SPECIAL ISSUE: **CLINICAL PATHWAYS**

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PATHWAY DEVELOPMENT

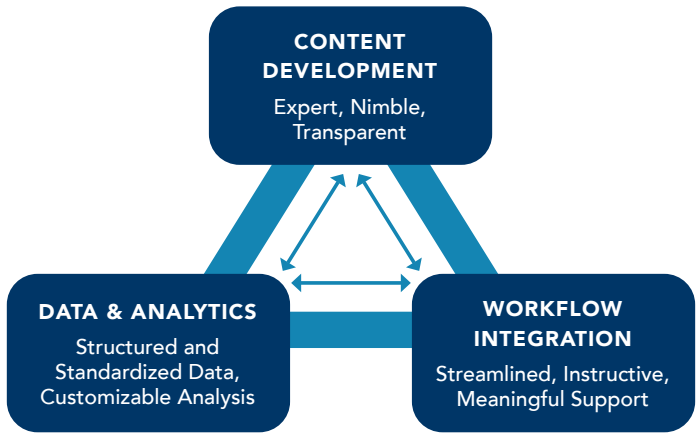
Lessons From the Front: Designing and Implementing Clinical Pathways by and for Clinicians

David M. Jackman, MD; Joanna Hamilton, MA, MS; Emily Foster, MPH; Craig A. Bunnell, MD, MPH, MBA; Louis Culot, MA; Carole Tremonti, RN, MBA; Joseph O. Jacobson, MD, MSc

OVER THE PAST DECADE, the use of clinical cancer pathways has increased. In its 2017 State of Cancer Care in America report, the American Society of Clinical Oncology (ASCO) noted a 42% increase from 2014 to 2016 in practices using a clinical pathways program.[1] This growing trend reflects a need for structured decision support among clinicians, clinical practices, and payer systems. As cancer care becomes more complex and more expensive, these decision-support algorithms offer a mechanism to define best practice, reduce unwarranted variation, and control costs across growing networks.[2-4]

At the heart of the pathways movement lies a desire to improve treatment—its outcomes, its tolerability, its efficiency, and its value. Achieving these goals requires commitment not just to an electronic platform but also to a broader pathways program. At the Dana-Farber Cancer Institute (DFCI), we believe that this requires a tripartite dedication to expert content development; integration into physician and practice workflow; and the capture, analysis, and practical use of data (**Figure 1**). These are, in fact, the same 3 areas identified as key for high-quality pathways programs by the ASCO Pathways Committee.[5] Ultimately, the successful creation and implementation of a pathways program within any institution or network depends on understanding the interdependence of these 3 areas and using each to improve the others.

FIGURE 1. The Interdependence of Content Development, Workflow Integration, and Data and Analytics.



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PATHWAY ADOPTION

Clinical Pathways: Reducing Costs and Improving Quality Across a Network

Marcus Neubauer, MD

TODAY, AS ONCOLOGISTS STRIVE to meet the needs of a growing population of patients with cancer in 2020,[1] they must remain abreast of rapidly emerging treatments to deliver positive patient outcomes, while meeting increasing demands from government and private payers. To do so, clinical pathways have emerged as a key tool driving informed decision making and providing more efficient, cost-effective, value-based care.

Across the practice of oncology, there is often a high variation of choices available to physicians in how best to treat patients. Adopting evidence-based clinical pathways helps align patient care and reduce unnecessary variation. These pathways provide a succinct, clinically proven list of treatment options that offer increased value to the healthcare system and the patient through a careful balance of cost sensitivity, treatment toxicity, and clinical outcomes.

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COMMENTARY

Clinical Pathways: A Critical Component of Success in Episodes of Care

Lili Brillstein, MPH, and Brian Currie

THE EPISODES OF CARE MODEL is a value-based model that incorporates all the care rendered to an individual patient over the course of treatment for a particular procedure, diagnosis, or healthcare event, across the full continuum of care. This construct gives clinicians and their interdisciplinary partners a framework to explicitly and consciously collaborate in treating individuals who are clinically similar and therefore would be expected to have clinically similar outcomes. It is a model that focuses on consistently achieving the best of those outcomes.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Brukinsa™
zanubrutinib 80 mg capsules

BRUKINSA™ (zanubrutinib) IS A KINASE INHIBITOR INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY.

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

Learn more at BRUKINSA.com

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose.

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 in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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

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

BeiGene

BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA™ (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. 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 (8.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

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 in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥ 75 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CLcr ≥ 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rashǁ	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis
† Hemorrhage includes all related terms containing hemorrhage, hematoma
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis
§ Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral
ǁ Rash includes all related terms containing rash
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, 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. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. 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 BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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FROM THE EDITOR-IN-CHIEF

The End of the Beginning

Now, this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.

Winston Churchill, 1942


ALVARNAS

AT THE BREAK OF 2020, we were greeted with good news from the American Cancer Society (ACS) that cancer survival rates had improved by the largest 1-year margin ever reported.[1] In sharing this news, the ACS provided even more extraordinary context: between 1991 and 2017 cancer death rates fell by 29%.[1] The improvements in survival for patients with lung cancer were particularly striking, with mortality "declines accelerated for lung cancer, from 3% annually during 2008 through 2013 to 5% during 2013 to 2017 in men and from 2% to almost 4% in women, spurring the largest even single-year drop in overall cancer mortality of 2.2% from 2016 to 2017."[1]

This profound decline in cancer mortality reflects a massive systemic set of efforts, including more effective cancer prevention, earlier detection, and advances in cancer treatments. It is in this latter regard that advances in the application of genomic and molecular diagnostic testing and increasingly effective targeted therapeutic matching to individual patient needs has validated in gratifyingly tangible ways the promise of the "precision medicine" paradigm of cancer care.

Lest we walk away from this great news believing that we have won the war against cancer, it is best to think of this momentous occasion instead as the end of the beginning of our advances into increasingly effective, innovative cancer care. There are reasons for looking at this news with a tempered sense of optimism. Although improvements in lung cancer and melanoma survival rates are unprecedented, survival improvements for other cancer types for some cancer types (female breast cancer, colorectal cancer, hepatic cancer) were far more modest; for some cancer types there have been little recent improvement (prostate cancer).[1] Patients, physicians, healthcare systems, and payers face a number of new challenges in adapting to this new era in cancer care. The cost of care has risen precipitously with the advent of targeted anticancer therapeutics and immune-oncological agents. The cost of these agents may range from nearly $6000 to more than $11,000 per cycle.[2] High costs have created significant concern about how such treatments can be delivered in a financially sustainably way by both government and private payers. Moreover, the high cost of these therapeutics has led to the phenomenon of financial toxicity, which is the harm suffered by patients and families as they cope with their cost-sharing payments for these treatments.[3] Additionally, there is growing evidence that a significant number of patients who could potentially benefit from these innovative treatments may never get them.[4,5]

As we move from the end of the beginning into the next phase in our foray into the world of increasingly effective cancers treatments we will need to build better systems for delivery these treatments. This will require more effective physician decision support that can help deliver these treatments based upon individually tailored assessments of the patient's own cancer. This will also require that we build more effective systems that can empower better patient access, more robust value systems to increase transparency over care costs, and increasingly effective inter-stakeholder collaborations navigate this bold new future. ◆

Joseph Alvarnas, MD
Editor-in-Chief

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EDITORIAL MISSION

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

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Do I think I payers have been the people who have been lagging behind and have been an impediment? Frankly, there's no question.

Stuart Goldberg, MD

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FEBRUARY 2020, VOLUME 26, ISSUE 2

At its best, clinical pathway development should be a team-based approach that involves physicians who will use the resulting pathways at every stage of the process.

FROM THE CHAIRMAN

Pathways to Better Cancer Care

WHEN THE TERM *MANAGED CARE* appeared more than a generation ago, it promised the idea that patients would get the right care without wasting money on tests or procedures that made little difference. As Lili Brillstein, MPH, and Brian Currie write in this issue of *Evidence-Based Oncology*™, the first wave of reform proved a mixed bag for all involved—doctors had to hire staff to navigate the bureaucracy of getting their patients certain lab work or an appointment with a specialist. Patients fretted about waiting for the green light for a procedure that a trusted doctor said was needed. And insurance companies were cast as the greedy "Dr No," always ready to deny, deny, deny necessary care that might be too expensive.

Today, that "management" is undergoing a transformation. Especially in oncology, physicians are taking back control through the development of clinical pathways. As we read in this issue, panels of physicians are working in partnership with leaders in technology to use data to drive decision making. Sometimes, the decision will be to use the more expensive therapy. Sometimes, it won't. But the decisions are based on the evidence, unless there is a compelling reason to deviate from the pathway, which must be documented. Pathways are used in all kinds of settings—both academic medical centers and in community oncology. This issue provides an outstanding example of collaboration on pathway development between Dana-Farber Cancer Institute and Philips. The chief medical officer of The US Oncology Network describes how pathways are used across a broad group of practices. Brillstein and Currie explain how the episode of care or "bundled payment" fits into the pathway concept. It's all about delivering the right amount of care—not too much, not too little. It's about consistency based on the evidence, with allowances for a physician's best clinical judgment.

This issue also reports on important trends in cancer mortality. Overall, cancer deaths are trending downward; in fact, they saw their biggest drop last year—a testament to decades of innovation and efforts to curb smoking. But there's troubling news, too. Cancers associated with obesity are rising, especially liver cancer, and we still see sharp disparities linked to race and income. Public policy leaders must confront the challenge of how to ensure that life-saving treatments reach everyone, not just those who can afford to pay. Clinical pathways can help in this regard, as cost-effectiveness can be a factor in decision making. But the criteria must include *effectiveness*, not just cost. As we learn in an interview with Stuart Goldberg, MD, that's been a criticism of Medicare's Oncology Care Model.

We are exceptionally pleased to bring you this issue focused on clinical pathways in cancer care, and we look forward to your feedback. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND FOUNDER

Speaking of Employers: Purchasers Detail the Challenges of Getting a Handle on Oncology Care Costs

Mary Caffrey

A tradition of not questioning what the doctor says, because it's cancer, and a person could die.

A shifting financial landscape that lets some patients with cancer choose between an academic center and a community practice, whereas others have no choice at all.

Million-dollar treatments. And patients who have no idea what their health plan covers.

THESE ARE ASPECTS of the world that today's employers face as the workforce ages,[1] the price of cancer treatment rises,[2] and the obesity epidemic means millennials face double the risk of cancers that baby boomers did a generation ago.[3]

Good health benefits are essential to attracting top talent, but for employers, this comes at a price. An initiative by the Northeast Business Group on Health estimated that US employers spent $125 million on cancer care in 2015, or 12% of their entire health-care spend.[4] Cancer therapy costs have increased substantially since then, with the expanded use of immunotherapy, including the introduction of chimeric antigen receptor (CAR) T-cell therapy.

As today's employers try to balance the need to provide healthcare for their workers while keeping an eye on cost, they are banding together to learn more about cancer care and how to gain value for the millions they are spending. Meanwhile, provider groups like the Community Oncology Alliance (COA) are reaching out to employer and purchasing coalitions to discuss how community oncologists can help hold down costs.

Last fall, the 2 came together during COA's Payer Exchange Summit, held October 28 and 29, 2019, in Tysons Corner, Virginia. *Evidence-Based Oncology*™ listened as leaders from employer and purchasing groups shared experiences from their members in a roundtable discussion.

The participants were the following:

ASHLEY TAIT-DINGER, MBA, director of quality and value measurement for the Florida Health Care Coalition, based in Orlando

CHRIS SYVERSON, chief executive officer of Nevada Business Group on Health/Nevada Health Partners, based in Reno

MARIANNE FAZEN, PHD, president and chief executive officer, Texas Business Group on Health/Dallas-Fort Worth Business Group on Health

MAGDA RUSINOWSKI, vice president of health care cost and delivery, Business Group on Health, Washington, DC

RANDY VOGENBERG, PHD, principal, Institute for Integrated Healthcare, and board chair, Employer-Provider Interface Council of the Hospital Quality Foundation, Greenville, South Carolina

BRET JACKSON, president, Economic Alliance for Michigan, a bipartisan business and labor coalition

KYLE MONROE, MBA, vice president of network development and provider relations, The Alliance, based in Madison, Wisconsin

RUTH ANTONIADES, MS, executive director, Labor Health Alliance, New York, New York

Participants were asked a simple question: What does value in cancer care mean to your organization? And the discussion flowed from there. Tait-Dinger said her group's employers have been learning about bundled payments and value of navigators and whether it makes sense to use large providers. Fazen said her members also are learning about the value of navigators, and both said these professionals not only coordinate care but also can help members understand the details of the benefit package.

"The idea is to focus on the patient experience," Fazen said. "That's a big trend."

One item that emerged: ensuring that employees have help understanding the details of their short-term disability policies. In some cases, they can use individual benefit days for treatment.

Vogenberg said he sees "value" through more than 1 lens because he previously worked in Massachusetts and now works in South Carolina, where cancer care options can be limited, depending on where patients live. In South Carolina, partnerships among stakeholders in cancer care are still relatively new, he said. "Leapfrog and Leapfrog-like" activities are happening, he added, referring to the watchdog organization best known for its safety ratings.[5]

Site of Care Is Critical

Several participants discussed how site of care drives cost and considered ways employer coalitions can push back, assuming choices are available. Monroe said that in rural Wisconsin and Minnesota, some community oncology clinics have been acquired by area hospital systems, so patients no longer have real options—and neither do the people paying the bills. "If you're in the system, they're getting their pound of flesh," he said.

There are success stories, too. Syverson discussed how her members banded together and negotiated lower-cost care and better transition arrangements through Huntsman Cancer Institute at University of Utah for patients who needed specialty care, so they didn't need to go for care at one of the medical centers in the University of California system.

"You Can't Control Demand"

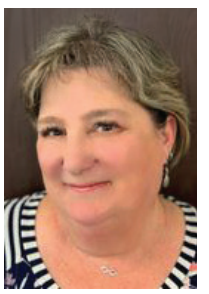
Talk of escalating drug costs was never far from the surface. If anything, the participants said, the 6-figure blockbuster therapies of recent years have finally pushed oncology off its untouchable perch; employers are finally seeking management strategies years after taking similar steps in cardiology, orthopedics, and other high-cost areas.

According to Jackson, when employers did an end run on the payers and the hospitals and talked directly to oncologists, it was an eye-opener. "Employers have been so focused on trying to control the demand side of healthcare," he said. That makes sense in some areas, such as setting limits on physical therapy. "When you get to oncology, you can't control demand," he said. "If they have cancer, they need treatment—otherwise, they are going to die."

Talks with oncologists revealed a great desire to stick to evidence-based guidelines, limit scans, and use just the right amount of therapy. But there are other forces at work. "They can't get the administration of their health system or their hospital to buy into those things," Jackson said. Less radiation means "fewer trips through the machine, and the bean counters at the hospital don't like that," he said. »

TAIT-DINGER

Ashley Tait-Dinger, MBA, director of quality and measurement, Florida Health Care Coalition



SYVERSON

Chris Syverson, chief executive officer, Nevada Business Group on Health/ Nevada Health Partners

FAZEN

Marianne Fazen, PhD, president and chief executive officer, Texas Business Group on Health/Dallas-Fort Worth Business Group on Health

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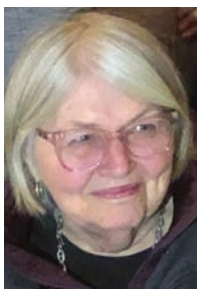
MONROE

Kyle Monroe, MBA, vice president, network development and provider relations, The Alliance



ANTONIADES

Ruth Antoniades, MS, Labor Health Alliance

Jackson's Economic Alliance convened a multistakeholder group that brought oncologists, payers, purchasers, and consumer groups to the table to ask how to improve the delivery system for everyone. "We need the employer community to stand up for the right thing with the CEO [chief executive officer] and the CFO [chief financial officer] of the health system to make it all happen," he said. "And, of course, we need to pay for it. We need the insurance companies to buy in this." That means prior authorization and step therapy must follow evidence-based guidelines, as well.

Blockbuster Therapies Shape Coverage

Both Rusinowski and Syverson discussed the distortions caused by the rise of extremely expensive gene therapies. CAR T-cell therapy starts at $373,000 just for the treatment; with administration costs, it can rise to $1 million.[6] With financial models that require the assumption of more risk and more of these therapies in the pipeline, small employers in particular are worried, Rusinowski said: "This is not going away."

"Employers have been so focused on trying to control the demand side of healthcare. ...When you get to oncology, you can't control demand. If they have cancer, they need treatment—otherwise they are going to die."

—Bret Jackson, Economic Alliance for Michigan

Others discussed how solutions for self-insured employers, such as carve-outs for high-cost therapies that call for these treatments to be packaged in a reinsurance pool, are no free lunch. Reinsurance costs are going up, too; for small employers, especially, the rise of high-cost curative therapies is beginning to drive coverage decisions and will make self-insurance off limits. One employer in Syverson's area that had been self-insured had to rejoin a commercial plan because it hired a man with a hard-to-treat chronic blood disorder. "They were going to go bankrupt based on 1 employee," she said.

"With all the new drugs that are coming out, we are coming up what I consider to be ethical decisions on plan design issues," Syverson said. "And they write their plan any way they want."

One small casino in Nevada stopped paying for specialty drugs because the owner could no longer afford to pay for high-cost drugs. "And that's not unusual," Syverson said.

Paying for six-figure therapies when the average tenure of an employee is 2 years is also an issue. Tait-Dinger said in the Orlando area, where she is based, employer groups are coming to grips with the idea that if everyone commits to taking on the high-cost therapies that emerge in the employee base, even if there is employer turnover, every employer will pay a fair share for these new therapies over time.

Monroe said that when it comes to cancer care, historically, the conversation has been about quality. When his group, which represents 120,000 lives, tried to talk about value, there was pushback. "Traditionally, our employers stay away from this," he said. "We wanted the providers to have those conversations."

But in the past year or so, there's been a shift, he said: "The million-dollar therapies in the pipeline have raised the level of awareness and a reasonable concern."

Finding Their Place at the Table

For years, employers have focused on running their business, and the cost of cancer care has not been on their radar. It's something that Rusinowski can relate to from her days on that side, but she said that attitude is changing. Today, she said, employers are learning just how "opaque" the drug pricing system is: They know what they don't know and are not willing to accept the lack of information.

"My employers are really struggling," Syverson said, with all the new terms, such as *biosimilars* and *orphan drugs*. It's a lot to learn, she said. Employees still tend to do whatever the doctor tells them to do, and it's still hard for the employer or someone on the employer's behalf to step in and ask if there's a better solution.

It's important for employers to ask who works for whom in the cancer care process, according to the participants. Does the navigator work for the physician? Is the navigator independent? Or does the navigator work for the health plan? Because if it's the latter, one participant said, that's like "the fox watching the henhouse."

Rusinowski said the lack of transparency around drug pricing, including the rebate system, is designed to keep employers from understanding the big picture. A self-insured employer that gets a big check might not ask questions, but, Rusinowski said, the questions need to be asked: "Are there rebates? Are the rebates properly assessed?" Cleaner pricing models, she said, might be more beneficial in the long run.

In the end, Antoniades said, it comes down to matching care with what the patient wants. She described at length how her own views on value-based care shifted after seeing her son live, work, and travel with Hodgkin lymphoma for the past 2 years.

"It seems like we have to think about a different kind of approach," she said. "Even if the diagnosis is the same, one size doesn't fit all. There needs to be a way to connect with people, to get them the treatment they're entitled to, while recognizing that everyone isn't going to accept everything they're offered." ◆

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Biomarker Testing Can Direct Care, but Only if Clinicians Perform the Right Tests

Interview by Allison Inserro

THE PROMISE OF PRECISION MEDICINE calls for directing the right therapy to the right patient based on genomic profiling to identify mutations that will predict responses and guide the course of care. But these opportunities are lost if clinicians do not perform biomarker testing or if the testing is insufficient.

How often does this happen? More often than cancer specialists may realize, and payers may be part of the reason, according to Stuart Goldberg, MD, a hematologist/oncologist and chief of the Division of Outcomes and Value Research at the John Theurer Cancer Center at Hackensack University Medical Center in New Jersey.

Previously, Goldberg was involved with COTA Healthcare, a company conceived and built by cancer physicians who wanted to tap electronic health records for insights that would guide better care. As reported last year by *Evidence-Based Oncology*™ (*EBO*), COTA has assembled a database of records from both academic centers and community practices, representing the breadth of care offered in the United States.[1]

Goldberg and several coauthors used the COTA database for a study whose results showed that patients receiving cancer treatment are not being tested for all the relevant mutations in evidence-based guidelines. He recently spoke with *EBO* about the findings, which appeared in *JCO Precision Oncology*,[2] published by the American Society of Clinical Oncology (ASCO).

The following has been edited slightly for clarity.

EBO: In your study, you note the promise of genomic profiling for mutations that can predict outcomes or response to treatment. But you found that biomarker testing rates are suboptimal. Can you briefly describe the results?

GOLDBERG: We've known for many years that biomarker testing for genomic mutations is an important part of treating colon cancer. This is an important part of the ASCO guidelines; they've been part of the [National Comprehensive Cancer Center] guidelines and the [College of American Pathologists] guidelines for many, many years. And we know that, for example, [patients with an *EGFR* mutation] may not respond to certain monoclonal antibodies. So for the main part, the testing makes the patient not eligible for certain therapies; we don't, therefore, give them expensive treatments that aren't going to work.

We wanted to find out [whether] these biomarker tests [are being done] in the real-world community. So we went to the COTA database, which is a large database taken from the electronic health records of patients throughout the country.[1] We looked at multiple states, in both academic centers as well as community [oncology] centers. We pulled the electronic health records for patients with newly diagnosed colon cancer, metastatic colon cancer, and we looked to see [whether] patients had the genomic testing that was done for the year in which [they received their diagnosis] because over the past decade, we've added new markers and new genomic [markers]. So we wanted to make sure that the patient in that year—whatever year they [received their diagnosis]—got all the [biomarker tests] recommended under the guidelines. One hypothesis was that…as doctors got more familiar with genomics, the rates would go up. What we found, however, when we looked at over a thousand patients, was that the rates did not go up, and a little bit went down. Yes, doctors were more familiar with genomics and were ordering the tests more often, but because more markers [and] more genomic mutations were now required, they weren't keeping up and getting all the right testing. So only about 40% of patients were actually tested for all the genomics recommended for that particular year in this retrospective chart review.

EBO: What are some of the barriers to testing, and what are some of the possible solutions? In other words, what can be done to help educate these doctors about the newer tests now available?

GOLDBERG: In our study—we were doing a retrospective study—we were looking at the charts, so we really couldn't say exactly why the tests weren't being done. But we have some hypotheses from other work we've done in the past. Part of it is education. Physicians do know that genomics are part of this, and they were ordering tests, but new tests keep coming to them. For markers such as *BRAF* and HER2, which are some of the newer ones being added to the guidelines, physicians aren't catching up. They're ordering the older tests but maybe not catching the newer tests. So [continuing medical education], paying attention to what's changing, and watching the guidelines are important for [physicians] to stay up-to-date on what needs to be done.

GOLDBERG

Stuart Goldberg, MD, chief, Division of Outcomes and Value Research, John Theurer Cancer Center, Hackensack University Medical Center

"We really have to explain to the insurance industry that payment for these tests in the long run is good for the patient and may be cost-effective. What we saw in our study was that if every single patient had undergone the testing, it probably would have been cost-effective. It actually would have been cheaper because many of the patients ended up getting the monoclonal antibodies that don't work."

—Stuart Goldberg, MD

The second piece is educating the insurance industry. The insurance industry wants to pay for as little as possible. And as you know, if you have to order individual tests and the insurance industry says, "Well, we only want to pay for tests A and B, but we're not going to pay for these large panels," well, they're going to end up missing things. So we have to really explain to the insurance industry that payment for these tests in the long run is good for the patient and may be cost-effective. What we saw in our study is that if every single patient had undergone the testing, it probably would have been cost-effective. It actually would been cheaper because many of the patients who weren't tested ended up getting the monoclonal antibodies that don't work. So you're paying for an expensive treatment that doesn't work and giving the patient no benefit. In the long run, that money could have been used to get the right tests for everybody in the whole group. And it wasn't that [expensive] because the tests are relatively inexpensive compared with the cost of the therapy. »

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We also need to work on coordinating care among the different physicians. Often the [gastroenterologist] does the biopsy. That biopsy goes to the pathologist; the hematologist-oncologist doesn't have access to it. It's done in a different hospital that can't get the tests. Now we're stuck with, "Oh, do we get a liquid biopsy, [or] do we try to track down the tissue?" So there's a lot of coordination that needs to be worked out in not only colon cancer, we found, [but also] in lung cancer. Coordination of care is still fragmented in our society, especially when patients cross different specialties and different hospitals.

EBO: Does the process become even more complicated if a patient has more than 1 type of cancer that needs to be profiled?

GOLDBERG: Fortunately, many patients don't have more than 1 cancer. But the more complex the disease is, the more complex everything becomes. It's really not so much a question of different diagnoses, but crossing medical systems. [If patients are] treated in one hospital system and then go to another hospital system, getting that biopsy [and] getting the coordination of care often become very difficult. Because, as you know, our electronic health records don't talk to each other, and our insurance [carriers] and our doctors don't talk to one another. So coordination of care becomes a big issue in trying to do simple things like getting genomic profiling.

EBO: What are the implications for patient care if insufficient genotyping occurs?

GOLDBERG: If we want to move to the world of precision medicine, which is where we want to be, [we need to give] the right therapy to the right patient, and I also argue in my other hat that we should be giving it at the right value. But if we want to give the right therapy to the right patient, we need to be able to know what that [patient's] genomics are. So we really need to be thinking about getting all the genomics and explaining to the patients the importance of this, and trying to make sure we get all the right tests. And that's another area where we are lacking, in explaining the importance of these tests to the patients.

EBO: You just mentioned your other hat that you wear in your work. Would you say that precision medicine is perhaps another form of value-based care? And can you describe the work that you're doing now, as you've been in a new position for about a year?

GOLDBERG: At our hospital, I run our new Division of Outcomes and Value Research. We realized that as medicine moves to a value-based world, we really need to have somebody at our center who focuses on the outcomes, the value. [Over are] the days of doing old-fashioned chart reducing and once a year writing my [American Society of Hematology (ASH)] paper or writing my ASCO abstract and sending my residents or fellows or students [to the meetings]. That's gone. We have electronic records, so we can mine the data in real time for all our patients and learn what we're doing. And we hope that by doing that, we will actually see the better outcomes—see what things are working, what things aren't working—and then start moving toward better outcomes, better value.

This is important, not just for academics but also for our pocketbook. Our practices participate in the Oncology Care Model [OCM],[3] and we're going to get paid based on whether we are practicing value-based medicine. Are we being the most effective and most efficient in what we're doing? So we felt at our center that we needed a physician who's going to be looking at the outcomes, who's going to be able to talk to the other physicians in our practice and say, "Hey, you're doing this, but you know, this biosimilar might be cheaper and give you the same outcomes," or, "Spend a little more money on a genomic test because in the long run, yes, it's going to be cheaper for the patient."

We actually proved that at our center several years ago when we did a study on Oncotype DX.[4] [It costs] several thousand dollars [to do each] Oncotype DX test. We would say, well, we're going to add several thousand dollars to every single case of breast cancer. Well, it turns out that Oncotype DX often will move patients from getting expensive chemotherapy to getting less expensive and equally as effective hormonal therapy. So [by performing] the test on every single patient, we ended up moving a lot of patients from chemotherapy to hormones. The patients benefited, and in the long run, it was cheaper. Therefore, we were much more value based, and it helped our practice.

Now, you could argue that in a patient who is 9 years old, you're not going to [give] chemotherapy, so there's no reason to do an Oncotype DX. Don't spend on the genomics. Likewise, if you have a stage I early tumor, very small, you probably don't need to do the Oncotype [DX test] because you're not going to give that patient chemotherapy. But in stage II disease, which is what we found in our analysis, where the patient was in the middle, where the doctors—we actually looked at what our doctors were doing— were giving a lot of those patients chemotherapy, and the Oncotype DX test moved enough of them over that they saved money that it paid for the genomic testing.

EBO: You mentioned the OCM. As you know, next year and for the next several years, your practice and many others will be looking at Oncology Care First (OCF). How will the use of Oncotype DX and genomic profiling play a role in savings for your practices?

GOLDBERG: The [current] OCM…is a 6-month model, which is a little dangerous for some physicians when we talk about genomics because if you're going to spend $3000 or $4000 for the test now, and you're going to be graded, what happens in the next 6 months, you've got to recoup that money pretty quickly, to make it balance.… We actually found that we saved enough money in those first 6 months to make it worthwhile. So [not only do] some of these genomic tests, although they're expensive, help the patient, but we actually could [achieve savings] that fit within the short models. Our hope is that as value-based medicine becomes more common, we'll go away from a 6-month model to a longer model where you can start doing things and hope it's going to help patients down the road. But right now, we're stuck with these short models. That's one of the problems with it, with some of the models, but we're still learning in the value-based world. So I think we'll see that.

EBO: Have you seen a big difference regarding the uptake of biosimilars when it comes to genomic profiling and these other tests?

GOLDBERG: Biosimilars are another important area in value-based medicine, meaning that when we look at the OCM, [we ask], "What are the things that are driving up the costs?" Drugs certainly are at the top. And if we can shift some of those drug costs down by using biosimilars, that [is] going to help everyone. Now the [issue] is, when we change from one drug to a different drug, we don't want to do it based on just cost—we want to make sure we're continuing to see the same outcomes.

That's why looking at value is important. To the medical economist, *value* is a very specific term—it's outcomes divided by cost. You must have a similar outcome or a better outcome. I don't mind paying a little more for a brand-name white bread because it tastes a lot better than store-brand bread. I feel that I'm getting my value. I'm getting my money's worth. But I don't want to be paying extra for something [that is not worth my money]. Value is not just what's cheapest. Unfortunately, I will tell you the OCM model is often based a lot more on cost—trying to reduce costs—than looking at outcomes. In fact, I think the biggest problem with the current OCM is that outcomes are not even considered.

EBO: Do you think the OCF is an improvement?

GOLDBERG: OCM is the first step. And, hopefully, the OCF model, will be another iteration. We learned a lot from the OCM. January 2020 is a critical point because now we're going into 2-sided risk, and our practice decided to go to 2-sided risk.[5] This is the first time that the OCM is going to hit our pocketbooks—until now, the first 3 years were only 1-sided risk. There was no downside to it. So [by] participating, you got your [Monthly Enhanced Oncology Services] payment, and you got your $1000 extra per patient. And that was supposed to help you transform your practice to do better things. Now we're going to see whether all that practice transformation translates to [practices learning to] reduce costs as we go to 2-sided risk, now that we really have to put our money where our mouth is. We'll see. If that's successful, we might see other practices join the next iteration of the OCM, which should be coming in the next 2 years.

EBO: Going back to the study on metastatic colon cancer, did any other findings surprise you?

GOLDBERG: I was very surprised by that study. I knew from our work in lung cancer that we weren't going to see all the patients being genotyped properly. We knew that already. We know that education is lacking.… Our hypothesis in doing the study was

that yes, doctors were familiar [with the fact] that there are certain genes you have to test for in colon cancer and that over time, [doctors] would learn, and they would get better and better. What I didn't anticipate was that over time, we got new genes that needed to be added, and physicians weren't keeping up. That means doctors actually ordered more genomic testing at the end of this study than they did at the beginning. But did they get all the tests they were supposed to get for that particular year? The answer is this actually went down. So yes, we're familiar with genomics. No, we're not keeping up with which genomics to order. And I think that was the big surprise to me. I expected [physicians] were going to get better on both sides, and they didn't.

EBO: Whose responsibility is it to alert physicians, to educate them about the new tests coming out?

GOLDBERG: I think that's the doctor's job. … And if you don't feel comfortable and know what the latest changes are, you have to go to continuing medical education. You must pay attention; you've got to do your work. The field is changing. And it is very, very difficult for oncologists and hematologists today to keep up, especially as things are changing. [It's hard] to just get back from ASH, to just get back from ASCO, and [see] whole things change overnight. And that's part of the challenge of our field, which is actually what makes it exciting for many of us. But at the same time, you have to do the work; you have to keep up. And you have to be looking at the guidelines, and you have to be saying, "OK, I know something I knew 2 years ago, but what has changed when I see the patient in front of me?" For each patient you see, you have to go back and start all over again. And that's what I think we learned from the study, that doctors now [know] they're going to do genomics—but then we're using what they learned 2 years ago or 5 years ago and not saying, "OK, genomics is now part of it, but what are the tests I have to order today?" And they're always lagging behind, and that's not good for the patients.

EBO: Any final thoughts on educating payers on this issue?

GOLDBERG: Do I think payers have been the people who have been lagging behind and have been an impediment? Frankly, there's no question. They often will tell us that they want to pay for an individual tissue marker—they will pay for just the 3 tissue tests and won't pay for the big panel. But we know that there are many drugs in the pipeline. There are big basket trials being run by ASH and by ASCO, by commercial pharmaceutical [companies], that say, "Look, do a whole gene panel. And depending on which genes mutated, you might be eligible for this particular trial, that particular trial, with these new drugs." That is world we're moving to. The approval of immunotherapy for [microsatellite instability-high or mismatch repair-deficient solid tumors], where it's approved across all cancers,[5] just based on the genetics has really changed the field. We're now we're starting to think of cancer not just as breast cancer, colon cancer, or lung cancer but as a genetic genomic disease, that based on the mutation, we're going to take different drugs.

That's a culture shift that is happening in the oncology world. We're going to have to explain that and teach that to our insurance carriers. Otherwise, they're going to just clamp down, and we're never going to get paid. But I think we're starting to see that sea change even in the insurance industry, but it's something we're really going to need to work on over the next several years.

EBO: Is there anything else in oncology that you're excited to see in 2020?

GOLDBERG: As a hematologist, I'm extremely excited that the [chimeric antigen receptor (CAR)] T-cell treatments are coming out. And the whole world of immunotherapy—in the solid tumors, yes, with the immunotherapy drugs in hematology, this is another quiver to our group—we have surgery, radiation, we had chemotherapy when I was training, then we added transplantation. Then we added targeted therapies. And now we're seeing the development of immunotherapies. And very shortly we're going to see the genomic diagnostic being revolutionized. Where I think we're going next over the next several years is the data, the mining of the electronic health records, and the use of all these real-world data—which we're just starting to see—this will shape things so that you won't need to wait 50 years to get a randomized trial, if you start to see the data and start seeing where things are pointing. The data revolution that's coming will then direct all these other areas of interest.

For an oncologist, this has been extremely fun 5, 6, 7 years, as we've added targeted [therapies] and now immunotherapy. And we see some new things happening with transplants and with CAR T. And I think the data revolution is going to really change everything. We'll have to see whether it's cost-effective, whether there's value, because that could be the thing that really kicks us up. Or it could be the thing that really clamps us back down. And that's going to be the healthcare debate going on in the country. ◆

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Impact of Next-Generation Sequencing Tests on Clinical Pathways for Cancer Care

Lance Baldo, MD

BALDO
Lance Baldo, MD, chief medical officer, Adaptive Technologies

THE HALLMARK OF CLINICAL PATHWAYS is the adoption of evidence-based practices to ensure quality care for patients. Such pathways bring standardization to patient care, with the goal of improving outcomes while reducing risks in a cost-effective manner. Critical to the success of clinical pathways is the use of high-quality diagnostic tools to inform patient management.

Cancer care is an excellent demonstration of the potential benefit of clinical pathways to both patients and the healthcare system. We are now firmly in the era of targeted cancer treatments and moving toward more frequent use of immunotherapies and even cellular therapies. In this paradigm, therapeutics developers, diagnostic innovators, payers, healthcare providers, and, most important, patients are aligned in their wish to see the adoption of diagnostic tools that can deliver effective and efficient care. With patients living longer thanks to new therapies, we need more accurate, sensitive, and standardized tools to guide their therapy.

Today, companion and complementary diagnostics offer a cost-effective way to help manage and tailor patient care.[1] Next-generation sequencing (NGS) is a powerful technology platform that investigators and clinicians are employing across various cancers to:

- Identify biomarkers that inform treatment decisions
- Detect the presence of disease
- Assess prognosis
- Evaluate depth of response to therapy
- Monitor disease burden over time

NGS tests have already had an significant impact on patient care and demonstrated potential value to the healthcare system, when appropriately used. In a study published in *JCO Precision Oncology*, investigators used the FoundationOne comprehensive genomic profiling (GCP) test to match patients to targeted therapies based on their tumor's genetic profile. The study demonstrated that patients who received CGP early in their therapy showed improved outcomes with reduced costs.[2] This is one of many studies that validate the importance of molecular testing in clinical practice and demonstrate the value of real-world evidence to inform use of target therapies and improve patient outcomes. Cancer centers like Texas Oncology are developing pathways that allow a physician to input the diagnosis and stage of the disease into the tool for testing recommended by National Comprehensive Cancer Network guidelines to tailor treatment based on the patient's disease.

Some NGS tests may directly assess the extent of underlying disease, which is essential to patient care for hematologic malignancies, as the tests can determine response to treatment, monitor changes in disease burden, and detect early signs of relapse. A key example is the assessment of minimal residual disease (MRD), the small number of cancer cells that can remain after treatment, in hematologic cancers. Although MRD is not a new concept, the recent availability of highly standardized, sensitive, and quantitative assessment methods has dramatically changed the way it is influencing patient management and drug development. Adaptive's clonoSEQ Assay is the only FDA-cleared diagnostic test for the detection and monitoring of MRD in multiple myeloma and B-cell acute lymphoblastic leukemia (ALL) from bone marrow, and it represents the first commercial application using NGS to directly track tumors.[3]

Clear examples already exist of how providers are using MRD to facilitate more cost-effective delivery of care:

- Practitioners use assessment of MRD following induction therapy in ALL to determine whether a patient should be a candidate for a novel therapy to further reduce disease, whereas patients who have achieved MRD negativity following induction may proceed to a less intensive, less expensive course of therapy.[4]
- Patients with multiple myeloma who achieve deep and sustained levels of undetectable MRD negativity may potentially discontinue maintenance therapy or move to limited-duration therapy.[5]
- MRD assessment following chimeric antigen receptor (CAR) T-cell therapy can assess response and determine whether long-term outcomes are likely to be favorable or whether additional treatment (ie, transplant) may be needed.[6]

To realize the benefits of molecular diagnostics more broadly, the oncology community must expand patient access and integrate innovative new technologies into clinical practice and therapeutic pathways. Despite the supporting data, challenges remain. Working within the existing system takes considerable time and investment, moving stepwise to validate emerging clinical uses. Expanded access to advanced molecular testing is essential to realize the promise of precision medicine. Advanced technologies are accelerating our ability to develop novel diagnostics, which will continue to address barriers to access now, before the next wave of NGS-based diagnostics are here. This is critical, because the next wave of applications is likely to continue to have a significant impact on outcomes.

As diagnostic technologies continue to improve, assessment and monitoring of cancer at the molecular level is transforming patient care and lowering costs to the system, making precision medicine a reality. For the medical community to realize the potential of NGS-based technologies, payers, diagnostic developers, and therapeutics companies need to work together to develop models that foster and encourage the standardized, guideline-driven use of these tools in clinical pathways. ◆

AUTHOR INFORMATION
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REGULATORY UPDATE

Faster Drug Approvals, Weaker Data? Study Raise Questions About FDA Process

Deana Ferreri, PhD

AN ARTICLE IN *JAMA* raises concerns that special and accelerated drug approval programs at the FDA in recent decades may have resulted in a process that approves drugs based on weaker data, without reducing overall drug development time.

An accompanying editorial describes the current regulatory process as "a thicket of special programs, flexible review criteria, and generous incentives" and suggests starting points for reforms, including improving access to biosimilars.

In the article, Darrow et al describe the evolution of FDA's approach to drug approval from 1983 to 2018 based on federal laws, FDA regulations, drug approval records, and user fee records.[1]

Special approval programs have increased FDA administrative costs (paid for mostly by user fees), and postponements of generic competition have been costly to the US healthcare system, according to a recent article in *JAMA*.

The FDA must balance rigorous testing of new drugs to clearly define benefits and risks against timely approval for drugmakers and access for patients. The agency instituted special development, protection from generic competition, and expedited approval programs, such as orphan drug, fast track, accelerated approval, priority review, and breakthrough therapy, to support drug development, especially for rare and serious diseases.[2] However, in 2018, 81% of all new drugs won regulatory approval through 1 or more of the expedited programs, the article noted.

Special approval programs have increased FDA administrative costs (paid for mostly by user fees), and postponements of generic competition have been costly to the US healthcare system, the authors noted.

Over the time period analyzed, the FDA accepted more surrogate measures; as a result, harder and more relevant clinical end points are studied less often. In 1995-1997, 80.6% of drug approvals were supported by at least 2 pivotal trials compared with 52.8% in 2015-2017. The authors caution that reliance on surrogate measures may accelerate the approval of drugs that pose significant risk but have little clinical value.

The article reports that although the FDA shortened its review times from more than 3 years in 1983 to less than 1 year in 2017, overall drug development time (from beginning human studies to approval) has not changed: approximately 8 years. The rate of new drug approvals (other than generics and biologics) has not increased substantially since 1983.

On the other hand, the authors acknowledge some positive outcomes. The median number of generic drugs rose following legislation to incentivize and accelerate their development. Plus, biologic approvals are increasing over time, reflecting technological advancement. Although drugs are now supported by fewer studies before approval, the number of patients in these studies has not declined.

In the accompanying editorial, Joshua M. Sharfstein, MD, the former principal deputy commissioner of the FDA, suggests 4 starting points for reforms[3]:

1. Rationalize and update programs to preclude unintended consequences (such as reducing competition) and limit fast track and breakthrough status to increase the likelihood that these treatments will offer major advances.
2. Strengthen postmarket safety oversight for drugs with the potential for both major benefits and serious risks, and take advantage of Risk Evaluation and Mitigation Strategies.
3. Recalibrate programs that provide drugmakers with special marketing protections to reduce costs and improve access to biosimilars.
4. Promote the generation of definitive evidence via use of clinically relevant end points with patent and pricing incentives.

"These changes would each reflect an evolution, not a revolution, of the FDA's approach to new drug approval," Sharfstein wrote. "These reforms also could bring greater order and thoughtfulness to the regulation of important new therapies, while enhancing safety and creating a greater capability to afford truly transformative medical products." ◆

FERRERI

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Overall US Cancer Mortality Rate Reaches 26-Year Decline, but Obesity-Related Cancer Deaths Rise

Matthew Gavidia

SIEGEL

Rebecca Siegel, MPH, scientific director of Surveillance Research, American Cancer Society

THE OVERALL CANCER DEATH RATE declined by 29% from 1991 to 2017, with a 2.2% decline from 2016 to 2017 serving as the largest single-year drop in reported cancer mortality, according to research published January 8, 2020, in *CA: A Cancer Journal for Clinicians*; however, obesity-related cancer deaths are rising and prostate cancer deaths remain stagnant.[1]

Cancer is the second leading cause of death in the United States, with researchers from the American Cancer Society predicting the disease will affect more than 1.7 million people and cause 600,000 deaths in the nation this year. Overall cancer mortality has seen an average drop of 1.5% per year in the last decade (2008-2017), with the steady decline from 1991 translating to approximately 2.9 million fewer cancer deaths (**Figure**).

The decline can be attributed to long-term drops in death rates for the 4 major cancers—lung, colorectal, breast, and prostate. Lung cancer mortality rates, which constitute a quarter of all cancer deaths, represent a chief influence on the historic decline in cancer mortality, as the pace of mortality reductions has doubled in recent years from 2% to 4%, with further significant declines made over the long term among the other 3 major cancers:

- The death rate for breast cancer dropped by 40% from 1989 to 2017.
- The death rate for prostate cancer dropped by 52% from 1993 to 2017.
- The death rate for colorectal cancer dropped by 53% from 1980 to 2017 among men and by 57% from 1969 to 2017 among women.

Progress in treatment for melanoma of the skin drove the most rapid death rate decline seen in the research, as the overall melanoma death rate dropped by 7% per year during 2013 to 2017 in people aged 20 to 64 years. Before the FDA approval of 2 melanoma treatments, ipilimumab and vemurafenib, these death rates decreased by 2% to 3% each year among people aged 20 to 49 years, with a minimal decline of 1% in those aged 50 to 64 years. Since 2010, the 1-year survival rate for patients diagnosed with metastatic disease rose from 42% (2008-2010) to 55% during 2013 to 2015.

Although these long-term declines show promise, reductions in death rates slowed for female breast and colorectal cancers and halted for prostate cancer, causing lead study author Rebecca Siegel, MPH, scientific director of Surveillance Research at the American Cancer Society, to describe the significance of the study findings as mixed.

"The exciting gains in reducing mortality for melanoma and lung cancer are tempered by slowing progress for colorectal, breast, and prostate cancers, which are amenable to early detection," she said.[2]

Furthermore, cancers that exhibited increases in death rates, such as thyroid, pancreas, and uterus, were all linked to obesity, stressing the ongoing public health crisis caused by this epidemic, a challenge explored at length in the October issue[3] of *Evidence-Based Oncology*.™ As African American (46.8%) and Hispanic (47%) adults were shown to be disproportionately affected by obesity, these minority groups represent definite at-risk groups.

"It's a reminder that increasing our investment in the equitable application of existing cancer control interventions, as well as basic and clinical research to further advance treatment, would undoubtedly accelerate progress against cancer," said Siegel. ◆

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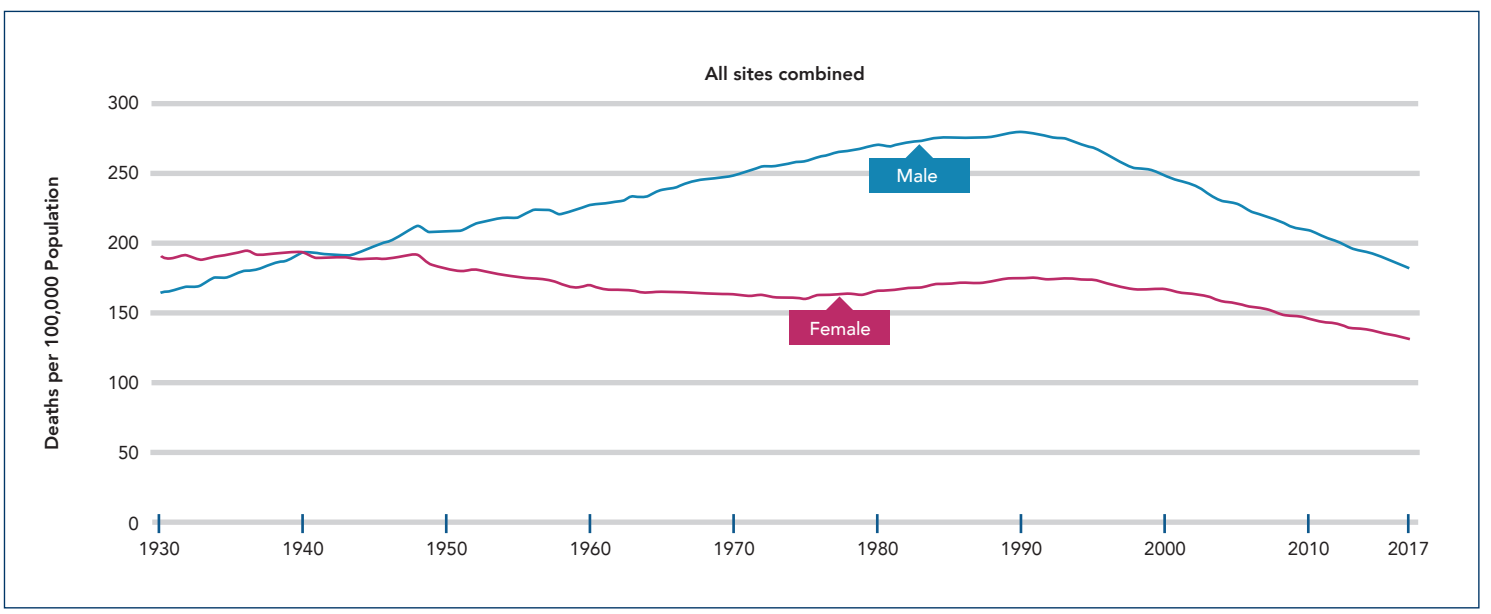
FIGURE. Cancer Mortality, All Sites



Source: American Cancer Society

Coalition Advocates for Biosimilar Uptake to Help Lower Employers' Drug Cost Burden

Gianna Melillo

RISING DRUG COSTS in the United States are a pressing concern not only for patients who need to receive those drugs, but for providers, who in many cases are employers.

The Employers' Prescription for Affordable Drugs is a coalition that aims to tackle this problem by working with policymakers and stakeholders to encourage and facilitate more transparency, competition, and value into the healthcare system. The coalition is composed of the Pacific Business Group on Health, the National Alliance of Healthcare Purchaser Coalitions, The ERISA Industry Committee, and the Silicon Valley Employers Forum.

MITCHELL

Elizabeth Mitchell, president and chief executive officer of the Pacific Business Group on Health, emphasized the need for driving down the cost of prescription drugs.

"Drug costs in the United States are at an all-time high and actually increased by 41% in the last 10 years from $236 billion to $333 billion," she said during a January interview with The Center for Biosimilars®, a sister site of *The American Journal of Managed Care®*.

The biggest contributor to this growth is the rising cost of brand name drugs and biologics. In fact, when ranked by total amount spent, the top 2 drug products in that list were biologics, with employers spending more than $7.5 billion on those 2 treatments alone, Mitchell said.

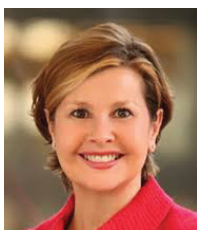
In 2016, large employers spent more than $83 billion on retail prescription drugs. Mitchell explained how these expenditures are siphoning away money from wages, growth, and innovation, and present "a real drag not only on employers, but also on the US economy."

Lauren Vela, senior director of member value at the Pacific Business Group on Health, agrees. In order to promote use of biosimilars and generic drugs among employers, Vela explained that challenges in the preferred provider organization marketplace must be addressed first.

"The first thing [employers] can do is dig in, identify the opportunity, and then…really understand specifically which obstacles are relevant to some of the larger opportunities," Vela said. Issues can include rebates attached to prescribed reference products, resulting in misaligned incentives, and lack of physician incentives to prescribe alternatives to brand name drugs.

In the United States, some physicians are paid based on the cost of drugs they prescribe. Vela argued that in the commercial market, physicians "may potentially make less money by prescribing a biosimilar" and are often hesitant to prescribe treatments they may not know enough about.

The organization urges employers to advocate for biosimilar use among network providers. "There have been 17 biosimilars approved in the United States that have been shown to have no clinical difference from their brand name counterpart, but only 7 have been launched and adoption has been sluggish," Vela said.



VELA

However, health economists estimate that the successful integration of biosimilars could reduce prescription drug spending by as much as $150 billion over the next 10 years.

One solution to the challenges of rebates, provider incentives, and provider education on biosimilars is the integration of value-based care.

"Moving away from fee-for-service and to value-based contracts will have the folks who are positioned to make the right kind of decisions for best clinical outcome and best accountability for total cost of care, able to make those decisions," Mitchell said.

Because so many different parties are present in the drug supply chain, cost containment won't take place unless employers and other payers actively work to change it, Vela explained. "Of course, pharmacy benefit managers (PBMs) have opaque rebates that just add to the challenge, so employers and purchasers can and must lead this," she added.

Added transparency to PBM practices would alleviate some burdens that are hindering the successful use of biosimilars, and "PBMs might actually be able to step in and be part of a solution where a health plan has failed in having a biosimilar-first policy," said Vela.

Effective legislation and policy enactment are also imperative to capping price increases that drug makers apply to products.

"We know that there is recognition on both sides of the aisle that this is an issue, that this can't be ignored," Mitchell said. "We know how powerful the pharma lobby is and we know how much effort they put into maintaining these prices."

Employer coverages of cost have been so helpful to employees, and employers "are increasingly willing to engage in this debate to seek legislative and policy intervention because the market is not working." Because of this, advocates are optimistic that Congress will recognize the absolute necessity of action.

The experts warn that even if price capping occurs in one sector, there are real concerns that those costs would be shifted to private purchasers who are challenged to negate the effects. Price controls or caps in Medicare or Medicaid would need to be extended to the commercial market as well, they argued. ◆

Spectrum Says Its Novel G-CSF Drug Will Be Reviewed by FDA

EBO Staff

IN LATE DECEMBER 2019, Spectrum Pharmaceuticals announced that the FDA has accepted for review a Biologics License Application for eflapegrastim, a novel drug that could, if approved, compete with existing granulocyte colony-stimulating factor (G-CSF) therapies and their biosimilars.

Eflapegrastim, which the company hopes to sell under the brand name Rolontis, is composed of 2 proteins: an analogue of G-CSF and an Fc antibody fragment. These components are joined by a polyethylene glycol linker. According to Spectrum, the Fc fragment is thought to interact with FcRn—expressed in endothelial cells and bone marrow—and to prolong the drug's retention in these tissues.

TURGEON

"If approved, Rolontis could be the first novel [G-CSF] available to healthcare providers in over 15 years," said the company's chief executive officer, Joe Turgeon, in a statement. "We have confidence in the future of Rolontis and are looking forward to potentially competing in this multibillion-dollar market."

The company expects a decision from the FDA by October 24, 2020.

The drug was studied in comparison with pegfilgrastim in a phase 3, randomized, open-label trial in 237 patients with breast cancer who were receiving chemotherapy. Patients were randomized to receive either the investigational drug (n = 118) or pegfilgrastim (n = 119), and the primary end point was the duration of severe neutropenia in cycle 1 of chemotherapy as measured by absolute neutrophil count. Results presented last year at the American Society of Clinical Oncology showed the study drug was non-inferior to pegfilgrastim. ◆

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Coverage by Mary Caffrey, Allison Inserro, Alison Rodriguez, and Maggie L. Shaw

CMS Agrees to Cover NGS for Medicare Patients With Breast, Ovarian, Other Cancers

CMS ANNOUNCED ON JANUARY 27, 2020, that it is expanding coverage of next-generation sequencing (NGS) as a diagnostic for patients with germline breast and ovarian cancers, paving the way for Medicare beneficiaries to receive more personalized medicine. CMS also gave Medicare contractors more leeway to use NGS for other cancers as well.

The national coverage decision (NCD)[1] applies to FDA-approved or -cleared laboratory diagnostic tests. However, an official with a leading advocacy organization for increasing access to testing said the NCD is not the positive step forward portrayed in the CMS announcement.

Lisa Schlager, vice president of community affairs and public policy at Facing Our Risk of Cancer Empowered (FORCE)[2], told *Evidence-Based Oncology*™ (*EBO*) that the precise wording of the NCD requires that germline NGS be "FDA approved," and at this point, no such testing exists. Thus, she said, the policy as written would actually limit access to germline NGS for women with breast and ovarian cancers.

Schlager told *EBO* that FORCE and other groups have notified CMS of this issue, but the wording remains unchanged. Congress may now have to address the matter, she added.

In a statement, CMS noted that Medicare first began covering laboratory diagnostic tests using NGS in March 2018 for patients with advanced cancer that met specific criteria.[3]

With this latest decision, CMS has determined that NGS is reasonable and necessary when performed in a Clinical Laboratory Improvement Amendments–certified laboratory, when ordered by a treating physician when the patient has ovarian or breast cancer, and as a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer.

In addition, the patient must have a risk factor for germline (inherited) breast or ovarian cancer and must not have been previously tested with the same germline test using NGS for the same germline genetic content. All the conditions must be met, CMS said. Besides being FDA approved, the diagnostic laboratory test using NGS must provide results to the treating physician for management of the patient using a report template to specify treatment options.

Given the speed at which the field is moving, CMS said it is also giving regional Medicare administrative contractors (MACs) discretion over whether to cover certain other indications. MACs may determine NGS coverage, in line with the first set of conditions, when the patients has (1) any cancer diagnosis, (2) has a clinical indication for germline (inherited) testing of hereditary cancers, (3) has a risk factor for germline (inherited) cancer, and (4) has not been previously tested with the same germline test using NGS for the same germline genetic content.

CMS also said it is clarifying the existing policy related to diagnostic tests for somatic (acquired) cancer.

"We recognize that cancer patients shoulder a heavy burden, so we're leaving no stone unturned in supporting women's health and getting all patients the care they need. NGS testing provides clinically valuable information to guide patients and physicians in developing a personalized treatment plan," said CMS Administrator Seema Verma.

The first FDA-approved test, FoundationOne CDx, received the go-ahead in December 2017.[2] ◆

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Data Show Risk of Heart Disease Among Childhood Cancer Survivors Falls Since 1970s

THE RISK OF HEART DISEASE is falling among survivors of childhood cancer, per recent statistics.

On January 15, 2020, the journal *BMJ Open* reported that efforts to protect children from the most toxic effects of cancer treatment, such as radiotherapy, appear to be working. Risk of coronary artery disease fell steadily, from 0.38% in the 1970s to 0.19% by the end of the 1990s.[1]

The findings are based on results from 23,462 adults in the Childhood Cancer Survivor Study who had the most common cancers diagnosed before age 21 from the 1970s through the 1990s. The median age at diagnosis was 6.1 years of age, and the mean age at the last follow-up was 27.7 years. A comparison group with 5067 siblings of cancer survivors was also included.

Although the number of survivors who had cardiotoxic treatments increased, the doses they received decreased. Radiation exposure fell from 77% in the 1970s to 40% in the 1990s.

Survivors of Hodgkin lymphoma accounted for most of the decline, and efforts to reduce radiotherapy among these patients likely explain the drop, the investigators report.

"These results suggest that efforts to modify cancer therapies in children and promote health surveillance are beginning to show benefits not only in overall survival but also in late adverse cardiac effects," the authors concluded.

The study asked questions about heart failure, coronary artery disease, heart valve defects, damage to heart tissue lining, and arrhythmias, and recorded the results. The researchers also recorded whether participants had risk factors such as diabetes, high blood pressure, or elevated levels of low-density lipoprotein cholesterol, whether they smoked or exercised, and their weight.

The 20-year incidence of heart failure first rose from 0.69% in the 1970s to 0.74% in the 1980s, before falling to 0.54% for those treated in the 1990s.

It was no surprise that having traditional cardiac risk factors fueled the risk of heart disease among cancer survivors, demonstrating the need for prevention of heart problems among this group. One problem with the study is that almost a third of possible participants opted not to answer the questionnaire, which could have affected the results.

As the number of cancer survivors rises, collaboration between oncologists and cardiologists is increasing to better protect patients from late treatment effects. Although heart failure results were not considered statistically significant in this study, heart failure is considered a risk of cancer treatment generally, as noted in 2019 by Kostakou et al.[2]

"If heart failure develops, even in the absence of overt clinical symptoms, standard heart treatment is to be followed and causal agent discontinued if possible," the authors wrote in *Heart Failure Reviews*. "One important question is whether and when to stop cardiac medication in case of heart dysfunction reversal, after completion of cancer treatment."

"Further cardio-oncology evolution can lead to a deeper understanding of the adverse mechanisms and effects causing heart failure, as well as the development of personalized treatment regimens in order to limit cardiotoxicity," the authors concluded. ◆

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Risk of Heart Failure Greater in Patients With AML, ALL on Anthracyclines

BECAUSE OF SCARCE KNOWLEDGE regarding the connection between acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) and risk of heart failure (HF) from anthracycline use in chemotherapy, researchers from the Hospital of the University of Pennsylvania (HUP) wanted to develop a risk score to help oncologists stratify their highest-risk patients. Such a score, they believe, will enable treatment to be tailored more to the individual patient. Their study was published in a recent issue of *JACC: CardioOncology*.[1]

Anthracyclines are a standard therapy to treat acute cases of leukemia, and they have led to increased survival rates in these patients to about 1% each year from 2006 to 2015, according to a statement.[2] The treatment is extremely toxic, however, and that combined with longer patient survival has focused attention on the cardiotoxic effects of this class of drugs.

The investigators analyzed data from a group of 450 patients treated at the Hospital of the University of Pennsylvania between January 2004 and April 2018, based on 6 risk factors, assigning a point value to each to classify patients as low (0-6 points), moderate (7-13 points), or high risk (14-21 points):

1. Baseline global longitudinal strain greater than –15% (6 points)
2. Baseline left ventricular ejection fraction (LVEF) less than 50% (4 points)
3. Preexisting heart disease (4 points)
4. AML (4 points)
5. Cumulative anthracycline dose of at least 250 mg/m^2 (2 points)
6. Age older than 60 years (1 point)

Follow-up began concurrent with start of anthracycline therapy and continued until death, event of interest (undefined in the study), or study end (June 30, 2018). Patients were excluded if an echocardiogram was not performed before starting anthracycline treatment, if the result was a poor-quality image, or there was no follow-up.

Almost 9.0% (40/450) of patients developed HF an average of 10 months after therapy initiation (range, 1-76 months), and 47.8% (215/450) died from noncardiac causes. These patients also had lower LVEF, and their global longitudinal strain was worse, which signified greater heart impairment. Close to 71.0% (318/450) of the patients were considered low risk; 24.9% (112/45), moderate risk; and 4.4% (20/450), high risk. The corresponding estimated rates of HF were 1.0%, 13.6%, and 35.0%, and more women fell into the low- (1.3% vs 0.8%) and high-risk (38.8% vs 33.7%) groups.

When broken down by acute leukemia subtype, HF occurred more often in patients with AML than acute lymphoblastic leukemia: 11.6% compared with 3.4%. This association remained after adjusting for older age and cumulative anthracycline dose.

What could be the reasons for these results? The authors propose 3 factors that accompany leukemia could be to blame: the possibility of high cytokine release, malignant cancer cells infiltrating the heart, or ischemic cardiac disease. Plus, reduced LVEF could mean less aggressive cancer treatment.

Despite study limitations that included possible selection bias (because patients with lack of follow-up were excluded) and lack of external or prospective risk score validation, the authors are calling for additional studies to explore the use of their risk scoring system.

"While this is a significant step toward identifying patient risk for heart failure, additional studies are needed to determine the effectiveness of such a risk score in clinical practice," stated the study's lead author Yu Kang, MD, PhD, a postdoctoral research fellow at University of Pennsylvania. ◆

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An Immune-Suppressing Target for Glioblastoma?

THE DISCOVERY OF IMMUNO-ONCOLOGY, which harnesses the body's own immune system to fight cancer, has brought hope where there was none in diseases such as metastatic melanoma and advanced lung cancer. Still, leaders in immuno-oncology recognized that their breakthrough treatments—checkpoint inhibitors—didn't work in every cancer. And they've wanted to know how to change that.

Perhaps the most stubborn outlier has been glioblastoma, the aggressive form of brain cancer that claimed the life of US Senator John McCain (R-Arizona). In the past year, some signs of hope led researchers to believe they were making progress in this most difficult and deadly of cancers.

Now, a team at The University of Texas MD Anderson Cancer Center in Houston led by original pioneers in the field have published an article in *Nature Medicine* that discusses an immune-suppressing enzyme that was strongly present in glioblastoma but not in 5 other tumor types the team studied.[1]

The team combined anti–programmed death-1 (PD-1) and anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) in mice bred to knock out the enzyme, CD73. They found the combination stifled tumor growth and led to increased survival.

"We're working with pharmaceutical companies that are developing agents to target CD73 to move forward with a glioblastoma clinical trial in combination with anti–PD-1 and anti–CTLA-4 checkpoint inhibitors," Padmanee Sharma, MD, PhD, professor of genitourinary medical oncology and immunology at MD Anderson, said in a statement.[2] Sharma, who is senior author on the research letter in *Nature Medicine*, worked on the original early trials with ipilimumab that led to the award of the 2018 Nobel Prize in Medicine or Physiology for James P. Allison, PhD, the MD Anderson immunologist who is also an author on the letter.[3]

The article in *Nature Medicine* identifies a subset of cells called *macrophages*—which can aid immune system responses—that had high levels of the CD73 enzyme. The work exemplifies current research that looks not just at the type of cancer but also at the common links of the drivers across different cancers. "By studying the immune microenvironments across tumor types, we've identified a rational combination therapy for glioblastoma," first author Sangeeta Goswami, MD, PhD, assistant professor of genitourinary medical oncology, said.

The approach of "reverse translation" calls on scientists to examine human tumors across multiple cancers to derive insights, which are then used to generate hypotheses to be tested on animal models—the inverse of the usual method. In this case, the team examined 94 human tumors from glioblastoma, lung cancer, kidney, prostate, and colorectal cancer to study clusters of immune cells.

This process revealed a concentration of immune cells among the glioblastoma tumors that expressed CD68, a marker for macrophages, along with CD73 and other immune-inhibiting molecules. They confirmed these findings in additional glioblastoma tumors. RNA sequencing revealed an immunosuppressive gene expression signature linked to the CD73 macrophages.

Their presence, the authors speculated, was likely the reason that immunotherapy designed to trigger T-cell responses has not worked in glioblastoma. But to test this theory, they used the CD73 knockout mice.

"We found that the absence of CD73 improved survival in a murine model of glioblastoma multiforme treated with anti–CTLA-4 and anti–PD-1," they wrote in *Nature Medicine*.

Now, the task ahead is to design a clinical trial that brings together the combination checkpoint inhibitors with a therapy to target CD73. And more than 1 company is working on this. Investigators presented data on an agent known as CPI-006 (Corvus Pharmaceuticals) at the annual meeting for the Society of the Immunotherapy of Cancer in November.[4] Another company working on a CD73 target, Surface Oncology, announced $25 million in financing in late November.[5] ◆ »

Coverage by Mary Caffrey; Allison Inserro; Alison Rodriguez; and Maggie L. Shaw

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Immunohistochemistry, Flow Cytometric Immunophenotyping Are Used in Subset of Lymphoplasmacytic Lymphoma

AN ANALYSIS OF 31 UNTREATED PATIENTS showed approximately one-third with Waldenström macroglobulinemia ([WM] a subset of lymphoplasmacytic lymphoma) had malignancies and all others had increased numbers of mast cells (MCs).

The study, published by *Annals of Laboratory Medicine*,[1] sought to identify the clinical, laboratory, and bone marrow (BM) findings of patients with WM. Additionally, the researchers were assessing the effectiveness of semiquantitative immunohistochemistry (CD20, CD138, tryptase, and CD154) for the diagnosis and prognosis of WM.

Bone marrow MCs have been reported in patients with WM with increasing frequency, the authors write. "This association could be a diagnostic feature of WM. Moreover, MCs could be potential therapeutic targets in WM. CD154 (CD40 ligand), a member of the tumor necrosis factor superfamily, has been reported to be expressed on "activated MCs" as a potent inducer of malignant B-cell growth," the authors said.

Medical records and BM studies or flow cytometric immunotyping were reviewed for 31 patients who had untreated WM. Of the 31 patients, 6 showed symptoms of hyperviscosity syndrome, whereas 11 patients had solid cancer and/or hematologic malignancy. The results also revealed that MCs increased in all samples. Furthermore, 5 patients had chromosomal abnormalities, according to the results.

"Most patients in our study had no specific symptoms of WM but showed abnormal laboratory findings such as rouleaux formation, reversal of albumin:-globulin ratio, anemia, and monoclonal gammopathy," the authors said. "They were thought to have plasma cell myeloma. Although WM is a lymphoma, most cases involve the BM, and some cases involve the lymph nodes and other extranodal sites. In our study, only 4 patients were diagnosed as having WM through a lymph node biopsy, and BM involvement of WM was confirmed via a subsequent BM study; the remaining 27 patients were diagnosed as having WM through BM examination."

The group of patients with high CD154-postive MCs had lower overall 5-year survival rates than the low CD154-positive MC group.

The authors concluded that immunohistochemistry and flow cytometric immunophenotyping may be useful for diagnosing WM, while increased CD154-positive MCs can indicate poor prognosis. ◆

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Quality-of-Life Improvement Is Shown With Docetaxel Plus Plinabulin vs Pegfilgrastim

PRELIMINARY DATA FROM the phase 2-3 multicenter, randomized, double-blind Protective-1 study show that intravenous plinabulin (BPI-2358),[1] meant to prevent chemotherapy-induced neutropenia (CIN), significantly improved quality of life (QOL), compared with pegfilgrastim (Neulasta), when taken with docetaxel for treatment of non-small cell lung cancer (NSCLC). The small molecule from BeyondSpring is currently in late-stage clinical development.[1]

CIN in patients undergoing treatment for cancer involves the destruction of neutrophils, "a patient's first line of defense against infections." The usual treatment calls for granulocyte-colony stimulating factor monotherapy (eg, pegfilgrastim). However, this has been shown to lead to grade 3-4 neutropenia, which can affect chemotherapy.[2]

In phase 2 of the current study, patients were assigned to docetaxel 75 mg/m^2 plus 1 of 3 doses of plinabulin—5 mg/m^2 (n = 14), 10 mg/m^2 (n = 13), or 20 mg/m^2 (n = 14)—on day 1 or docetaxel 75 mg/m^2 on day 1 and pegfilgrastim 6 mg on day 2. The plinabulin was administered 30 minutes after the docetaxel. The patients were evaluated before treatment on day 1 for 4 treatment cycles using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire across 3 categories: global health status/QOL, functional scales, and symptom scales. Scores were also summarized.[1]

The 20-mg/m^2 dose of plinabulin, which is the clinically effective dose for CIN, significantly improved QOL for the following measures[1]:

- Global health status (P <.0001)
- Symptom scale (P <.009)
- Summary score (P <.02)
- Fatigue (P <.03)
- Pain (P <.03)
- Insomnia (P <.05)

"While this analysis is exploratory, these preliminary results are statistically and clinically significant and indicate improvements with plinabulin in the QOL for patients being treated with docetaxel for advanced non-small cell lung cancer in addition to protecting against CIN," stated Douglas Blayney, MD, global principal investigator for BeyondSpring's CIN development program and professor of medicine at the Stanford University School of Medicine.[2]

Plinabulin works by binding to and essentially disrupting the protein tubulin, which forms microtubules within cells, affecting different cells in various ways. This activates the GEF-H1 protein, which spurs dendritic cells to activate T cells, enabling plinabulin to shrink tumors and increase survival. Data also indicate that plinabulin boosts production of primitive stem/progenitor cells in bone marrow, which produce mature immune cells.[3]

Plinabulin is currently in late-stage clinical development in NSCLC and for prevention of CIN. ◆

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Lessons From the Front: Designing and Implementing Clinical Pathways by and for Clinicians

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CONTINUED FROM COVER

Over the course of our own nearly decade-long experience with pathways, we have learned a lot from our stumbles and successes. We come to the pathways table bearing many perspectives—as creators of dynamic and expert content, as codevelopers of a wholly new pathways platform with Philips, as managers of care delivery across an academic institution and a larger network, and as clinical oncologists seeking to deliver the best care to the patient seated before us. The following are some of the key elements we deem worth sharing with others on their own journey down this road.

Development of Clinical Content

The quality of clinical content is the foundational component of any pathways platform. Content must be expert, it must be nimble, and it must be trusted.

Expert. Clinical pathways content requires the input of a diverse collection of providers with a wealth of clinical experience and mastery of the published evidence in a specific disease. To adequately compare clinical outcomes, toxicity, and costs, our clinical pathways committees comprise physicians and pharmacists with expertise in the clinical care and research of that disease, along with team members who provide up-to-date drug costs. Furthermore, to achieve content that is not only expertly sourced but also expertly applied in a pathways platform, it is critical that the creators of pathways content also be users of that same content. When physicians are contributing to a tool that they will use themselves, they have a vested interest in ensuring accurate, nuanced, and usable content.

Nimble. Keeping up with the staggering rate of new medical information—including FDA approvals, prominent publications and presentations, and safety alerts—is becoming increasingly difficult for an individual physician. Doing so across multiple cancer types while also managing a busy oncology practice is nearly impossible. Even at a programmatic level, keeping pathways up to date requires a commitment to infrastructure and process.

First, pathways need to be reviewed frequently enough to remain relevant. Within the DFCI pathways program, we conduct scheduled review meetings 2 to 4 times per year depending on the disease. For diseases with high rates of new approvals and changes, review meetings are scheduled 4 times per year. We intentionally time these reviews to follow major conferences including ASCO, the American Society of Hematology (ASH), and the European Society for Medical Oncology (ESMO) annual meetings or key disease-specific meetings such as the San Antonio Breast Cancer Symposium or the World Conference on Lung Cancer.

Second, we have designated medical directors for each pathway. If there is a major clinical breakthrough or a critical safety alert outside of the planned meeting schedule, we approach the corresponding director to triage the clinical urgency. If an ad hoc meeting is required instead of waiting for the next scheduled review, we proceed appropriately.

Third, timeliness applies not only to the decision-making process but also to the subsequent validation and implementation of content in the pathways platform. To reduce the time required to push content into production, Philips and Dana-Farber have designed the platform to be self-authoring. This allows our internal pathways project management team to model proposed changes, validate them with our physicians and pharmacists, and push them into production more quickly.

Trust. Trust in pathways content is derived from the expertise of the people and institutions creating the content, although that alone is not sufficient. To win the trust of physician users, a pathways program must provide a consistent and transparent decision-making process and succinct messaging about both the decisions made and the supporting rationale.

Contemporary references to transparency are often focused on conflicts of interest. Providers using a pathways platform deserve to know who is in the room when decisions are made and if and how they might be conflicted by ties to industry and other entities.

Transparency regarding what information is included in the decision-making process is just as important but often receives less attention. Providing this level of transparent data review requires significant programmatic commitment. To achieve this, Dana-Farber's disease-specific pathways medical directors, pharmacists, and pathways staff prepare extensively in advance of an upcoming review. These meetings start with a display of the current pathway selections, followed by a review of the trial design, outcomes, and adverse effects found in the publications and presentations supporting the proposed change. These results are then compared to those of the existing standard. Finally, before discussion and decision making, we present the drug costs of the proposed and existing regimens, calculated from the most recent Centers for Medicare & Medicaid Services Average Sales Price files.[6]

To achieve an additional level of transparency, we create succinct meeting minutes that summarize each agenda item, the sources cited, the decisions made, and the supporting rationale. The meeting slides and minutes are shared with all relevant users, and web-based recordings of the meetings are made available.

Integration Into Clinical and Institutional Workflow:

The success of a pathways program relies on physician adoption, and physician adoption in turn hinges significantly on integration into workflow. To optimize the user experience, the Philips Healthcare development team has involved DFCI physicians from the early planning stages in every aspect of the platform: medical content, design and layout, navigation, and workflow. To create a system that is sensitive to the clinical demands of busy practitioners, these collaborating teams have identified and addressed a number of areas for focus:

- ***Accessing the platform from within an Electronic Medical Record (EMR)*** rather than having to search for a separate application
- ***Opening the pathway tool with a single sign-on (SSO)*** from within a specific patient's chart. This not only expedites access but also potentiates the transfer of data among the pathways platform, the EMR, and other medical databases and applications.
- ***Visually displaying the treatment-support algorithms as a road map to be traversed.*** This allows the platform to present choices in the order and manner in which »

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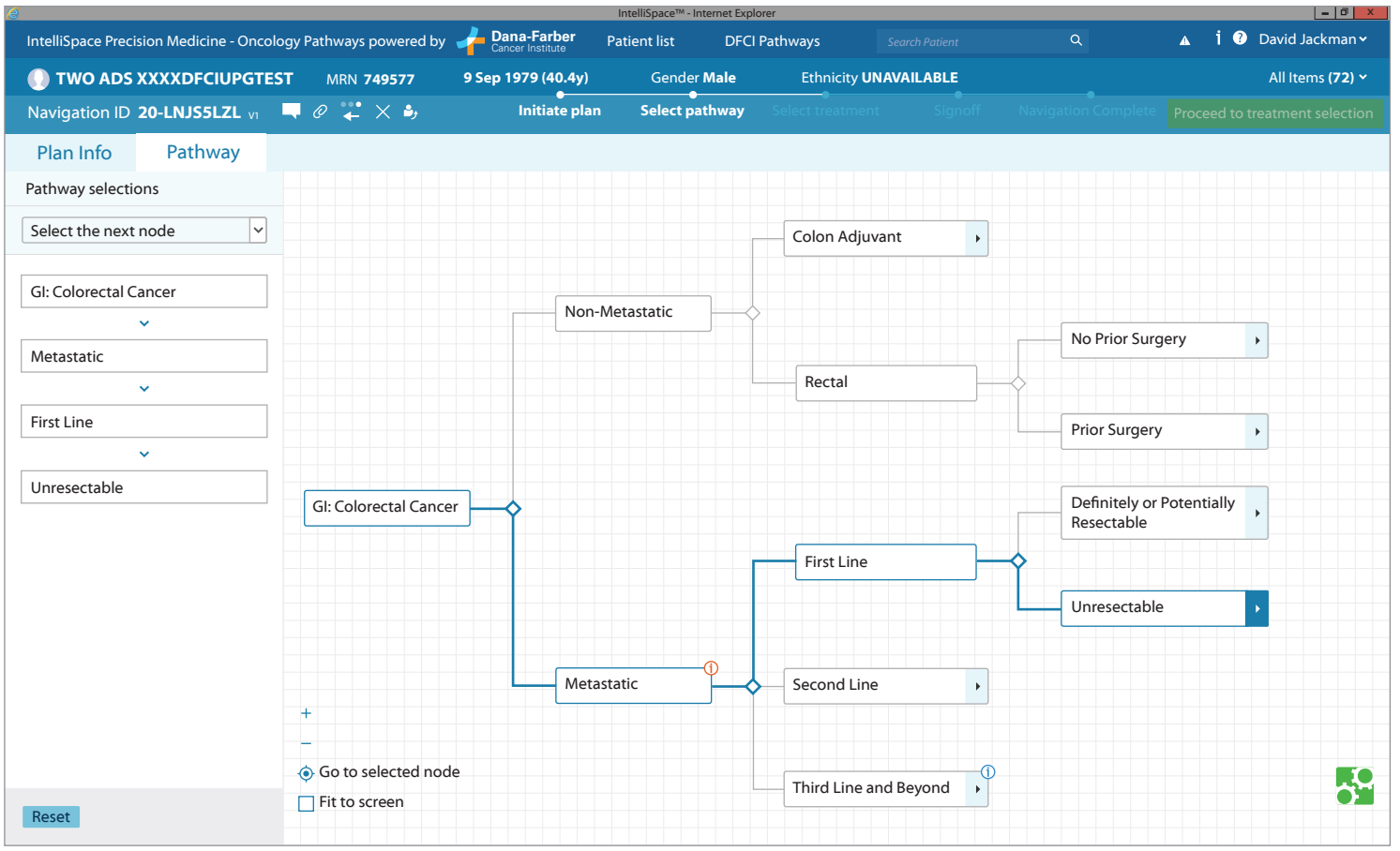
FIGURE 2. User Interface for Colorectal Cancer Within the Philips IntelliSpace Precision Medicine–Oncology Pathways Powered by the Dana-Farber Cancer Institute.



Source: Dana-Farber Cancer Institute

a clinician would consider them, and it allows users to understand how and why each successive choice leads to the next (**Figure 2**).

- ***Minimizing clicks wherever possible***, while ensuring safety and maintaining data integrity. Current medical practice risks "death by a thousand clicks,"[7] but we have sought to minimize these without compromising the platform's ability to impart medical nuance, provide critical information, or capture important data.
- ***Listing on-pathway treatment recommendations and clinical trial options in a single digestible page***, with supporting information, warnings, and other medical guidance clearly displayed.
- ***Creating lists of treatment-associated adverse effects for every regimen in our library***. For a multidrug treatment plan, these adverse effects represent the potential toxicities of the combination, not of each individual drug. They are curated by our pharmacists and physicians, are in patient-friendly language, and are incorporated into a consent form that is generated upon treatment selection. Automatically creating a consent form with regimen-specific adverse effects can result in significant time saved, in some cases winning back more than the time spent navigating the platform itself.

Although integrating a pathways platform into a provider's workflow is critical, it is equally important to integrate into institutional workflow. Beyond decision support, pathways can help to streamline operations and improve care delivery. For example, the data captured in the process of pathway navigation—histology, stage, line of therapy, performance status, genomic alterations, and other molecular biomarkers—are precisely the information that can support the prior authorization process. Pathways navigations in the Philips platform automatically generate treatment summary reports that outline the treatment selections and recapitulate the data elements that drove those selections.

Our goal is to reduce unwarranted variation throughout our practice—not just in treatment decision making but also in physician work itself. Forcing an individual provider to navigate different pathways platforms for each patient threatens to subvert some of the very goals that pathways aim to achieve. Working with multiple systems reduces individual and operational efficiency. Pathways cease to function as an effective learning system when navigations and data are dispersed among multiple platforms. Working with different sets of content—with different decisions, different review schedules, and varying degrees of transparency—adds an additional level of difficulty to the decision-making complexity that pathways should be seeking to minimize. If a high-quality pathways system with a transparent review process and sound decision making can gain broad acceptance from all necessary parties, the uniformity of the system can potentiate the true benefits to care delivery that clinical pathways were intended to address.

Data and Analytics

Data inform every part of a robust pathways program. Measurement ultimately facilitates management. A pathways platform should strive to capture and meaningfully analyze every discrete interaction with the system. In our platform, we accomplish this by building a data model that parses every component of the pathways navigation process into discrete, fundamental elements. This database enables many important functions:

- ***Data Capture and Analysis***. By breaking each successive node in the pathway decision tree into its component elements, we are able to learn from each click in a pathways navigation. Furthermore, we are able to extract and

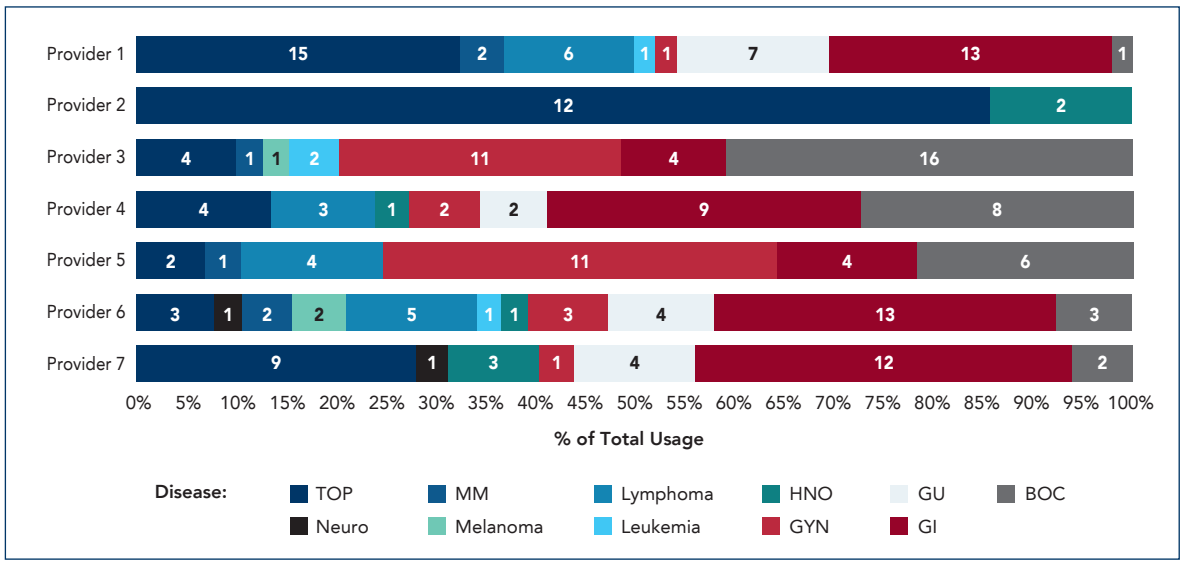
analyze this information in great detail across patients, users, and pathways.

- ***Data Import***. A platform-wide data model potentiates importing of existing, discrete data elements. Bringing in elements like stage, performance status, or genomic alterations from an EMR or other source could help drive assisted navigation of the pathways platform.
- ***Standardization.*** Wherever possible, the database is tied to accepted, existing standards (eg, tying histology to the International Classification of Diseases of Oncology, third revision or tying solid tumor staging to the American Joint Committee on Cancer, version 8). In addition, wherever appropriate, common data elements are used consistently across multiple pathways in the platform. This standardization enables analysis of data across institutions and across pathways.

Data derived from the pathways platform informs every other element of the program. Usage of the platform and on-pathway rates can be analyzed across our network by site, by department, by individual user, and by each branch of the pathway.

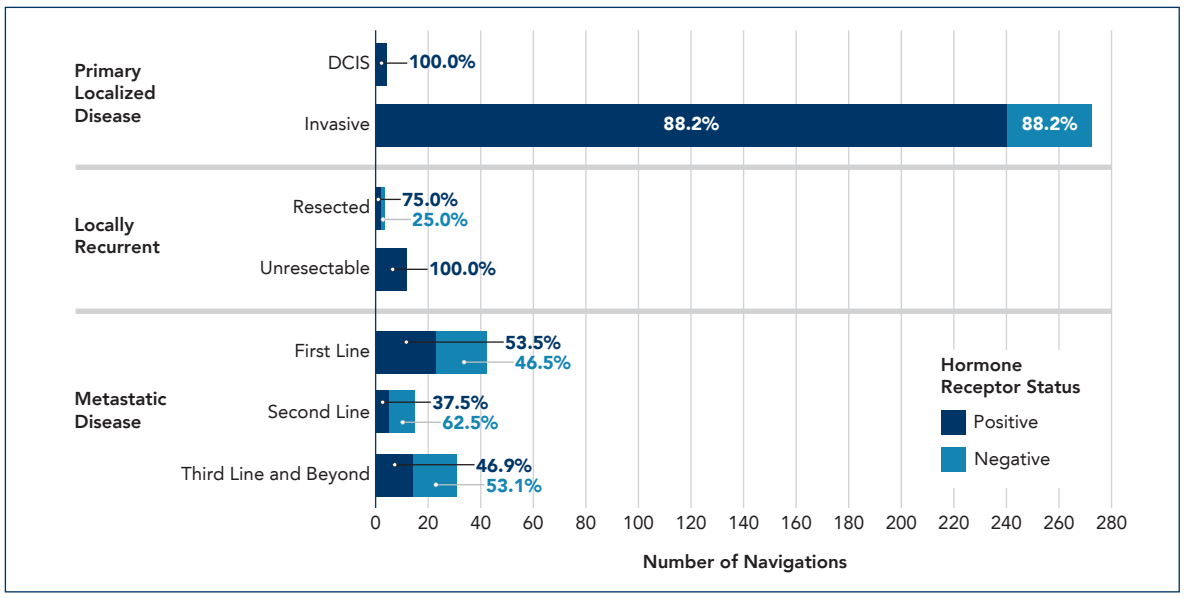
- This can provide a snapshot of institutional and provider case mix (**Figure 3**), helping to determine if this is the optimal use of physician resources.
- On-pathway data by disease, by physician, and by branch can help monitor the quality of care across our network. By analyzing each branch for where and why our physicians go off pathway and what they use in such situations, we can identify instances of potentially suboptimal care. Furthermore, repeated, similar off-pathway navigations at a specific branch may provide a signal that content for this branch may need to be re-evaluated.
- Analysis of a biomarker-based subset within different parts of a pathway can support research operations (**Figure 4**). For instance, knowing how many patients with breast cancer who have hormone-sensitive disease are treated with third-line therapy can inform grant applications or decisions about supporting trial enrollment in that setting.

FIGURE 3. Pathways Navigations by Disease Type Among Physicians at a Satellite Practice, September-December 2019



Source: Dana-Farber Cancer Institute

FIGURE 4. Number of Navigations by Clinical Context and Hormone Receptor Status, September-December 2019



Source: Dana-Farber Cancer Institute

Conclusion

When fully implemented, a clinical pathways program can affect and influence care delivery in a number of important ways. A rigorous and transparent review process of new clinical data affords an opportunity to consider not only what can be done but what should be done. A well-designed platform integrates those recommendations in a model that can be embraced by physicians not only for its ease of use but also for the support and tools that it can provide. And a carefully curated, clinical data model can transform a pathways platform from a decision support tool to a continuous learning system.

As Dana-Farber and Philips have collaborated over the last year and a half to design, build, and implement a new pathways platform, we have learned many key lessons. Perhaps the most important and fundamental is how we listen to each other. Improvement comes when developers, data analysts, and physicians (both as clinical experts and product users) communicate and appreciate each other's needs and limitations. Consistent and concerted efforts to bring these stakeholders together have allowed us to develop and evolve content, platform, and analytics in a way that can move oncology care forward. ◆

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Clinical Pathways: Reducing Costs and Improving Quality Across a Network

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Marcus Neubauer, MD, is the chief medical officer for The US Oncology Network.

CONTINUED FROM COVER

As the cost of oncology drugs only continues to rise, incorporating clinical pathways into cancer care helps streamline the integration of evidence-based best practices while improving quality and reducing costs for patients and payers.

The Pathway Process

The US Oncology Network—which today comprises more than 1400 physicians treating more than 1 million patients in 25 states annually—was a pioneer in the development of clinical pathways in the early 2000s. We identified a need early on to help oncologists determine which regimens may drive better value when there is overlap or duplication among certain therapies.

The network's clinical pathways are managed by our pathways committee, which is made up of 13 physicians who have a keen interest in delivering and supporting value-based care. The committee is supported by 5 pharmacists who scour the latest literature to absorb the rapid introduction of information into the cancer space. They are constantly looking for data on new therapies to inform our pathways. There has been an explosion of information concerning mutations that cause cancer, leading to rapid adoption of targeted therapies. Our team of pharmacists stays up to date on the latest information and presents this to our physicians to review, deliberate, and update our pathways.

Our review process allows us to move quickly to adopt the latest drugs and therapies backed by clinical evidence in order to achieve optimal outcomes for our patients. The pathways committee meets monthly to consider new literature, evaluate new treatments, and discuss what does and doesn't warrant consideration for adoption into our pathways. Once the committee has identified a new drug or therapy for a specific pathway, all network physicians take an active role in decision making through an "open comment period," which allows them to review and submit responses. This feedback is strongly weighed by the pathways committee before pathways are finalized, ensuring physician buy-in and network credibility.

What added significant validation to our pathways development process is the network's unique partnership with the National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 28 leading cancer centers devoted to patient care, research, and education.[2] The NCCN is focused on facilitating quality, effective, efficient, and accessible cancer care. Since 2013, we have worked with the NCCN to form a joint product, Value Pathways powered by NCCN,[3] for which they provide clinical expertise adding strength to our content.

These Value Pathways, along with the NCCN's larger suite of clinical practice guidelines, are easily integrated into the US Oncology Network's system-wide electronic medical record system, iKnowMed, through a decision support tool called Clear Value Plus.[4] This innovative tool can not only inform and educate physicians on the recommended pathways choices, it also enables input of clinical facts into the electronic medical record, subsequently allowing robust data collection. By offering physicians information at the point of care, it encourages accurate and real-time data entry so the network can track pathway adherence and outcomes. These invaluable data are used to inform future pathway refinement and patient care delivery to ensure we are supporting positive outcomes while managing the cost of care.

Further, the data collected through our decision support tool enable us to demonstrate the value of our clinical pathways to payers and reduce some of the barriers to timely coverage and care delivery such as prior authorization requirements. This has ultimately improved patient access to care and reduced administrative burden to our practices.

It is important to stress that the network's clinical pathways program is, at its core, a tool. It was never meant to substitute a physician's clinical judgment or independence. This is why we have put into place a collaborative process for physicians to engage in the development and refinement of Value Pathways. Further, there is an "exception to pathways" process, which allows physicians to treat patients outside of the identified Value Pathways when they feel it is clinically appropriate. We are proud of Value Pathways powered by the NCCN and remain fully committed to maintaining our physician-led process.

Data show that our pathways, previously known as Level I Pathways and, currently, as Value Pathways powered by NCCN, have been successful in shifting the delivery of cancer care from "volume to value."

Pathways to Success

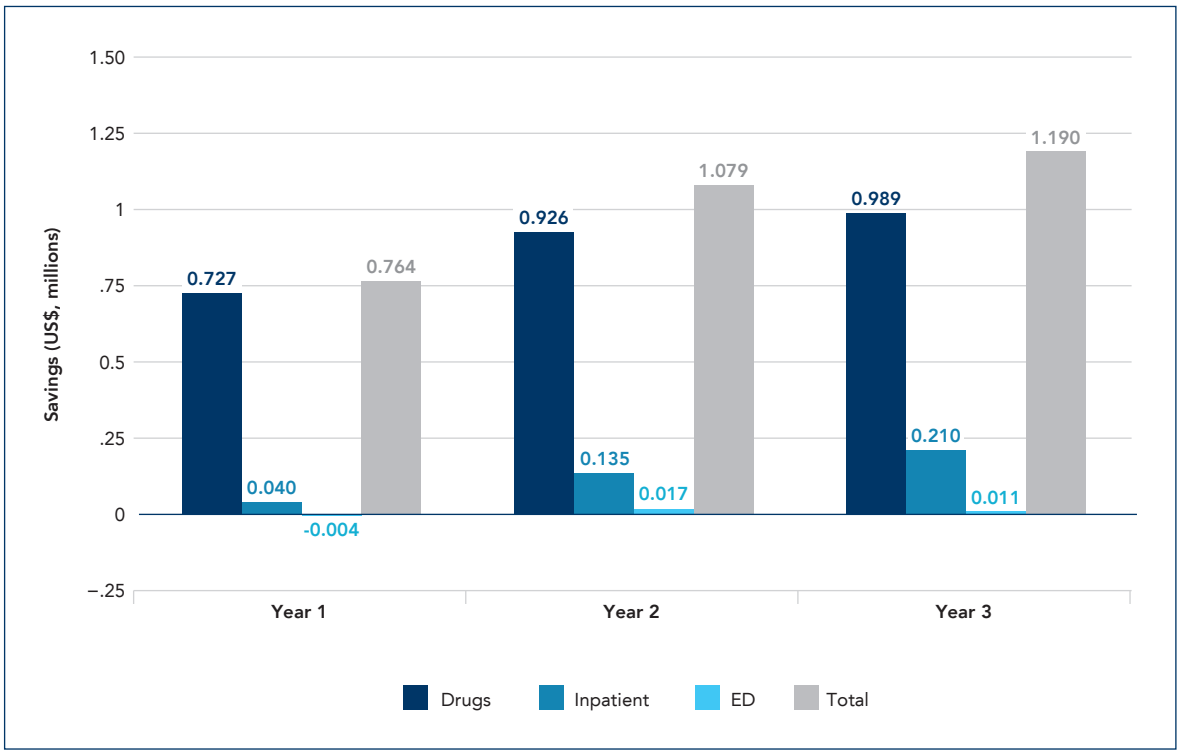
Since launching our clinical pathways program, the network has collected data on the economic impact and clinical outcomes associated with pathway adherence. Data show physician adherence to clinical treatment pathways can improve patient care while reducing costs.

Among the Medicare population, where patients are frailer and living with more comorbidities, a 3-year study of a practice-based, clinical pathways program coupled with a patient care-management program identified a cost savings of more than $3 million mainly due to a reduction in medication costs but also from a reduction in inpatient stays and emergency room visits.[5] The 2018 study concluded that "a practice-based program supported by a payer sponsor can reduce costs while maintaining high adherence to treatment pathways and patient satisfaction in older patients."

An earlier study examining our Innovent Oncology Program—to support pathway compliance and the use of patient support services in reducing chemotherapy-related emergency room and hospital admission costs—found that fewer emergency department visits and inpatient admissions occurred while costs declined and on-pathway adherence increased (**Figure**). Among patients participating in the Innovent Oncology Program over a 2-year period, the average in-patient days decreased from 2.1 to 1.2 days, which resulted in a total program savings of $506,481.[6]

Previous results of studies also show clinical pathways to be highly effective in the treatment of patients with colorectal cancer[7] and non-small cell lung cancer,[8] specifically.

FIGURE. Pathway Adherence Leads to Savings on Drugs, Hospital Admissions, ED Visits



ED indicates emergency department. Source: Hoverman JR, Klein I, Harrison DW, et al. J Oncol Pract 2014;10(1):63-67.

Conclusions

Because of our scale, The US Oncology Network has been able to successfully adopt pathways to the benefit of both patients and payers and publish our results. Data show that both our pathways previously known as Level I Pathways and, currently, Value Pathways powered by the NCCN have been successful in shifting the delivery of cancer care from "volume to value." Although data show pathways might not be appropriate for every specialty, they do work for the practice of oncology.

Our experience demonstrates that value-based clinical pathways—including the rapid integration of new research and treatments into standards of care—can be done safely and effectively. These pathways reduce the cost of cancer care, increase patient satisfaction, and ultimately improve clinical outcomes. ◆

AUTHOR INFORMATION

Marcus Neubauer, MD, is the chief medical officer for The US Oncology Network.

FINANCIAL DISCLOSURE

Dr Neubauer has no financial interests in the pathways programs used by the The US Oncology Network.

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COMMENTARY

Clinical Pathways: A Critical Component of Success in Episodes of Care

Lili Brillstein, MPH, and Brian Currie

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The goal of episodes of care (or bundled payments) is to create a comprehensive treatment model that places the individual patient at the center. The model encourages communication, collaboration, and coordination across all healthcare providers—with goals of reducing unnecessary care and related costs and standardizing and optimizing both.

Clinical pathways are the clinical processes and protocols that are designed to guide treatment decision making and ensure that all practitioners care for the individual patient in the most clinically appropriate manner. They are scientifically based best practice standards—that is, the therapeutic interventions with the highest likelihood of achieving the best outcome for the patient. When effectively developed and adhered to, these clinical protocols can help create success within the episodes of care construct and other value-based models.

Employing clinical pathways within a value-based model construct allows clinicians to standardize care to address the variations in care and costs of care among clinically similar individuals; these variations often lead to suboptimal experiences and outcomes and unnecessary costs. Clinical pathways are most often developed by teams of clinicians in the same specialty using big data—years of objective clinical outcomes results on specific diseases—to agree upon the best methods of treating patients with these diseases, while leaving room for individual patient variation.

Pathways alone, however, are insufficient to transform the healthcare industry and create the most efficient treatment models to address a wide spectrum of diseases. It is absolutely critical to identify and understand the variations in care and costs of care to inform and develop the most effective tools. It is healthcare payers, governmental and private, who have the required data and necessary analytical tools to effectively understand those prevailing variations in care.

Truly transforming care requires a close, trusted partnership between payers and providers—it requires an understanding of all the care required for the patient, not just the care rendered by one particular practitioner at a time, as is the focus in the traditional and often frail fee-for-service (FFS) reimbursement model. It requires a commitment to creating and adhering to evidence-based guidelines, as well as a regular review and refinement of those interdisciplinary guidelines, to ensure consistently optimal outcomes.

The FFS model unintentionally creates treatment silos, which do not allow coordination of care between, for example, a primary care physician, an oncologist, a cardiologist, an obstetrician/gynecologist, or another specialty practitioner caring for the same patient with the same condition or multiple chronic conditions. Clearly, this cannot be the path to a future of holistic disease management and treatment. A vexing challenge, however, is that only health plans are the custodians of much of the data that can help provide insights into individual patients' longitudinal experiences and care. Access to that data has historically been limited, at times inaccurate, and often difficult to discern for providers.

In response to the FFS models' failure to deliver high-quality care at the most efficient and affordable cost, the alternative, "managed care," was originally touted as a rigorous, private sector–based approach that could achieve both optimal patient outcomes and more consistent care, as well as help address healthcare costs that were steadily rising to unaffordable levels.

Unfortunately, in practice, the standard FFS model of managed care has in many cases simply devolved into a "Mother may I" activity, in which clinicians must seek permission in advance each time they want to provide an isolated service to an individual patient. The inherent constraints of this model have left health plans intensely involved in the process of approving each isolated aspect of caring for patients, rather than creating networks and clinical models that support providers in making the most effective treatment decisions and collaborating to provide optimal, long-term care for its members. In this environment, health plans have increasingly become managers of increments of quality of care rather than overseers of patient outcomes and experiences and have been only marginally successful in providing support for providers in their role of defining the processes that will lead to the best patient outcomes, both clinically and financially.

Employing clinical pathways within a value-based model construct allows clinicians to standardize care to address the variations in care and costs of care among clinically similar individuals; these variations often lead to suboptimal experiences and outcomes and unnecessary costs.

The focus in FFS is on each singular, independent service rendered by individual practitioners. Care is often disjointed, with little to no communication among various healthcare providers treating the individual, and individuals are often left to navigate the complex labyrinth of healthcare services on their own. This all has led to unnecessary care, unsustainable costs, and suboptimal outcomes.

The FFS, managed care model of approving increments of treatment has been especially problematic for individuals with chronic and comorbid conditions, as their successful treatment and recovery often depend upon coordinated care among a variety of practitioners.

Episodes of care models provide an opportunity to transcend that dynamic—to use health plans' own proprietary data to enable them to focus on overall patient outcomes and provide information to providers/clinicians to help them make decisions that create the best outcomes for patients at the most cost-effective price. These models respect the providers as the clinicians in charge of patient care and the health plans as oversight guardians of their members by providing support for those clinicians, as well as tools that ensure that providers and patients can see where unnecessary or unnecessarily costly care is being rendered. Using episodes of care models, the focus of the health plans becomes patient outcomes rather than increments of care. The focus of providers is on the process (that is, clinical decisions) to achieve the best outcomes

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tied to evidence-based best practices. Clinical pathways are critical tools that providers can use to standardize and achieve those best outcomes.

Episodes of care models have begun to take shape among clinicians caring for individuals with oncologic diagnoses. Evidence-based treatment protocols are widely disseminated and adopted by cross-specialty groups of providers who agree to closely collaborate in their treatment methodologies and evaluate outcomes within the construct of episode of care models. In many cases, surgical, chemotherapeutic, and radiation oncologists not only agree on which specific combinations of treatment are appropriate for an individual patient, based on the type and severity of the disease and its progression, but also adhere to specific time frames regarding the provision of each component of care and the seamless transition of care between and among collaborating providers. Perhaps most importantly for some of these conditions, both the evidence-based protocols and episodes of care models are rapidly being adapted in response to the burgeoning field of targeted biologics and personalized immunologic medicine, which will only exacerbate the need for a combination of evidence-based treatments within the construct of overall value-based treatment models.

Most clinicians believe they are taking the best care of their patients, and of course that is their intent; however, many have no idea that there may be significant variations between the care they deliver and that advocated by experts in their field using the most comprehensive, up-to-date, scientific evidence available. Health plans have the data that can clearly and reliably demonstrate to providers that these variations often can be easily addressed to improve outcomes, patient experience, and overall cost of care.

Physicians are often concerned that engaging in a value-based care model will reduce their ability to make decisions about their patients and about potentially losing their livelihood. If designed collaboratively and reviewed and refined regularly and with utmost respect for the roles of each partner, value-based models should support providers' decision-making ability and provide additional revenue to those whose outcomes and costs are optimized. These models should also prepare providers to adapt to the rapidly changing advances in clinical treatment of various diseases with the data necessary to manage the soaring costs of such treatment. A value-based partnership model, incorporating evidence-based clinical pathways, would seem to be the only successful path forward to achieve optimal patient outcomes, as well as reduce and eliminate unnecessary costs and burdens to patients and health plans. ◆

AUTHOR INFORMATION

Lili Brillstein, MPH, is a leading advocate for episodes of care/bundled payments, with a global reputation for successfully advancing and implementing value-based care models. She is a former director of specialty care value-based models for Horizon Blue Cross Blue Shield of New Jersey and built the largest, most progressive, and most collaborative episodes of care program for commercially insured patients in the country. In July 2019, Brillstein founded BCollaborative to provide strategic advisory services to boards and C-suite stakeholders across the healthcare industry that seek to craft strategy and engagement in specialty care value-based models. She works with providers, payers, pharma, start-ups, and others to help advance the move from fee-for-service to value-based care. She has served as an advisor to CMS and is a member of the advisory board to the US Women's Health Alliance and the Quality Cancer Care Alliance.

Brian Currie has been designing, negotiating, and implementing reimbursement solutions for major healthcare systems in the New York, New York, region for more than 25 years. He is the former senior vice president of reimbursement performance and outcomes at Northwell Health, where he created a financial framework for the system's first extensive regional network of freestanding surgical and urgent care centers. Previously, Currie was president and chief executive officer of Long Island Health Network, leading the first clinically integrated hospital network in the country; the network gained recognition for its clinical quality improvement and financial turnaround. Currie is presently a self-employed healthcare consultant in New York.

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