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 Calol, 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.

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.

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.

CONTINUED ON SP57 »

CONTINUED ON SP62 »
BRUKINSA IS NOW APPROVED

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) 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 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.

ADVERSE REACTIONS
The most common adverse reactions in >10% of patients who received BRUKINSA were (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

BRUKINSA and BeiGene are trademarks owned by BeiGene, Ltd.
© BeiGene, Ltd. 2019 All Rights Reserved. 0819-BRU-PRC-011 11/2019
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 (7.4.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**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 use a condom and avoid ejaculation into the female reproductive organs. BRUKINSA is not excreted in breast milk; however, breastfeeding is not recommended in women receiving BRUKINSA.

**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-AU-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 patients 524 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 (18%), pneumonia (18%), urinary tract infection (13%), hematrua (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

**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.

**5.4 Second Primary Malignancies**

Secondary malignancies, including non-skin carcinomas, 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.

**5.3 Cytophenias**

Grade 3 or 4 cytophenias, including neutropenia (27%), thrombocytopenia (17%), 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 support or transfusions, as needed.

**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)]
- **Cytophenias** [see Warnings and Precautions (5.3)]
- **Second Primary Malignancies** [see Warnings and Precautions (5.4)]
- **Cardiac Arrhythmias** [see Warnings and Precautions (5.5)]

**5.2 Infections**

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematologic malignancies treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to HPV in vaccinated patients (0.6%) 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 fewer or other signs of infection and treat appropriately.

**5.1 Hemorrhage**

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 the bleeding.

**5.4 Second Primary Malignancies**

Second primary malignancies, including non-skin carcinomas, 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.

**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 use a condom and avoid ejaculation into the female reproductive organs. BRUKINSA is not excreted in breast milk; however, breastfeeding is not recommended in women receiving BRUKINSA.

**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)]
- **Cytophenias** [see Warnings and Precautions (5.3)]
- **Second Primary Malignancies** [see Warnings and Precautions (5.4)]
- **Cardiac Arrhythmias** [see Warnings and Precautions (5.5)]

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-AU-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 patients 524 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 (18%), pneumonia (18%), urinary tract infection (13%), hematrua (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

**5.1 Hemorrhage**

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 the bleeding.

**5.2 Infections**

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematologic malignancies treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to HPV in vaccinated patients (0.6%) 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 fewer or other signs of infection and treat appropriately.

**5.3 Cytophenias**

Grade 3 or 4 cytophenias, including neutropenia (27%), thrombocytopenia (17%), 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 support or transfusions, as needed.

**5.4 Second Primary Malignancies**

Second primary malignancies, including non-skin carcinomas, 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)].
≥ 50 x 10⁹/L and an absolute neutrophil count ≥ 1 x 10⁹/L independent of growth factor support, hepatic enzymes ≤ 2.5 times upper limits of normal, and no history of hepatic disorders. The BGB-3111-206 trial required a platelet count ≥ 75 x 10⁹/L [see Clinical Studies (14.1)].

The median age of patients who received BRUKINSA in studies was 68 (range: 35 to 88). Males were 55% of the patients. Most patients (93% of patients receiving BRUKINSA monotherapy) had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 (i.e., no symptoms) or 1 (i.e., able to perform all activities of daily living but unable to carry out professional occupations).

Adverse Reactions:

-**Cardiac Arrhythmias**

-**Hemorrhage**

-**Pancreatitis**

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

-**Second Primary Malignancies**

-**Hematologic and Lymphoid System Disorders**

-**Infections**

-**Liver Disorders**

-**Clinical Laboratory Test Abnormalities**

-**Neural Tube Defects (NTDs)**

-**Pulmonary Embolism**

-**Pulmonary Hypertension**

-**Renal Impairment**

-**Skin and Subcutaneous Tissue Disorders**

-**Vascular Disorders**

-**Other Clinical Findings**

-**Gastrointestinal Disorders**

-**General Disorders and Administration Site Reactions**

-**Hepatic Impairment**

-**Neurological Disorders**

-**Respiratory, Thoracic and Mediastinal Disorders**

-**Endocrine Disorders**

-**Investigations**

-**Psychiatric Disorders**

-**Eye and Periorificial Disorders**

-**Musculoskeletal and Connective Tissue Disorders**

-**Metabolic and Nutritional Disorders**

-**Injury, Poisoning and Procedural Complications**

-**Hepatobiliary System Disorder**

-**Psychiatric Disorders**

-**Injury, Poisoning and Procedural Complications**

-**Hepatobiliary System Disorder**

-**Psychiatric Disorders**

-**Respiratory, Thoracic and Mediastinal Disorders**

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 (0- or 3-chambered heart) 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 of 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)).

**Drug Interactions**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Moderate and Strong CYP3A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib Cmax and AUC [see Clinical Pharmacology (12.3)] which may increase the risk of BRUKINSA toxicities.</td>
</tr>
<tr>
<td>Prevention or management</td>
<td>Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

**Table 5: Drug Interactions that Affect Zanubrutinib**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Moderate and Strong CYP3A Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib Cmax and AUC [see Clinical Pharmacology (12.3)] which may reduce BRUKINSA efficacy.</td>
</tr>
<tr>
<td>Prevention or management</td>
<td>Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

Distributed and Marketed by:
BeiGene USA, Inc.
San Mateo, CA 94403
BRUKINSA and BeiGene are trademarks owned by BeiGene, Ltd.
© BeiGene, Ltd. 2019 All Rights Reserved. 0919-BRU-PRE-045 11/2019
have created significant concern about how such treatments can be delivered in a financially sustainable 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.\(^1\) Additionally, there is growing evidence that a significant number of patients who could potentially benefit from these innovative treatments may never get them.\(^1,5\)

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 delivering 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**

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

**REFERENCES**


SP42

FROM THE EDITOR-IN-CHIEF

The End of the Beginning

JOSEPH ALVARNAS, MD

SP44

FROM THE CHAIRMAN

Pathways to Better Cancer Care

MARTY CAFFREY

FEATURES

SP57

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; LOUIS CULOT, MA; CAROLE TREMONTI, RN, MBA; JOSEPH O. JACOBSON, MD, MSC

SP60

PATHWAY ADOPTION

Clinical Pathways: Reducing Costs and Improving Quality Across a Network

MARCUS NEUBAUER, MD

SP62

COMMENTARY

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

LILI BRILLSTEIN, MPH, AND BRIAN CURRIE

INSIDE THIS ISSUE

SP45

PAYING FOR CANCER CARE

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

MARTY CAFFREY

SP47-SP50

PRECISION MEDICINE

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

INTERVIEW WITH STUART GOLDBERG, MD, MBA

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

LANCE BALDO, MD

SP51

REGULATORY UPDATE

Faster Drug Approvals, Weaker FDA Process

DEANA FERRERI, PHD

SP52

POPULATION HEALTH

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

MATTHEW GAVIDIA

WHO ARE THE AJMC® STRATEGIC ALLIANCE PARTNERS?

This symbol designates authors and faculty from our Strategic Alliance Partners®, who work with us to share important news and insights in oncology, reimbursement, and other areas. If your organization would like to become a Strategic Alliance Partner, email MARYCAFFREY@AJMC.COM with SAP in the subject field.
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.

CARDIO-ONCOLOGY UPDATES
Data Show Risk of Heart Disease Among Childhood Cancer Survivors Falls Since 1970s
Risk of Heart Failure Greater in Patients With AML, ALL on Anthracyclines

CLINICAL UPDATES
An Immune-Suppressing Target for Glioblastoma?
Immunohistochemistry, Flow Cytometric Immunophenotyping Are Used in Subset of Lymphoplasmacytic Lymphoma

QUALITY-OF-LIFE UPDATE
Quality-of-Life Improvement Is Shown With Docetaxel Plus Plinabulin vs Pegfilgrastim

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 physicians 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
Paying for Cancer Care

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, the price of cancer treatment rises, and the obesity epidemic means millennials face double the risk of cancers that baby boomers did a generation ago.

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 healthcare spend. 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 coalitions 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

Brett 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.

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.
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. 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.

“When 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.”
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.

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, 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. 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 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.

“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 didn’t get 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.”

Medical Utilization for Opioid-Related Diagnoses

ajmc.com/link/4488
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 have the right therapy to the right patient, and I also argue in my other hat that we should be giving it at the right time. 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 where 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 cancer who focuses on outcomes and value. We’re starting to see more and more models that are specific to value, and we’re starting to see outcomes become more important. So we really need to be thinking about 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 have the right therapy to the right patient, and I also argue in my other hat that we should be giving it at the right time. 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 outcomes and value. We’re starting to see more and more models that are specific to value, and we’re starting to see outcomes become more important. So we really need to be thinking about 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 have the right therapy to the right patient, and I also argue in my other hat that we should be giving it at the right time. 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 outcomes and value. We’re starting to see more and more models that are specific to value, and we’re starting to see outcomes become more important. So we really need to be thinking about 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 have the right therapy to the right patient, and I also argue in my other hat that we should be giving it at the right time. 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?
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 not keeping up with which genomics to order. And I think that was familiar with genomics. No, we're not 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?

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, 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.

EBO: What's your 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: 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.
Impact of Next-Generation Sequencing Tests on Clinical Pathways for Cancer Care

Lance Baldo, MD

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 immunotherapeutics and even cellular therapies. In this paradigm, therapeutic developers, diagnostic innovators, payers, and healthcare providers, and, most importantly, 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. Next-generation sequencing (NGS) is a powerful technology platform that investigationalists 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 a 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 (CGP) 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. 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.

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.
- 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.
- 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.

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 diagnostic tests, 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
Lance Baldo, MD, is chief medical officer of Adaptive Biotechnologies. Before joining Adaptive, Baldo served in various roles at升起Incand its affiliates from February 2010 to April 2019, including most recently as senior vice president and head of US medical affairs of Genentech.

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

Deana Ferreri, PhD

**REGULATORY UPDATE**

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. 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 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 starting points for reforms: 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.”

**REFERENCES**

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

Matthew Gavidia

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 issue3 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.◆

REFERENCES
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.

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.

However, health economist 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.

The Employers’ Prescription for Affordable Drugs coalition advocates for biosimilar uptake to help lower employers’ drug cost burden.

Gianna Melillo

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 efaloprostim, a novel drug that could, if approved, compete with existing granulocyte colony-stimulating factor (G-CSF) therapies and their biosimilars. Efaloprostim, 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.

“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.

REFERENCE


Gianna Melillo
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) 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®), 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.

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 for hereditary breast or ovarian cancer.

“The first FDA-approved test, FoundationOne CDx, received the go-ahead in December 2017. The first FDA-approved test, FoundationOne CDx, received the go-ahead in December 2017.

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. 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.

“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.

REFERENCES

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/m² (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 disease. Plus, reduced LVEF could mean less aggressive cancer treatment.

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.

REFERENCES

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 stilled 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.2

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 Govani, 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 multifforme 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.3 Another company working on a CD73 target, Surface Oncology, announced $25 million in financing in late November.4
CD154-positive MCs can indicate poor prognosis. Immunophenotyping may be useful for diagnosing WM, while increased survival rates than the low CD154-positive MC group.

In our study, only 4 patients were diagnosed as having WM through BM examination. The remaining 27 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.

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, which forms microtubules within cells, affects different cells in various ways. This activates the GEF-H1 protein, which spurs dendritic cells to activate T-cell growth,” the authors said.

Medical records and BM studies or flow cytometric immunophenotyping 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 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-positive 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.

**REFERENCES**


**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), 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.

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.

In phase 2 of the current study, patients were assigned to docetaxel 75 mg/m² plus 1 of 3 doses of plinabulin—5 mg/m² (n = 14), 10 mg/m² (n = 13), or 20 mg/m² (n = 14)—on day 1 or docetaxel 75 mg/m² 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.

The 20-mg/m² dose of plinabulin, which is the clinically effective dose for CIN, significantly improved QOL for the following measures:

- Global health status (P < .001)
- 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.

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

**REFERENCES**


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, MBA; Louis Calot, MA; Carole Tremonti, RN, MBA; Joseph O. Jacobson, MD, MSc

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, we proceed appropriately.

Third, nimbleness requires the integration of content, design and layout, navigation, and workflow. To create an 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.

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 they are intended.

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, we proceed appropriately.

Third, nimbleness requires the integration of content, design and layout, navigation, and workflow. To create an 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.

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.
PATHWAY DEVELOPMENT

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,” 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 a consent form with regimen-specific adverse effects can 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 (e.g., by tying histology to the International Classification of Diseases, 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.

**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.

**AUTHOR INFORMATION**

From Dana-Farber Cancer Institute, Boston, Massachusetts: David M. Jackman, MD, Medical Director of Clinical Pathways; Joaquina Hamilton, MA, MS, Senior Project Manager; Clinical Pathways program; Emily Foster, MPH, Senior Business Analyst; Craig A. Burnell, MD, MPH, MBA, Chief Medical Officer; Carolan Teitum, MBA, RN, Senior Director, Clinical Pathways Operations; Joseph O. Jacobsen, MD, MS, Chief Quality Officer. From Philips, Cambridge, Massachusetts: Louise Colut, MA, General Manager for Genomics and Oncology Informatics.

**FINANCIAL DISCLOSURE.** The authors employed by the Dana-Farber Cancer Institute derive no income from the clinical pathways program or from pharmaceutical industry sources. Colut is employed by Philips.

**REFERENCES**


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

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

Clinical Pathways: Reducing Costs and Improving Quality Across a Network

Marcus Neubauer, MD

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. 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 the NCCN and remain fully committed to maintaining our physician-led process.

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

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

Lili Brillstein, MPH, and Brian Currie

CONTINUED FROM COVER

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.
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 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 payment models, 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 and chief financial 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.
Blood cancer therapies are rapidly improving.

Is your plan enabling access to the latest advances in Minimal Residual Disease (MRD) assessment?

clonoSEQ®

The first & only FDA-cleared and Medicare covered assay for the detection and monitoring of MRD in bone marrow samples from multiple myeloma and B-cell acute lymphoblastic leukemia (ALL) patients.

clonoSEQ MRD testing is available to clinicians nationwide with positive payer decisions expanding access to over 165 million people.