEASURE INCUBATOR

The National Quality Forum (NQF) is a consensus-building organization that evaluates healthcare performance measures and facilitates a defined process to endorse these measures. Over the past decade, NQF has conducted several projects to evaluate and endorse cancer care measures under the guidance of multi-stakeholder committees that represented payer, consumer, quality improvement, provider, and patient perspectives. Some of these measures include areas such as access and cultural competence; prevention and screening; diagnosis and treatment of breast, colorectal, and prostate cancers; symptom management; and EOL care. In 2008, NQF led a workshop that highlighted key measurement gaps in cancer despite the rapid proliferation of measures across a number of clinical areas. These gaps included many of the topic areas identified by organizations such as ASCO, and emphasized that areas such as shared decision-making, EOL care, care coordination, and patient and family engagement were not adequately represented.[15]

In 2012, the Measure Applications Partnership (MAP), a public/private endeavor, enacted as part of the passage of the Affordable Care Act, and overseen by NQF to guide HHS on the selection of performance measures for federal programs, suggested there was an immediate need to address the fundamental cross-cutting aspects of care that are relevant to all cancer patients throughout the trajectory of their illness. Both NQF and MAP stated that a more comprehensive measurement system that focused on patients, rather than individual providers or distinct care settings, was preferable. However, the process of designing, testing, and disseminating quality measures to fill these priority gaps is burdensome, costly, and time consuming. On average, measure development and testing take approximately 2 to 3 years.

An additional difficulty arises from testing measures, which currently requires implementation across real-world practice sites in order to assure validity and feasibility across multiple clinical sites and vendors. Further, no linear pathway exists to coordinate and invest in measures most relevant for improving health outcomes. As a result, the persistence of measure gaps undermines the quality-management enterprise. NQF is addressing the market inadequacies in healthcare measure development and testing through its Measure Incubator, a platform that can shorten the time and decrease the burden of measure development and enable the focus on novel and needed measures. The Incubator creates the foundation for the next generation of performance measures, including measures of PRO-PMs, measures of resource use and population health, and electronic clinical quality and registry-based measures. It can also accelerate improvement in quality by creating a more collaborative model of measure development that focuses on leveraging the appropriate stakeholders, resources, and data assets, at the time the measure is created, to help complete the development process in an efficient and expeditious manner. This vision mirrors the "incubation" concept used in other contexts to support innovation and transformation of innovative ideas into timely solutions.

Although NQF is playing a facilitative role, the organization is not directly engaging in measure development. NQF also developed strict conflict-of-interest guidelines to prevent any incubated measure to receive preferential status for endorsement. The Incubator is building on the substantial base of priority setting—the result of the MAP and the NQF endorsement process. This new collaborative model can support the development of meaningful evidence-based measures for a wide range of clinical settings and disciplines. Through greater upstream collaboration with guideline developers and downstream collaboration with stakeholders who support the measure, the development of a measure can be focused where there is the highest likelihood for meaningful improvement in patient outcomes.

THE USE OF THE NQF MEASURE INCUBATOR TO DEVELOP PRO-PMS IN PALLIATIVE CARE

The NQF Measure Incubator can utilize the information gathered through these instruments to help develop robust and valid PRO-PMs by following a pathway outlined in the 2013 report by NQF, Patient Reported Outcomes (PROs) in Performance Measurement. This pathway was designed to ensure that the data from the validated instrument is used at the beginning of the process to develop the measure in a manner that is both meaningful to patients and implementable to providers. The pathway consists of the following overarching components:

Identifying a PRO for development. Each of the tools currently used to assess a patient's feelings about palliative care focuses on the most relevant and meaningful issues to them, including their priority of choice of treatment for their cancer and their wishes for medical care. Recent studies indicate that physicians must understand the importance of communication in the context of advanced illness, when the achievement of a patient's specific needs assumes priority over inappropriate prolongation of care. These data could lay the foundation for the development of a PRO-PM in palliative care, as this is one meaningful area that could be developed into a measure using existing survey tools, which would ensure that the most important quality issue is developed into a measure concept.

Each of the referenced tools deals with relevant QoL issues, such as treatment choices and preferred outcomes. Through the use of the Incubator, NQF staff examines the data at the beginning of the development process, bringing together the appropriate subject matter experts in palliative care and the expertise in measurement science from NQF, to understand how various interventions affect the outcomes that are important to patients in a comprehensive manner. For example, a 2004 study that used the PLQI indicated that cancer patients in palliative care need the support of their family and friends when considering treatment options. Therefore, understanding how the provider brings them into the decision-making process and how that would affect the overall choice of treatment could lead to a PRO-PM that would be relevant to both patients and providers.

Suitability of the PRO-PM for use in palliative care. Part of the measure incubation process is examining the suitability for the development of PRO-PMs in palliative care, which encompasses multiple concepts, including whether the measure addresses an unmet measurement need, and the instruments are reliable and valid to support the development of a PRO-PM. The data used to both develop and test the measure would come from instruments that have been psychometrically tested and embrace concepts that are meaningful to patients—this would ensure protection against the development of a measure that would not be directly applicable to cancer patients in palliative care. The parameters of the measure would be tightly defined so as to increase its usability in these types of settings and with patients diagnosed with various forms of cancer.

Specifying and testing the measure. Although it should, again, be noted that NQF does not participate in the development of

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The NQF Measure Incubator is a platform that can shorten the time and decrease the burden of measure development and enable the focus on novel and needed measures.

The data used to both develop and test a measure would come from instruments that have been psychometrically tested and embrace concepts that are meaningful to patients.

the measure, NQF has promulgated criteria that represent a "gold standard" for both development and use. The NQF Measure Incubator assists measure developers in applying those criteria to ensure that their measures are reliable, valid, and feasible and can be implemented in the settings for which they are intended. Additionally, given that the measure can be initially tested with data from a validated instrument, it can be determined early on if the metric generated from the measure is useful for providers to better understand patient needs. Upon the completion of the process, the organization that funded the measure and the developer can determine if the measure should be considered for NQF endorsement. This is an independent process and does not involve any input from NQF, nor does participation in the Incubator ensure that endorsement is guaranteed.

The NQF Measure Incubator provides a unique opportunity to allow organizations, measure developers, subject matter experts, and other stakeholder to collectively develop measures that fill existing gaps in quality measurement. By creating a process that is both efficient and cost-effective, the ability to get to "measures that matter" for both patients and providers is not as burdensome or time-consuming. It also allows for the development of PRO-PMs in specific areas, such as palliative cancer care, that lend a voice to patient needs and concerns, and develop much needed quality measures that improve their overall QoL. **EBO**

REFERENCES

1. Cancer facts and figures 2016. American Cancer Society website. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed May 3, 2016.
2. Spinks TE, Walters R, Feeley TW, et al. Improving cancer care through public reporting of meaningful quality measures. *Health Aff (Millwood)*. 2011;30(4):664-672. doi:10.1377/hlthaff.2011.0089.
3. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*. 2009;27(17):2758-2765. doi:10.1200/JCO.2008.20.8983.
4. Hassett MJ, McNiff KK, Dicker AP, et al. High-priority topics for cancer quality measure development: results of the 2012 American Society of Clinical Oncology Collaborative Cancer Measure Summit. *J Oncol Pract*. 2014;10(3):e160-e166. doi:10.1200/JOP.2013.001240.
5. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board; Hewitt ME, Simone JV, eds. Cancer care quality assurance. In: *Ensuring Quality Cancer Care*. Washington, DC: National Academies Press; 1999.
6. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635-2645. doi:10.1056/nejmsa022615.
7. Blayney DW. Defining quality: QOPI is a start. *J Oncol Pract*. 2006;2(5):203. doi:10.1200/jop.2.5.203.
8. Seow H, Snyder CF, Shugarman LR, et al. Developing quality indicators for cancer end-of-life care: proceedings from a national symposium. *Cancer*. 2009;115(17):3820-3829. doi:10.1002/cncr.24439.
9. Lorenz KA, Lynn J, Dy SM, et al. Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med*. 2008;148(2):147-159. doi:10.7326/0003-4819-148-2-200801150-00010.
10. Mularski RA, Dy SM, Shugarman LR, et al. A systematic review of measures of end-of-life care and its outcomes. *Health Serv Res*. 2007;42(5):1848-1870. doi:10.1111/j.1475-6773.2007.00721.x.
11. Bauswein C, Simon ST, Benalia H, et al; PRISMA. Implementing patient reported outcome measures (PROMs) in palliative care–users' cry for help. *Health Qual Life Outcomes*. 2011;9:27. doi:10.1186/1477-7525-9-27.
12. Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. *Qual Health Care*. 1999;8(4):219-227. doi:10.1136/qshc.8.4.219.
13. Jack B, Hillier V, Williams A, Oldham J. Hospital based palliative care teams improve the insight of cancer patients into their disease. *Palliat Med*. 2004;18(1):46-52. doi:10.1191/0268216304pm846oa.
14. Baumrucker SJ. The Palliative Care Quality of Life Instrument (PQLI): a new tool for measuring quality of life. *Am J Hosp Palliat Care*. 2004;21(2):87-89. doi:10.1177/104990910402100203.
15. *National Voluntary Consensus Standards for Quality of Cancer Care*. Washington, DC: National Quality Forum; 2009.

UTILIZATION MANAGEMENT

Integrative Oncology Program Improves Efficiency and Outcomes in Oncology Care

AMIT GUPTA, MD

Rapidly developing medical technology presents both benefits and challenges to cancer patients and physicians. Although the number of treatment options now available improve quality of life and survival rates for patients, they also make physicians' selection and coordination of treatments more complex. Care is further complicated by the rising cost of cancer treatment. Total costs are projected to be between $158 billion and $173 billion in 2020, a 39% increase from 2010.[1] In addition, some newer cancer drugs now cost $10,000 to $30,000 per month. Patients typically pay 20% to 30% out-of-pocket for drugs, so an average year's worth of new drugs could cost $24,000 to $36,000 in addition to health insurance premiums.[2] These expenses exceed many patients' ability to pay, and many are forced to simply forego treatments.[3] It is critical that patients receive the best possible treatment at the lowest possible cost.

INTEGRATIVE ONCOLOGY

Achieving efficiency and optimization of treatment is the goal of HealthHelp's new Integrative Oncology program. HealthHelp uses evidence-based guidelines to advise and educate physicians on the most appropriate tests and procedures based on their patients' symptoms and health history. The goal is to improve provider compliance with oncology care guidelines, which improves patient care and outcomes, while reducing waste caused by unnecessary testing and procedures.

HealthHelp is the first specialty-benefits manager in the nation to offer an Integrative Oncology program. The process begins by identifying a patient's risk level and, through adaptive algorithms, determining the most appropriate care alongside specialty nursing and physician support. As a patient's risk level changes, clinical decisions adapt to the patient. HealthHelp is unique in the utilization management in-

dustry in that its specialists, drawn from major academic and medical institutions, will proactively call physicians before they even make an authorization request for their patients, in order to provide guidance on their choice of testing and treatment. This physician peer-to-peer program gives the provider a sounding board to discuss appropriate care and offers education on the best treatment for each patient. This multi-institution advanced treatment planning can also influence tumor board decisions on how to best care for patients.

The Integrative Oncology program considers the totality of the patient receiving a full array of services, encompassing the management of 3 modes of therapy:

- Radiation therapy, including intensity-modulated radiation therapy (IMRT), brachytherapy, 2D/3D conformal radiation, stereotactic radiosurgery and radiotherapy, and proton beam therapy.
- Medical oncology, including chemotherapy, hormone therapy, prophylactics, and biologic agents.
- Oncology surgery, including wedge resections, lobectomy, lumpectomy, and others.

This integrative approach to cancer care makes it easy for physicians in different specialties to collaborate and coordinate the treatment a patient receives, developing one cohesive continuum of care. Since patients with cancer frequently work with multiple physicians, cross-specialty coordination is especially important to ensure quality care. The Integrative Oncology program gives radiology and oncology providers access to patient information that may have been administered by a provider in an alternate department or even an alternate facility. This helps to eliminate duplicate or unnecessary testing, which increase patient risk and costs.

The main components of the Integrative Oncology program are:

- Risk assessment and screening. Patient risk is calculated in real time during the authorization process, and the patient is categorized into a risk population based on published, evidence-based literature. Based on his or her category of risk, the patient will be steered to the most cost-effective and appropriate treatment.
- Imaging and staging work-up. This follows a patient when a positive screening has occurred or a request for an authorization comes in for incidental findings, such as lumps, nodules, or masses. There are extensive prediagnosis guidelines for the initial work-up to ensure physicians select the proper sequence of imaging to prevent overtesting or unnecessary testing.
- Biopsies and interventions. HealthHelp's risk segmentation ensures that high-risk individuals get timely diagnosis and early resection of low-stage cancerous findings, while low-risk individuals do not receive excessive interventions and imaging due to high false-positive rates. Proper upfront screening and imaging schedules are also used to prevent unnecessary biopsies and interventions that are inconvenient and cause anxiety among patients.
- Prognostic assessment. Oncologists and the clinical team reach out and gather information on cancer patients who are undergoing staging and work-up for prognostic assessment. This takes into account the patient's disease stage, clinical parameters, histopathology, and molecular characterization to determine the patient's prognosis. This is key to treatment planning and distinguishing between a curative or a palliative path for the patient.
- Treatments and surgeries. This includes chemotherapy, biotherapeutics, ancillaries, radiation therapy, excisions, and surgeries.
- End-of-life care with palliative and curative pathways. By constantly reevaluating a patient's stage and prognostic indicators, and through case management, the patient's wishes can be more closely followed if palliative care is needed. If a palliative pathway is determined, to ensure maximum patient comfort, HealthHelp coordinates physical therapy/occupational therapy, pain management, home health nursing, and other services.
- Advocacy/peer oncologist. HealthHelp monitors a patient's timeline of diagnosis, staging, treatments, and other care needs, so that when appropriate, a peer oncologist can intervene in the process. The peer oncologist creates personalized interactions with both providers and patients to ensure coordination of care, treatment planning, and shared decision making.
- Genetic testing and precision testing. Not everyone is a candidate for genetic testing. Whereas it may be warranted for patients identified as being at greater risk for cancer, it's an unnecessary expense for many patients. Similarly, certain chemotherapy drugs target specific cancers caused by genetic mutations, such as Avastin (bevacizumab) for recurrent glioblastoma, a type of brain cancer. With precision testing, a biopsy will show whether a patient's tissue responds to the medication. If it does, the drug is authorized because it clearly works on that patient. If the tissue doesn't respond, there is no point in prescribing the medication.

By design, our integrative oncology management strategy achieves 3 objectives:

1. Ensuring patient safety. This is the most crucial objective of the program. It ensures safety through pathways and treatment guidelines that enhance outcomes for patients undergoing cancer treatment. Patients who need emergency therapy are exempt from review.
2. Following evidence-based guidelines. Leveraging evidence-based guidelines eliminates variations in cancer treatment, promotes consistent care, and reduces toxicity. The Integrative Oncology program establishes pathways and treatment plans based on:
   - Nationally and internationally recognized standards of care
   - Peer-reviewed literature published by societies such as the American Society for Radiation Oncology, American Society of Clinical Oncology, American Society of Hypertension, and National Institute for Health and Care Excellence, as well as *Journal of the National Comprehensive Cancer Network*,
   - Landmark studies and phase 3 trials
3. Striving for cost-effective care. Evaluating current scientific literature when developing clinical pathways identifies treatments that produce the highest efficacy at the lowest toxicity and cost for each stage and state of cancer. HealthHelp's current radiation therapy and medical oncology programs save payers 15% to 30% and 12% to 25%, respectively, prior to their integration into one continuous process as part of the new integrative oncology program.

NONDENIAL MODEL

The Integrative Oncology program leverages HealthHelp's proven benefits management platform, which is based on a nondenial model of preauthorization. If an initial review finds that a physician's request does not meet clinical guidelines for approval, the request escalates to a specialty nurse and, if necessary, a peer-to-peer consultation with a specialty physician. The specialist collaborates with the requesting physician to determine the best test or treatment, which usually leads to an agreed-upon change in the procedure or the procedure being withdrawn. However, physicians can be reassured that their requested tests or treatments will be approved even if they don't align with the preauthorization recommendation. Although HealthHelp will deny a physician's authorization re-

(continued on **SP291)**

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HealthHelp's current radiation therapy and medical oncology programs save payers 15% to 30% and 12% to 25%, respectively, prior to their integration into one continuous process as part of the new integrative oncology program.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

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%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

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

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

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

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

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

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended overall survival vs chlorambucil

Statistically significant reduction in risk of death[1]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

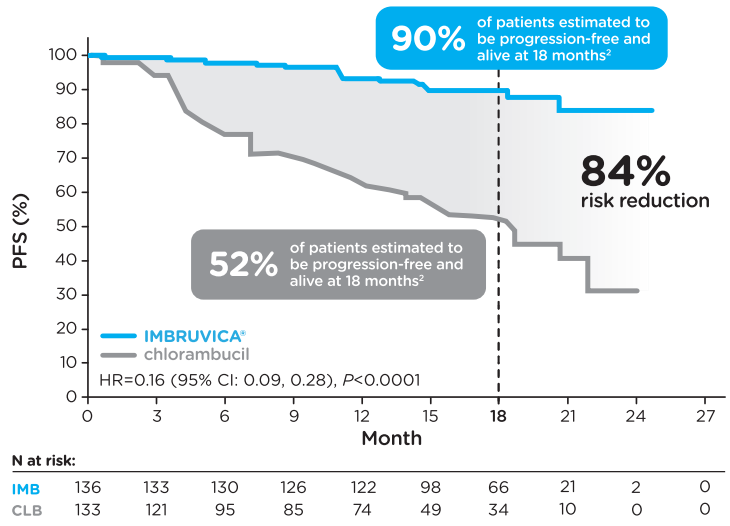
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS)

- Median follow-up was 28 months[1]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil



N at risk:

IMB	136	133	130	126	122	98	66	21	2	0
CLB	133	121	95	85	74	49	34	10	0	0

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS)

- Median follow-up was 18 months[2]
- IMBRUVICA® median PFS not reached[1]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[1]
- PFS was assessed by an Independent Review Committee (IRC) per revised International Workshop on CLL (IWCLL) criteria[1]

Adverse reactions ≥20% across CLL/SLL registration studies[1]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia* (64%), thrombocytopenia* (63%), diarrhea (43%), anemia* (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

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

The most common Grade 3 or 4 non-hematologic 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/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration 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 see the Brief Summary on the following pages.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **2.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) 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 (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

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

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

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%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

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

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

Second Primary Malignancies: Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* 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/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

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

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

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

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

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 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

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

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The 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.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

IMBRUVICA® (ibrutinib) capsules

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

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

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

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

Waldenström's Macroglobulinemia: 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 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
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 preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: 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.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

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

Hepatobiliary disorders: hepatic failure (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A).

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: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data].* If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

IMBRUVICA® (ibrutinib) capsules

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

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

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

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

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

Contraception:

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

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

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

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA *[see Clinical Studies (14.2) in Full Prescribing Information].*

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

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

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

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial fibrillation:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions].*
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

PRC-01957

(continued from **SP285**)

quest if there is concern for patient safety or quality of care (such as overtesting, overtreating, or risk of complications), the real focus is on educating providers to order the right test or procedure for a given patient. Over time, by managing the use of medical and radiation oncology, the peer consultation program enhances physicians' knowledge and sustains savings by changing long-term ordering patterns as ordering physicians increasingly adhere to best practices.

One recent study of a large state Medicaid program clearly demonstrated the sustainable effects of the HealthHelp model. Over a period of 2 years, the HealthHelp program was responsible for a 46.3% decrease in advanced imaging, resulting in over $42 million in savings. Although there was a sharp decline in utilization immediately after program implementation, a steady decline in utilization over the entire 2-year period was also observed. This continual decrease in utilization supports the efficacy of HealthHelp's unique education-focused model. Furthermore, the focus on physician education enhances patient outcomes and safety by ensuring patients receive the right test or procedure at the right place at the right time.

PEER COLLABORATION

HealthHelp's physician-collaborative peer consultation model has helped thousands of ordering physicians decide the best treatment for their patients. Real-time access to peer experts provides timely and invaluable insight into treatment options. HealthHelp's clinical pathways were developed in collaboration with leading medical and oncology experts from across the country. The company employs independent radiologists, medical and radiation oncologists, orthopedic surgeons, cardiologists, and sleep specialists from established academic institutions and top teaching hospitals in the world to determine medical necessity based on nationally recognized standards of care.

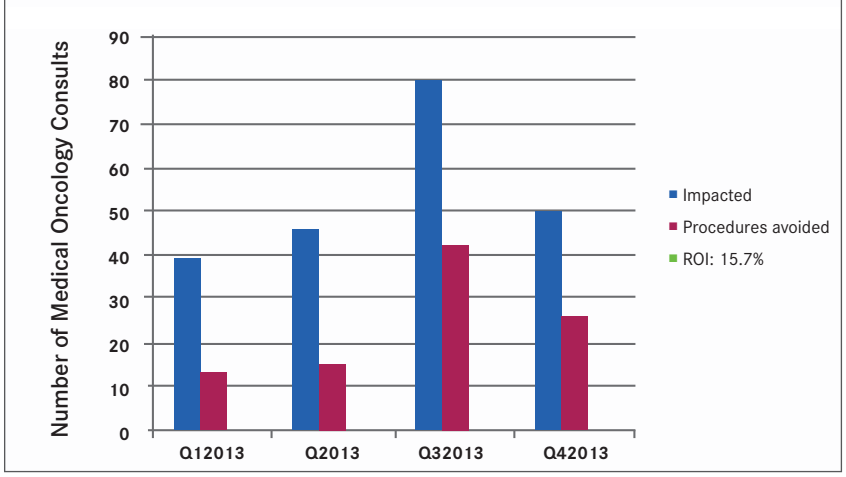
MEDICAL ONCOLOGY

The success and effectiveness of the Medical Oncology program is exemplified by a case study of one of HealthHelp's clients, a regional health plan in the Southwest. In 2013, the plan saw that 3 of 4 medical oncology requests resulted in a peer-to-peer consultation, resulting in a relatively high percentage change in treatment plan or withdrawal of request (**TABLE 1**). Due to the high-cost nature of medical oncology, even a slight change results in large savings and a sizeable return on investment (ROI). For this client, 216 cases were impacted, resulting in a 15.7% ROI (**FIGURE**).

TABLE 1. Number of Requests and Impact of HealthHelp's Medical Oncology Program for a Regional Health Plan (2013)

MEDICAL ONCOLOGY	Q1 2013		Q2 2013		Q3 2013		Q4 2013		TOTAL	
Measures	n	%	n	%	n	%	n	%	n	%
Peer-to-peer	230	82.4	196	73.7	394	74.6	345	70.1	1165	74.4
Impacted	39	14.0	47	17.7	80	15.2	50	10.2	216	13.8
Procedures avoided	14	5.0	16	16.0	43	8.1	27	5.5	100	6.4
Total	279	100.0	266	100.0	528	100.0	492	100.0	1565	100.0

FIGURE. Count of Medical Oncology Consults by Type for a Regional Health Plan (2013)



Savings are achieved by shifting to more cost-effective treatments and following clinical guidelines. For example, a switch from Neulasta to Neupogen means the average cost shifts from $4360 to $450. Colon cancer with KRAS mutation does not respond to erbitux (cetuximab); physicians should avoid this and other ineffective treatments that may only result in toxicity among patients. Thus, payers and patients save money while improving safety and outcomes for patients.

RADIATION THERAPY

HealthHelp's Radiation Therapy rogram improves quality and safety by reducing 4 undesirable outcomes:

1. Excessive radiation exposure. The radiation dose per treatment is too high or the total radiation dose exceeds a recommended level, which could result in secondary cancers.
2. Insufficient radiation dose to eradicate a tumor. The radiation dose per treatment is too low, or the total radiation dose is less than recommended.
3. Procedures with limited evidence to support improved survival. For example, stereotactic and proton-beam therapy have less than 5 years of data to show that they improve survival, whereas 2D/3D and IMRT have more than 10 years of data to support improved survival.
4. Significant complications. Understanding patient clinical information and using best-practices guidelines can ensure patients receive medically appropriate procedures. Further, HealthHelp's program provides continuity of care through triage to approg-priate wellness services, care advocates, and palliative care, which prevent many avoidable complications.

Savings are achieved by shifting to more cost-effective treatments and following clinical guidelines. For example, a switch from Neulasta to Neupogen means the average cost shifts from $4360 to $450.

Overall, about 30% of preauthorization consultations go to a peer-to-peer physician review, 14% are impacted, and 5% are withdrawn (TABLE 2). Recent study results confirm that while the consultative preauthorization process reduces utilization, it still provides doctors and patients access to appropriate testing. The study analyzed 4 years of clinical data, looking at cases where physicians' preauthorization review with a consulting radiologist led to a modified test request.

TABLE 2. Percentage of Requests in Radiation Therapy Receiving Peer-to-Peer Review, and National Impact (2013)

RADIATION THERAPY	2013 TOTAL	
Measures	Commercial	Medicare
Peer-to-peer	28.8%	37.2%
Impacted	15.3%	13.7%
Procedures avoided	5.3%	4.4%

The research examined data from 4 common neuroimaging sequences:

1. Request for head computed tomography (CT) modified to head magnetic resonance imaging (MRI)
2. Request for both head CT and intracranial computed tomography angiography (CTA) or both head MRI and intracranial magnetic resonance angiography (MRA) modified to a request for a single study
3. Request for a CT of both the head and sinuses modified to a request for a single study
4. Request for an MRI of the head and orbits modified to a request for a single study.

In 3 of the sequences, no provider reinitiated a study within 30 days. (Researchers chose a 30-day test period because it seemed a reasonable time frame for a doctor to order follow-up testing for a somewhat urgent problem if the first test was inadequate.) In the fourth sequence, only 4 of 64 (6%) withdrawn requests for head CT/MRI or head CTA/MRA were re-initiated within 30 days. Overall, for 99.2% of the requests that were modified through peer-to-peer consultation, the original requested test was not performed in the subsequent 30 days. This low re-initiation rate confirms that the collaborative consultation fulfilled the providers' clinical objective.[4] Again, patients received the right test at the right time, the first time.

SUMMARY

HealthHelp's Integrative Oncology Specialty Health Management program brings together a continual pathway for managing each cancer type, which creates cost savings and improved patient outcomes by utilizing the adaptive and unique program design. It enables patients to receive medically appropriate care, care management, and end-of-life services; provides education and risk management for providers; and generates significant savings for payers. Long-term improved outcomes are achieved by reforming the behavior of providers through a consultative and educative process. The focus is on giving the right care at the right time across the entire cancer continuum. This model program delivers sustainable cost savings to payers and patients while promoting patient safety and quality of treatment. **EBO**

REFERENCES

1. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-128. doi:10.1093/jnci/djq495.
2. Glover L. Oncologists worry about rising costs of cancer treatment. *US News & World Report* website. http://health.usnews.com/health-news/patient-advice/articles/2015/07/01/oncologists-worry-about-rising-costs-of-cancer-treatment. Published July 1, 2015. Accessed April 18, 2016.
3. Young RC. Value-based cancer care. *N Engl J Med*. 2015;373(27):2593-2595. doi:10.1056/NEJMp1508387.
4. Powell AC, Hippe DS, Long JW, Robinson JD. Reinitiation of withdrawn or modified neuroimaging requests after collaborative consultation. *Acad Radiol*. 2015;22(11):1433-1438. doi:10.1016/j.acra.2015.08.005.

Quality Metrics for Oncology in a Value-Based Reimbursement World

KIM CHARLAND, BA, RHIT, CCS, AND ROBIN ZWEIFEL, BS, MT (ASCP)

Healthcare is rapidly transitioning from a fee-for-service (FFS) to a value-based reimbursement world. This transition accelerated in January 2015, when HHS announced a new set of goals and a timeline for tying Medicare payments to quality or value through alternative payment models.[1]

HHS goals included linking 30% (up from 20%) of traditional Medicare payments through accountable care organizations and bundled payments by the end of 2016, and 50% by the end of 2018. HHS also set a goal of linking 85% of all traditional Medicare payments to quality or value by 2016, and 90% by 2018, through programs such as Hospital Value-Based Purchasing[2] and the Hospital Readmission Reduction Program.[3]

WHAT DOES THIS MEAN FOR ONCOLOGY SERVICES?

Cancer is one of the most common diseases in the United States, with more than 1.6 million individuals receiving a cancer diagnosis each year. About 77% of all cancers are diagnosed in people 55 years and older.[4] According to CMS,[5] the majority of those diagnosed are over 65 years and Medicare beneficiaries.

A *British Medical Journal*[6] article reported that the waste from cancer drugs costs Medicare and private insurers billions of dollars each year. In addition, chemotherapy services can include many post-acute care services (eg, physician follow-up visits, medication management, laboratory services, home care, hospice, etc) and impact the patient's quality of care, requiring a high level of care coordination between the various providers and services. Based on the HHS goals to increase quality-of-care outcomes and improve patient satisfaction while reducing costs, it is clear why the CMS chose oncology services as one of its specialty care models. (The first was the Comprehensive End-stage Renal Disease Care Model.)

The Oncology Care Model (OCM) is a multi-payer model where physician practices enter into payment arrangements that include financial and performance accountability for episodes of care surrounding chemotherapy administration to cancer patients.[7] The goal of this model is to provide higher-quality and more coordinated oncology care at a lower cost.

The OCM—a 5-year model with plans to begin in the spring of 2016—combines financial incentives, including performance-based payments, to improve care coordination, appropriateness of care, and access for beneficiaries undergoing chemotherapy. It will target beneficiaries receiving chemotherapy treatment and the spectrum of care provided to a patient during a 6-month episode following the start of chemotherapy. Physician practices that furnish chemotherapy treatment may also participate in the OCM.

Participating physician practices will be eligible for 3 payments under the OCM:

- Regular FFS payments (including average sales price + 6% for drugs and biologicals)
- $160 per-beneficiary-per-month payment for care management (up to $960 per beneficiary per episode)
- Performance-based payment where participants may receive up to the full difference between a target spending price and their actual expenditures, based on their performance on a range of quality measures. This payment offers an opportunity to share in the savings from this model.

The OCM requires that participating physician practices meet certain practice transformation requirements to improve management and coordination of care. They include the following:

- 24/7 patient access to a clinician who has real-time access to the practice's medical records
- Attestation and use of the Office of the National Coordinator for Health Information Technology–certified electronic health record (EHR)
- Utilize data for continuous quality improvement
- Provide core functions of patient navigation
- Document care in accordance with the Health and Medicine Division (HMD; formerly the Institute of Medicine) Care Management Plan
- Treat patients with therapies consistent with nationally recognized clinical guidelines.

Physician practices also will be required to meet certain quality and performance measures to receive their performance-based payment. CMS provided a primary list of over 30 quality metrics and indicated that it will continue to work with stakeholders to finalize a reasonable set of measures. A complete list of quality and performance measures can be found on pages 25 to 28 of the OCM Request for Applications.[8]

ADOPTING QUALITY STANDARDS

So what can physician oncology practices be doing from a quality-metric perspective to ensure appropriate documentation and reporting of chemotherapy services? There are several processes to consider adopting, including the following.

Responsible Staff Members

Participating practices must be adequately staffed and prepared to coordinate appointments for diagnostic and therapeutic services. When indicated, the practice must ensure that the complete medical record is available at the time of all scheduled appointments. Coordination of care will include maintaining communication with the patient and/or family members. At times it may be necessary to arrange for, or assist with arrangements for, translation or interpretation services, transportation to/from appointments, child care or elder care, follow-up service, and financial support. The provider or staff may be called upon to provide access to clinical trials, to advise on participation in a trial, or to provide referral to services such as support groups. Additionally, processes must be in place to monitor patient satisfaction levels.

Documentation

Participation in the OCM requires development of a plan that contains the 13 components listed in the HMD Care Management Plan for each patient participant. The provider's determination to follow a nationally recognized clinical guideline or to deviate from the clinical guidelines for a particular patient should be explained within the record. An explanation that justifies the clinical decision making that impacted the treatment choice for each patient (eg, participation in a clinical trial) should be included. The care plan should reflect the patient's participation in its development and should refer to the patient's decision to move forward with the chemotherapy treatment plan.

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Quality data collection and reporting done by different staff utilizing different processes results in an uncoordinated effort. When everyone works in their own silos, the reported data often conflicts and not everyone collecting that data fully understands what it means.

Be sure to include information that provides an estimated total of the treatment cost and the expected out-of-pocket costs to be paid by the patient. Depending on the drug regimen, it is possible that the Medicare drug spending[9] dashboard would provide supporting data; it may address drug-specific estimates for per-patient annual spending and the average annual beneficiary cost share for Part B and Part D prescription drugs being studied by Medicare due to the high cost.

ELECTRONIC HEALTH RECORD

Care coordination requires communication among service providers in order to track hospital admissions (including the number of Intensive Care admissions), hospital readmissions, emergency department visits, and/or hospice admissions. Tracking of this information extends beyond the treatment phase to 6 months following the OCM FFS episode of care.

Compatibility among the reporting systems of the diagnostic service providers, such as a hospital or an independent reference laboratory, interpreting physicians (eg, pathologist, radiology), or genetic counselors is essential. This ensures that everyone involved has access to necessary diagnostic information including "specific tissue information, relevant biomarkers, and stage." *Remember:* Participating providers must attest to their accessibility 24/7, the effective use of EHRs, and real-time access to the medical record and comprehensive plans.

Reporting

Specific quality measures are in place for colorectal cancer and breast cancer. Clinical quality-of-care monitoring is outlined for colon cancer, breast cancer, and prostate cancer. All quality measures required by the program must be documented by the participating providers and reported to CMS. (Required components can be found in Appendix C of the OCM request for application.) A provider's reimbursement could decrease if the required quality measures are not reported.

We have found that quality data collection and reporting done by different staff utilizing different processes results in an uncoordinated effort. When everyone works in their own silos, the reported data often conflicts and not everyone collecting that data fully understands what it means. The goal, instead, is for those involved to understand how their piece of the quality puzzle affects others pieces. They also must understand all of the processes related to quality data collection and reporting. The following steps may help achieve that goal:

- Identify a multidisciplinary team to develop workflow and shared processes. It is critical to establish a single point of reference for providers. Be sure to promote a culture of transparency and integrity. It is important that your team members understand what your data is showing so that they know how to address issues and opportunities that may be identified.
- Perform an operational review of all quality data collection and reporting functions in each relevant practice area. Assess data collection and reporting processes, as well as the actual data reporting and outcomes. It is important to ensure that processes are working and that everyone understands what your data is showing.
- Consider a focused review (internal and/or external) of all reporting and audit mechanisms to eliminate duplicate efforts. Ensure consistent data reporting by investing in a comprehensive system. Develop a corrective action plan for your practice that includes documentation guidelines and clinical definitions for nonclinical and clinical staff. Use technology whenever you can to work more efficiently, but be careful not to become too technology-dependent. You still need a person to interpret and analyze the data.
- Assess documentation and EHR capabilities at your practice. Is your EHR optimally set up for collecting quality data?
- From a financial perspective, know where your practice stands on each selected measure for the baseline period and identify which measures have the best rate of return. You also want to ensure that your pricing is competitive and defensible.
- Educate your entire multidisciplinary team. All staff should have a baseline starting point and a way to maintain their knowledge levels, as quality-related information is being released sometimes on a daily basis.

Practices must begin to review their quality practices and data collection on an annual basis much like they review their other processes (such as coding and charge masters). External auditors could be brought in to conduct reviews once a year, supplemented by an internal team, with one person assigned to lead and coordinate. This will be the only way to ensure that processes are working optimally and data is being reported accurately.

While this article has focused on the OCM for physicians, it is important to look ahead and be prepared for similar programs on the hospital side, which CMS addressed in the proposed rules for the 2016 Hospital Outpatient Prospective Payment System.[10] Insights of topics that may be targeted in the future can be found in the comments submitted by the American Society of Clinical Oncology (ASCO) to CMS on August 31, 2015. ASCO focused on reimbursement for cancer drugs, packaging of drugs and drug administration add-on codes, and increasing high-quality, high-value cancer care in outpatient hospital settings.[11] **EBO**

REFERENCES

1. Better, smarter, healthier: in historic announcement, HHS sets clear goals and timeline for shifting Medicare reimbursements from volume to value [press release]. Washington, DC: HHS website; January 26, 2015. https://www.hhs.gov/about/news/2015/01/26/better-smarter-healthier-in-historic-announcement-hhs-sets-clear-goals-and-timeline-for-shifting-medicare-reimbursements-from-volume-to-value.html.
2. Hospital-based purchasing. CMS website. https://www.cms.gov/Medicare/Quality-initiatives-patient-assessment-instruments/hospital-value-based-purchasing/index.html. Updated October 30, 2015. Accessed May 23, 2016.
3. Readmissions Reduction Program. CMS website. https://www.cms.gov/medicare/medicare-fee-for-service-payment/acuteinpatientpps/readmissions-reduction-program.html. Updated April 18, 2016. Accessed May 23, 2016.
4. Cancer facts and figures 2014. American Cancer Society website. www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/. Accessed May 23, 2016.
5. Oncology care model fact sheet. CMS website. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2015-Fact-sheets-items/2015-02-12.html#_ftn1. Published February 12, 2015. Accessed May 23, 2016.
6. Bach PB, Conti RM, Muller RJ, Schnorr GC, Saltz LB. Overspending driven by oversized single dose vials of cancer drugs. *BMJ.* 2016;352:i788. doi:10.1136/bmj.i788.
7. Oncology Care Model. CMS website. https://innovation.cms.gov/initiatives/oncology-care/. Updated March 3, 2016. Accessed May 23, 2016.
8. Oncology Care Model, request for applications, February 2015. CMS website. https://innovation.cms.gov/Files/x/ocmrfa.pdf. Updated June 3, 2015. Accessed May 23, 2016.
9. Medicare drug spending dashboard 2014. CMS website. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/Medicare-Drug-Spending/Drug_Spending_Dashboard.html. Accessed May 23, 2016.
10. Department of Health and Human Services. *Federal Register.* 2015;80(130). https://www.gpo.gov/fdsys/pkg/FR-2015-07-08/pdf/2015-16577.pdf. Published July 8, 2015. Accessed May 23, 2016.
11. ASCO responds to proposed rules on 2016 hospital outpatient prospective payment system. American Society of Clinical Oncology website. https://www.asco.org/advocacy-policy/asco-in-action/asco-responds-proposed-rules-2016-hospital-outpatient-prospective. Published September 1, 2015. Accessed May 22, 2016.

A Discussion on Oncology Quality Tools:

Filling in the Gaps

SURABHI DANGI-GARIMELLA, PHD

Improving the services that an organization provides—whether these are commercial services or those related to healthcare—is not possible unless one gathers information on the service, collates it, improves on it, and implements the changes in the field. This process is fraught with challenges at every step as it continues to evolve and develop.

Evidence-Based Oncology organized a discussion on the topic among experts who evaluate and utilize quality measurement tools at the point of care. Linda Bosserman, MD, assistant clinical professor and staff physician, City of Hope; Jason C. Goldwater, MA, MPA, senior director, National Quality Forum (NQF); and Jennifer Malin, MD, staff vice president, Clinical Strategy, Anthem, joined me to talk about processes that help identify the most valuable metrics and the importance of making these metrics relevant for use in the clinic. The panelists also discussed the challenges with extracting data from electronic health records (EHRs) across independent data systems, evaluating and implementing the metrics, and data gaps that currently exist in the field of quality measurement.

According to Bosserman, quality measurement is an indicator of the real care that is delivered; it provides insight into what we know about care and helps improve on it. "You can only [improve quality] if you measure it and try to understand it," she said.

Malin said that although quality measurements have been integrated into the operations of most other industries, healthcare has arrived late in the game. She thinks that for a long time now, we have been doing things a certain way in healthcare without knowing why. "As Dr Bosserman says, in order to know what we're doing, we have to measure it so that we have an idea of what we're doing today and how we can improve. We can only identify the areas that we need to improve if we measure what we're doing," Malin said.

There are 3 important qualifiers for measuring quality, according to Goldwater.

- Ensures that the best evidence-based practices and the best science are being used in patient care by developing and maintaining a good quality metric.
- Helps set a threshold for what is construed as good quality care and can improve care where it is lagging. It also helps compare the quality of care delivered across various practice settings.
- Allows us to keep pace with the way healthcare is evolving.

Back in the 90s, as the field was evolving, researchers were baffled about converting clinical outcomes into process measures. "Now, you flash forward to 2016. There are more than 600 NQF-endorsed measures and probably approximately 2500 quality measures overall. Because we've been able to develop measures and figure out ways of evaluating clinical outcomes and processes and structures, it's allowed us to keep in line with the advances in medicine," Goldwater explained.

DEFINING A GOOD METRIC IN ONCOLOGY

Goldwater provided an overview of the process that NQF follows when evaluating these quality measures. A standing committee of experts from diverse groups—payers, clinicians, and hospitals—reviews the metrics and their applicability and ease of use in the clinic. Explaining the rigor of the evaluation process, Goldwater said, "The measure has to be reliable; it really does have to be able to produce a metric of value. It has to be valid, so the metric is measuring what it intends to measure. It has to be feasible, so it is something that could actually be used, particularly with the rapid implementation of electronic health records over the last 10 years."

He believes that the measure should be implemented into an EHR or a registry, and should not significantly interrupt the provider workflow or steal time away from patient care. "That's never the intent. The intent is to continue to spend time with the patient by also understanding what the best practices are for quality and being able to have data populate that measure to indicate the threshold at which we know quality is being reached," Goldwater explained.

MEASURING PERFORMANCE: WHAT'S IMPORTANT FOR WHOM

Payer

Quality metrics play a significant role in informing health plans on the performance of clinics and health systems. So when payers evaluate the clinical and performance outcomes of a clinic, what are the most important quality metrics? Malin said that the field of quality measurement is still in its infancy, and current data systems are constrained in their capacity to convert clinical data into meaningful quality measures—especially in cancer care. "It's very challenging to get quality measures that are really meaningful that don't put a burden on the practice," she said.

Malin explained that for health plans, the interests of their members are the primary concern. Patients and their caregivers want to know which practice can provide them with the highest quality care—information that is still somewhat elusive. Malin believes that existing quality measures are merely conversation starters between payers and providers. "As a health plan, we really want to get to that next step of transparency and being able to share the quality scores of practices with our members so that they can use that information in helping to decide where to go to get care."

When asked to comment on how payers weigh process measures versus outcomes measures, Malin said it has to do with the context. She provided an example of postsurgical outcomes in patients diagnosed with pancreatic or esophageal cancer, and how the site of surgery—the hospital where the surgery is conducted—can influence 30-day mortality, anywhere from 5% to 25%. According to Malin, documented evidence has shown that low-volume hospitals have higher mortality rates, information that a patient may not be aware of when he or she selects a hospital for treatment.

This is changing, Malin said, although slowly, and the California Healthcare Foundation has launched an initiative to promote patient awareness on the performance of healthcare clinics and bigger health systems. One such effort is a website that allows visitors to compare and contrast different healthcare providers and access their quality scores on patient experience, rehospitalization, and patient safety.[1]

Commonly used metrics, like the 5-year survival rate, are "not very helpful in the setting of looking at quality of care where you really want to know what is happening now. It doesn't really help me to know how this practice was doing 5 years ago. I want to know how they're doing now when they're taking care of patients," said Malin. Process measures would definitely be more valuable in that situation, she added. Malin

ABOUT THE EXPERTS

JASON GOLDWATER, MA, MPA

Mr Goldwater is senior director, Natonal Quality Forum.

JENNIFER MALIN, MD

Dr Malin is staff vice president, Clinical Strategy, Anthem.

> **"As a health plan, we really want to get to that next step of transparency and being able to share the quality scores of practices with our members."**
>
> —JENNIFER MALIN, MD

ABOUT THE EXPERT

LINDA BOSSERMAN, MD

Dr Bosserman is assistant clinical professor and staff physician, City of Hope.

believes in evaluating both process and outcomes measures to see an improvement in care quality, because "if you have an outcome measure it does not really tell you what you need to do to improve the quality of care."

Provider

Bosserman distinguished between the clinical and the patient perspectives. For patients, their primary concern is to see their health improve. If clinics fail to measure patient performance, then the information they gather would only be an extension of clinical trial data. She explained that trial data alone are not the best indicator of outcomes, because trials are conducted in a controlled environment and may not always account for differences in age, ethnic diversity, or comorbidities. "Patients want to be engaged. They want to know what they can expect. They want a good experience. They want to have their issues addressed. They also want to know the cost," Bosserman said.

For a clinician, the ultimate goal is to improve the outcomes of patients with multiple comorbidities from the care they receive, hopefully with the adequate use of EHRs. But a continuous improvement is not possible without a learning system that provides feedback. "Once you start measuring, you keep learning and you keep improving your processes and you standardize more," Bosserman said. She firmly believes that patient engagement and targeting the right treatment to the right patient can transform the system, for both the patient and the care team.

BUILDING PRO TOOLS

Although there has been movement in healthcare to incorporate patient-reported outcomes (PROs) into quality measurement, it's been a long, winding road to identifying the measures to include. Gathering this data is a challenge that researchers are still struggling with.

There are several barriers to PRO measurement, Bosserman said, starting with what measures should be included. "How can we prompt our patients to give us information so we can walk into that visit and make it really effective—whether it's a phone visit or an office visit or an interval visit?" She then explained the strategy developed by her own practice with respect to PROs. The physicians/nurses at her practice believe that interactions with patients should be all about the medications they are taking, and whether they have any issues with their treatment, and if they want those issues addressed. She added that clinics should also track whether the patient received any alternate care between visits.

"If we can integrate the patient-reported outcomes into our decision making and our clinic visit, whether it's a phone call or however that visit goes, we can much better address patient symptoms and hopefully minimize them so they're not getting sick between treatments and we're keeping them as healthy as possible," Bosserman said.

Goldwater believes that PRO tools are hard to build, especially since they need to perfectly capture the patient's viewpoint on relevant and meaningful outcomes. The tool should ultimately be able to let the patient perform an action to improve their quality of care or aid the physician in doing so. "It's a lot easier when you have an outcome measure that says if somebody comes in with a heart attack, give them aspirin right away—which now is somewhat of a common practice. It's much more difficult to try to understand what the patients really want if they come in with these symptoms or if they have these signs or specific concerns."

The background information that is captured to help build the quality measurement tool is extremely important, Goldwater stressed, and the patients need to understand the information they are being asked to provide and then fill it out accurately as it relates to them. The measure then has to align with what the patient filled out. Testing these measures is a challenge in itself, he said, with sometimes more than a year needed "to find the appropriate sites, to deploy the measure, get the data, and look at the data in comparison to the measure. It is also important to ensure that the measure is reliable, valid, feasible, usable, and then make the necessary refinements as necessary."

Added dimensions to testing the PRO measures include identifying the right sites and the right patients to fill out the tool that will populate the measure. Goldwater said that while progress has been made, with patients more capable of self-reporting on information associated with their health, a lot remains to be achieved.

OVERCOMING DATA SILOS IN QUALITY MEASUREMENT

The lack of interoperability across data systems remains a significant barrier to improving healthcare quality. The panel continued their discussion on ways to overcome this issue. Interoperability across data banks is key to make data more meaningful. "While we have the Office of the National Coordinator promulgating a variety of data standards and vocabularies to control what that information looks like and how that information reads, there's no mandate that they have to be using these particular standards for laboratory tests, for laboratory orders, for diagnoses, or for procedures," said Goldwater.

He clarified that there are specific codes in oncology that define a certain service or clinical information, but that the use of these codes is not mandated. Subsequently, the lack of standardization and diverse vocabularies across data systems complicates matters. Goldwater went on to suggest one particular solution to this problem: creating a unique patient identifier. Having a unique patient identifier for every patient would help track their health records and make it easier to pull their information out from various sources, he said.

We are in the transition phase with interoperability, said Bosserman. "Projects like CancerLinQ[2] that are now linking up multiple different electronic records and different data sets and CMS sets and SEER data sets—they can begin to feed all that information on a specific patient back to the practitioners." Hoping for a bigger role for the federal government, Bosserman added that just submitting information to meet compliance requirements may not be the best practice for clinics to follow. "We need to start moving from these volume-control measures to value-based compliance measures," she said.

As a payer, Malin provided a very different perspective. The challenge she experiences with the diversity of clinical practices that Anthem's members are enrolled in extends beyond data silos. "Not all of our oncologists and physicians use EHRs, so extracting member data faces the biggest challenge right there, which can then increase the burden on those practices if we try to gather that data from them," she said. To circumvent the issue, Anthem is using data from its prior-authorization and clinical pathways program, the Cancer Care Quality Program. "We can use that data, which we then get across all practices and members, in order to look at the quality of care being provided," Malin explained.

Although Anthem has been working with EHR vendors to create an interactive system with a 2-way data transfer, problems arise when some practices have very sophisticated EHRs that link to their billing system and have in-built quality measures, while others are a solo practice that is completely paper-based. "Thinking of it from a health plan perspective, I have to come up with a solution that bridges all of those practice settings," Malin said.

Bosserman is quite confident about the potential of CancerLinQ in promoting the quality of cancer care. "I think that

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> —JASON GOLDWATER, MA, MPA

platform under the SAP group is going international and will be a foundation of a system that can help us going forward on a larger level. It's an evolution," she said. NQF is interested in knowing how ASCO is planning to leverage the data that they gather via CancerLinQ. Will it be used "to populate measures that are already existing or to, perhaps, gain a better understanding of measures?" Goldwater asked. He believes that the platform could have a tremendous impact if it can help develop a new measure or provide updates on an existing measure.

Bosserman said that CancerLinQ has already had a significant impact on data accuracy. In her mind, the bigger challenge is with "structuring the processes in the clinics or the apps to collect the discrete data in both systems of identified data accuracy and data entry blanks."

STANDARDIZING ONCOLOGY QUALITY MEASURES

How does a health plan finalize its reporting requirements of oncology clinics and practices? Does Anthem, for example, follow CMS' data-reporting requirements?

"What we have been focusing on, and reports that we're going to be providing to practices sometime [in June 2016], include adherence to our pathways, [emergency department] utilization, hospitalizations during treatment, and access to hospice and other end-of-life care," Malin said. She added that these measures are a part of the Oncology Care Model (OCM)[3] and have been advocated by the Community Oncology Alliance and other groups. For Anthem, "Developing a smaller set of meaningful measures that can be implemented across their entire network is a substantial challenge." Malin said that Anthem has tried to develop measures that can help practices compare the quality of care they deliver with other practices that treat Anthem members. Whereas these measures may not match up with the requirements of the Physician Quality Reporting System, she said they are in synch with the OCM.

As for the administrative burden of all the reporting on physician practices, Malin said that America's Health Insurance Plans, commonly refereed to as AHIP, has a working group that has tried to short-list measures across commercial plans and CMS, and some of these measures are a part of the OCM. "Figuring out the most efficient, and least burdensome, way for [physicians] to report data is a big challenge," Malin said. Commending the rigor and the standards used by NQF in evaluating these measures, she said, "Measures that really get used for pay-for-performance and accountability, most eventually end up being reviewed by NQF."

GAPS IN CARE MEASUREMENT

The presence of an exhaustive list of measures is not necessarily an indicator of a flawless system, as data gaps may still exist. Malin agreed, identifying several different gaps:

- Quality measures may be too general to differentiate between high and low-quality care
- There remains a need for cross-cutting aggregate measures, especially in cancer, with so many different tumor types and subtypes
- Succinct measures are necessary, but rare cancers cannot be left out.

Goldwater said that NQF leads the Measure Application Partnership,[4] a product of the Affordable Care Act, which brings together leading experts in oncology from numerous sectors: payers, providers, and consumers, to discuss measure gaps that need to be filled. These recommendations are, in turn, forwarded to CMS. He said that NQF has, over the years, identified gaps in palliative and end-of-life care in oncology. Additionally, there is a lack of information that can help understand where the disparities in cancer care lie, "to effectively then know what sort of treatments are necessary, what sort of preventions or screenings are needed, and where to emphasize efforts."

Bosserman expressed her faith in the potential of the 2-way EHR system that Malin discussed, which will help doctors keep track of alternate care that their patients seek. "We don't always get that real time in the practice unless you put some system in place that asks the patients, measures it, and somehow keeps track of it," Bosserman said. She believes that such gaps in information can be filled via a partnership between providers and payers. "The exciting thing is that the conversations between providers and health plans have really opened up. Dr Malin is one of the leaders in the field, and others at Aetna and United have really begun to reach out and try to partner with practices to start finding more solutions." **EBO**

> **"The exciting thing is that the conversations between providers and health plans have really opened up."**
>
> —LINDA BOSSERMAN, MD

REFERENCE

1. CalQualityCare.org website. http://www.calqualitycare.org/. Accessed May 31, 2016.
2. Caffrey M. ASCO announces partner for groundbreaking CancerLinQ platform. *The American Journal of Managed Care* website. http://www.ajmc.com/focus-of-the-week/0115/asco-announces-partner-for-groundbreaking-cancerlinq-platform. Published January 21, 2015. Accessed May 31, 2016.
3. Dangi-Garimella S. Experts discuss Medicare's new Oncology Care Model. *Am J Manag Care*. 2015;21(SP8):SP288.
4. Cassel CK. Making measurement meaningful. *Am J Manag Care*. 2015;21(5):332b-c.

Oncology Payment Reform: *Payers and Providers Discuss APM and Beyond*

SURABHI DANGI-GARIMELLA, PHD

Everyone in healthcare is currently grappling with what payment reform will look like in the coming years, and oncology is no exception. How do payers, providers, and health policy experts view existing transitions within healthcare, and where do they foresee potential changes in the future?

An expert panel at The Community Oncology Conference: Innovation in Cancer Care, held in Orlando, Florida, April 13-15, 2016, provided their insight. Panel members included, Jeremy Behling, MBA, vice president of operations & practice innovation, Florida Cancer Specialists and Research Institute; Michael Kolodziej, MD, national medical director, Oncology Strategies, Aetna, Inc; Edward J. Licitra, MD, PhD, medical oncologist from the Regional Cancer Care Associates, LLC; Kavita Patel, MD, senior fellow, The Brookings Institution, Washington, DC; Bhuvana Sagar, MD, medical director, Cigna Healthcare; and Mark E. Thompson, MD, Oncologist, The Mark H. Zangmeister Center.

Commenting on the new alternative payment models (APMs), in particular, the recent Medicare Part B demonstration project,[1] Patel said, "Medicare is doing a sprint here. The provisions in Part B represent just a slice of the pattern that we are seeing within, say, the orthopedic space."

Thompson responded that there is a demonstration project in the APM space that has been proposed, but that it's still in the making. "Many of us are feeling that time is ticking very quickly since MACRA [Medicare Access and CHIP Reauthorization Act of 2015]," he said. "And the only APM out there now is the OCM [Oncology Care Model]. But I am not sure that OCM is the right model for everyone."

How about the payers? Are they developing innovative reimbursement methods in the APM space for oncology? Kolodziej said that Aetna has been collaborating with providers who have participated in the Oncology Medical Home (OMH) project and has successfully implement structured clinical pathways. "United, Anthem, and Cigna all have their own perspectives. They all look at reducing the cost of care and also improve the quality of care," he said.

"Cigna has been in the primary care space for a while in oncology, and the model has the same intent as others in the field: simple for physicians to navigate, emphasizing a shared decision-making process and patient-centricity," Sagar told the audience. To which, Kolodziej responded, "It's important to note that even if we criticize CMS for all the pilots they are experimenting with, they are doing the exact same thing."

Providers, on their end, have also been working with health plans to develop payment models that suit their practice. "We have a good relationship with Horizon in New Jersey," said Licitra. "Many of these are episode-based pilots. To better understand where we stand in New Jersey and to understand variance in sites of service or physicians. We are working with Horizon to provide value for the choice of care patients choose," he said.

So what's not working? What do physicians, oncology clinics, and those who cover these services think has failed within the system? "The biggest is lack of data transparency," said Behling. "We are involved in accountable care organizations (ACOs) and other models, and it's difficult to assess quality for the various health conditions of each patient if we don't have easy access to their health data. OCM and Medicare's model are a good start," he added

However, measuring the quality of care delivered under OMH has been a challenge for Cigna, said Sagar. "How we measure quality and keep it meaningful is important. How do we understand building episodes? That's what we are trying." With the multitude of molecular subtypes of each cancer, defining episodes of care is very complicated," she explained. "We are definitely trying to change in-patient utilization and the Medical Home model is useful for that."

How about the strength of the data that payers actually gather? Are there gaps in the data that payers receive from clinics? Kolodziej pointed out that the data gaps create opportunities to improve on the payment models and also leave room to improve on things, such as length of stay. He emphasized, however, that the data from smaller practices are not big enough to draw meaningful conclusions. "These clinics just don't have the volume, the number of patients you need to draw conclusions." Since the data are not well powered, outliers can create a huge problem, according to Kolodziej.

The discussion then moved on to payment reform and what's failing and what needs to change. "Practices that are a part of the ACO model have done well with the value-based modifier payment models, but they have no idea why," said Patel. "On the contrary, there are practices that are proactive with quality improvement and monitoring their care delivery meticulously, but they often don't seem to perform well with the model. My biggest fear with some of the MACRA pieces is that we are going to have every subspecialty offer their own APM."

Patel said that payers, including commercial, Medicare, and Medicaid cannot completely revamp their operations. They do need small, pilot demonstration projects to experiment with. "It's nicer to have models that look cleaner," she said.

Speculating on the future of the world of payment models, Sagar said, "There's value-based contracting in the drug space." She explained that while there are several pathways being developed in oncology, it's important to figure out who's the best person to define them and also to understand best practices that can target drug savings. "Things like unnecessary imaging can be avoided to reduce utilization. The question remains, 'Can we develop episodes that can include some of these nuances?'"

For Kolodziej, the future in oncology care lies with episode-based payment. "What is happening is that both oncologists and payers are looking at what constitutes the outcomes-based trajectory. A local payer and provider can do it by sitting across the table. But I can't…I have to think about all 50 states," he said. He also believes that elimination of buy-and-bill and introduction of a management fee for oncologists—something that UnitedHealth did—is coming.

For Licitra, as a provider, care management is a challenge. "It's about figuring out where do we stand with respect to our physicians and how do you modify physician behavior at every level. And, at the end, how do you provide value-based services?" Behling added that at their practice, their focus is on providing patients with a more comprehensive care. "We are trying to add value for our patients on the front end—navigation, nutrition, and social work," he said.

According to Thompson, only 2 things change physician behavior: what's in their wallet and how they perform compared with their peers. "So value does not trouble me. Because value is finally derived by physicians and their staff," he said. **EBO**

ABOUT THE PANELISTS

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Dr Sagar is medical director, Cigna Healthcare.

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Dr Licitra is medical oncologist, Regional Cancer Care Associates, LLC.

JEREMY BEHLING, MBA

Mr Behling is vice president of Operations & Practice Innovation, Florida Cancer Specialists and Research Institute.

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Dr Patel is senior fellow, The Brookings Institution.

MICHAEL KOLODZIEJ, MD

Dr Kolodziej is national medical director, Oncology Strategies, Aetna Inc.

REFERENCE

1. Dangi-Garimella S. Oncology payment reform: payers and providers discuss APM and beyond. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/new-payment-model-will-test-high-value-prescription-drug-use-under-part-b. Published April 15, 2016. Accessed May 24, 2016.

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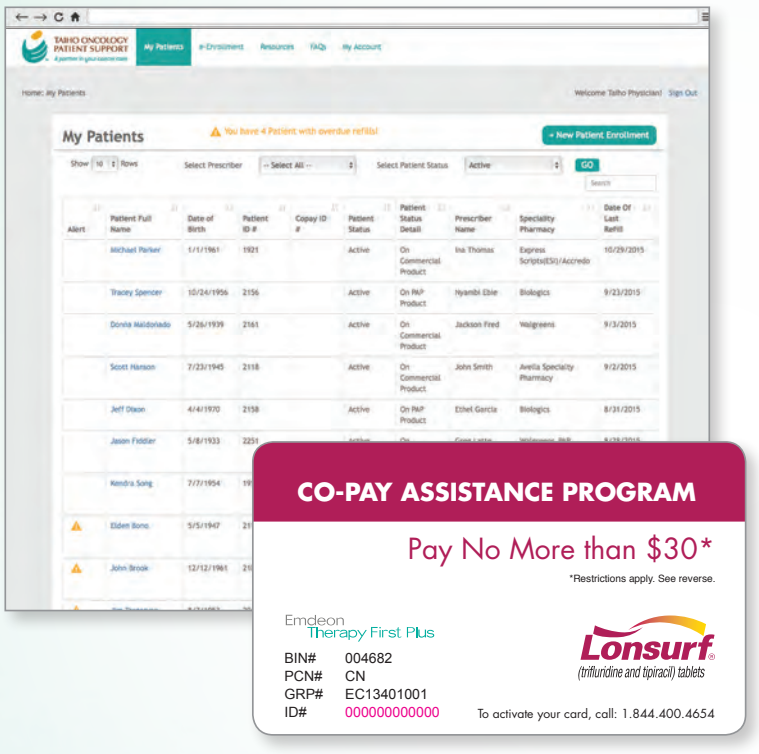

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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.

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.

An Update on the Oncology Medical Home Model at the COA Conference

SURABHI DANGI-GARIMELLA, PHD

Providing quality care that values the requirements and needs of individual patients in an integrated and comprehensive manner, and at lower costs, is the premise of the Oncology Medical Home (OMH). There have been several advances and improvements in the OMH, and accreditation of the model by the American College of Surgeons' Commission on Cancer (CoC)[1] has further strengthened the process to ensure the delivery of quality cancer care.

Representatives from 3 clinics that successfully participated in the CoC accreditation process sat on a panel on the first day of The Community Oncology Conference: Innovation in Cancer Care. The panelists included, Marsha DeVita, ANP-BC, chief clinical officer, Hematology Oncology Associates of Central New York; Bruce J. Gould, MD, president and medical director, Northwest Georgia Oncology Centers, PC; and Barbara McAneny, MD, chief executive officer, New Mexico Cancer Center & Innovative Oncology Business Solutions.

Gould provided a historic perspective on how the OMH evolved years ago. The Community Oncology Alliance (COA) had a board member, John Sprandio, MD, who presented a new oncology care practice model to the COA board in early 2011. "This was a model that he followed in his clinic in Philadelphia—a more patient-centered model that was cost saving. He called it the OMH model," Gould said. "But this was a single practice in Philadelphia. So COA decided to expand on it and gathered input from diverse stakeholders, including patients, patient advocates, payers, and providers. We refined and defined the model with input from our steering committee," he added.

Gould explained that the model places tremendous emphasis on patient values. "Patients want more engagement in decision making, easy access to patients, insurance navigation, not wanting to call 911, etc. Payers are more focused on standardizing care and differences in reimbursement based on site of care."

But there's a lot that physicians do for patients, such as financial counseling, that cannot be reimbursed. "So we came up with processes of care, such as a triage pathways; having frank, end-of-life discussions—and generating the relevant paperwork for it—among many others. We also developed quality measures that are reported to payers and other stakeholders. But the focus is on the patient," added Gould. "We then developed a patient survey to understand how they view the value of their quality of care. This has been adopted by payers such as Aetna, as well." Practices can access patient feedback and try to improve and reengineer how things are managed in the clinic so they can meet their patients' expectations. "We have been working with CoC to develop the medical accreditation program. We have had 10 accredited medical homes in a span of 1 year," said Gould.

McAneny, who has initiated the COME HOME project at her clinic in New Mexico, introduced the audience to the triage system followed at their clinic, which has a substantial impact on the efficiency, patient quality of care, and cost. "In my practice in New Mexico, where we take care of a significant number of less-privileged patients, we have to deal with a lot of issues with how we ensure patients get the care they need," she said. Considering the increasing cost of care, cancer patients are twice as likely to go bankrupt she said.

McAneny explained that her clinic received funding from the Center for Medicare & Medicaid Innovation (CMMI) to develop a model that can redefine quality care and save costs. "Through this model, we defined episodes of care and quality measures. We also asked, 'What do patients value most?'" she said. The COME HOME project was the result of the CMMI grant, and it incorporated patient and practice experience.

An important focus of their model is triage. "We made sure that when patients call in, they could speak to someone who understood their case, the drugs they took, and the side effects they are susceptible to," all in an effort to ensure quality and keep costs low. "If they can stay out of the hospital, it can't just control costs, but also keep patients healthy," she emphasized.

McAneny said that their triage pathways are built to understand the symptom-specific pathways. "We are working hard to ensure our nurses are trained to do that. We found that we can ensure savings for patients, practices, and the healthcare system, as a whole, by keeping the patient out of the hospital." She then provided details on the triage system and the patient data that the nurses access to help them manage their symptoms when they call in.

"We have to be able to manage the patients, have to ensure that they get what they need, and we need to have an adequate system in place to support the process. This will help keep patients out of the hospital and to keep the costs low," she affirmed.

DeVita, a nurse practitioner, provided insight into the working of their practice in New York. "We were part of the CoC pilot of the OMH. It's all about the quality of care, value of care, and being patient-centered. This being central to our practice, it helped us get structure to what we did and to do it right." Patient access was most important, according to DeVita. "OMH gave us better handle on our daily working to ensure patients get access as they call in." Telephone triage is also extremely important, she said. "This has been very valuable to help take care of patients at the early stage before there is an emergency."

DeVita emphasized that patient education is of utmost importance to ensure patients understand the process. Their clinic has developed the most comprehensive approach to care, with services that include financial navigation and clinical and psychosocial support. "Our practice provides team-based care which involves a physician, a nurse practitioner, a registered nurse, and a navigator." Every morning, the team holds a "huddle" to exchange information on all the patients scheduled for a clinic visit that day. The broader team, she said, includes social workers, a dietician, and a cancer rehabilitation specialist.

"Quality feedback from the patient is extremely important to help improve our performance. So the OMH helps restructure the clinic's functioning and also allows continuous feedback-based improvements. We do consider individualized values and needs of each patient and translate them into the care delivered to them," said DeVita. **EBO**

REFERENCE

1. McKellar DP, Bane C, Carter MA, Knutson A, Chiappetta V, Gamble B. The Oncology Medical Home—beyond clinical pathways. *Am J Manag Care*. 2016;22(SP5):SP164-SP165.

ABOUT THE PANELISTS

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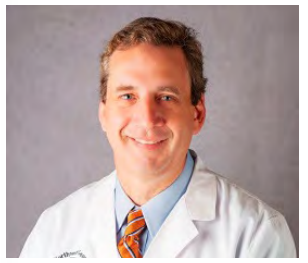

BRUCE J. GOULD, MD

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> **"We have to be able to manage the patients, have to ensure that they get what they need, and we need to have an adequate system in place to support the process."**
>
> —BARBARA MCANENY, MD

Aligning Reimbursement With Quality: *Are We There Yet?*

SURABHI DANGI-GARIMELLA, PHD

ABOUT THE PANELISTS

RANDY BROUN, MD

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RICH SCHIANO

Mr Schiano is chief executive officer of Oncology Hematology Care.

> **"We have a weekend clinic, which helps patients. We also have patient navigators to help patients navigate the healthcare system, as well as the financial aspects of care."**
>
> —RANDY BROUN, MD

On the first day of The Community Oncology Conference: Innovation in Cancer Care, held in Orlando, Florida, April 13-15, 2016, oncologists discussed how their practices are coping with the transition toward quality- and value-based reimbursement. The discussion also spanned the challenges they face and the changes they have been making in their clinic to provide evidence that the care they deliver follows guidelines and supports quality care.

The panel, Aligning Physician Compensation to Quality and Value, saw participation by Randy Broun, MD, president and chairman of the Board of Directors, Oncology Hematology Care, Inc; Michael Diaz, MD, an oncologist with the Florida Cancer Specialists & Research Institute; Rich Schiano, CEO of Oncology Hematology Care; and Todd Schonherz, COO, Florida Cancer Specialists and Research Institute, participated on the panel.

Lucio Gordon, MD, medical oncologist with Florida Cancer Specialists & Research Institute, moderated the discussion and asked the panelists about their efforts to inculcate quality metrics in their practice and associating it with their compensation.

Schiano said, "We used an outside consultant to align quality with reimbursement. They initially built a metric of specific measures, satisfaction, compliance, adherence to pathways, etc, into the system. Then, later we included metrics for advanced practice providers as well."

"We want the entire practice to achieve its quality and value metrics," explained Diaz. "We are still in the process of defining value—there's still a lot of debate about optimal quality measures. So focusing on moving targets wouldn't help us." Diaz emphasized that their overall approach is that every physician should have the opportunity to succeed, and Todd Schonherz, he said, helped their practice with implementing value and quality metrics.

Schonherz said that NCCN guidelines have been the standard used for care delivery at their clinic. "We have many clinics with extended and weekend hours, and we are also planning on a walk-in clinic," he said. This provides a lot of flexibility to the patients and can prevent them from getting to the emergency department (ED) or a hospital setting for any complications or side effects. Schonherz emphasized the importance of patient feedback in the performance of their practice. "Our compensation is driven by how we perform and how our patients rate us," he added.

Broun explained how their clinic has been working to adapt to this transition. "Our computer systems were also redone by a consultant who built quality measures into the system. It's important however, that these metrics be specific for each department—metrics that apply to medical oncologists may not apply to radiation oncologists or to those who conduct bone marrow transplants," Broun said.

Schiano said that while their physicians are extremely competitive, "There is a net promoter in each practice among consumers—our patients. This patient can be held as an ideal for all doctors to achieve," he said and the patients in their turn help and bring value back to the practice.

"We have talked to payers about the volume-to-value movement. These are not simple agreements that we can draw out—they are not a sprint, more a marathon. We have been developing programs and creating infrastructure to support that because we want to be here for the long-term for our patients," said Schonherz.

Broun then made a point about data analytics. "Doctors do not like bad analytics," he said. "Bad numbers always mean doctors get upset with the data they are presented with." When asked to prove otherwise, they pull out the individual patient charts as proof.

This then led to the discussion on how the analytics can then be translated into real-time use in the clinic. "We are focused on developing a level of real-time transparency that would be readily visible to the doctors to build and apply," Schiano said. He insisted however, that the entire staff at the clinic needs to be trained and on board to make this system work. "You need to get this data out in front of the staff and discuss it with them. We are constantly thinking about engaging every segment of the office, including those at the front desk."

"How about the patients? Do they care that we are aligning our compensation with quality?" asked Gordon. "I think they would be," replied Diaz. "In the big picture of things, they are aware of other surveys and what other patients think. Beyond that, it might be too technical for them to grasp additional details."

The bottom line though is gathering sufficient data. "Data is an important driver. If data shows you are operating within pathways, you are operating at low costs, and you take it back to the healthcare system, it helps," explained Schiano. "Analytics help support your clinic's performance. We need to ensure we have the right architecture and that we are gathering the right data that can help sculpture the information being presented to guarantee it tells the real story," he added.

The Oncology Medical Home model has been initiated by several clinics within the country, and Gordon wanted the panelists to comment on where the model stands.

"We have a weekend clinic, which helps patients. They can just walk in and be able to see a provider, usually an advanced practice nurse. We also have patient navigators to help patients navigate the healthcare system as well as the financial aspects of care," Broun said.

Schonherz said that Florida Cancer Specialists, too, has extended and weekend hours at their clinics. "We have been initiating discussions with urgent care centers to use them as a way to avoid ED or other hospital visits that are more expensive.

"Ideally, we want a universal agreement on the quality metrics. We have to take it one step at a time," said Diaz. **EBO**

Industry Insight on the Challenges With Developing and Adopting Biosimilars

SURABHI DANGI-GARIMELLA, PHD

With a growing number of expensive biologicals entering the market across a broad range of therapeutic areas, payers and pharmacy benefit managers are exploring ways to curb the growing expense of biologicals, which sometimes cost more than 22 times that of small molecules. We now have 2 biosimilars approved in the United States: a biosimilar to filgrastim[1] and a biosimilar to infliximab.[2]

Although cost savings with biosimilars remain debatable, there have been questions about whether physicians and pharmacists would be able to prescribe these drugs versus the originator product. There's also the question of acceptance by these prescribers.

At the annual meeting of the Community Oncology Alliance, a panel, "The Now and Future of Biosimilars: Implications for Practice Management," discussed these issues and more. Moderated by Jim Koeller, PharmD, professor, University of Texas at Austin & the Health Science Center, participants included Earl Dye, PhD, director, Technical Regulatory Policy, Genentech; Thomas Felix, MD, director, R & D Policy, Amgen; Jim McKay, PhD, director, Clinical Development and Medical Affairs, Sandoz Biopharmaceuticals; and Sue Naeyaert, senior director, Biosimilars Policy, EMD Serono. Each panelist provided an overview of distinct aspects of the biosimilar development process.

"What we understand is biosimilars are not generics. It needs reverse engineering back to the innovator biologic," said Naeyaert. "Biologics are never the same, and they are very different from generics—these variabilities can occur from batch-to-batch production. Even slight changes in the manufacturing process, to improve the product, result in changes in the final product," she explained.

Dye explained that the FDA has created an abbreviated approval process for biosimilars. "The objective was to allow continued innovation, but also allow cheaper copies of already approved biologicals. The abbreviated approval process has lower submission requirements of preclinical and clinical data for FDA review," he said, adding that submission requirements include data from analytical and pre-clinical toxicity studies of the biosimilar. "Unlike the extensive 3-phase clinical studies required of the company that develops the innovator biological, the biosimilar developer does extensive functional comparison with the reference product and also some additional preclinical studies and clinical studies to show that any differences from the innovator does not translate into significant clinical differences." Dye also indicated that biosimilar manufacturers, who intend to extend the indications of their product beyond those of the reference product, must provide scientific justification for this.

"Biosimilar clinical studies are not designed or powered to conduct safety-efficacy studies," according to McKay. "So the purpose of clinical studies for biosimilars is very different from that for the reference product. While labels are mostly alike, slight differences may exist, such as indications for use."

Addressing the question of interchangeability, he said extra clinical data are needed to prove that switching between the biosimilar and reference will not affect efficacy or safety in patients. Interchangeability is, of course, not yet allowed in the United States.

Felix, a regulatory expert, said, "Pharmacovigilance is very important for biologicals, overall. Biosimilar manufacturers need the ability to analyze safety of their products. There are issues of misattribution of adverse events, where even if use of the originator product declines, adverse events are attributed to the originator." He said better control of this process is needed.

Felix explained that naming of the follow-on products is still not clear. The FDA has released a draft naming guidance for biologicals, which indicates the need for a hyphenated suffix, but "this is still being worked on. There is also a global discussion involving the World Health Organization for standardizing a naming approach across countries, and that, too, is still being finalized."

Felix identified significant challenges that exist with coding for biosimilars with respect to reimbursement. "CMS has finalized having a fixed code for all biosimilars to a reference product. But the impact of this on the Sentinel system that monitors adverse events would be interesting to watch," he said. "State bills are also being passed for substituting with a biosimilar product, where self-administered biosimilars can be dispensed by a pharmacist without need for approval," he told the audience.

When asked to share thoughts on how an institution would switch out a product for a biosimilar, McKay said that it would need to be an FDA-approved product for a hospital to make that decision. "There's clinical data, a lot from Europe, that switching the products is not a big issue," he affirmed.

"I believe physicians should have more control on this switching," Naeyaert said, adding that physician acceptance of biosimilars is growing, with data supporting the switch by rheumatologists over the past year. "It is starting to move, but there is still a lot of education that needs to happen," she added.

"Maybe physicians have reservations to switch a patient, but they could think of starting a new patient on the biosimilar," Dye said. **EBO**

REFERENCE

1. Joszt L. FDA approves first biosimilar in US. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/fda-approves-first-biosimilar-in-us. Published March 6, 2015. Accessed May 24, 2016.

2. Dangi-Garimella S. A second biosimilar has been approved in the United States, a follow-on to infliximab. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/a-second-biosimilar-has-been-approved-in-the-united-states-a-follow-on-to-infliximab. Published April 5, 2016. Accessed May 24, 2016.

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> **"Biosimilar clinical studies are not designed or powered to conduct safety-efficacy studies. The purpose of clinical studies for biosimilars is very different from that for the reference product."**
>
> —JIM MCKAY, PHD

ASCO Releases an Updated Value Framework

SURABHI DANGI-GARIMELLA, PHD

The American Society of Clinical Oncology (ASCO)'s Value in Cancer Care Task Force has published an updated value framework that can help clinicians and patients assess the relative value of cancer therapies that have been compared in clinical trials.

The conceptual framework, published last year right after ASCO's annual meeting,[1] was aimed at easing the shared decision-making process for patients and oncologists as they weigh the numerous treatment options available to them. ASCO claims that its framework incorporates elements of clinics benefit, toxicity, and symptom palliation—all drawn from clinical trial data—to develop a net health benefit (NHB) score. Patients are also provided information on the cost of the regimens to help understand the financial impact of their treatment.

The revised framework, published May 31, 2016, in the *Journal of Clinical Oncology*,[2] defines value as a combination of clinical benefit, side effects, and improvement in patient symptoms or quality of life in the context of cost, according to an associated press release.[3] The current updates are based on the feedback that ASCO received—from patients, patient advocates, physicians, representatives of the pharmaceutical industry, and other members of the cancer community—during a 60-day comment period following the release of the value framework.

The following are updates to the framework:

1. ASCO has modified the NHB score to better reflect true differences between treatments. For example, to calculate the efficacy of a treatment, the framework now uses hazard ratios rather than absolute survival measures. Hazard ratios provide a more complete assessment of the relative differences between therapies.
2. All side effects, not just high-grade toxicities, will be used to calculate the NHB score, following patient recommendations. So, in addition to awarding bonus points for symptom palliation, additional points are given for improvement in quality of life.
3. The revised framework will continue to only evaluate treatments that were studied head-to-head in prospective randomized clinical trials.
4. The framework will continue to focus on cancer drugs, rather than other interventions, since drug costs are the most rapidly rising component of cancer care and among patients' biggest concerns.
5. Although patient-reported outcomes (PROs) are important and may be included in future versions of the framework, clinical trials are yet to adequately measure or report PROs. ASCO hopes to be able to consider these data as they are more rigorously collected and reported in future trials.

Speaking with *Evidence-Based Oncology*, ASCO's CMO Richard Schilsky, MD, FACP, FASCO, said, "What we are planning to do later this year is to develop a software application that incorporates all the elements of the Value Framework into an easy-to-use software that can be used on a laptop or a tablet at the point of care, where doctors can actually use it to engage patients in a conversation [around value]."[3] According to the press release, ASCO will work closely with stakeholders, particularly patient advocates, to help ensure that the tool fully considers the needs and preferences of patients. Once it is developed, physicians will be provided with educational resources so that they can best apply the tool in their discussions with patients. **EBO**

REFERENCE

1. Dangi-Garimella S. ASCO's conceptual value framework released: tool for shared decision making. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/ascos-conceptual-value-framework-released-tool-for-shared-decision-making. Published June 22, 2015. Accessed May 31, 2016.
2. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received [published online May 31, 2016]. *J Clin Oncol*. doi: 10.1200/JCO.2016.68.2518.
3. ASCO value framework update: Statement by ASCO president Julie M. Vose, MD, MBA, FASCO [press release]. Alexandria, VA: American Society of Clinical Oncology; May 31, 2016. http://www.asco.org/about-asco/press-center/news-releases/asco-value-framework-update.
4. In conversation with ASCO's Richard Schilsky. *The American Journal of Managed Care* website. http://www.ajmc.com/journals/evidence-based-oncology/2016/peer-exchange-oncology-stakeholders-summit/in-conversation-with-ascos-richard-schilsky. Published May 11, 2016. Accessed May 31, 2016.

MSK Survey Indicates Misbelief Responsible for Dismal Cancer Trial Participation

SURABHI DANGI-GARIMELLA, PHD

A survey conducted by MaPS/Millward Brown Analytics, on behalf of Memorial Sloan Kettering Cancer Center (MSK), has identified multiple concerns of American consumers with cancer clinical trial participation, which could be responsible for the dismal 4% national enrollment rate in clinical trials.[1]

The survey was conducted across the country among 1511 consumers, between 18 and 69 years old, and 594 practicing physicians who have discussed clinical trials with their patients. Physicians were specialists in oncology/hematology, OB/GYN, gastroenterology, urology, ear/nose/throat medicine, neurology, pulmonology, or dermatology. Of the surveyed individuals, only 35% indicated that they'd be willing to enroll themselves in a trial, and less than half (40%) seemed to have an overall positive impression of clinical trials.

These results corroborate findings of a study published late last year by 4 other cancer centers in the country: Robert Lurie Comprehensive Cancer Center at Northwestern University, Cleveland Clinic Foundation, Fox Chase Cancer Center, and Karmanos Cancer Institute at Wayne State University. The survey found that 21% of 1255 cancer patients chose to participate in clinical trials—much greater than the 4% to 5% trial participation that is typically observed. The high numbers in this particular study were the result of patient education on clinical trials (PRE-ACT). The study, which was published in the *Journal of Clinical Oncology* (*JCO*), found that the knowledge and attitude of patients in the PRE-ACT greatly improved, and it crumpled the barrier to participation.[2]

Clinical trials are the stepping stone for drug discovery, and increased trial participation can have a tremendous impact on bringing newer and better drugs to the market. The primary concerns with trial participation, noted by the survey participants, were:

- Worry over side effects/safety (55%)
- Uncertainty about insurance and out-of-pocket costs (50%)
- Inconvenience of trial locations (48%)
- Concerns about getting a placebo (46%)
- Skeptical of a treatment that is not yet proven to work (35%)
- Worries over feeling like "guinea pigs" (34%)

However, similar to the *JCO* study, attitudes changed following a bit of education on what clinical trials are and how they are conducted: 60% of those surveyed said they'd be open to enrolling in a trial, up from the initial 40%.

José Baselga, MD, PhD, physician-in-chief and chief medical officer at MSK, reacted to the results of the survey by saying, "When it comes to advancing cancer care, clinical research is the rocket fuel for better treatments, more accurate diagnoses, and, ultimately, cures. If this trend of low enrollment continues, we will face a crisis in cancer research and discovery. Further education is the key to participation and progress."

Surprisingly, surveyed physicians, too, seemed to have inhibitions about enrolling their patients in a trial: 53% expressed concern that individuals would not want to feel like guinea pigs.

"While concerns regarding clinical trials are understandable, it is critical that the cancer community address common myths and misunderstandings around issues like effectiveness, safety, use of placebo, and at which point in treatment a trial should be considered," said Paul Sabbatini, MD, deputy physician-in-chief for Clinical Research at MSK. "For example, the vast majority of clinical trials do not involve a placebo."

Community support could play a significant role in washing away some of these misconceptions. In an interview with *The American Journal of Managed Care*, Kim Thiboldeaux, chief executive officer of the Cancer Support Community, explained the important role that patient advocates can play in this process.[3] "From our standpoint and the patient advocacy community, we believe that we need to do some basic education, that we need to train patients, we need to get them the information about clinical trials, as a starting point, so that they can think about a clinical trial as a treatment option when they are diagnosed with cancer and not something that is a last-ditch effort or something that they would only have access to when everything else has failed," she said. **EBO**

REFERENCES

1. Despite pressing need, survey finds most Americans unlikely to enroll in clinical trials [press release]. New York, NY: Memorial Sloan Kettering Cancer Center; May 23, 2016. https://www.mskcc.org/press-releases/despite-pressing-need-survey-finds-most-americans-unlikely-enroll-clinical-trials.
2. Dangi-Garimella S. Improving cancer trial participation via Web-based interventions. *The American Journal of Managed Care* website. http://www.ajmc.com/newsroom/improving-cancer-trial-participation-via-web-based-interventions. Published December 28, 2015. Accessed May 24, 2016.
3. Kim Thiboldeaux explains patient misconceptions of cancer clinical trials. *The American Journal of Managed Care* website. http://www.ajmc.com/interviews/kim-thiboldeaux-explains-patient-misconceptions-of-cancer-clinical-trials. Published September 10, 2015. Accessed May 24, 2016.

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- Panel: Oncology care 2017

CancerLinQ—ASCO's Rapid Learning System to Improve Quality and Personalize Insights

(CONTINUED FROM COVER)

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CANCERLINQ BACKGROUND AND HISTORY

The 2013 IOM report, Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis, identified contemporary challenges to the delivery of high-quality cancer care and specified 10 core recommendations for remediation.[1] A technology-based "learning healthcare system" was identified as essential to make cancer care more evidence-based and patient-centric. The authors described a learning health system as one that uses HIT to "…continuously and automatically collect and compile from clinical practice, disease registries, clinical trials, and other sources of information, the evidence needed to deliver the best, most up-to-date care that is personalized for each patient."[2]

In a learning health system, research and practice inform each other in a virtuous cycle, one in which the findings from everyday care experiences continuously improve both practice and the discovery of new knowledge. In March 2011, the ASCO Board of Directors adopted strategic initiatives to begin the development of a rapid learning system (RLS) in oncology. Over the next 4 years, ASCO undertook a number of steps to make this RLS a reality. ASCO formed a separate Quality Department to house all of the Society's quality programs, including CancerLinQ, and dedicated staff, volunteer committees, and external advisors were brought together to define goals and strategy and to create a business plan. A pilot of an RLS that focused on breast cancer began in 2012, using mostly open-source software, and the prototype was publicly demonstrated, albeit with limited functionality, at ASCO's Quality Care Symposium in 2012.

After the Board approved full build-out of the system, in 2013, ASCO commenced a rigorous process to gather requirements, leading to the release of a Request for Proposals for vendors in 2014. Also in 2014, the ASCO Board created a separate limited liability company, CancerLinQ LLC,[3] as a nonprofit, wholly-owned subsidiary of ASCO, with its own board and advisory committees and numerous new staff. In January 2015, ASCO announced that SAP, a German multinational corporation that makes enterprise software, was chosen to develop and deploy CancerLinQ in a co-innovation partnership with ASCO. ASCO provides the oncology subject matter expertise and controls the data, services, and products that stem from CancerLinQ, while SAP provides access to its global healthcare technical platform and engineering support to create customized tools unique to CancerLinQ's needs.

ASCO had previously engaged a number of early adopters from the oncology community in the United States to serve as "vanguard practices," and between 2015 and 2016, the pace of practice engagement increased sharply. As of May 1, 2016, 37 vanguard practices had signed Business Associate Agreements with CancerLinQ, representing over 700 physicians, and nearly 600,000 patient records. Data ingestion is ongoing as new practices are added, and data connections to the EHR, established. The vanguard practice group comprises a mixture of small, community-based, single-specialty, hematology-oncology practices; larger, multisite cancer centers and integrated delivery networks; and academic medical centers. With the first release of the platform, anticipated in proximity to the ASCO Annual Meeting in Chicago, June 3-7, 2016, participating practices will have access to a full suite of features to be delivered as part of the initial version, including quality performance measures, analytic reports, and a data exploration tool known as CancerLinQ Insights (CLQI).

In a learning health system, research and practice inform each other in a virtuous cycle, one in which the findings from everyday care experiences continuously improve both practice and the discovery of new knowledge.

CANCERLINQ DATA ARCHITECTURE

CancerLinQ is a cloud-based solution built on SAP's HANA, an in-memory data management and application platform providing analytics and data visualization, and hosted in a secure data center within the United States. CancerLinQ consists of a series of logical databases in the HANA Enterprise Cloud (HEC) environment, through which data flow and undergo progressive normalization and deidentification. There are several models by which data are extracted from the EHR and flow into CancerLinQ. In the default option, the CancerLinQ engineering team deploys a third-party software agent called CancerLinQ Connect, which is installed behind the practice firewall and pulls the required data elements, both structured and unstructured, from the EHR database. A customized data file known as an HIX file is created and securely transferred to the HEC. Several "push" options are also supported, among them data warehouse extracts. Regardless of the initial data extraction methodology, incremental updates, uploaded nightly, will occur to ensure the timeliness of the clinical data in the system.

Once the data are ingested into the HEC, they flow into a data staging area or, "data lake," which contains fully identifiable protected health information (PHI) and personably identifiable information (PII). So that the clinical quality measures can fire and the clinical concepts queried, the data are standardized via a rules engine, based on a terminologies database known as the National Cancer Institute Metathesaurus.[4] The unstructured data run through a natural language processing engine for conversion to structured elements. The data land in the clinical database containing PHI and PII that can be queried by the end-user based on access privileges. Physician-users will only be able to view patient data with PHI for their own patients or, in some cases, the patients of other physicians within their practice. From there, the data then undergo deidentification via a third-party software tool and land in an analytical database for users to access the aggregated, deidentified data set. The CancerLinQ informatics team will use this database to create customized analytic reports for participating practices and other parties, pursuant to CancerLinQ data governance principles.

The end-user accesses CancerLinQ through a web browser. Product features include a set of clinical quality performance indicators based on ASCO-developed electronically specified clinical quality measures (eCQMs), discussed in the next section; the CLQI tool for customized cohort and data exploration; a patient timeline tool to visually represent oncologic milestones in the patient history; and a suite of parameterized analytic reports.

Additional data sources contemplated for CancerLinQ ingestion in future versions, include practice management systems (financial and administrative data), tumor registry data, claims data, genomic and other molecularly derived datasets, and data warehouse datasets.

QUALITY MEASUREMENT AND BENCHMARKING

The ASCO Board of Directors, from the time of its earliest strategic decisions to create CancerLinQ as a learning health system for oncology, envisioned that the primary function of the platform would be as an extension of ASCO's quality portfolio, most notably the Quality Oncology Practice Initiative (QOPI).[5] QOPI is ASCO's signature quality assessment program for outpatient hematology-oncology practices, designed to create a culture of self-examination and improvement through periodic measurement of practice performance on established clinical quality measures, many of which are derived from ASCO's own clinical practice guidelines. However, QOPI is a retrospective analysis, describing clinical events at least 6 months back, by which time, the opportunity to influence the care of any individual patient, has generally long passed.

By comparison, CancerLinQ provides real-time assessment of practice performance on a subset of embedded eCQMs, both disease- and domain-specific, derived from the QOPI program. The eCQM results are displayed graphically in the user portal of the CancerLinQ web interface using tools in SAP HANA for measure definitions and visualization. The initial measure set, which includes eCQMs that are adapted from measures endorsed by the National Quality Forum, is shown in the **TABLE**.

TABLE. CancerLinQ Clinical Quality Measures[a]

Staging documented within 1 month of first office visit.
Pain addressed by second office visit.
Pain intensity quantified by second office visit.
Test for HER2/neu overexpression or gene amplification.
Tamoxifen or aromatase inhibitor received within 1 year of diagnosis by patients with AJCC stage IA(T1c) and IB-III estrogen or progesterone receptor-positive breast cancer.
CEA within 4 months of curative resection for colorectal cancer.
Adjuvant chemotherapy received within 4 months of diagnosis by patients with AJCC stage III colon cancer.
Smoking status/tobacco use documented in past year.
Rituximab administered when CD-antigen expression is negative or undocumented (lower score = better).
Hepatitis B surface antigen and hepatitis B core antibody test within 3 months prior to initiation of rituximab for patients with NHL.

[a]initial release 2016.
AJCC indicates American Joint Committee on Cancer; CD, cluster of differentiation; CEA, carcinoembryonic antigen; NHL, non-Hodgkin's lymphoma.

Oncologists participating in CancerLinQ have the ability to see quality performance results on their own patient population, and they can drill down to individual patient-level detail. They are able to compare their results to aggregated data from all participating practices, but they are shielded from seeing performance metrics of other participants other than in the aggregate, and no PHI is exposed, other than that of their own patient population. Designated "clinical supervisors" in each practice, typically the lead physician or practice manager, can be given access to view the quality performance results of all physicians in the practice, based on the local security model, but not that of any other practice at the detailed level.

The real-time nature of quality measurement in CancerLinQ allows for the concept of "*actionability*." Embedded in the software is functionality that enables the individual user to view a measure-by-measure depiction of his or her performance in a dashboard characterizing patients as measure concordant or non-concordant. The non-concordant patients can be sorted based on whether they are in an actionable time frame, meaning the patient does not yet satisfy the requirements of the measure, but is still within a timeframe permitting a diagnostic or therapeutic intervention under the physician's control (eg, administration of adjuvant chemotherapy for a patient with stage III colon carcinoma within 4 months of diagnosis). This "early warning system" can improve care by surfacing such patients when there is still an opportunity to deliver a guideline-specified intervention. In the circumstance where there may be a valid clinical contraindication (eg, due to a comorbidity), relevant patient-level detail can be accessed directly from the quality dashboard.

By virtue of the sheer number of cases contained in the database—at least 1 million by mid-2016, and expected to grow sharply from there—CancerLinQ may very well represent the most accurate depiction of practice quality in the real world, since it generates metrics based on the actual care rendered and outcomes achieved. Furthermore, all patients eligible for a quality measure, subject to the denominator exclusions incorporated into the measure itself, will be included automatically, without an ability to "cherry pick" patient charts, as is the case for most other quality assessment programs where chart selection is controlled by the practice. However, it is important to reemphasize that each practice's quality reports are only viewable by that practice, and the aggregated reports from all participants have safeguards built in that makes it impossible to identify individual practices by name, location, or characteristic.

LEARNING FROM OBSERVATIONAL DATA—HAZARD OR OPPORTUNITY?

As described, CancerLinQ enables oncologists to use data collected from EHRs to assess quality and inform clinical decisions. Presumably, physicians can learn from the quality performance data of peers to improve their own care. But, is this a reasonable assumption? Moreover, how should observational data such as that derived from CancerLinQ be considered in the context of clinical decision making for individual patients? In this era of big data, there are no straightforward answers yet. Even if one acknowledges that patient populations encountered in practice have little resemblance to those studied in the majority of clinical trials—where the patients tend to be healthier, younger, and less diverse from a racial and socioeconomic status—using the data from observational studies remains fraught with hazards, since risk adjustment and controlling for confounding variables remain challenging. For example, a report looking at the breast cancer radiotherapy endpoints of overall mortality and cause-specific mortality, comparing findings from a public-use dataset from the Surveillance, Epidemiology, and End Results Program (observational data) to the randomized trials that were part of recent meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (clinical trial data), showed substantially divergent results, even when all potential confounders were controlled using full stratification.[6]

On the topic of using observational data in comparative effectiveness research, Curtis and Krumholz, opined in an editorial, in *Annals of Internal Medicine*:

> "Much work remains before comparative effectiveness studies using observational data become meaningful for influencing clinical practice, including improving the quality of data, strengthening analytic methods with attention to assessing comparative effects and modifying factors, and reaching consensus on validation approaches. Meanwhile, these studies remain interesting, yet fall short in altering our assessments of the comparative performance of each strategy."[7]

However, how is an individual clinician to proceed when faced with a patient in the exam room with a rare tumor for which evidence-based clinical practice guidelines do not exist, and the patient is not a candidate for a trial? Or a patient with a common malignancy like breast cancer coexisting with a myelodysplastic syndrome with del[5q]? Or the much more common scenario of a patient with compromised renal function faced with the decision as to the advisability of potentially nephrotoxic, but curative adjuvant chemotherapy? The availability of a powerful tool like, CancerLinQ, that can provide insights into the real world outcomes of similar patients, when combined with existing trial-generated evidence

By virtue of the sheer number of cases contained in the database—at least 1 million by mid-2016, and expected to grow sharply from there—CancerLinQ may very well represent the most accurate depiction of practice quality in the real world.

and full patient consent, may be transformative to the practice of the art of medicine in these difficult situations. **EBO**

REFERENCES

1. Delivering high-quality cancer care: charting a new course for a system in crisis. Institute of Medicine website. http://www.nationalacademies.org/hmd/Reports/2013/Delivering-High-Quality-Cancer-Care-Charting-a-New-Course-for-a-System-in-Crisis.aspx. Published September 10, 2013. Accessed May 1, 2016.
2. A learning health care information technology system for cancer. In: Delivering high-quality cancer care: charting a new course for a system in crisis. Institute of Medicine website. http://www.nap.edu/read/18359/chapter/8#238. Published September 10, 2013. Accessed May 1, 2016.
3. CancerLinQ website. http://www.cancerlinq.org. Accessed May 1, 2016.
4. NCImetathesaurus. National Cancer Institute website. https://ncimeta.nci.nih.gov/ncim-browser/. Accessed May 1, 2016.
5. Blayney DW, McNiff K, Eisenberg PD, et al. Development and future of the American Society of Clinical Oncology's Quality Oncology Practice Initiative. *J Clin Oncol.* 2014;32(35):3907-3913. doi:10.1200/JCO.2014.56.8899.
6. Henson KE, Jagsi R, Cutter D, McGale P, Taylor C, Darby SC. Inferring the effects of cancer treatment: divergent results from Early Breast Cancer Trialists' Collaborative Group meta-analyses of randomized trials and observational data from SEER registries. *J Clin Oncol.* 2016;34(8):803-809. doi:10.1200/JCO.2015.62.0294.
7. Curtis JP, Krumholz HM. The predicament of comparative effectiveness research using observational data. *Ann Intern Med.* 2015;163(10):799-800. doi:10.7326/M15-2490.

MEASURING PROS

Partnering With Patients to Rapidly Develop a Quality-of-Life Measure in Mycosis Fungoides/Sézary Syndrome Type Cutaneous T-cell Lymphoma

(CONTINUED FROM COVER)

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tion, both cancer-specific (eg, FACT-G) and skin-specific (eg, Skindex-29) measures are often administered in trials, which are shown to be responsive to change, but, at 56 questions, these measures can be burdensome for patients.[11]

There is a dearth of literature on aspects of QoL impairment by specific MF/SS CTCL subgroups selected by gender, age, clinical type, treatment, or clinical status.[12] Traditional clinical assessments (such as extent of lesion, lymph node involvement, or flow cytometry) do not capture patient perspective on how disease manifestation can have a major impact on many domains related to QoL,[13] such as role function or psychological distress. As a result, there is little data on the relationship between MF/SS CTCL symptom burden and health-related QoL, and researchers have sought to answer whether the connotation of having a poorly understood form of cancer causes distress, over and above the consequences of cutaneous manifestations of disease.[13]

Addressing these gaps in the literature is challenging, because new condition-specific measures have traditionally been expensive and time consuming to develop. According to some estimates, the time taken may be as much as 2 to 4 years, and the costs range from $725,000 to $2.1 million, depending on the extent of rigor required for developing them.[14,15] A robust research program requires:

- A researcher trained in psychometrics
- Ready access to a sizable sample of participants
- Identification and licensing of relevant comparator measures
- Staff to collect and analyze data
- Longitudinal follow-up to determine minimally important differences
- Efforts to disseminate the findings and support the instrument once released.

Even when resources are available, PROs, developed by researchers in isolation, risk measuring things that don't really matter to patients.[16] Despite the fact that the perspective of patients is increasingly recognized as crucial across many aspects of medical research,[17] several legacy measures in widespread use today were developed with little or no patient input. These are significant challenges that are amplified when the condition of interest is as rare as MF/SS CTCL.

Early experiences have shown that patients using the internet to share information about their condition and to connect with peers can contribute their experiences to PRO developers in a rigorous fashion that helps overcome some of the aforementioned challenges.[18-22] Methodology studies undertaken to evaluate the quality and representativeness of data gathered online has found that it is similar in nature to data gathered through more traditional means such as guided interview.[23] Legitimate questions remain as to how online tools can verify patients identity, obtain objective data of their diagnosis and status, and overcome biases inherent in the use of online tools.[24]

Funded by a grant from the Robert Wood Johnson Foundation, PatientsLikeMe, built the Open Research Exchange (ORE),[25] an online software platform with tools that simplify the process of developing, testing, and sharing new PROs (**FIGURE**). The instrument development process is based on a sequential multi-step, iterative process that complies with widely acceptable scientific recommendations[26-28] and FDA guidelines.[29]

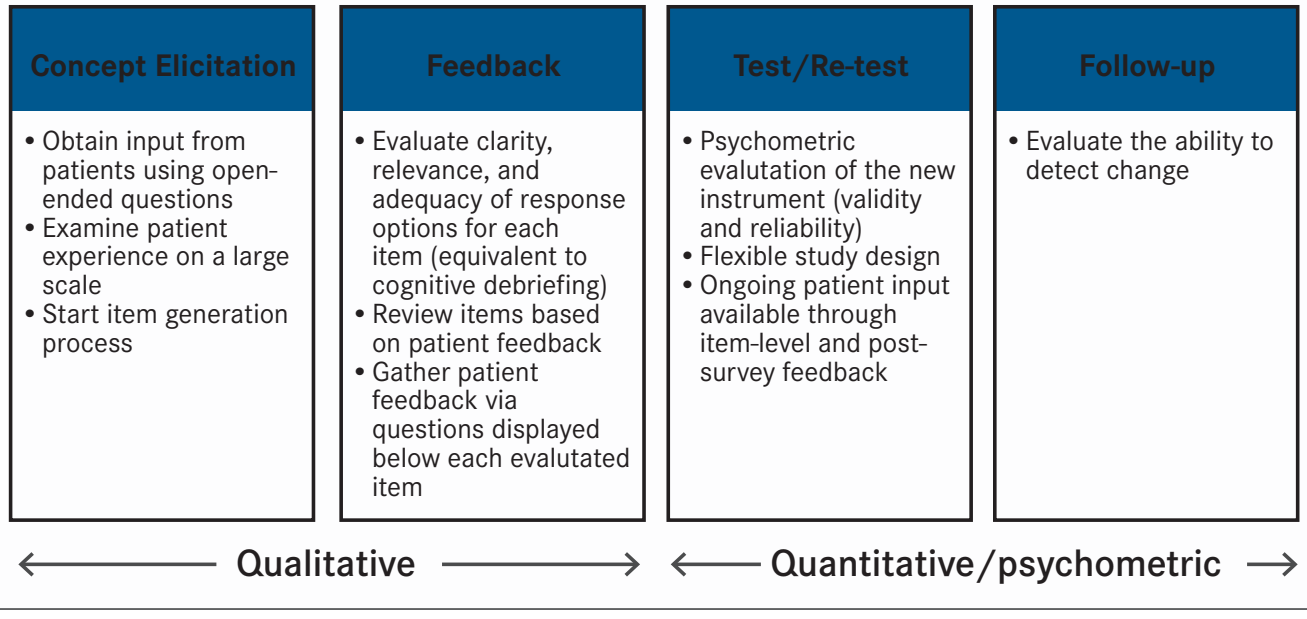
The process consists of the following steps:

1. Construct definition and conceptual framework
2. Concept elicitation
3. Feedback
4. Psychometric evaluation
5. Test-retest

ORE is connected to an online platform where more than 400,000 patients currently track their health, connect with others for information and support, and contribute data for research. Consequently, the challenges of recruitment, data collection, and follow-up are rendered more manageable. To date, more than 20 new instruments have been developed using the platform, including published measures of treatment burden,[30] extracampine hallucinations, Parkinson's disease,[31] and hypertension.[32]

Recognizing the need for an MF CTCL–specific HRQoL instrument, Actelion Pharmaceuticals and PatientsLikeMe sought to harness new technology to rapidly develop, prototype, and psychometrically validate a new instrument with patient input throughout. Our objective was to create an instrument that could be used to better understand patient unmet need (eg, disease burden, treatment satisfaction, and health-related QoL), and help characterize the experience of patients living with MF/SS-CTCL. We also sought to contribute the tool to the wider community in a Creative Commons ShareAlike 3.0 license, so that it could be used, expanded upon, and improved by other researchers.

FIGURE. Phases of PRO Tool Development on the Open Research Exchange (ORE)



DEVELOPING THE INSTRUMENT

Although a full description of the study methods is beyond the scope of this article (for more, see Towers et al[33]), we will summarize the approach taken. Following a literature review and interviews with clinical experts, 21 patients reporting a physician-confirmed diagnosis of MF/SS CTCL were invited to complete open-text concept elicitation items (eg, "How is your physical well-being affected by MF/SS CTCL?"). In addition, 10 patients out of the 21 were invited for further telephone interview to probe their answers. Qualitative analysis suggested that content saturation was reached after 15 patients and thematic content analysis identified 6 major themes that were subsequently used to generate a preliminary version of the 31-item questionnaire. This long-form questionnaire was administered to 42 patients for their item-level feedback, where multiple-choice and open text survey items allowed patients to identify issues with any items they found lacked clarity or relevance. After removing redundant items, an abbreviated 14-item scale was administered to a sample of 126 patients for psychometric validation, including comparator measures. Sixty-six patients completed test-retest performance 5 days later with known-group validity analysis.

Psychometric analysis showed good internal consistency, test-retest reliability, and that the items were appropriately ordered in terms of severity. We also found that the MF/SS CTCL QoL is capable of discriminating between individuals with low and high levels of interference in their QoL, and that the items adequately covered the varying levels of interference with QoL due to MF/SS CTCL. Further work detailing the validation process and final instrument is under preparation.

DISCUSSION

The use of the ORE platform enabled patient feedback to be easily incorporated throughout every step of the development process. Additionally, thanks in large part to a relationship with the Chronic Lymphoma Foundation, recruitment was faster and more cost effective than traditional methods of sourcing patients through clinical centers. Information collected from key opinion leaders and the literature helped to inform a scientifically grounded and relevant measure that accurately depicts the patient experience with MF/SS CTCL, particularly given the variability that patients often encounter, as they cope with the daily demands of the condition. Online feedback replaced more time and resource-expensive interviewer-led cognitive debriefing interviews. In all, the process took less than a year, and the total cost was a fraction of what traditional instrument development costs.

LIMITATIONS

The greatest limitation of the study is the sample size, due in part to the rarity of the condition. A number of psychometric validation measures were, therefore, unable to be completed and could be addressed in future research. Additionally, while it is impossible to guarantee that those who registered on the website actually have MF/SS CTCL, a recent study in other conditions, on PatientsLikeMe, found that around 95% of patients could be identified via IMS Health medical and pharmacy claims (Eicher et al, *In Press*). Further, the sample of patients who participated in this study were largely in Stage 1 of mycosis fungoides, or Sézary syndrome, with few patients reporting more advanced stages of the syndrome (stage III, n = 2; stage IVa, n = 4; stage IVb, n = 1). Inclusion of more individuals at later stages of the syndrome would allow for empirical testing of differential item function by later stages of the syndrome.

CONCLUSION

The MF/SS CTCL PRO tool project represented a unique collaboration between a pharmaceutical company and a patient network, using an innovative platform to work on a new measure for a rare disease that would otherwise have never been developed. We hope use of the MF/SS CTCL–QoL tool, which is freely available, will enable better communications about QoL between patients and their care teams, and improve and inform clinical management and treatment decision making related to MF/SS CTCL. **EBO**

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REFERENCES

1. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. *J Am Acad Dermatol*. 2014;70(2):205:e1–16; quiz 221-222. doi:10.1016/j.jaad.2013.07.049.

2. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. *Arch Dermatol*. 2007;143(7):854-859. doi:10.1001/archderm.143.7.854.

3. Weiyun A, Keegan T, Press D, et al. Outcomes After diagnosis of mycosis fungoides and Sézary Syndrome before 30 years of age. *JAMA Dermatol*. 2014;150(7):709-715. doi:10.1001/jamadermatol.2013.7747.

4. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous t-cell lymphoma. *JAMA Dermatol*. 2013;149(11):1295-1299. doi:10.1001/jamadermatol.2013.5526.

5. Demierre MF, Kim YH, Zackheim HS. Prognosis, clinical outcomes and quality of life issues in cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 2003;17(6):1485-1507.

6. Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot qual-

ity-of-life instrument for pruritus. *J Am Acad Dermatol*. 2008;59(2):234-244. doi:10.1016/j.jaad.2008.04.006.
7. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216.
8. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol*. 1996;107(5):707-713.
9. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
10. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570-579.
11. Demierre MF, Ferzli P, Miller D. Measuring HRQOL in patients with cutaneous T-cell lymphoma undergoing therapy with oral bexarotene and extracorporeal photopheresis. *Arch Dermatol*. 2007;143(5):659-661. doi:10.1001/archderm.143.5.659.
12. Sampogna F, Frontani M, Baliva G, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. *Br J Dermatol*. 2009;160(4):815-822. doi:10.1111/j.1365-2133.2008.08992.x.
13. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer*. 2006;107(10):2504-2511. doi:10.1002/cncr.22252.
14. Rosen R. Development of patient reported outcome (PRO) measures: how feasible is a PRO for asymptomatic PCa treatment? FDA website. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM350175.pdf. Accessed May 3, 2016.
15. Hayes R. Patient-reported outcome (PRO) instruments as drug development tools (Session III). In: Washington, DC; 2011. FDA website. https://c-path.org/wp-content/uploads/2014/05/2014-Session-4-SocialDigitalMedia.pdf.
16. Wicks P. Commentary: Measuring what matters: the case for patient generated PROMS. *BMJ*. 2015;350:h54. doi:10.1136/bmj.h54.
17. de Wit M, Abma T, Loon MK-V, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. *BMJ Open*. 2013;3(5):piie002241. doi:10.1136/bmjopen-2012-002241.
18. Wicks P, Massagli MP, Wolf C, Heywood J. Measuring function in advanced ALS: validation of ALSFRS-EX extension items. *Eur J Neurol*. 2009;16(3):353-359. doi:10.1111/j.1468-1331.2008.02434.x.
19. Wicks P, Vaughan TE, Massagli MP. The multiple sclerosis rating scale, revised (MSRS-R): development, refinement, and psychometric validation using an online community. *Health Qual Life Outcomes*. 2012;10:70. doi:10.1186/1477-7525-10-70.
20. Bove R, Secor E, Healy BC, et al. Evaluation of an online platform for multiple sclerosis research: patient description, validation of severity scale, and exploration of BMI effects on disease course. Oreja-Guevara C, ed. *PLoS ONE*. 2013;8(3):e59707. doi:10.1371/journal.pone.0059707.
21. Wicks P, Massagli M, Kulkarni A, Dastani H. Use of an online community to develop patient-reported outcome instruments: the Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ). *J Med Internet Res*. 2011;13(1):e12. doi:10.2196/jmir.1687.
22. Smith RA, Wicks P, Yagi N, Scheinker D, Thisted R. Development of a self report bulbar function scale. *Neurology*. March 2011:A48-A49. PatientsLikeMe website. http://patients-likeme_posters.s3.amazonaws.com/2011_Development%20of%20a%20self%20reported%20bulbar%20function%20scale%20.pdf.
23. McCarrier KP, Bull S, Fleming S, et al. Concept elicitation within patient-powered research networks: a feasibility study in chronic lymphocytic leukemia. *Value Health*. 2016;19(1):42-52. doi:10.1016/j.jval.2015.10.013.
24. Rothman M, Gnanasakthy A, Wicks P, Papadopoulos EJ. Can we use social media to support content validity of patient reported outcome (PRO) instruments in Medical development? *Value Health*. 2015;18(1):1-4. doi:10.1016/j.jval.2014.10.001.
25. Open Research Exchange website. https://www.openresearchexchange.com/. Accessed May 2, 2016.
26. Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. *Patient-Reported Outcomes: Measurement, Implementation and Interpretation*. Boca Raton, Fl: Chapman & Hall/CRC Press; 2013.
27. DeVellis RF. *Scale Development: Theory and Applications*. 3rd ed: Vol 26. Thousand Oaks, CA: Sage Publishing; 2012.
28. Kane RL, Radosevich DM. *Conducting Health Outcomes Research*. Sudbury, MA: Jones & Bartlett Learning; 2010.
29. FDA. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. *Federal Register*. 2009;74(235):65132-65133.
30. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med*. 2014;12(1):109. doi:10.1186/1741-7015-12-109.
31. Wood RA, Hopkins SA, Moodley KK, Chan D. Fifty percent prevalence of extracampine hallucinations in Parkinson's disease patients. *Front Neurol*. 2015;6:263. doi:10.3389/fneur.2015.00263.
32. Kear T, Harrington M, Bhattacharya A. Partnering with patients using social media to develop a hypertension management instrument. *J Am Soc Hypertens*. 2015;9(9):725-734. doi:10.1016/j.jash.2015.07.006.
33. Towner A, Raja P, Braverman J, et al. Patients' experiences with mycosis fungoides/sézary syndrome-cutaneous t-cell lymphoma (Mf/Ss-Ctcl): evidence from qualitative research of a patient reported outcome (Pro) Measure developed on an online research platform.*Value Health*. 2015;18(3):A25. doi:http://dx.doi.org/10.1016/j.jval.2015.03.155.

PHYSICIAN PERSPECTIVE

So Many Metrics, Yet So Little Known About Quality and Value in Cancer Care

(CONTINUED FROM COVER)

others whose unique expertise and ability to evaluate and endorse rigorous quality measures make them important contributors to this process.

Despite a wealth of cancer quality measures, a number of lingering questions persist:

- Do these measures actually work to improve care?
- Do they measure what matters most to patients and their families?
- Are they robust enough to discern which hospitals and physicians provide excellent care from those who do not?
- Do they constitute the most important or relevant measures in an era in which we are asked to deliver personalized medicine and precision cancer care solutions?

From this perspective, the effectiveness and utility of many of the endorsed cancer care measures appear to be questionable. Their central role in determining payment, patient referral patterns, and crafting a national health care strategy needs to be viewed with greater skepticism. This is not to cast doubt upon the value of quality measures; rather, this skepticism is based on inadequacies of the current measure sets when viewed from the prism of the extraordinary diversity of cancer patients, the importance of molecular biology in care decisions, the centrality of patient risk-assessment in care decision making, and our highly imperfect methods for collecting and analyzing data. Even those who view cancer care metrics as an important set of tools for improving care processes and outcomes, the complexity of this task is clear. Spinks et al

note, "Cancer represents a set of diseases with some common traits but tremendous variability, unlike more homogeneous conditions such as diabetes. Cancers vary greatly depending on location, type, stage, and molecular and genetic characteristics. Treatment may involve medical, surgical, and radiation oncologists, which presents a unique challenge for attributing patient outcomes to a particular provider...These factors underlie the formidable challenge of representing a disparate set of diseases with a uniform set of quality measures."[3]

As cancer care stakeholders move through processes of creating, deploying, and reporting quality metrics, it is important to remember that these measures alone are not sufficient to bring better care to patients. Cancer care quality measures are not the equivalent of baseball sabermetrics;[7] there is no easy, metric-based fast-track toward creating a less costly, more effective cancer care delivery system. Our national enthusiasm for metrics often blinds us to broader complexities of delivering excellent care, and our need to meet the distinct (and sometimes non overlapping) needs of many cancer care stakeholders in the process.

CHARACTERIZING VALUE IN HEALTHCARE

In his *New England Journal of Medicine* paper on value in health care, Michael Porter notes that, "Value—neither an abstract ideal nor a code word for cost reduction—should define the framework for performance improvement in healthcare. Rigorous, disciplined measurement and improvement of value is the best way to drive system progress." Yet, value in healthcare remains largely unmeasured and misunderstood.

Value should always be defined around the customer, and in a well-functioning healthcare system, the creation of value for patients should determine the rewards for all other actors in the system.[8] If we are ever to bring a system of cancer care that fully ensures safe, effective, patient-centered, timely, efficient, and equitable care to fruition,[9] then we need to better understand the limitations of our current quality measures, so that future measures can more effectively center around patient and stakeholder needs, rather than simply assess what is most easily measurable.

In order to get to better quality metrics, we need to recognize the following concerns with our current set of measures:

1. Quality and value are multidimensional, but the narrow focus of many quality measures undermines their effectiveness and meaningfulness.[8]
2. Quality and value measures are all too often based on isolated care transactions, rather than the continuum-of-care model that is an essential part of effective cancer care.[8]
3. Few quality/cost/value measures include risk as part of their formulation or expression.[3,4,10]
4. Electronic health records do not facilitate capture or assessment of key outcomes data.[11]
5. Few quality measures are linked to care strategy, healthcare facility/provider strategic planning, or the development of more effective care systems.[12]
6. Our measures for assessing patient-reported outcomes are weak, and rarely measure those things which matter most to patients.[13,14]

A number of cancer care stakeholders are in the process of creating value models from which more meaningful patient and care delivery metrics can be derived. Important leaders, in this domain, include ASCO[15] and the National Comprehensive Cancer Network.[16]

In their *Harvard Business Review* article, "The Strategy that Will Fix Health Care," Porter and Lee recommend that in care planning and effectiveness assessment, the focus should be placed upon the patient and the effectiveness, efficiency, and patient-centeredness of longitudinal care delivery.[17] A model like this is more likely to empower metrics that measure what matters most to patients, their families, and other key healthcare stakeholders. This shift from a short-term to a long-term mindset over cancer metrics will be important to ensure that our metrics help drive meaningful change in our cancer care system. The importance of carefully defining value in a multidimensional, patient-centered manner is essential to achieving meaningful improvements in care delivery.

As Porter notes in his *New England Journal of Medicine* article on value, "The failure to prioritize value improvement in health care delivery and to measure value has slowed innovation, led to ill-advised cost containment, and encouraged micromanagement of physicians' practices, which imposes substantial costs of its own. Aligning reimbursement with value in this way rewards providers for efficiency in achieving good outcomes while creating accountability for substandard care."[8] **EBO**

REFERENCES

1. Linking quality to payment. Medicare.gov website. https://www.medicare.gov/hospitalcompare/linking-quality-to-payment.html. Accessed May 31, 2016.
2. Burwell SM. Setting value-based payment goals–HHS efforts to improve U.S. health care. *N Engl J Med.* 2015;372(10):897-899. doi:10.1056/NEJMp1500445.
3. Spinks TE, Walters R, Feeley TW, et al. Improving cancer care through public reporting of meaningful quality measures. Health Aff (Millwood). 2011;30(4):664-672. doi:10.1377/hlthaff.2011.0089.
4. National Quality Forum website. http://www.qualityforum.org/Home.aspx. Accessed May 31, 2016.
5. Commission on Cancer website. https://www.facs.org/quality-programs/cancer/coc. Accessed May 31, 2016.
6. Measures overview. ASCO Institute for Quality website. http://www.instituteforquality.org/qopi/measures. Accessed May 31, 2016.
7. Albert J. An introduction to Sabermetrics. Bowling Green State University website. http://www-math.bgsu.edu/~albert/papers/saber.html. Accessed May 31, 2016.
8. Porter ME. What is value in health care? *N Engl J Med*. 2010;363(26):2477-2481. doi:10.1056/NEJMp1011024.
9. The six domains of healthcare quality. Agency for Healthcare Research and Quality website. http://www.ahrq.gov/professionals/quality-patient-safety/talkingquality/create/sixdomains.html. Reviewed March 2016. Accessed May 31, 2016.
10. Methodology employed for annual report on hematopoietic cell transplant center-specific survival rates. Center for International Blood and Marrow Transplant Research website. https://www.cibmtr.org/ReferenceCenter/SlidesReports/USStats/Documents/CIBMTR_HCT_Center_Survival_Report_Methodology.pdf. Updated February 5, 2016. Accessed May 31, 2016.
11. Klumpp TR. Electronic medical records and quality of cancer care. *Curr Oncol Rep*. 2013;15(6):588-594. doi:10.1007/s11912-013-0347-z.
12. Porter ME, Lee TH. Why strategy matters now. *N Engl J Med*. 2015;372(18)1681-1684. doi:10.1056/NEJMp1502419.
13. Johnson CY. The burden of cancer isn't just cancer. *The Washington Post* website. https://www.washingtonpost.com/news/wonk/wp/2016/04/08/cancers-sinister-side-effect-financial-toxicity/?tid=a_inl. Published April 8, 2016. Accessed May 31, 2016.
14. de Boer AG, Verbeek JH, Spelten ER, et al. Work ability and return-to-work in cancer patients. *Br J Cancer*. 2008;98(8):1342-1347. doi:10.1038/sj.bjc.6604302.
15. Cavallo J. ASCO develops new strategy to increase value in cancer care. *The ASCO Post* website. http://www.ascopost.com/issues/may-15-2014/asco-develops-new-strategy-to-increase-value-in-cancer-care/. Published May 15, 2014. Accessed May 31, 2016.
16. NCCN unveils evidence blocks for CML and multiple myeloma. National Comprehensive Cancer Network website. https://www.nccn.org/about/news/newsinfo.aspx?NewsID=546. Accessed May 31, 2016.
17. Porter ME, Lee TH. The strategy that will fix health care. *Harvard Business Review* website. https://hbr.org/2013/10/the-strategy-that-will-fix-health-care. Published October 2013. Accessed May 31, 2016.

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As cancer care stakeholders move through processes of creating, deploying, and reporting quality metrics, it is important to remember that these measures alone are not sufficient to bring better care to patients.

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