Bridging the gap among payer, provider, and patient perspectives

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Evidence-Based Oncology

SPECIAL ISSUE: COST SHARING IN ONCOLOGY

Policy

Improve Medicare Policy to Remove Barriers to Bone Marrow and Cord Blood Transplants

JEFFREY W. CHELL, MD

Every 3 minutes, an American is diagnosed with blood cancer, and every 9 minutes the disease takes another life. All in all, there are more than a million people in the United States living with or in remission from lymphoma, myeloma, or leukemia alone—and approximately 170,000 individuals will be newly diagnosed in 2016.[1]

Reducing barriers to hematopoetic stem cell (HPC) transplant is critical to supporting patients with one of the more than 70 blood cancers and other blood disorders (such as leukemia, lymphoma, and myloplastic dysplasia) for which a transplant may be the only therapy remaining with curative intent. Healthy HPCs replace marrow that will no longer recover post therapy or secondary to the underlying disease. Depending on the diagnosis, HPCs may also exhibit a graft versus tumor effect, eliminating residual disease.[2]

Historically, finding a suitably matched adult donor or cord blood unit(s) has been the primary barrier to accessing an HPC transplant. This is related to the precision matching at a DNA level. Only 30% of patients have a perfect match in their family. However, with growth of the Be The Match Registry, improving international cooperation, and the emergence of successful multiple mis-matched transplants, finding a suitable donor no longer represents the most significant barrier to access.

Recognizing that bone marrow and cord blood transplants often

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Provider Perspective

Proton Therapy Eliminates Unnecessary Radiation Exposure and Is Medically Necessary

STEVEN J. FRANK, MD

When it comes to health coverage, most Americans face an unnerving reality—they have no idea what is covered under their health insurance policy until after they are affected by illness or disease. Further complicating matters are the often illogical differences in why certain treatments are covered by some insurance providers and others are not.

As an oncologist at one of the world's leading cancer centers, these unexplainable discrepancies in insurance coverage—which inhibit physicians from prescribing and patients from receiving the most appropriate treatment for their illness—have become a part of my everyday work life, and they are far too common in the field of proton therapy.

Picture yourself as having just received a diagnosis of cancer. After the immense shock of hearing that diagnosis, you consult a doctor about the path that lies ahead. A medical team consisting of a surgical oncologist, a medical oncologist, and a radiation oncologist weigh the most recent clinical evidence to date, and prescribe proton therapy to treat the cancer. This seems like great news because proton therapy is a highly precise form of treatment that can specifically target and destroy cancer cells while eliminating unnecessary radiation exposure to surrounding healthy tissues.

At that point, the anxiety over the cancer diagnosis and potential

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Patient Advocacy

Finding Solutions for Cancer Patients: The American Cancer Society's Health Insurance Assistance Service

KATHERINE SHARPE, MTS; MELISSA FELLERS; AND MANDI BATTAGLIA SEILER

The American Cancer Society (ACS) has worked tirelessly to ensure that the voices of cancer patients, survivors, and caregivers are heard and that every cancer patient can access timely, high-quality cancer care. Since 2005, ACS has sponsored the Health Insurance Assistance Service (HIAS), a unique initiative to help cancer patients navigate the private coverage system and to educate policy makers about how coverage works for patients with this serious and chronic condition.

The HIAS program has helped monitor the progress of healthcare implementation as it evolves through the cancer lens, in a manner that is readily understandable to a broad public audience, the media, and policy makers. Additionally, the program offers patients and their caregivers much needed resources to help them bridge the all too frequent financial barriers they experience relative to their care.

GROWING BURDEN ON THE PATIENT'S WALLET

The costs of cancer care have been increasing and are projected to continue to rise over the next decade. Increasing out-of-pocket (OOP) expenses can affect cancer patient's care, often resulting in a lack of treatment adherence due to inadequate or unaffordable health insurance.[1] ACS' HIAS,

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Also in This Issue...

AJMC® Managed Markets Network®

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NEW DATA: IMBRUVICA® EXTENDED OVERALL SURVIVAL VS CHLORAMBUCIL IN FRONTLINE CLL/SLL

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1]
- CLL/SLL with 17p deletion[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended overall survival vs chlorambucil

Statistically significant reduction in risk of death[1]

56%

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

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

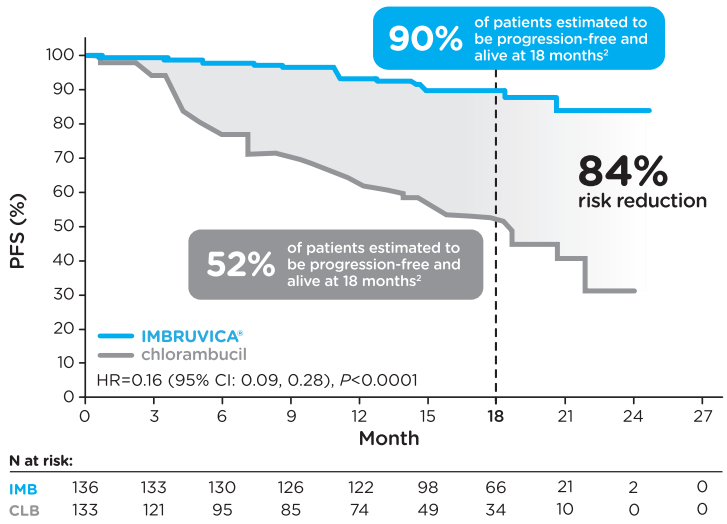
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS)

- Median follow-up was 28 months[1]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil



PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS)

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

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

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

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

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

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

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

Monitor complete blood counts monthly.

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

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

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

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

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

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

* One patient death due to histiocytic sarcoma.

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

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

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

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

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

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

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

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

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

* Based on laboratory measurements per IWCLL criteria.

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

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

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

IMBRUVICA® (ibrutinib) capsules

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

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

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

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

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

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

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

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

Waldenström's Macroglobulinemia: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

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

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

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

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

* Based on laboratory measurements.

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

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

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

Hepatobiliary disorders: hepatic failure (includes multiple terms)

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

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

IMBRUVICA® (ibrutinib) capsules

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

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

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

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

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

Contraception:

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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Closing the Loop on Precision Medicine, Improved Outcomes, and Paying for It All

Innovation is expensive, whether it's for healthcare or consumer goods, and paying for innovation is a choice that usually rests with the consumer. Healthcare, of course, is unique because the decision to use a particular treatment or service is made by multiple stakeholders, not by the patient alone.

In our August issue of *Evidence-Based Oncology*, we hear from several of these stakeholders—providers, a diagnostic device manufacturer, patient advocates, and those in charge of patient assistance programs.

Dr Jeffrey Chell, who leads the National Marrow Donor Program and Be The Match foundation, narrates how Medicare coverage of bone marrow and cord blood transplants could transform patient lives. Medicare's restrictive policies, he writes, currently cover only 6 conditions, and expanded coverage is determined on an indication-specific basis. Dr Chell believes this is an unnecessary risk for our elders.

We also hear from Dr Steven Frank from MD Anderson Cancer Center. A strong proponent of proton beam therapy (PBT), he wants a consistent definition of "medical necessity" and uniform coverage that ensures patient access to proton therapy when that therapy is recommended by a multidisciplinary medical team. But, PBT is expensive and payers have been hesitant. To prove this point, MD Anderson has developed a program in collaboration with The University of Texas System's employee benefit program and Blue Cross Blue Shield of Texas to allow proton therapy to be covered for employees of The University of Texas and their families for cancer of the head and neck, esophagus, breast, and lung, as well as for patients participating in clinical trials of proton therapy.


MIKE HENNESSY, SR

The Samfund and the Leukemia and Lymphoma Foundation discuss the support they provide for young adult (YA) survivors and patients, respectively. Samfund is developing a program, "Finances 101: A Toolkit for Young Adults With Cancer," that can support YAs with financial, healthcare, and other challenges during their cancer journey. The Leukemia and Lymphoma Foundation is working on aspects of public policy, research on barriers to access, patient assistance programs, and working with stakeholders to help patients surmount their cost-sharing challenges.

I hope you will appreciate the viewpoints we present in this issue. As always, thank you for your readership, and please visit the Oncology Compendium on our website, www.ajmc.com, for the latest clinical and managed care updates.

Do not forget to register for our meeting, Patient-Centered Oncology Care (http://www.ajmc.com/meetings/pcoc16), which is celebrating its 5th anniversary this year. In addition to insightful presentations and panel discussions, the meeting, scheduled to be held in Baltimore on November 17-18, 2016, also provides opportunity for participants to present their research as posters.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

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

The Toll of Cancer Care—Clinical and Financial Toxicity

These are times of extraordinary change for patients, families, physicians, healthcare systems, and payers who are engaged in the perpetual battle against cancer. For decades, the distant promise of "magic bullets" that could attack cancer with unprecedented effectiveness and safety has now culminated in an era in which molecular diagnostic testing empowers the use of a rapidly growing armamentarium of lifesaving targeted therapeutics. The long-known fears surrounding a new cancer diagnosis are yielding to a new found sense of optimism and soaring rhetoric that heralds a new era of precision medicine and "Moonshot" initiatives.[1] Data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program now show that for the period between 2006 to 2012, 5-year cancer survival rates rose to 66.9%, up from 48.9% for the period between 1975 to 1977 (the initial years of the SEER data registry).[2]

These successes, however, have not come without significant challenges. The challenge of ensuring that precision medicine solutions can be made equitably available to all patients has involved the growing realization that innovation does not come cheap. The costs of precision-medicine cancer care are enormous. As of 2010, national cancer care costs amounted to $124.6 billion and the NCI predicted that expenditures would grow by 39% through the year 2010.[3] The rate of cancer care cost inflation far exceeds the inflation rate for the domestic economy. Cancer care diagnostic testing and pharmaceutical costs are key drivers of this increase. Molecular diagnostic testing costs are rapidly growing and, as of 2010, were projected to exceed $8 billion in annual expenditures.[4]

In parallel with the growth in diagnostic testing costs, cancer drug costs have also increased in an unprecedented fashion. In the *Journal of Oncology Practice*, Kantarjian and colleagues noted. The average cancer drug price for approximately 1 year of therapy or a total treatment duration was less than $10,000 before 2000, and had increased to $30,000 to $50,000 by 2005. In 2012, 12 of the 13 new drugs approved for cancer indications were priced above $100,000 per year of therapy.[5]

This rapid escalation in cancer care costs has had a significant toll on patients and families faced with a cancer diagnosis. The term "financial toxicity" has entered the lexicon in acknowledgement of the profound adverse impact that these costs have had upon patients and their families.[6]

The issue of cost sharing in oncology care sits squarely at the intersection of our aspirations to deliver precision-medicine solutions while attempting to foster an economically sustainable cancer care system. This issue of *Evidence-Based Oncology* is dedicated to understanding the implications, scope, and opportunities within the realm of cost sharing in oncology. Our contributors include, The Samfund, which represents young adults and helps to prepare them for the financial implications of a cancer diagnosis through their program, "Finances 101: A Toolkit for Young Adults With Cancer." Dr Jeffrey Chell, from Be The Match, discusses some of the financial barriers and coverage gaps affecting patients in need of hematopoietic cell transplantation. The Leukemia and Lymphoma Foundation shares its perspective on how the issue of cost sharing may limit access to essential pharmaceutics for patients with blood cancers. Dr Steven Frank, from MD Anderson Cancer Center, shares his perspective on the issue of medical necessity and lends his insights on how higher upfront costs may actually result in decreased long-term costs and improved quality of life for cancer patients.

As patients, families, physicians, and other stakeholders who battle cancer daily, it is easy to become swept up in the rhetorical poetry of the precision medicine era. Our ongoing challenges, however, are far more prosaic and are grounded in the financial realities of delivering complex, innovative care solutions. As our healthcare system continues to grapple with how best to deliver these solutions in a financially responsible way, conversations such as these may help lay the groundwork for creating the tools that can ensure equitable and sustainable access for all patients. **EBO**

ABOUT THE EIC

JOSEPH ALVARNAS, MD

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

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Solutions for Reducing Patient Cost Sharing for Medications

MARIALANNA LEE, MSC; BRIAN CONNELL; ELISA WEISS, PHD; AND LOUIS J. DEGENNARO, PHD

ABOUT THE AUTHORS

MARIALANNA LEE, MSC

Ms Lee is senior director, State Government Affairs, The Leukemia & Lymphoma Society.

BRIAN CONNELL

Mr Connell is senior director, Federal Affairs, The Leukemia & Lymphoma Society.

In 2010, Fletcher was diagnosed with chronic lymphocytic leukemia. Within 6 months of starting treatment, his disease was in remission. But this good news did not last as he relapsed just 9 months later. He began treatment again, but the results were poor: Fletcher developed congested lungs, a persistent cough, and cataracts that left him temporarily blind. So, his doctor proposed a different treatment. Exhausted, but hopeful, Fletcher was ready to try the new drug until he heard what it would cost him—$2310 out of pocket (OOP) for just 1 month of treatment. His best chance of survival would consume nearly his entire month's take-home pay.

It was not long before Jody's medical bills ate through her family's savings following her diagnosis with acute lymphoblastic leukemia in 2009. To keep her cancer in remission, Jody is taking a kinase inhibitor that she will likely need for the rest of her life. But when she went to pick up her first dose at the pharmacy, she, too, was shocked to learn how much that life-saving drug would cost her—$5640 for the first month alone. Everything that she and her husband had put away for their children's college educations has gone to keeping Jody alive.

Besides leukemia, Fletcher and Jody have something in common: they have had health insurance throughout their cancer treatment journey. Yet, because of the high cost sharing associated with their medications, Fletcher and Jody have faced profound difficulty accessing the treatments prescribed for them. At The Leukemia & Lymphoma Society (LLS), our mission drives us to find cures for blood cancers, but we recognize that finding cures is not enough. We must also work to facilitate access to these life-saving medications, for Fletcher, Jody and many other blood cancer patients struggling to live under similar circumstances.

THE IMPACT OF THE RISING COST OF TREATMENT ON PATIENTS

Over the last decade, employers and other providers of health insurance have shifted more costs onto patients due to a multitude of factors that includes the rising cost of healthcare services. This trend is especially troubling for patients living with a blood cancer diagnosis, since available treatments typically consist of high-priced specialty drugs and other cost-intensive healthcare services.

A common discussion with this cost-shifting trend is the steady increase in consumer premium payments, as employee premium contributions have increased 83% since 2006 (compared with a 54% increase for employers over the same period).[1] Although premium increases have captured the headlines in recent years, the rising OOP costs that patients face, *after* they pay their premiums, have proven to be even more dramatic (**FIGURE**[1]). In 2003, almost half of patients in employer-provided insurance had no deductible to cover. Ten years later, less than 20% of patients had the same benefit.[2] In fact, as insurers have recognized that increasing deductibles can discourage consumers from accessing their benefits, plans have accelerated this trend. In 2015, the average deductible in an employer-provided insurance plan had increased more than 250% from a decade earlier—increasing 3-times faster than premiums over the same period.[1]

Of specific concern to blood cancer patients are benefit designs that increase the portion of drug costs borne by consumers. This trend is particularly striking in the Medicare Part D marketplace—in 2015, every stand-alone prescription drug plan had adopted a "specialty tier."[3] Placing a drug in a specialty tier allows the plan to charge patients a percentage of a drug's list price rather than a fixed dollar amount and simultaneously prevents a patient from accessing Medicare's cost-sharing appeals process. The impact on affordability is reflected in increases in the number of medications placed on the specialty tier each year. In the past 4 years alone, Part D plans have shifted 50% more drugs onto their specialty tiers,[3] subjecting many patients relying on those medications to thousands of dollars in additional cost sharing.

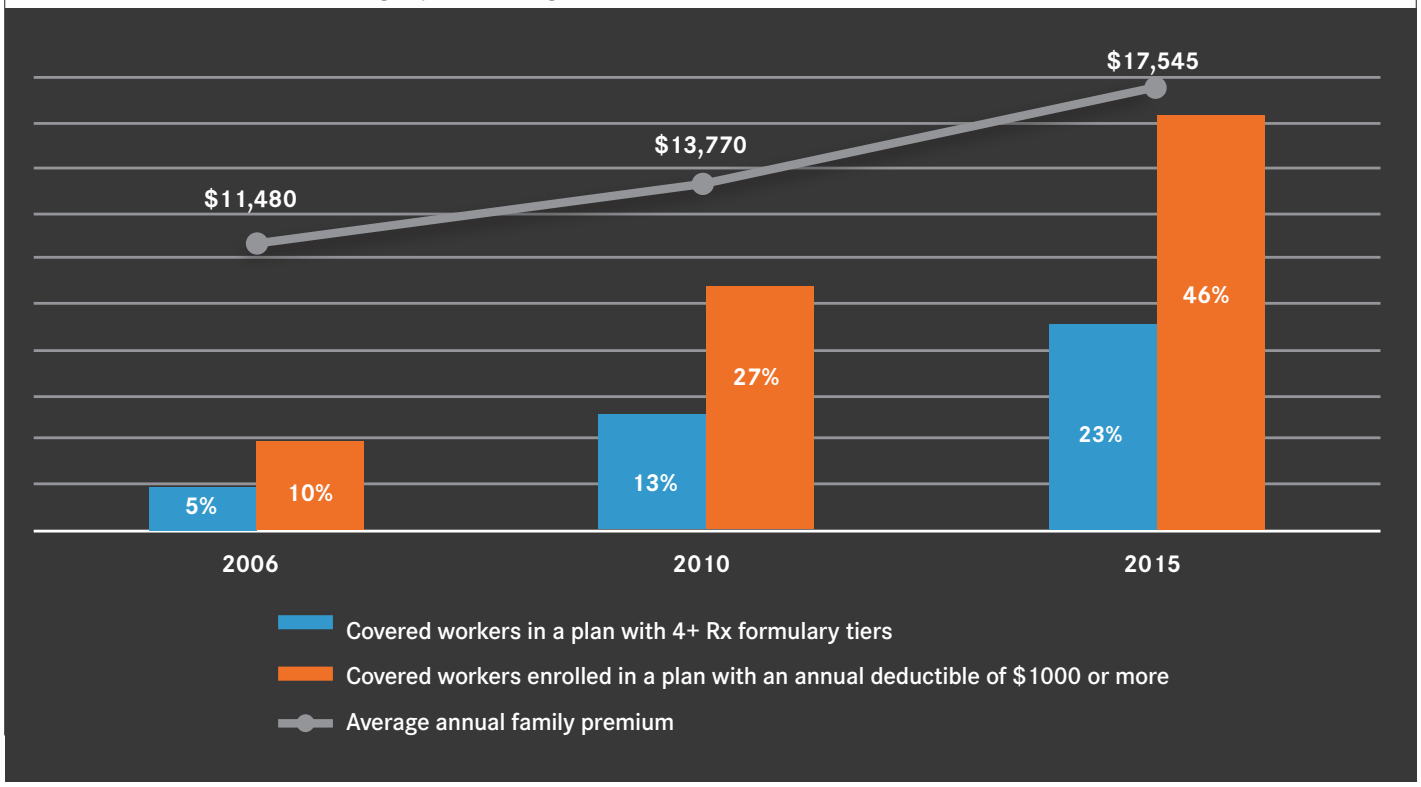
Every day, across the country, blood cancer patients face decisions that pit their health against their family's finances. And while policy makers, payers, and drug manufacturers engage in debates on drug pricing and a host of related topics—debates that seem far from reaching a productive resolution—patients, like Fletcher and Jody, struggle day to day to access critical medications. Evidence indicates that once cost sharing exceeds $100, adherence to prescribed medications begins to drop off significantly,[4,5] likely due to the trade-off between paying for medical care and the prospect of damaging the family's financial stability. Data also show that decreases in adherence correspond to worse outcomes[6,7] and increases in costly medical interventions[8,9] that, in many cases, could have been avoided with proper adherence. It is unacceptable and tragic when a patient knows that a potential cure is waiting behind the pharmacy counter but cannot receive it due to his/her inability to pay.

THE IMPERATIVE TO IMPLEMENT A SOLUTION

LLS believes that policy makers ought to take immediate action to ensure that consumers, especially those living with chronic and life-threatening diseases and conditions, can benefit from approved therapies that offer appropriate medical benefit. Fortunately, solutions have been identified that, if embraced by policy makers, could have a significant impact on patients with practically no discernable impact on premiums. One of these solutions is to limit the OOP costs associated with prescription drugs. This finding emerged in an actuarial analysis[10] that LLS and other partners commissioned last spring, to explore the financial impact of applying limits of $100 and $200 to the cost share for a 30-day supply of a single medication. Given the access barriers associated with increasingly high deductibles, the modeling conducted in the analysis considered these dollar caps to function in a pre-deductible manner. That is the $100 and $200 limits would apply to a consumer's OOP costs regardless of whether the plan's deductible has been reached.

To quantify the potential impact for patients, the analysis drew on claims data for patients taking 1 of 6 specialty medications typically used to treat either cancer, HIV, or rheumatoid arthritis. The results of the analysis showed potentially dramatic reductions in total annual costs for the patients utilizing these medications, ranging as high as 32% for blood cancer, 42% for rheumatoid arthritis, and 55% for HIV. Critically, these reductions include not just savings on medicines,

FIGURE. Patients' Increasing Exposure to High Out-of-Pocket Costs[1]



but reflect the potential impact on cost sharing for medical benefits, as well.

Regarding premiums, the analysis tested these cost-sharing limits in all 4 metal tiers established by the Affordable Care Act (ACA). The results demonstrated that, in silver, gold, and platinum coverage levels, a $100 limit would potentially trigger a small premium increase, ranging from just 0.2% to 0.8% annually ($9 to $35), which could be offset with minor changes in another component of the plan design. For bronze coverage, the analysis indicated that a $200 limit could produce an annual premium increase of up to 1.6% ($55), but here, too, the analysis showed that the potential increase could be offset with simple modifications to another component of the plan design. For example, this could be achieved through relatively small adjustments to the total OOP costs that a consumer may be required to cover for all benefits and services utilized over the course of the plan year. In the bronze plan designs studied in the analysis, this would mean increasing the OOP maximum from $6250 to $6600.

In short, this analysis illustrates both the viability and potential positive impact of applying modest dollar limits to what patients can be required to cover as their share of the cost of a prescription medication. Certainly, the results of this analysis do not eliminate the possibility that an alternative approach could similarly improve patient access to medications. This could include policies that limit the use of high, combined deductibles; obligate payers to offer plans that utilize only co-pays, rather than coinsurance, as a method for determining cost sharing for medications; or some combination of the two. LLS invites policy makers, patient advocates, payers, and drug manufacturers to come forward with other evidence-based solutions to this critical and complex access issue. From our perspective, policy makers ought to give priority consideration to solutions that would meet the following criteria:

- Patients would experience a meaningful improvement in access to care
- Payers could reasonably implement the proposed solution from both a financial and administrative perspective
- The proposed solution will not prohibit a health plan from complying with existing laws and regulations, in particular, actuarial value requirements as established by the ACA

CONCLUSION

To be clear, the cost of medication is just 1 cost that blood cancer patients and their families must face. Consequently, LLS is taking a proactive and multi-faceted approach to addressing cost and access issues for our community. This includes:

- Working to secure public policies that can reduce the barriers associated with high OOP costs
- Conducting research into how cost acts as a barrier for treatment access
- Providing assistance through our copay program to help patients who cannot afford their insurance premiums or drug co-pays
- Calling on the pharmaceutical and biotechnology industries to share real-world quality of life and outcomes data to support the pricing for their medications.

We are confident that by collaborating with key stakeholders we can dramatically improve patient access to these important therapies. **EBO**

ABOUT THE AUTHORS

ELISA WEISS, PHD

Dr Weiss is vice president, Patient Access & Outcomes, The Leukemia & Lymphoma Society.

LOUIS J. DEGENNARO, PHD

Dr DeGennaro is president and chief executive officer, The Leukemia & Lymphoma Society.

Address for correspondence
Louis J. DeGennaro, PhD
President and CEO
The Leukemia & Lymphoma Society
3 International Drive, Rye Brook, NY 10573

Louis.degennaro@lls.org

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Does the Cost-Sharing Burden Influence Cancer Outcomes?

SURABHI DANGI-GARIMELLA, PHD

Cost sharing has been identified as a significant burden on patients, often being a barrier that prevents individuals from seeking much needed care. With this realization, the Affordable Care Act (ACA) made provisions to both ensure coverage and create a ceiling for maximum out-of-pocket (OOP) spending for patients.

The ACA limits the total annual spending of an individual or a family on medical care by forcing all health plans in the individual and group markets to have maximum OOP limits.[1] Once the OOP maximum has been reached, the health plan has to absorb the cost of all in-network care that the enrollees seek. The value of these efforts have been realized by several organizations, including America's Health Insurance Plans (or AHIP), a trade organization of health insurance companies; the American Cancer Society; the American Heart Association, and the Center on Budget and Policy Priorities.[1]

87% of uninsured patients were billed more than insured patients who used the same service, and 23% were billed 200% more than their insured counterparts.

NEED FOR BETTER COVERAGE AND PRICE TRANSPARENCY

Healthcare coverage policies can create roadblocks for patients to access much needed care, especially in oncology; this has been shown in both the Medicare and commercially insured populations. A study published by Dusetzina and colleagues found that in 2012, Medicare, on average, reimbursed less than 40% of charges for chemotherapy while private insurance shared a little over 55% of the enrollee's costs. Overall, one-third of chemotherapy agents that the authors examined were reimbursed at higher rates by commercial health plans.[2]

Further, service charges vary widely depending on the medication being administered. As Dusetzina and colleagues found out, the range was $59 per infusion (for 500 mg of fluorouracil) to $9225 per infusion (for 10 mg of bevacizumab). Additionally, charges varied for the same drug depending on the provider; for example, a patient could be charged anywhere between $3889 and $6675 for a single infusion of trastuzumab. The source of this data was Medicare and large employer-sponsored private plans.[2]

Privately insured patients, at least in the population studied by Dusetzina's team, had the least OOP responsibility across all chemotherapy agents and across all visit types. Uninsured patients, on the other hand, faced bills that could be as much as 43 times the Medicare allowed amount.

Studies have also found discrepancy in the rates at which uninsured patients were billed in the outpatient setting: 87% of uninsured patients were billed more than insured patients who used the same service, and 23% were billed 200% more than their insured counterparts. This led the authors to conclude that physicians provide negative uncompensated care to the uninsured and earn more on uninsured patients than on insured patients with comparable treatments.[3] Similarly, a bias was seen in the billing rates for uninsured patients for inpatient services: uninsured patients were charged 2.5 times that of commercially insured and 3-times that of Medicare or Medicaid insured patients.[2]

INSURANCE STATUS, ACCESS TO CARE, AND PATIENT OUTCOMES

Financial burden is a potential nonclinical adverse event in cancer patients. As patients, especially those in the lower income ranges and the middle class, struggle to meet their medical bills, the likelihood of them skipping doses or doctor's visits is quite high. The impact, of course, is on clinical outcomes, be it disease progression or survival. And this has been documented.

A study published in *Cancer Medicine* reported that insurance status was a primary predictor of 5-year cause-specific survival among 18-to-64-year-old patients diagnosed with one of 7 cancer types in New Jersey.[4] These 7 cancers—breast, colorectal cancer (CRC), lung cancer, non-Hodgkin lymphoma (NHL), prostate cancer, bladder cancer, and cervical cancer—accounted for 61% of incident cancers and 56% of cancer deaths in New Jersey between 2005 and 2009.

Retrospective analysis of the data, which was drawn from the New Jersey State Cancer Registry, showed that among individuals diagnosed with breast, CRC, lung, NHL, and prostate cancer, those who were uninsured or enrolled in Medicaid had a much higher risk of death than those who had private insurance coverage. Overall, patients diagnosed with any of the 7 cancers had a 41% to 97% higher risk of dying within 5 years of diagnosis if uninsured compared with privately insured. Medicaid-insured patients in the cohort (except those with bladder cancer) had a 21% to 198% risk of dying within 5 years

of diagnosis compared with privately insured.[4]

The authors attribute their findings to several factors:

- Poor health: comorbidities, unhealthy behaviors
- Inadequate preventive healthcare
- Barriers to access and adhering to treatment regimens due to cost concerns
- Inability to navigate the healthcare system
- Misinformation about the healthcare system
- Practical issues with lack of transportation, lack of time off from work
- Provider barriers: do not accept uninsured/Medicaid patients
- Lower-quality care by providers who treat uninsured/Medicaid patients

A broader national study retrospectively analyzed data collected between 2007 and 2010 from the SEER database, which is maintained by the National Cancer Institute. The researchers analyzed data on 473,722 patients—from the same age group as the above cohort (aged 18 to 64 years)—who were diagnosed with one of 10 cancers (breast, prostate, lung, CRC, head and neck, NHL, liver, pancreatic, ovarian, or esophageal). The primary outcome of interest was to determine the association of the patient's insurance status with disease stage at presentation, treatment received, and survival.[5]

Insurance status of the patients was defined as non-Medicaid insurance (insured/no specifics), Medicaid insured, or uninsured. The SEER definition of insured includes those with private insurance, Medicare, and coverage from the military or Veterans Affairs when initially diagnosed and/or treated. However, since the authors restricted the current study to those under 64 years, that eliminated the Medicare-eligible population.

The outcomes are quite eye-opening: only 16.9% of patients on non-Medicaid insurance initially presented with advanced disease compared with 29.1% on Medicaid and 34.7% without insurance. Nearly 80% of the non-Medicaid insured received cancer-directed surgery or radiation compared with only 67.9% of Medicaid insured and 62.1% of uninsured. The most significant outcome of the analysis was that patients were more likely to die as a result of their disease if they had Medicaid coverage (HR, 1.44; 95% CI, 1.41-1.47; *P*<.001) or no insurance (HR, 1.47; 95% CI, 1.42-1.51; *P*<.001) compared with non-Medicaid insurance.[5]

IS MEDICAID EXPANSION THE ANSWER?

The fact that patients with non-Medicaid insurance presented with more localized disease meant that their disease might still be responsive to treatment and yield better outcomes. Further, the uninsured who presented with a more advanced stage disease were less likely to receive cancer-directed surgery and radiation treatment, and had worse survival as a result.

The question here is whether Medicaid expansion, one of the biggest undertakings of the ACA, might help reduce this disparity in the long term. As of July 11, 2016, only 26 states were reported to have made the decision to expand Medicaid, 6 states were using an alternative to traditional expansion,[6] and governors of other states, such as Oklahoma,[7] have realized the importance of participating in the expansion.

Politics aside, we need more long-term sustainable policies to reduce these discrepancies that are rampant across healthcare. Policies to reduce patient burden through a limit on OOP spending, greater transparency on service charges, and coverage plans that do not discriminate based on a patient's insurance status could be potential solutions. **EBO**

Medicaid-insured patients in the cohort had a 21% to 198% risk of dying within 5 years of diagnosis compared with privately insured.

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DIAGNOSTIC TESTING

Precision Oncology: *Why Payers Should Initiate CGP Coverage Now!*

JERRY CONWAY AND INGRID MARINO, MS, CGC

According to the 2016 Genentech Oncology Trends Survey Report,[1] the top 3 most pressing challenges faced by the 100 payers surveyed are:

1. Control of cancer specialty drug costs
2. Control of overall cancer care costs
3. Balancing treatment standardization with personalization

Payers are responding to these challenges by implementing a number of alternative payment models or APMs (eg, clinical pathways, medical home, and bundled payments) that are designed to shift from a "pay for volume" to a "pay for value" paradigm. Precision oncology, or the clinically and financially efficient use of genomically matched treatments and clinical trials, is evolving as a potentially important starting point for cancer care within successful APMs.

The use of validated comprehensive genomic profiling (CGP)[2] at initial diagnosis for patients with particularly aggressive or metastatic cancer is playing an important role in routine clinical care and new payment approaches. This is due to

ABOUT THE AUTHORS

FOUNDATION MEDICINE®

JERRY CONWAY

Mr Conway is vice president, payer relations and reimbursement, Foundation Medicine.

Address for correspondence
Jerry Conway
150 Second Street
Cambridge, MA 02141

jconway@foundation-medicine.com

INGRID MARINO, MS, CGC

Ms Marino is director, Payer Medical Affairs, at Foundation Medicine.

CGP being a clinically efficient and cost-effective[3-5] means of identifying the presence or absence of genomically matched targets to FDA-approved drugs covered by payers (typically those with National Comprehensive Cancer Network [NCCN] Category 1 and 2A levels of evidence). CGP also has the potential to provide clinical trial alternatives to patients when covered drugs are not an option, as well as accurately identifying clinically relevant mechanisms of resistance or even a complete lack of genomically matched treatment options to help eliminate futile or potentially harmful treatment. This biomechanistic and highly personalized precision oncology approach ensures that the mechanism of action or sensitivity is truly present before approving access to high-cost, FDA-approved specialty oncology drugs. Therefore, CGP is becoming a pragmatic solution that drives successful management strategies to effectively address the top 3 challenges identified by payers, and therefore, should justify the necessity of payer coverage today when used in the appropriate clinical setting.

CURRENT SITUATION

Approximately 14.5 million Americans with a history of cancer were alive in 2014[6] and that number is slated to grow to 18.1 million in 2020.[7] Cancer care costs in the United States were estimated to be $124.57 billion in 2010 and are projected to increase to between $158 billion and $173 billion by 2020, a 27% to 39% increase.[7] Factors driving these dynamics include the growth and aging of the US population, an overall reduction in mortality due to increase in cancer survival, the earlier detection of cancer, the shift of care delivery to hospital outpatient settings,[8,9-12] and the rapid growth of new and often very expensive oncology care products and services.

The projected cost increase by 2020 assumes that past trends continue: the 5-year survival rate for all cancers diagnosed between 2005 and 2011 was 69%, up from 49% during 1975 to 1977,[6] and a 2012 study identified a 1.5% annual decline in cancer mortality for the decade examined.[13] However, despite substantial advances in diagnosis and treatment, the 5-year relative survival for advanced or metastatic (ie, Stage IV) cancers has remained relatively stagnant since 1973, which is when such data was first collected in the SEER database.[14,15]

Alarmingly, the costs associated with the use of biologic therapies are growing faster than any other aspect of cancer care and have escalated to 335% growth in Medicare and 485% in the commercial payer market between 2004 and 2014.[16] As precision oncology continues to gain traction, these trends will be further accelerated with the broadened utilization of the existing 50-plus FDA-approved targeted drugs and immuno-oncology agents, the majority of which were approved after 2010. This is compounded by the coming bolus of new drugs—770 targeted and immuno-oncology agents in various stages of FDA review, which are currently being evaluated in more than 3000 clinical trials.[17] Another important trend is the use of high-cost targeted and immuno-oncology agents in sequence and/or in combination, and perhaps for longer durations, as the number of responding patients grows.

The growth of precision oncology therapies and molecular or companion diagnostic testing options used to guide the selection of these therapies is overwhelming the ability of physicians, payers, patients, and other stakeholders to keep pace with innovation. When researchers from the National Institutes of Health conducted a landscape scan of test offerings as part of the Institutes' Genetic Testing Registry in February 2016, they found that oncology test options had grown considerably to more than 5000 tests—a 153% increase over the previous 12 months.[18] Uncontrolled costs associated with trying to manage this high volume of expanding test options, while addressing quality issues that have been recently documented with standard-of-care (SOC) companion diagnostic tests, further complicate the situation.[19-23]

Combining these findings with those of the Genentech survey described earlier,[1] clearly shows an urgent need for innovative clinical and cost management strategies and tools to ensure that patients have affordable access to next-generation diagnostics and therapies. The current SOC in oncology is often based on trial and error, without the benefit of biomarker data to inform treatment decisions, thus resulting in suboptimal outcomes and wasted dollars. Adverse events associated with invasive procedures, non-targeted treatment toxicity and unnecessary testing, as well as unnecessary emergency department (ED) visits and hospitalizations, all drive substantial human and financial costs associated with comorbidity, reduced quality of life, and even mortality.[24] The idea of 1 empiric treatment approach for every patient with a particular cancer (eg, breast cancer) is not yielding the results required to make meaningful improvements in care.[14,15] Because of failures with the empiric approach and the new understanding that cancer is a disease of the genome, testing and treatment are rapidly moving toward precision oncology care.

THE VALUE OF PRECISION ONCOLOGY

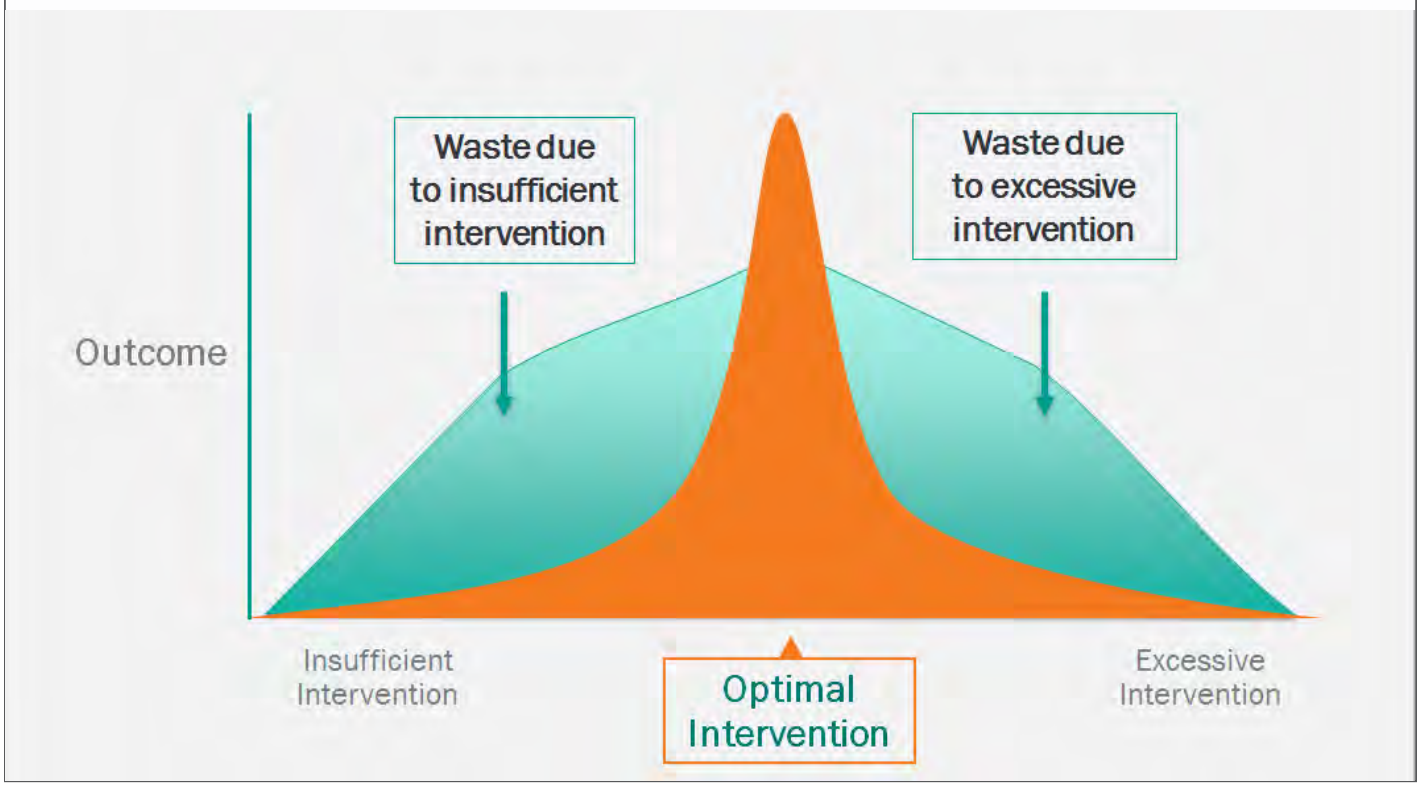
As discussed in earlier issues of *Evidence-Based Oncology*,[15,25] cancer diagnosis and treatment is being transformed with the knowledge that cancer is a disease of the genome,[26-29] and the genomic "blueprint" responsible for driving cancer is unique to each patient—the so-called personalized "malignant snowflake."[30] Data indicate that genomically matched treatments and clinical trials, or precision oncology, are often less toxic, more efficacious,[19,31-39] and less expensive than traditional cytotoxic chemotherapy. Targeted and immuno-oncology therapies have the potential to improve patient outcomes and quality of life, in addition to yielding cost savings.[3-5,34-37] This is especially true when used as a first-line treatment option in the advanced or metastatic setting.[3] Integrating CGP into the initial diagnostic work-up optimizes interventional efficiency by enabling genomic data to be immediately available in the medical record. This enables informed treatment decision making in real time versus using CGP as a "rescue" strategy after a patient has already failed multiple lines of therapy. Bottom line is that investing in precision oncology to transition patients from cytotoxic to genomically matched treatments and clinical trials is a smart solution that meets the core objectives of payer-initiated APMs—evidence-based care coordination that yields improved outcomes and quality of life through increased safety, efficacy, and cost-effectiveness of treatment (**FIGURE**).

Several *in silico* modeling data published recently indicate the potential for substantial health and economic benefits of genomic sequencing in non–small cell lung cancer (NSCLC) and melanoma.[4-5] However, one of these studies relies on directionally correct, but overly aggressive assumptions that are not reflected in current practice such as precipitous reductions in cytotoxic utilization (decrease from 83% to 20%), and impractical expectations for clinical trial enrollment (increase from 4% to 54%).[5] As outlined in a real-world study by Newcomer et al,[24] increased treatment costs can be significantly offset by the total cost-effectiveness achieved, primarily by:

- Eliminating unnecessary molecular tests[19-23]
- Eliminating unnecessary biopsies[19,40]
- Reducing cytotoxic chemotherapy use[4,5]
- Optimizing FDA-approved targeted and immuno-oncology therapy utilization[19,31-39]
  - Increasing clinical trial enrollment as an alternative to noncovered off-label use[15,41]
- Reducing emergency department visits[24]

Because of failures with the empiric approach and the new understanding that cancer is a disease of the genome, testing and treatment are rapidly moving toward precision oncology care.

FIGURE. Investing in Precision Oncology Helps Optimize Utilization of Genomically Matched Treatments and Clinical Trials



- Reducing hospitalizations[24]
- Reducing futile treatment[4,5]

IMPORTANCE OF CGP: ACHIEVING THE GOALS OF CANCER MOONSHOT

The White House Cancer Moonshot initiative, announced at President Obama's State of the Union address on January 12, 2016, and subsequently led by Vice President Biden, relies heavily on precision oncology as its central feature. CGP is a key component of routine clinical care and national initiatives like "Moonshot." The journey from "more precise" to "precision" diagnosis and treatment will require multi-stakeholder standardization, integration, and data sharing[42,43] to simultaneously match patients with covered treatment options while advancing the genomic knowledge base. The administration can play a key role in energizing "Moonshot" by using its authority to overcome reluctance by CMS and private payers to pay for the personalized diagnostics and therapies that the administration champions. In an editorial published by *Science* in April of this year, Harold Varmus, MD, former director of the National Cancer Institute, recommended that "The Administration could also exercise its regulatory authority—most potently, to direct the Centers for Medicare and Medicaid Services (CMS) to allow reimbursement for molecular profiling of cancers. That would vastly increase the data available for analysis, accelerate interpretation of genetic profiles, provide a test bed for true sharing of clinical information, and allow future coverage determinations by CMS to be made more quickly and sensibly."[44]

For select patients with life-threatening advanced cancer, access to a single, clinically effective and cost-efficient test with a rapid turnaround time and posttest decision support is essential. However, a value-based CGP program includes much more than the testing alone. CGP should include, but not be limited to, robust provider education on appropriate ordering and interpretation, benefit investigation and prior authorization to enable patient out-of-pocket cost transparency, electronic workflow integration and data sharing, patient assistance programs, and effective medical decision support and clinical trial navigation services. These additional value-added investments, beyond the testing portion only, must be adequately reflected in payer reimbursement.

A significant advantage of CGP is the opportunity to eliminate workflow inefficiency, costly use of suboptimal tests, and unnecessary biopsy procedures. As evidence rapidly evolves, updates in the CGP knowledge base happen in real time to reflect the very latest in curated data, translating into additional value at no extra cost to payers and patients. For stakeholders who would otherwise struggle to keep pace with the rapid advances in precision oncology, this is a critical advantage. Further, emerging evidence shows that CGP can enable effective utilization and cost management of the increasing number of targeted and immuno-oncology therapies available within the patient's medical and pharmacy benefit.

For a majority of patients, if genomically matched options are not available, at the time of profiling, alternatives can be offered that forego the expensive use of futile and potentially harmful treatment. Finally, clinical trial options and navigational support available through CGP providers represent a cost-effective alternative for patients and payers when no covered treatment is recommended, or is otherwise unavailable. This is a result of drug costs in clinical trials being borne by the biopharma manufacturer. Clearly, investing in CGP, even at a price point of $3000 to $4000 or higher, is smart business when one considers decisions involving coverage, especially in the face of the price of precision oncology drugs, which can easily cost considerably more than $100,000 per patient per year.[45]

CGP is a valuable, core navigational aid for payer coverage, payment, and cancer care management programs when used as a frontline solution at initial diagnosis of particularly aggressive or metastatic disease. It enables standardization, personalization, and timely consideration for all available genomically matched treatment and clinical trial options consistent with coverage policies and relevant guidelines, including those from the NCCN (Category 1 and 2A levels of evidence), American Society of Clinical Oncology (ASCO), and the FDA. In essence, CGP is becoming a standardized "universal

Integrating [comprehensive genomic profiling] into the initial diagnostic work-up optimizes interventional efficiency by enabling genomic data to be immediately available in the medical record.

genomic pathway solution" for payers, specialty pharmacies, pathways organizations, and all other stakeholders engaged in managing the quality and costs of cancer care. This is entirely consistent with ASCO's Choosing Wisely top 10 list for oncology.[46]

> ***#10 -Do not use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy.***

A TIPPING POINT: THE UNIVERSAL GENOMIC PATHWAY SOLUTION

There is a growing body of published literature to demonstrate, characterize, or quantify *the positive* impact of precision oncology in the context of specific and broad ranges of tumors and clinical settings. Recent publications, health economic models, and positive coverage decisions indicate that early-adopter payers are proactively pivoting toward embracing precision oncology as an opportunity to align the need for improved clinical outcomes with cost-effectiveness.

Clearly, investing in [comprehensive genomic profiling], even at a price point of $3000 to $4000 or higher, is smart business when precision oncology drugs can cost more than $100,000 per patient per year.

Since 2014, NCCN has endorsed broad molecular profiling, like CGP, in the NCCN NSCLC Guidelines.[47] Suh et al[23] have proposed that CGP is clinically efficient and cost-effective by facilitating implementation of the NCCN Guidelines for NSCLC, including the identification of "pan-negative" patients who may benefit from enrollment in mechanism-driven clinical trials without additional tissue use or cost. The Center for Medical Technology Policy published a consensus white paper, *Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology,* outlining coverage guidelines for CGP—several national payers participated in developing the paper (CMS, Palmetto GBA, Anthem, Aetna, and Humana),[48] and a number of national and regional payers have started to cover, and are in the process of reimbursing academic and commercial providers such as Foundation Medicine for CGP.[49-53] These early-adopter payers recognize the pragmatic value of precision oncology informed by validated CGP. They realize that a biomechanistic approach ensures that patient-specific sensitivity and unique mechanisms of resistance are identified before approving or restricting access to expensive, FDA-approved specialty oncology drugs, or referring patients to clinical trial alternatives in the absence of FDA-approved options. CGP effectively addresses the 3 top challenges identified by payers.

Payers can benefit, now, by proactively taking strategic steps to integrate precision oncology into coverage and alternative payment models, by:

1. Acknowledging cancer as a disease of the genome by modifying the existing coverage and payment policy framework to align with cancer biology, the N-of-1 personalized reality of treatment decision making, and first-line coverage at initial diagnosis in the particularly aggressive or metastatic cancer setting.
2. Recognizing CGP as a "universal genomic pathway solution" for genomically matched treatment and clinical trial decision making; managing medically indicated specialty drug growth cost-effectively while reducing total costs of care by minimizing the use of ineffective drugs and costs associated with unnecessary biopsies, testing, cytotoxic treatments, and downstream ED visits and hospitalizations.
3. Establishing Pan-Cancer precision oncology coverage and payment policies for members with particularly aggressive or metastatic cancer, based on a CGP first-line testing "universal genomic pathway solution" strategy to successfully manage the rapidly growing costs associated with diagnostic testing and genomically matched treatments.
4. Creating a genomic benefit management program that seamlessly integrates highly validated CGP data with expert decision support, and other value-added services as the primary tools informing evidence-based treatment utilization and cost management solutions;
    - For example, integrate CGP as part of the first-line pathway to optimized use of genomically matched treatments and clinical trials in accountable care organizations, oncology medical homes, pay-for-performance partnerships, bundled payments, limited provider networks, nurse navigator programs, end-of-life support and survivorship support programs, and/or personalized treatment pathways.
5. Partnering only with a limited network of CGP providers capable of committing to long term "pay for value" relationships based upon consistently meeting or exceeding high-performance standards[2] (ie, analytic validation, clinical validation, clinical utility, and cost-effectiveness), providing comprehensive data integration solutions with decision support, and a willingness to participate in data sharing with public databases.[42,43]

Harnessing the power of comprehensive genomic profiling will allow the field of oncology to more rationally match patients to efficacious therapies, and ultimately enable all stakeholders to recognize the true potential of precision oncology. **EBO**

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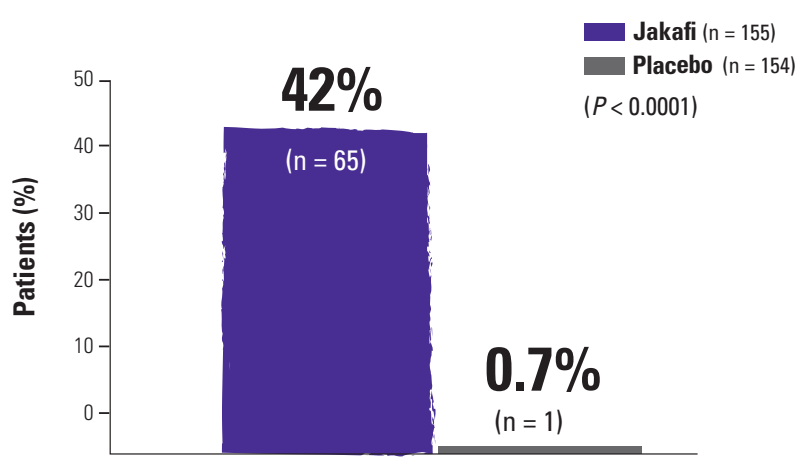
Provide your members with the option that's

FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

Significantly more patients with intermediate-2–risk or high-risk myelofibrosis receiving Jakafi® (ruxolitinib) achieved the primary end point compared with placebo (COMFORT-I*) or best available therapy† (COMFORT-II‡)[1-3]

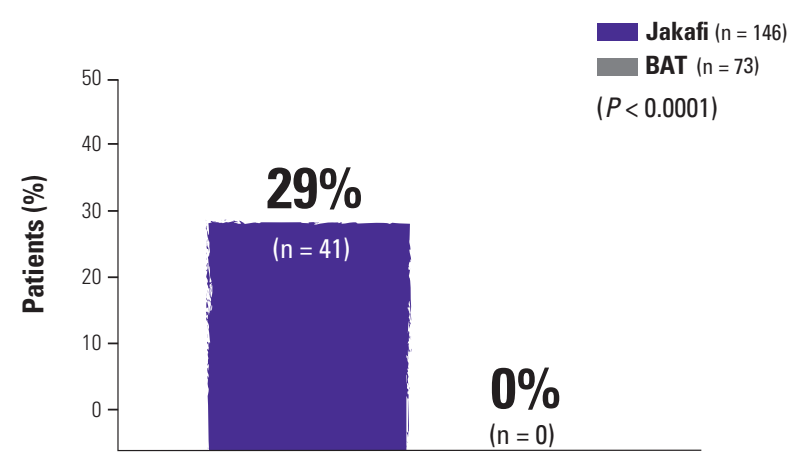
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk and high-risk myelofibrosis.[1,2]

† Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

‡ COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk and high-risk myelofibrosis.[1,3]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Jakafi® ruxolitinib (tablets)

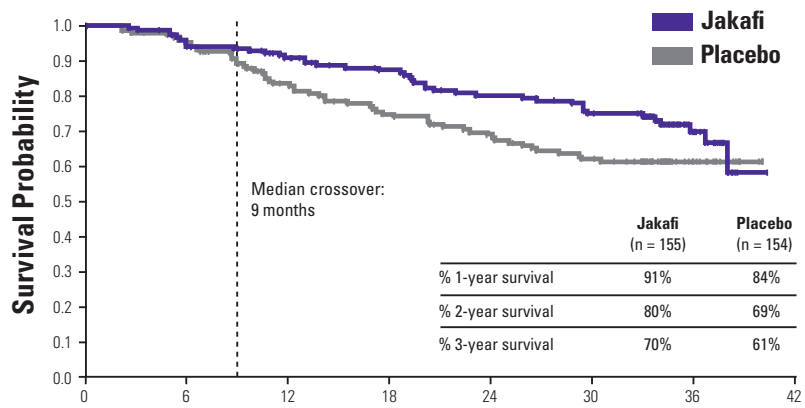
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]

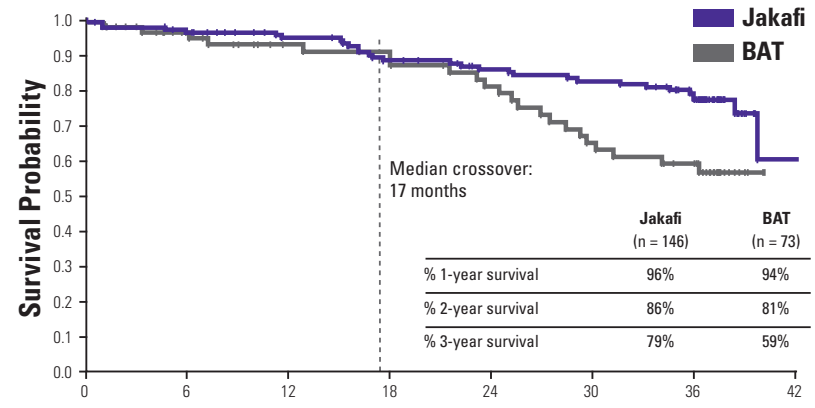


	Jakafi (n = 155)	Placebo (n = 154)
% 1-year survival	91%	84%
% 2-year survival	80%	69%
% 3-year survival	70%	61%

Number of patients at risk

Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



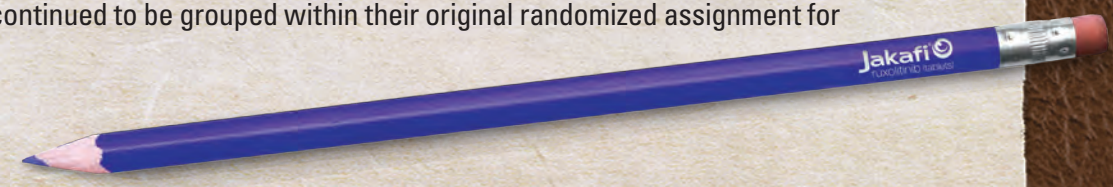
	Jakafi (n = 146)	BAT (n = 73)
% 1-year survival	96%	94%
% 2-year survival	86%	81%
% 3-year survival	79%	59%

Number of patients at risk

Jakafi	146	135	126	115	107	104	33	0
BAT	73	58	50	47	42	33	9	0

BAT, best available therapy.

- Because of progression-driven events or at the physician's discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes[4]



- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *PML* Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. 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. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions **Anemia** In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Fluconazole:** The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively [*see Pharmacokinetics (12.3) in Full Prescribing Information*]. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Pharmacokinetics (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: *Risk Summary* There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [*see Dosage and Administration (2.4) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

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Young Adult Cancer Survivors Disproportionately Affected by Treatment Costs

SAMANTHA WATSON, MBA, AND MICHELLE LANDWEHR, MPH

ABOUT THE AUTHORS

SAMANTHA WATSON, MBA

Ms Watson is the chief executive officer, The Samfund.

Address for correspondence
Samantha Watson
The Samfund
89 South Street, LL02
Boston, MA 02111

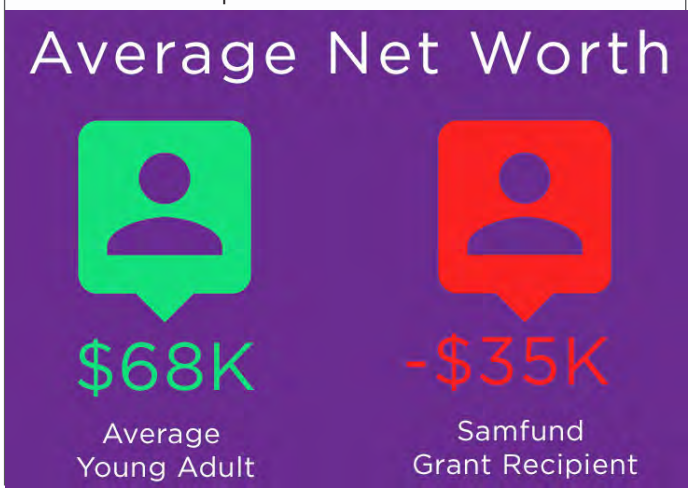
sam@thesamfund.org

MICHELLE LANDWEHR, MPH

Ms Landwehr is the chief operating officer, The Samfund.

Young adult (YA) cancer survivors are hit the hardest in the wallet by their treatment. In fact, as we discovered while analyzing our data for our research paper published in February 2016 in *Cancer Medicine*,[1] the average net worth of YAs who have received grants from The Samfund is a staggering –$35,000 (yes, that's a negative sign), while that of their counterparts, in the general population, is $68,000—*a difference of more than $100,000* (see **FIGURE**). This disparity exists on top of the emotional, physical, and psychosocial deficits that YAs face. What's more, YA patients with cancer and those newly deemed cancer-free are the least likely to be employed.[2]

FIGURE. Average Net Worth of a Young Adult Versus a Samfund Grant Recipient



Compared with their siblings or peers who do not have a history of cancer, YA patients with cancer are less likely to be working for reasons that include:

- Their inability to report to work due to physical symptoms resulting from their treatment
- Medical appointments
- Hospitalization
- Medical isolation due to a compromised immune system.[2]

This starts a pattern from which it can seem impossible to escape: a YA has to leave his job to undergo treatment, receives bills for his treatment that are difficult to pay without an income, stays out of work after treatment (while continuing to receive bills) because of the treatment's effects, and then avoids necessary follow-up care because he cannot afford additional bills.[3,4] In addition to the obvious financial stress, a YA also faces significant emotional and psychological stress that can become paralyzing.

WHAT TRIGGERS THIS VICIOUS CYCLE?

To begin to understand the financial impact of treatment specific to YA cancer survivors, we must recognize the forces at play:

1. *The "I don't know what to ask" factor.* Many YAs don't know how to start a conversation about finances with their doctors, even though they feel this is important.[5] For YA patients, the priority at the time of diagnosis is, understandably, survival, and they don't want to feel like they are sacrificing their care by asking for a less expensive treatment protocol. Conversations about finances frequently take a back seat until it's too late and debt has already spiraled out of control. In his 2015 study, Yousuf Zafar, MD, MHS, found that only 19% of patients reported having discussed the cost of cancer treatment with their physician.[6]
2. *The "I'm too embarrassed to ask" factor.* Many of our YAs have expressed feelings of shame, fear, or reluctance to talk with their doctors because they cannot afford their care. As one of our recipients confirms, "I would feel uncomfortable discussing financial concerns with my doctor, thinking perhaps they would not want to treat me, or would not be as eager to treat me if they were afraid my bills would end up in collections." Some are afraid that their doctors will not be reimbursed if they, the patients, do not pay their hospital bills. YAs express guilt at this fact, since they feel they owe their lives to their clinicians.
3. *The "I can't afford it" factor.* On a most basic level, YAs who have been through treatment just cannot afford their ongoing care. Treatment does not end when chemotherapy and radiation do. Every day, we hear from YAs who are skipping medications and meals, among other necessities, due to their treatment costs.[7] One survivor, when discussing the challenges of turning 26 and losing her parents' insurance, wrote in her application: "Now that I am 26 years old and no longer covered under my parents' health insurance, I am responsible for the cost of my annual [magnetic resonance imaging], seizure medication, and doctor visits. The cost of a brain scan is $6000 or more for each scan, and I am required to have one on an annual basis."

Another points to the unique challenge of being hit with an expensive medical condition when trying to survive financially on their own for the first time: "This obstacle in my life made me move backwards financially right when I thought I was going to start being on my own. I cannot keep up with all these medical bills that come with getting cancer, and it is affecting my credit. I cannot get a credit card and I feel like I am financially stuck at the moment."

What happens when YAs are diagnosed with cancer, taken out of the workforce, and buried under medical debt? The result is what is described as "financial toxicity," which ripples out into society at large.[6] YAs have seen more than their fair share of this phenomenon, as evidenced in the thousands of grant applications we've received over the past decade. In the **TABLE** below, we illustrate some of the common debts and medical expenses our population shoulders. It's no wonder that YAs are stuck making impossible decisions about their care.

TABLE. Mean Debts/Monthly Payments in Screened Samfund Applicant Population (2014 to 2016, n = 524)

Mean total medical debt	$5016.95
Mean total credit card debt	$4941.55
Mean monthly medical payments	$185.41

As one YA writes:
I am barely able to keep up with living expenses—specifically food and housing, along with financing my education and medical ex-

penses. While this is true for anyone, being a cancer survivor is an even greater challenge due to a weakened immune system, lower stamina, continuing medical follow-up care, and the anxiety that comes from worry of a future recurrence. I've been forced to borrow from family/friends occasionally to cover things like the fee for storing my frozen eggs, cost of medical insurance premiums, prescriptions, and medical follow-up appointments. I've held off on scans and routine female health exams to eliminate additional medical debt.

Another discusses the burden of medical costs on her overall expenses [slightly modified]:
With cancer, I have dedicated a large portion of my financial resources to medical expenses including previous bills, doctor's visits, and surveillance scans, as well as unanticipated visits to the [emergency room], procedures, and lab work. This has been a very difficult situation for me, as I am a medical student with no source of income and I rely completely on student loans. Unfortunately, my student loans do not take into account the additional cost of my medical expenses, and I have not received supplemental income from any other source. As a consequence, I have skipped appointments that I could not afford and pushed back appointments in order to avoid the expense.

The impact of patients' financial toxicity goes beyond a zero bank account balance. The far-reaching consequences for YA survivors include a decrease in quality of life and overall health, plus an increase in negative stress.[8,9] We've shown how financial limitations and treatments, both primary and follow-up, are inseparable for many YAs. Once overwhelming stress becomes a contributing factor, the pattern explained above worsens. One of our grant recipients explains: "The stress from my money issues due to cancer has not only led to a diagnosis of severe anxiety and depression (for which I now have to buy medication for and pay for [doctor's] visits with my primary), but it literally causes fatigue and bone pain. I feel it has limited me in my social life, how I perform at work, my personal happiness, my relationships with others, and I truly feel like my youth has been stolen from me."

IDENTIFYING SOLUTIONS

The good news is that the best and brightest minds in oncology are working hard to address financial toxicity. At this year's annual conference for the American Society of Clinical Oncology, Zafar; Veena Shankaran, MD, MS; and Jill Hershman, MD, MS, presented research illustrating the impact of financial toxicity on patient outcomes and adherence.

At The Samfund, we're working on new ways to help YAs manage these costs and reduce the associated stress. We find that by the time YAs come to us for a grant, many are in dire straits: drowning in credit card debt (charging all of their medical bills without realizing that even minimum payments could keep them out of collections), making astronomical car payments (because they needed a way to get to and from treatment), declaring bankruptcy in their 20s, and so on. In many instances, the YAs do not have the luxury of time or information to research better choices, and end up choosing what seems like the quickest or easiest alternative in the short term. But in almost all cases, early guidance in the decision-making process could have prevented these crises from happening.

With this in mind, The Samfund, in collaboration with Triage Cancer, is developing a new program: "Finances 101: A Toolkit for Young Adults With Cancer." The main goal of this program is to equip the YA community with the tools necessary to make educated decisions about their finances, healthcare, and other related challenges during key moments in their cancer journey (diagnosis, during treatment, or after treatment), so that recovering financially from cancer does not become a lifelong struggle.

We hope that increasingly inclusive discussions regarding the cost of cancer treatment, health insurance coverage, developments in research, and the importance of healthcare for all shed light on not only overall trends, but also on the issues of specific populations including YA cancer survivors. With limited employment history, a newly or not-yet-formed family unit, and minimal savings, the costs of care add up much faster for this population. An increase in financial stress often leads YAs to experience emotional, psychological, and social stresses which negatively impact quality of life and compromise their recovery and overall health. Despite all of these undue hardships, we are witness to an astounding and common resiliency in many of the YAs we speak with every day. We are proud to represent the YA patient voice in larger conversations about costs of cancer, and are hopeful that, collaboratively, we can begin to develop more comprehensive and effective responses to financial toxicity. **EBO**

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> **"I feel [financial stress] has limited me in my social life, how I perform at work, my personal happiness, my relationships with others, and I truly feel like my youth has been stolen from me."**
>
> —SAMFUND GRANT RECIPIENT

The Samfund, in collaboration with Triage Cancer, is developing a new program to equip the YA community with the tools necessary to make educated decisions about their finances, healthcare, and other related challenges.

Charitable Assistance Among Economically Vulnerable Cancer Patients: *Patient Access Network Foundation Summary Statistics 2011-2015*

HELAINE E. RESNICK PHD, MPH; BRUCE BARTH; AND DANIEL KLEIN, MHS

ABOUT THE AUTHORS

PAN Foundation

HELAINE E. RESNICK, PHD, MPH

Dr Resnick is president, Resnick, Chodorow and Associates.

BRUCE BARTH

Mr Barth is manager of Data Analytics and Reporting, Patient Access Network Foundation.

DANIEL KLEIN, MHS

Mr Klein is president and chief executive officer, Patient Access Network Foundation.

Address for correspondence
Daniel Klein
President and Chief Executive Officer
Patient Access Network Foundation
1331 F Street NW, Suite 975
Washington, DC 20004

dklein@panfoundation.org

The American Cancer Society estimates that about 1.7 million Americans will receive a cancer diagnosis in 2016, and about 596,000 people will die from cancer this year. Although these statistics may seem bleak, the United States has witnessed major reductions in cancer mortality in recent decades. The drop in cancer mortality is largely attributable to 3 factors: reductions in smoking, improvements in early detection (screening), and the availability of better cancer treatments. Together, these factors contributed to a 23% reduction in cancer mortality between 1991 and 2012.[1]

Given the marked improvements in cancer mortality—arguably the most important indication of progress in the fight against cancer—why do warnings about the threat of cancer to the public health seem to be increasing, rather than decreasing over time? One reason is the dramatic increase in patients' out-of-pocket (OOP) cancer treatment costs that arise from several sources: insurance premiums, co-payments, co-insurance, deductibles, and tiered formularies. In addition to costs that are directly associated with care, indirect OOP costs add to the burden. These include factors such as lost income and travel expenses for both patients and caregivers. Despite the many sources of OOP costs for cancer patients, OOP costs for cancer medications have received the most attention, in part due to the marked increases in the cost of cancer drugs. National data show that retail expenditures on prescription cancer medications increased 5-fold in the decade between 2001 and 2011, from $2.0 billion to $10.0 billion.[2]

Increased spending on cancer drugs is driven by a combination of factors, including an aging US population and complex changes in the oncology drug development pipeline and marketplace. The latter involve:

- An active drug development pipeline (45 new drugs were launched between 2010 and 2014)
- Availability of new drugs that often provide better outcomes with fewer side effects than traditional options
- Development of immunotherapeutic products and a push to develop new therapies, as well as new drug classes, and increased use of new targeted therapies
- A sharp increase in the number of protected brands and new product launches
- A slowing of patent expirations[3]

Although these trends account for much of the recent increase in spending for cancer drugs, many of the medications that are involved in the debate over skyrocketing cancer drug costs are the same drugs that are responsible for marked improvements in cancer outcomes.[3]

It is against this complex backdrop that the increasing cost of cancer medications has received attention from the federal government,[4] advocacy organizations,[5] and professional societies.[6] For patients, increased OOP costs associated with cancer medications directly impact financial well-being, especially among patients who have low incomes and those who are uninsured or underinsured. One high-profile study that analyzed data from 1995 to 2009 in Washington State showed that cancer patients had bankruptcy rates that were 2.65 times higher than people without cancer; a sobering reflection of the financial strain that a cancer diagnosis places on many families.[7] A more recent study of financial hardship among people with cancer (borrowing money or going into debt, filing for bankruptcy, being unable to cover OOP costs, or making other financial sacrifices) showed that 20.4% of cancer survivors experienced 1 or more of these hardships. Among these individuals, 7.1% had to borrow money to pay for cancer treatment, 11.9% could not cover OOP cancer treatment expenses, and 9.4% made other financial sacrifices to deal with their cancer diagnosis.[8] The growing literature on the financial impact of cancer leaves little debate concerning both the short- and long-term impact of this diagnosis among economically vulnerable patients and their families.

It is perhaps not surprising that the term "financial toxicity" has taken root to describe the consequence to patients who choose cancer treatments with high OOP.[9] Although national data provide a glimpse into the characteristics of relatively small numbers of economically vulnerable cancer patients, overall, very little is known about these individuals—and there are few published data that exclusively focus on this group. Using a unique data source, the objective of our report is to provide an overview of this patient population.

DATA UTILIZED FOR CURRENT ANALYSIS

The Patient Access Network (PAN) Foundation is an independent, national 501(c)(3) organization that assists federally and commercially insured individuals living with chronic, life-threatening, and rare diseases, with their OOP costs for prescribed medications.[10] Patients who seek support from PAN must demonstrate eligibility by providing required information to a call center, or online through self-service portals on PAN's website.[11] During the application process, patients provide demographic and insurance information. Support is reserved for people whose household income is less than or equal to 400% or 500% of the federal poverty level (FPL). FPL is calculated based on reported total household income and the number of people living in the patient's household. Once a patient is determined to be eligible for support from PAN, claims can be immediately submitted to PAN. Pharmacies, physician practices, and other entities that dispense prescriptions submit claims to PAN and are reimbursed for eligible patients' OOP drug expenses. Claims that were filed by pharmacies are for self-administered prescription drugs that are covered under Medicare Part D, while physician-based claims are for Medicare Part B prescription drugs that are typically administered by physicians in a hospital or office setting. PAN maintains a database that details patient-level information on these claims.

PAN maintains a number of disease funds that provide support for OOP medication expenses for specific health conditions. Fluctuations in resources for these disease funds result in some year-to-year variability in which financial resources are available to support OOP medication expenses for specific conditions. Between 2011 and 2016, 84 funds provided support for OOP health expenses for distinct conditions, and of these, 33 provided support for various cancers.

This report presents descriptive data on trends over time in PAN's support of OOP medication expenses for cancer patients. The analytic data set covers the period from January 1, 2011, through December 31, 2015. The variables of central interest included:

- The year in which PAN support was provided
- The number of patients and claims that were made each year

(continued on **SP455**)

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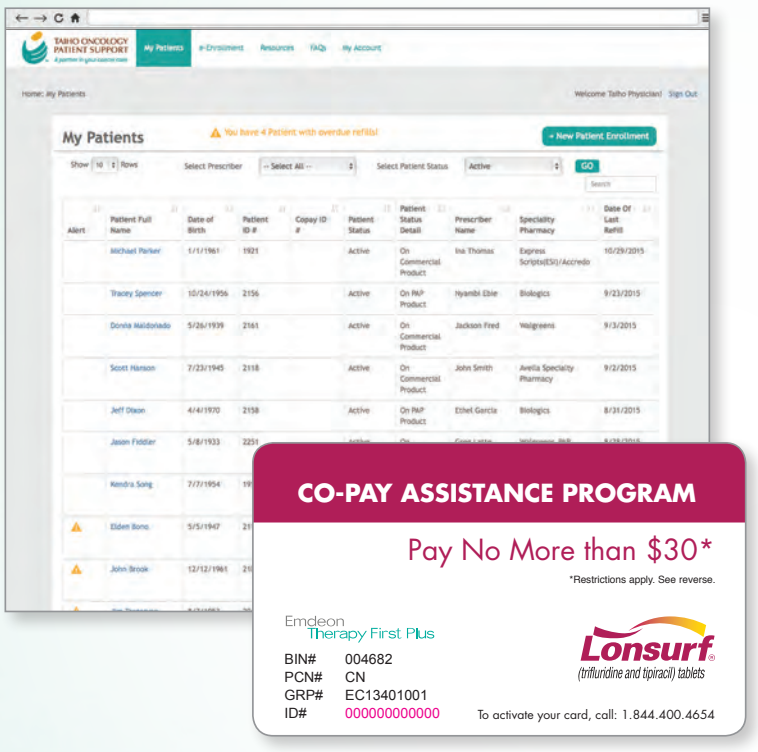

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Important Safety Information

WARNINGS AND PRECAUTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

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

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

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

4 CONTRAINDICATIONS
None.

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

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

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

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

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

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

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

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

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

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

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

Table 2 Laboratory Test Abnormalities

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

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

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

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

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

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

Contraception

Females

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

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

Males

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

8.4 Pediatric Use

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

Animal Data

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

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

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

8.8 Ethnicity

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

10 OVERDOSAGE

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

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

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

Gastrointestinal toxicity:

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

Administration Instructions:

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

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

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

Embryo-Fetal Toxicity:

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

Lactation:

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

TAIHO ONCOLOGY, INC.

(*continued from* **SP450**)

- Patients' primary type of insurance at the time PAN support was sought (Medicare or commercial insurance)
- Whether the claim originated from a pharmacy or physician's office
- The amount of each claim
- Whether patients were receiving support from a cancer or noncancer fund.

Patients with more than 1 diagnosis could access multiple disease funds, patients could have multiple claims in a given year, and patients could receive support over multiple years.

RESULTS

The analysis data set contains information for 834,819 patients who received support from PAN for OOP medication expenses between 2011 and 2015. Among these individuals, there were 2,917,524 claims, 80.6% of which originated from pharmacies and 14.2% from physician offices.

During the 5-year study period, there was a 13-fold increase in the number of individuals who received OOP support from PAN, and these numbers increased markedly for both cancer-related and noncancer–related illnesses. In 2011, PAN provided support to 14,373 individuals for cancer-related OOP expenses, and the number rose to 159,130 in 2015 (**FIGURE 1**). Overall, 41.6% of people who received support from PAN between 2011 and 2015 were patients with cancer who directed PAN support toward OOP expenses for their cancer drugs. Medicare was the primary source of insurance for 91% of patients with cancer who received support from PAN for their OOP drug costs, and there was a dramatic increase in the number of Medicare beneficiaries receiving OOP support for their cancer medications during the study period (**FIGURE 2**): from 11,453 patients in 2011 to 275,481 patients in 2015.

The total number of claims for patients with cancer rose from 33,871 in 2011 to 572,407 in 2015—a 17-fold increase. Cancer medications accounted for 39% of the total number of claims during the study period (**FIGURE 3**).

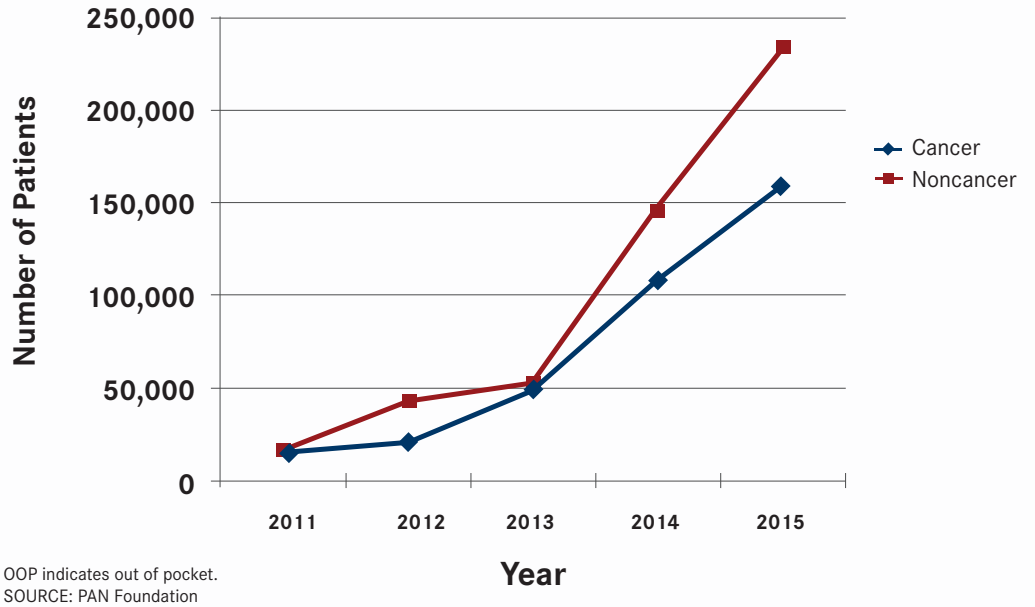
PAN provided $2.1 billion in support for OOP medication expenses between 2011 and 2015, with a sharp upward trend beginning in 2013. Support for cancer medications rose from $60 billion in 2011 to $542 billion in 2015 (**FIGURE 4**). Although 39% of all claims between 2011 and 2015 were for cancer drugs, these claims accounted for 55% of all OOP financial support that PAN provided during this time. Throughout the study period, patients with cancer had higher OOP costs for their medications, both on a per-claim and a per-person basis (**FIGURE 5**).

During the study period, the proportion of claims from patients with cancer to cover OOP medication expenses that originated from a pharmacy was lower than that of patients with other conditions (72.7% vs 85.7%, respectively); interestingly, the proportion of the pharmacy claims increased steadily over time—from 39.9% in 2011 to 76.4% in 2015 (**FIGURE 6**). Although the average number of pharmacy claims was lower throughout the study period among patients with cancer compared with their counterparts with other health conditions (2.4 vs 3.1 claims), the average number of pharmacy claims among patients with cancer rose steadily during this time while pharmacy claims increased less dramatically among patients without cancer (**FIGURE 7**).

CONCLUSIONS

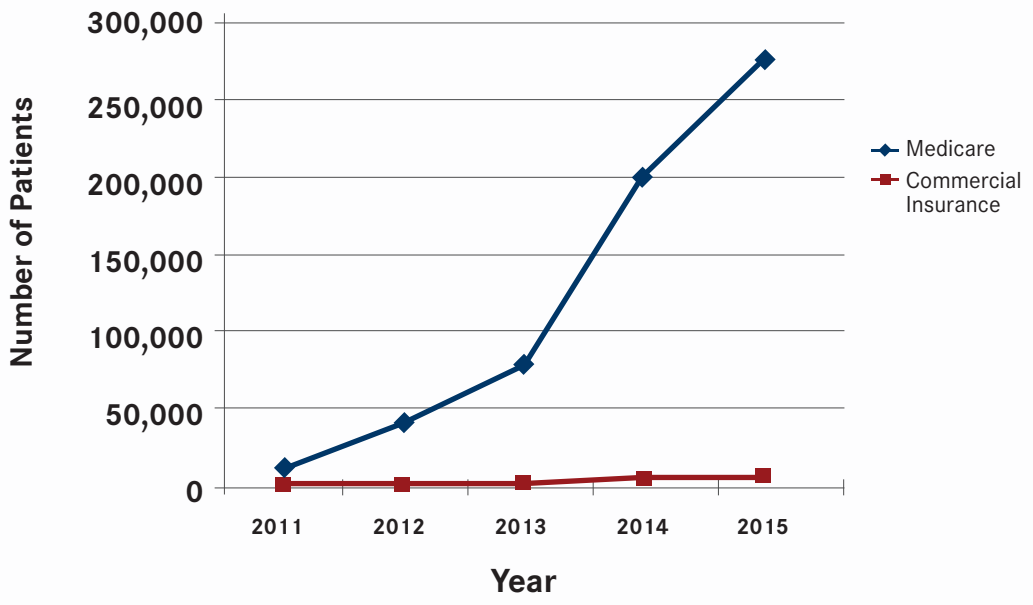
Increasingly, large numbers of economically vulnerable patients are utilizing charitable assistance to cover their OOP medication expenses. Recognizing this trend, PAN convened a roundtable in February 2016 to explore the challenges imposed by cost sharing on patients and families. The roundtable covered a variety of topics, including the special circumstances faced by those diagnosed with cancer. These patients, along with their families, must often choose between access-

FIGURE 1. Number of Patients Receiving Charitable Assistance for OOP Medication Costs, by Fund Type and Year



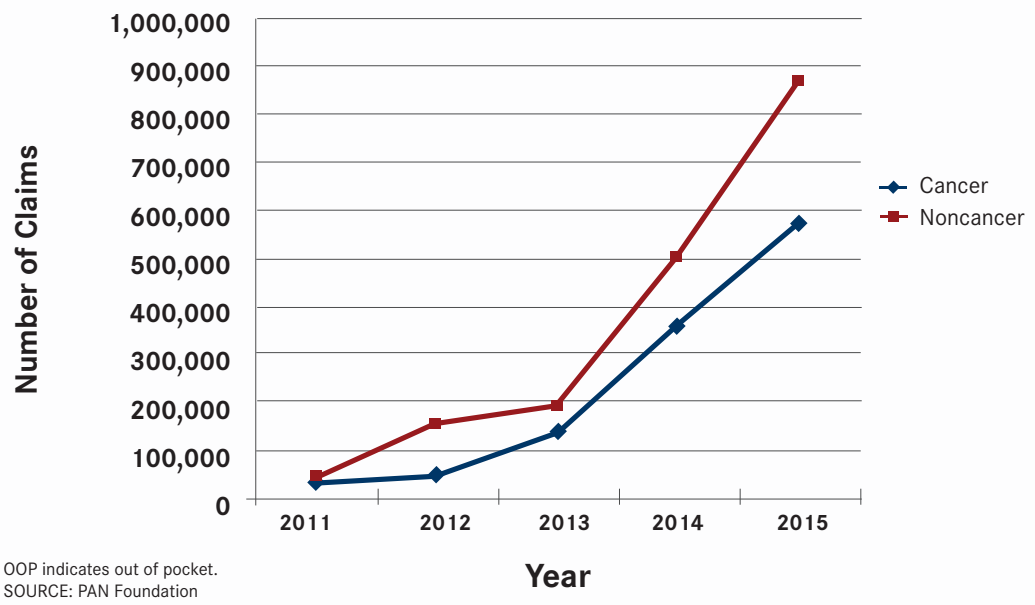
OOP indicates out of pocket.
SOURCE: PAN Foundation

FIGURE 2. Number of Cancer Patients Receiving Support for OOP Medication Costs, by Insurance Type and Year



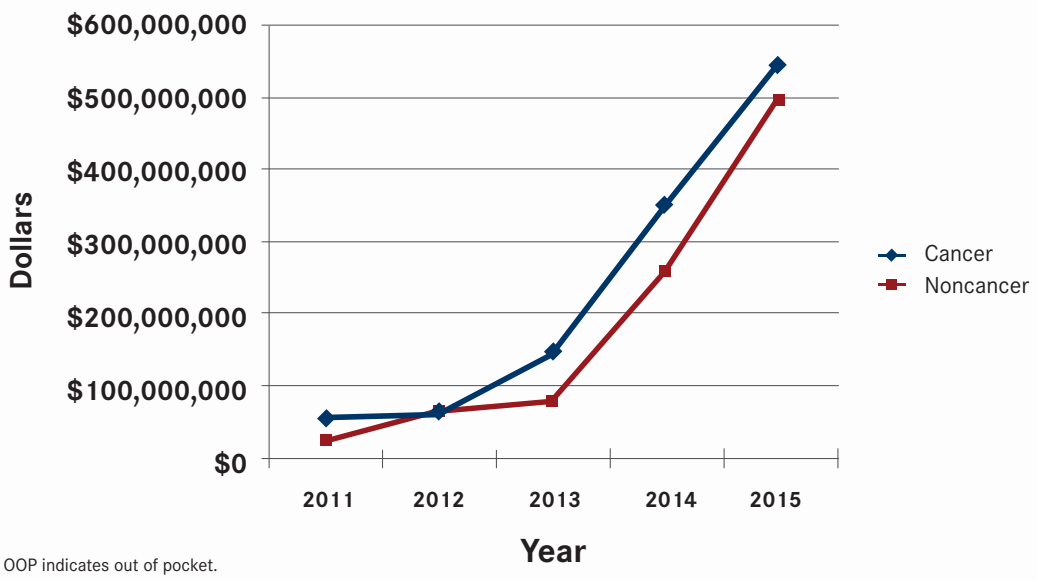
OOP indicates out of pocket.
SOURCE: PAN Foundation

FIGURE 3. Total Number of Claims for OOP Medication Costs, by Fund Type and Year



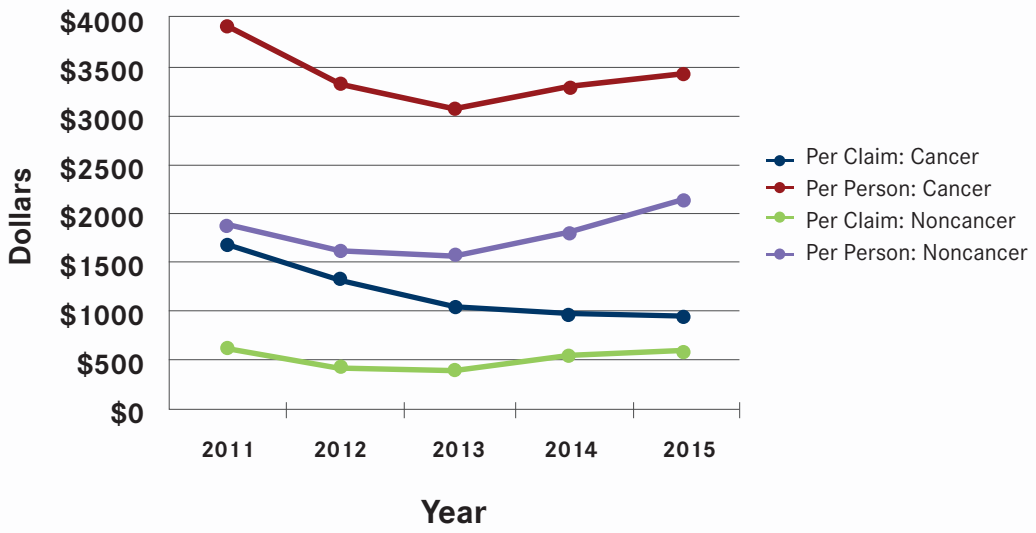
OOP indicates out of pocket.
SOURCE: PAN Foundation

FIGURE 4. Value of Claims for OOP Medication Expenses, by Fund Type and Year



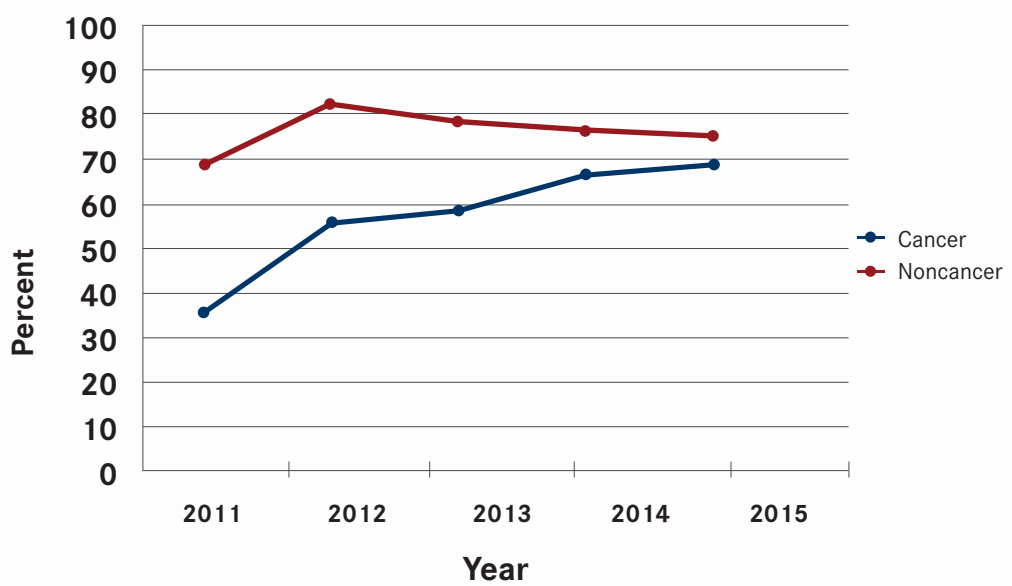
OOP indicates out of pocket.
SOURCE: PAN Foundation

FIGURE 5. Average Per Claim and Per Patient Support for OOP Medication Expenses, by Cost and Year



OOP indicates out of pocket.
SOURCE: PAN Foundation

FIGURE 6. Percent OOP Medication Expenses Attributable to Pharmacy Claims, by Fund Type and Year



OOP indicates out of pocket.
SOURCE: PAN Foundation

ing the life-saving benefits of the newest treatments, and the financial ruin that results from the OOP expenses that come with this access.[12]

New research among Medicare beneficiaries—the group that receives the vast majority of charitable assistance from PAN—demonstrates the link between high cost sharing and access to effective cancer treatment.[13] The new report shows that among beneficiaries who were newly diagnosed with chronic myeloid leukemia (CML), those with low cost sharing (less than or equal to $5 throughout the year) were more likely than those with high cost sharing (greater than $2600 per fill) to initiate therapy with oral tyrosine kinase inhibitors, a new class of targeted cancer therapy that offers most CML patients the opportunity to enjoy a near normal life span.[14] The latter report puts CML patients' OOP costs into sharp focus, and offers appropriate context for the data presented in the current report, which describe all cancer patients who received charitable assistance for OOP medication costs over a recent 5-year period.

In 2011, PAN provided charitable assistance for OOP medication expenses to 14,373 cancer patients who were at or below 500% of the FPL. This number had risen to nearly 160,000 in 2015, and in that year, patients received more than $542 million to cover the OOP costs of their medications. These findings, along with the observation that OOP drug costs were higher for patients with cancer than for their counterparts with other health conditions, provide further evidence concerning the financial hardship faced by those being treated for cancer.

In 2015, less than half (40.5%) of the individuals who received charitable assistance from PAN to cover their OOP drug costs had cancer, yet their claims accounted for more than half (52.2%) of all funds that were disbursed that year. It was, therefore, not surprising that OOP medication costs for patients with cancer were higher on both a per-claim and per-patient basis compared with patients with other conditions, and these trends were evident throughout the 5 years of our study. Our data—which reflect the experience of an especially vulnerable segment of the patient population—demonstrate that OOP costs for drugs have a disproportionate impact on cancer patients relative to economically challenged people with other health problems. Our findings are consistent with a growing body of literature that focuses on the financial toxicity of a cancer diagnosis, and the specific role that is played by OOP drug costs among cancer patients.[1,15,16] Our data also show that the per-patient annual cost of OOP support for cancer drugs was considerably higher than the same support for non-cancer drugs, and this gap increased during the 5 years between 2011 and 2015. This finding suggests that the "financial burden gap" is increasing among patients with cancer—even those who are economically vulnerable enough to be eligible for charitable assistance for their OOP medication costs.

Although the vast majority of claims for charitable support to cover OOP costs for cancer medications is currently directed at pharmacy claims, the proportion of these claims has risen steadily—from 39.9% of all claims in 2011 to 76.4% of claims in 2015. We observed a parallel increase in the average number of pharmacy claims per cancer patient during this time—0.94 claims per patient in 2011 to 2.7 claims per patient in 2015. As expected, the shift toward increasing pharmacy claims was accompanied by a corresponding decrease in the proportion of cancer drug claims originating from physician offices. This pattern likely reflects a relative increase in utilization of new oral medications and a relative decrease in chemotherapies that are typically administered in hospital- or office-based settings. These cancer-specific trends were also discussed during our recent Cost-Sharing Roundtable.[12] Our findings are consistent with the rapid approval of new oral cancer medications that are dispensed from pharmacies. Of the 21 oncolytic

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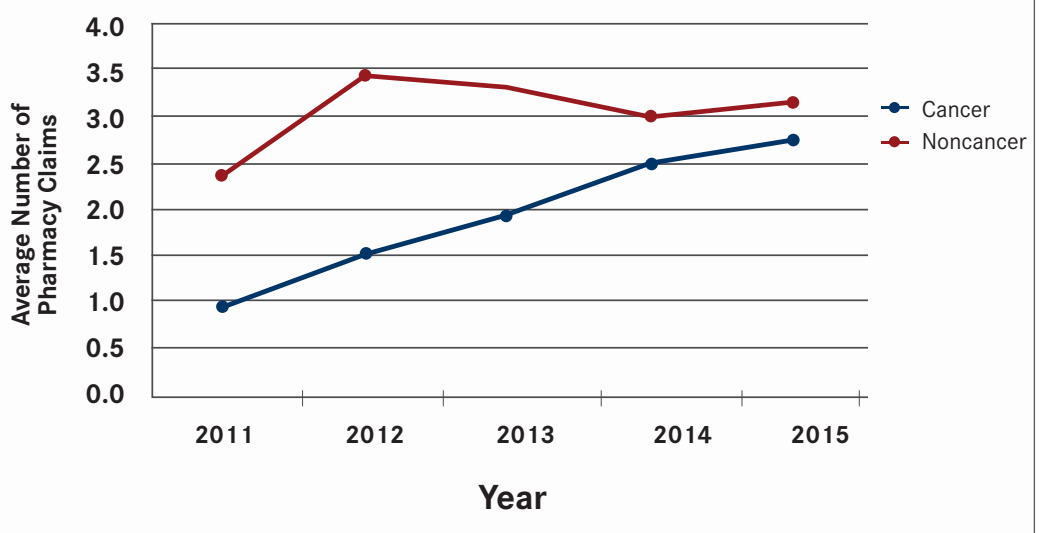
drugs that were approved in 2015, 12 were oral formulations. As of June, 2016, 3 of the 5 drugs that have been approved for cancer are oral medications.[17]

Cost sharing has far-reaching implications concerning the connection between access and health. A report from the Robert Wood Johnson Foundation found that increased cost sharing was associated with adverse health outcomes for vulnerable populations including the elderly, chronically ill, and those on public assistance programs.[18] Cost sharing creates a 2-class system with respect to pharmaceutical access. People who can afford their OOP drug costs can access the full spectrum of health benefits from recent advances in biotechnology and drug development, whereas those with insufficient resources to cover their OOP drug costs must settle for medications that may be less effective than newer options; alternatively, patients may have to forgo the medications altogether.

PAN's database of individuals who meet income-based criteria for receipt of charitable assistance with their OOP drug costs provides an opportunity to understand trends in the need and disposition of this assistance in large samples of economically vulnerable patients. These data show that the number of charitable grants to assist with OOP cancer treatment costs has increased dramatically, and that OOP costs for drugs have a disproportionate impact on people with cancer. **EBO**

FIGURE 7. Average Number of Pharmacy Claims for OOP Medication Expenses, by Fund Type and Year



OOP indicates out of pocket.
SOURCE: PAN Foundation

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MANAGED CARE UPDATES

Patient Access to Reference Pricing Prompts Choice of Lower-Cost Testing Laboratories, Cost Savings

SURABHI DANGI-GARIMELLA, PHD

A study by researchers at the University of California, Berkeley, found that patients who have access to the prices charged by a testing laboratory, as well as reference pricing, choose lower-cost laboratories, a move that results in overall cost savings.

A common practice in Europe, a reference price is the reimbursement limit set by insurers for medications and services; anything above that limit is paid for by the patient as the out-of-pocket (OOP) share. In the United States, some health plans are using reference pricing for surgical and diagnostic procedures, and for the current study, the authors sourced data from health insurer Anthem, which provides health coverage for employees of the grocery store network Safeway. Anthem negotiates reference prices for laboratory testing based on the geographic region, and Safeway employees who choose a laboratory that charges less than or equal to the established reference price do not see any additional charges beyond their deductible.

With a large sample size of more than 30,000 employees, the study, published in *JAMA Internal Medicine*, documented changes in laboratory pricing and the selection of a testing laboratory by the employees following the implementation of a reference pricing policy.[1] The comparator group included more than 180,000 policy holders of a large national insurer that did not implement reference pricing. The authors write that Anthem established an upper limit at the 60th percentile of the distribution for each laboratory in a particular geographic region and policy holders were given access to information on pricing at all laboratories through a mobile digital platform.

For the period between 2010 and 2013, 2.13 million claims for 285 types of in vitro diagnostic tests were analyzed, with the primary outcomes of interest being patient choice of laboratory, price paid per test, patient OOP costs, and employer spending. Safeway employees had an average of 5 to 6 tests per year, which remained the same over time. What changed following implementation of the reference pricing policy was the site where the tests were conducted: before 2011, 50% of tests were conducted at laboratories that charged more than Anthem's reference price; by 2013, the number dropped to 16%.

The results of the analysis were quite compelling. Within 3 years of implementing reference pricing, Anthem saw a 31.9% (95% CI, 20.6%-41.6%) reduction in the average price paid per test, with $2.57 million (95% CI, $1.59-$3.35 million) in savings from reduced spending. By choosing cheaper alternatives, patients reduced their OOP spending by $1.05 million (95% CI, $0.73-$1.37 million) and simultaneously saved their employer $1.7 million (95% CI, $920,000-$2.48 million).

James Robinson, PhD, professor and head of health policy and management at UC Berkeley's School of Public Health, who led the study, told *Reuters*, "Reference pricing can't be used across all types of healthcare. While being treated for cancer, we don't expect the patient to shop the market." However, most of medicine is nonemergency, he said.[2]

Robinson added that patients do not pay attention to the price being paid when their employer is paying for their healthcare. With reference pricing, when the patients have to share the cost burden, they are forced to shop around for lower-cost services. However, it is important to ensure that patients are made aware that a reference price is being implemented on the service they seek. Communicating this information falls on the shoulders of the health plan. **EBO**

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California Experiment Will Let Pathologists Report Cancer Diagnoses in Real Time

SURABHI DANGI-GARIMELLA, PHD

A collaborative pilot that involves the California Department of Public Health, St. Joseph Health in Orange County, and UCSF Benioff Children's Hospital in Oakland is studying whether near–real-time reporting of cancer diagnoses by pathologists, using standardized electronic forms, will permit providers to make more informed and timely treatment decisions.

As part of the project, pathologists at a dozen hospitals in the state will document cancer diagnoses to the California Cancer Registry as soon as it is possible, quite unlike the traditional method that often saw reliance on data that could be as much as 2 years old. According to Kaiser Health News (KHN), the registry is a treasure trove of information—diagnoses, screening, patient demographics, initial treatments, and outcomes—on over 4.5 million cancer patients. With access to more real-time information, oncologists would be better situated when choosing treatment options for their patients.

This also opens up a window of opportunity for directing patients to the appropriate clinical trial. "Our driving force is making sure we can get the patient to the right treatment, the right trials, as quickly as possible," Michelle Woodley, chief nursing information officer at St. Joseph Health System, told KHN.

The most significant impact of adding this capability to the registry is the potential for prospective analysis instead of retrospective analysis that researchers have resorted to with the database. The California Cancer Registry is often used by researchers to identify disparities in cancer screening and outcomes, as well as to confirm hot spots of specific cancer types. Although such information is very useful for population-based surveillance studies, they may not be as efficient when providing more individualized care.

With access to more real-time information, oncologists would be better situated when choosing treatment options for their patients.

Bob Achermann, executive director of the California Society of Pathologists, told KHN, "The current system is not working as well as it should. There are long delays… You would assume that a program that has been around as long as it has would be more sophisticated, but it is not." Whereas the state mandates reporting of all cancer diagnoses, it wants real-time reporting to increase to 10% by next June, from the current 5%, and to 65% by 2022.

Transition from paper charts to electronic health records and an upgrade to information systems used by hospitals and cancer clinics could provide a significant boost to this project. Programs are also being piloted to make it easier for pathologists to provide their diagnoses—such as creating a checklist instead of a summary paragraph for easier interpretation.

The California Department of Public Health, meanwhile, hopes to expand such programs statewide. "As technology in every aspect of our lives has drastically changed, so has the expectation of physicians, laboratories, facilities, and facility groups about what types of data they need," said a statement released by the department. **EBO**

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Breakthrough for Daratumumab for Use as Second-Line Treatment With Standard of Care in Multiple Myeloma

SURABHI DANGI-GARIMELLA, PHD

The monoclonal antibody daratumumab (Darzalex) has been granted Breakthrough designation, the second for this drug, for use in combination with either lenalidomide (Revlimid) and dexamethasone or bortezomib (Velcade) and dexamethasone for patients with multiple myeloma who have received at least 1 prior therapy.[1] The drug was first approved in November 2015 in heavily pretreated patients diagnosed with multiple myeloma.

The new breakthrough status was based on the results of 2 pivotal phase 3 studies, both finding that including daratumumab reduced the risk of disease progression, as well as death, in patients with multiple myeloma:

- MMY3004 (CASTOR) trial, which evaluated daratumumab in combination with the immunomodulatory agent dexamethasone and the proteasomal inhibitor bortezomib compared with bortezomib and dexamethasone alone, in patients who had received just a single prior line of therapy.
- MMY3003 (POLLUX) trial, which evaluated daratumumab in combination with dexamethasone and the immunomodulatory agent lenalidomide compared with dexamethasone and lenalidomide alone, in patients who had received just a single prior line of therapy.

> **"We are pleased that the FDA continues to recognize the potential of daratumumab to help patients with multiple myeloma."**
>
> – JAN VAN DE WINKLE, PHD

"This is the second time daratumumab has earned the distinction of a Breakthrough Therapy designation. We are pleased that the FDA continues to recognize the potential of daratumumab to help patients with multiple myeloma. We continue to work with our strategic partner Janssen and the regulatory authorities to advance daratumumab to bring this treatment to more patients suffering from multiple myeloma as quickly as possible," said Jan van de Winkel, PhD, chief executive officer of Genmab, which is developing the drug in collaboration with Janssen Research and Development.[1]

Craig L. Tendler, MD, vice president, Late-Stage Development and Global Medical Affairs for Oncology, Hematology and Supportive Care, Janssen, said, "This is an important recognition of the transformative potential of daratumumab and its possible benefit as a backbone therapy in combination with two of the most widely used regimens for multiple myeloma."[2] **EBO**

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NEJM Study First to Identify Mutations Responsible for Relapse in PD-1 Inhibitor–Treated Melanoma

SURABHI DANGI-GARIMELLA, PHD

Loss-of-function mutations in Janus kinase 1 (JAK1) or Janus kinase 2 (JAK2), deletion of the wild-type allele of JAK1 or JAK2, and truncation in the antigen-presenting protein beta-2-microglobulin (*B2M*) gene have been found responsible for lack of response to interferon gamma in patients with melanoma.[1]

The group that has identified these mutations recently published another study that showed that 25% of patients with melanoma who had an objective response (OR) to antibodies against the programmed death 1 (PD-1) receptor showed disease progression at a median follow-up of 21 months.[2] To pinpoint the triggers for this resistance, the authors analyzed the genomic evolution of the disease in patients who had been treated with the anti–PD-1 antibodies.

Seventy-eight patients with metastatic melanoma were treated with pembrolizumab at the University of California at Los Angeles (UCLA); 42 had OR, of whom 15 progressed. Further analysis of the tumor samples of 4 of the 15 patients was conducted, which included pathological analysis, DNA and RNA analysis, and trying to establish cell lines to identify resistance mechanisms.

Following whole-genome sequencing, the authors identified loss-of-function mutations in kinases associated with the interferon-receptor pathway—specifically, a Q503* nonsense mutation in JAK1 in patient 1 and a F547 splice-site mutation in JAK2 in patient 2. Comparing the response of the primary cell lines that were derived from the tumor of patient 2—at baseline and following relapse—the authors found an absence of JAK2 protein expression following relapse and a consequent lack of response to interferon gamma. The cell line also failed to upregulate a wider panel of interferon-induced transcripts involved in antigen presentation and T-cell chemotaxis, the authors write. In patient 3, mutation in the *B2M* gene resulted in loss of outer membrane localization of MHC class I molecules, which has previously been identified as a mechanism of acquired resistance to immunotherapy.

Commenting on the findings of their study, senior author Antoni Ribas, MD, PhD, who directs the tumor immunology program at UCLA said, "This will help us to better design the next generation of treatment."[3] He believes that their findings may not be restricted to Merck's pembrolizumab (Keytruda) and could be generalized to the entire class of PD-1 inhibitors. "If we understand the process, we may be able to tailor the treatment better. We are not there yet," Ribas added. **EBO**

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Medical World News®

CLINICAL UPDATES

Nivolumab Passes QOL Test in Melanoma

SURABHI DANGI-GARIMELLA, PHD

Results from the CheckMate 066 study found that the checkpoint inhibitor nivolumab, which has proven highly efficient in the treatment of melanoma, also performs well in improving the patient's long-term quality of survival benefit in patients with advanced melanoma.

Immunotherapy, particularly the checkpoint inhibitors that belong to the programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 or CTLA-4, have reformed the treatment landscape in melanoma as well as in lung cancer and created more hope. Although only 20% to 30% of patients respond to these drugs, the extent and duration of response are robust, and results from Checkmate 066 convinced the FDA late last year to grant approval to nivolumab as a single agent in treatment-naïve patients with advanced melanoma who express wild type BRaf.

However, concerns with the toxicity of these agents remain, toxicities that can influence a patient's health-related quality of life (HRQOL). Even if a patient is an ideal candidate to being treated with nivolumab, with high chances of longer survival, is he or she ready to face the accompanying toxicity? This is an important question that also finds a place in the various value tools that have been developed in healthcare. With this in mind, Checkmate 066 was designed to gather data on HRQOL measures, comparing the impact of nivolumab and dacarbazine on patient-reported outcomes.

No deterioration of HRQOL was identified with nivolumab. When added to the survival benefit of nivolumab, the benefit-to-risk ratio favors nivolumab over dacarbazine.

For the study, researchers evaluated HRQOL at baseline and every 6 weeks on treatment using the European Organisation for Research and Treatment of Care (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and the EuroQoL Five Dimensions Questionnaire (EQ-5D). Patients were treated with nivolumab 3 mg/kg every 2 weeks or dacarbazine 1000 mg/m2 every 3 weeks. The completion rate for both questionnaires was 65% and 70% for dacarbazine and nivolumab.

The analysis found that the average baseline HRQOL scores were similar for patients in both cohorts, and the baseline HRQOL score levels were maintained with nivolumab over time. However, a difference as observed with the EQ-5D utility index and clinically meaningful EQ-5D improvements from baseline at several time points for patients on nivolumab, the authors write. Nivolumab also did not increase their symptom burden, the patients reported via EORTC QLQ-C30. Patients on dacarbazine, on the other hand, had a high attrition rate after 13 weeks, which prevented meaningful data analyses, although there was no change in the HRQOL information.

Time to deterioration was much greater in the nivolumab-treated cohort, the authors report as measured by the EORTC QLQ-C30 scale, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, and constipation, as well as EQ-5D utility index.

"No deterioration of HRQOL was identified with nivolumab. When added to the survival benefit of nivolumab, the benefit-to-risk ratio favors nivolumab over dacarbazine," they conclude. **EBO**

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The Risk of T2D in Individuals With Benign Adrenal Tumors

SURABHI DANGI-GARIMELLA, PHD

Adrenal gland tumors that are defined as being nonfunctional may not really be so, and the hormones that these tumors secrete could increase an individual's risk of cardiometabolic irregularities, according to a new study published in *Annals of Internal Medicine*.

Tumors in the adrenal glands—abdominal glands that produce hormones and are included in the endocrine system—are classified as benign, functional, and malignant. The benign tumors are typically defined as being noncancerous and are found by chance when diagnostic tests are being conducted to evaluate some other symptoms. However, one of the hormones secreted by these tumors is cortisol, which can increase the risk of cardiovascular and metabolic diseases.

To further study the relation between the development of these tumors and an individual's risk for cardiometabolic outcomes, researchers conducted a retrospective analysis of medical data gathered from 166 individuals who were documented as having developed the tumors. The control group of 740 individuals did not have adrenal tumors; inclusion criteria was a 3-year follow up period. Patient records were evaluated for an average period of 7.7 years from the time of abdominal imaging following incidental outcomes of hypertension, composite diabetes (prediabetes or type 2 diabetes [T2D]), hyperlipidemia, cardiovascular events, or chronic kidney disease.

"Our results indicated that patients with nonfunctional adrenal tumors developed diabetes twice as often as patients without any adrenal tumors."

– ANAND VAIDYA, MD, MMSC

When the association between exposure status and incident outcomes was analyzed, it was discovered that individuals with the benign tumors had significantly higher risk for incident composite diabetes than those without the tumors. Specifically, 27.3% of those carrying the tumors had an absolute risk of 15.6% (95% CI, 6.9% to 24.3%) and an adjusted risk ratio of 1.87 (CI, 1.17 to 2.98). On the other hand, less than half (11.7%) the participants in the control group developed the risk of composite diabetes. While there was no significant association between nonfunctional adrenal tumors and any of the other cardiovascular outcomes being evaluated, cortisol levels were found associated with the size of the tumors and higher prevalence of T2D.

"Our results indicated that patients with nonfunctional adrenal tumors developed diabetes twice as often as patients without any adrenal tumors. This suggests that even adrenal tumors we deem to have no health risks are in fact associated with an increased risk of developing diabetes," said Anand Vaidya, MD, MMSc, senior author on the study, in a statement. He recommends that adrenal tumors sould be considered a potential risk factor for the development of diabetes. **EBO**

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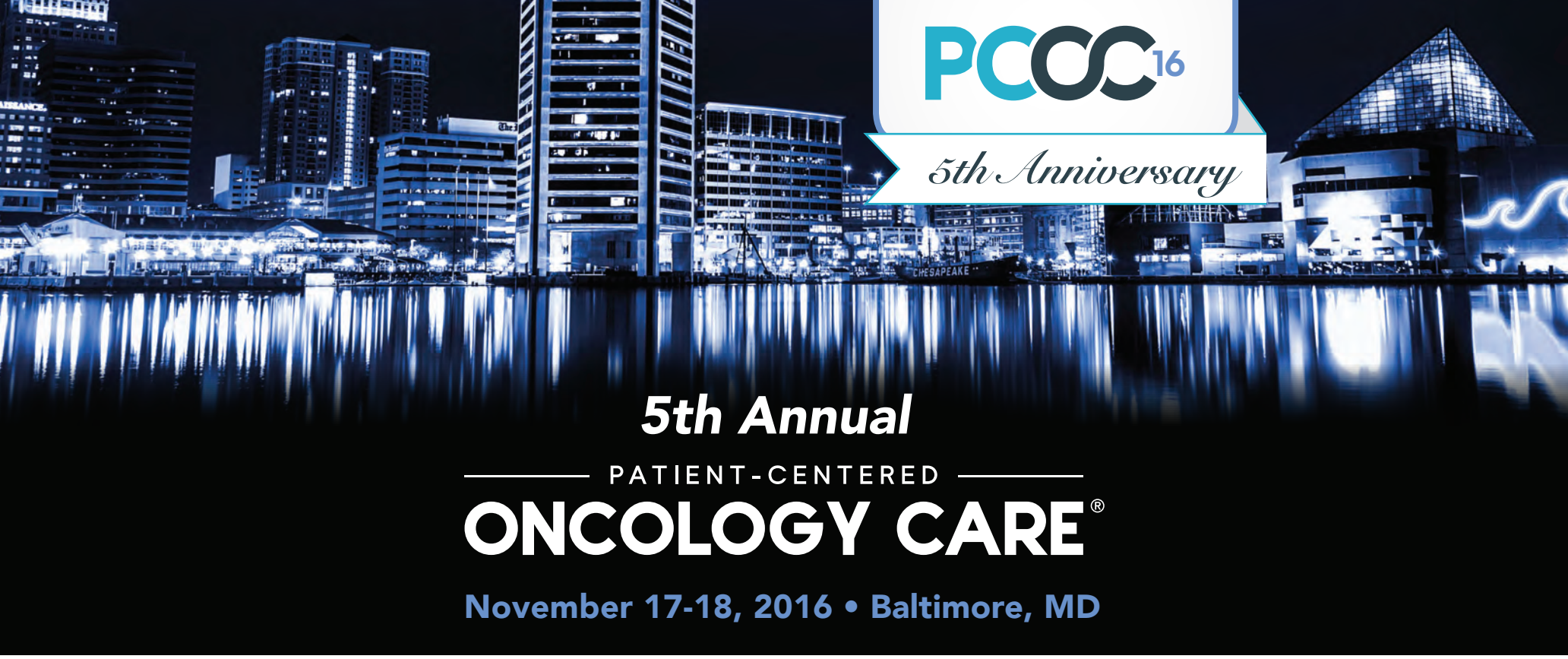


CALL FOR POSTERS

for *The American Journal of Managed Care*'s 5th Annual Patient-Centered Oncology Care® meeting

The American Journal of Managed Care (*AJMC*) is issuing a call for posters to be presented at its *5th Annual* **Patient-Centered Oncology Care®** (PCOC) meeting, to be held November 17-18, 2016, in Baltimore, Maryland. Participants at PCOC include a diverse mix of payers, healthcare providers, patient advocates, and health outcomes researchers (academic and industry).

In commemoration of the 5th anniversary of PCOC, we'd like to invite our attendees to present their research data, in the form of posters, during PCOC. Topics that can be submitted for presentation include:

- Patient access
- Barriers to reimbursement
- Utilization management
- Cost-sharing
- Coverage gaps
- New treatments/indications
- Tools for quality improvement
- Assessing value in oncology care
- And more…

Objectives and results of the research should be included in the abstract, which should be organized into 4 sections (Background, Methods, Results, and Conclusions) and should not exceed 400 words. The abstract submission deadline is September 1, 2016. Abstracts can be submitted by emailing Nicole Beagin at nbeagin@ajmc.com or Surabhi Dangi-Garimella at sgarimella@ajmc.com.

Posters will be displayed at the venue throughout the meeting. The top 3 posters will be selected by attendees of PCOC. Abstracts will be published in a special issue of *AJMC*'s *Evidence-Based Oncology* (*EBO*) and can be converted into papers for publication in a regular issue of *EBO*.

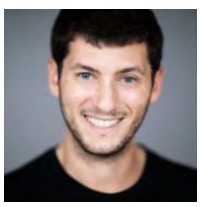
AJMC® Managed Markets Network®

Paying to Make Health IT Meaningful: *A Discussion at the NCCN Policy Summit*

SURABHI DANGI-GARIMELLA, PHD


ROESELER


ABERNETHY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KOLODZIEJ

Maximizing the utility of technology platforms and making them meaningful to ensure quality cancer care was the underlying theme of Emerging Issues and Opportunities in Health Information Technology, a National Comprehensive Cancer Network Policy Summit, held June 27, 2016, in Washington, DC.

The first panel discussion, Readiness to Support Alternative Payment Models and Reporting for Precision Medicine and Quality Care, saw participation by a payer, providers, and developers of technology platforms. Participants included Amy Abernethy, MD, PhD, Flatiron Health; Jonathan Hirsch, Syapse; Michael Kolodziej, MD, Aetna (who has since joined FlatIron Health); Mia Levy, MD, PhD, Vanderbilt Ingram Cancer Center; Alexandra Mugge, MPH, CMS; Marcus Neubauer, MD, McKesson Specialty Health; Allen Roeseler, NantHealth; and Bret Shillingstad, MD; Epic Systems Corporation.

Data silos that emerge because systems do not speak with each other is a significant problem. How does this absence of information affect patient care? Neubauer said that interoperability is a problem for healthcare systems. "Within our system, we are internally networked well enough to not have any such issues. Otherwise, clinics have to significantly depend on patient reporting," he said, which can sometimes be a challenge.

With respect to measuring the quality of care delivered, the more information the better. "Clinical pathways involve a design component, and then there's compliance," explained Neubauer. They are both distinct. We have [developed] capabilities to generate and share reports on compliance with payers."

Mugge said that at CMS, "We try to listen to clinicians to make measures more meaningful. They could be targeted. Like just for [electronic health records (EHRs)]."

What is the most significant barrier for data mining across systems? According to Levy, it's how the data is extracted. "Quality metrics have been around for a long time, but they have not been grounded in the feasibility of measuring something—while measures may be process-oriented, they are not easy to extract," Levy said. "The feasibility of being able to extract data in a more automated fashion is important," she said. Roeseler agreed. "We have these vast data sets…the question is, how do you access this information?" According to Shillingstad, specialty organizations and registries play a very important role in the process, and a registry of standards for data extraction can be established for oncology.

"The interesting thing with oncology is that some of the new data sources lend the opportunity to monitor and implement workflow changes and process changes. We have been able to work with one of these to institute such workflow changes," added Hirsch.

But the necessary changes have to be implemented now, at the point where physicians and clinics are preparing to submit their reports for the Merit-Based Incentive Payment System (MIPS), a measurement tool of the Medicare Access & CHIP Reauthorization Act of 2015, and its other option, alternative payment models (APMs). "So, Flatiron is working to get data organized to introduce it into registries and data sources," Abernethy said. "It's also important to record those quality measures that matter, and I foresee 2 challenges with that: the need for quality measures that are aligned with the current data systems and developing measures that are flexible enough to alter, based on outcomes."

Neubauer complimented the way in which CMS' Oncology Care Model (OCM)[1] has been developed. "Initially, there were 20 quality measures within the OCM, and now they have been reduced to 12, 4 of which are requirements of the [Physician Quality Reporting System]. So, quality metrics change as the program evolves. They were smart to do that with [the] OCM," he said. "While decision support tools are a good idea, they should contribute to making the physician workflow smoother, and not add to their burden," Neubauer added.

Abernethy pointed out that physicians should remember to only add information that they need to enter. "If it's not necessary information, the physician's quality report drops off."

How can health IT platforms support APMs? Kolodziej said, "Oncologists are responsible for understanding the clinical profile before they treat the patient. MIPS and OCM are transitional models, not the end game. To understand the clinical information and then come up with alternatives for care…we need health IT."

Shillingstad believes that although EHRs can support models, such as bundled payment and episodes-of-care, the complexity rises several notches with oncology. According to Abernethy, software solutions that guide physicians and buyers to the right solutions is the basic requirement. Additionally, predicting risks by using algorithms that can forecast which patient is at risk for specific problems. "EHRs create a community practice. They create a mechanism for community oncologists to relate to each other and help each other," Abernethy said, which was the objective behind FlatIron's cloud-based EHRs.

"Cloud-based technologies and machine learning can provide increased data access. Cloud-based technologies and aggregated data can provide the solution," said Roeseler. Hirsch agreed. "Cloud-based systems, as Amy said, can help physicians share and learn from each other. We are currently collaborating with health systems on this."

"Most of what is coming back is that customers are driving development," Shillingstad added. **EBO**

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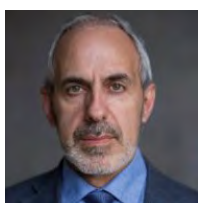
Health IT Essential for the Success of Cancer Moonshot

SURABHI DANGI-GARIMELLA, PHD


SIMON

Gregory C. Simon, executive director, White House Cancer Task Force, spoke at the National Comprehensive Cancer Network Policy Summit in Washington, DC. Highlighting the overall progress over the past decade, Simon said, "Every field has advanced, except for the way research has been done at the NIH [National Institutes of Health]. Hardly anything has changed at the NIH since World War II."

Simon emphasized that there is really no limit on what can be done. "It's about what we want to do. Changing culture is the most powerful thing on the planet." He argued that science is not hard; rather, its people who make things difficult. The moonshot, he said, is organized around promoting collaboration between the government and outside players. The National Cancer Advisory Board of the NIH has selected a blue ribbon panel of 29 experts who will create a report for the board, "which reaches the National Cancer Institute and finally to us," said Simon. The blue ribbon panel will provide guidance on projects that are worth investing in to achieve the objectives of the Cancer Moonshot.[1]

"Just like the original moonshot, the Cancer Moonshot is about using technology and the resulting information," according to Simon. A cancer survivor himself, Simon alluded to how the removal of data silos and providing access to information had influenced his own treatment. "My leukemia treatment was at MSKCC [Memorial Sloan Kettering Cancer Center], and subsequent care was at George Washington University," he said. Data was shared seamlessly between providers at the 2 institutions, without any restrictions, he added. "We need to know how to get to our data, who can get to it, how they use it, and how they share it," Simon explained. "Information that I publish should be available instantly—especially if it is government-sponsored—not 2 years later when it might be too late."

Simon believes that both raw and published form of government-sponsored data should be readily accessible to whoever seeks it. "How can a physician find out more about a patient's disease? How can the doctor get his hands on this information so he can treat his patient better?" he asked. "We need a blending of disciplines," he said. That's how ideas will evolve—ideas that tell us that it might be sufficient to contain cancer, rather than curing it. Such ideas need cross-disciplinary collaborations to blossom. Simon also emphasized the importance of patient engagement.

"Researchers who do not gain input from patients will stand to lose," he said. "We need to include patient-reported outcomes, unexpected beneficial events, [adverse events] with researchers," he said, adding, "So, there is nothing but a role for [health IT] in cancer care." **EBO**

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Dissolving Data Silos and Improving Access to Health IT Essential in Oncology Care

SURABHI DANGI-GARIMELLA, PHD

COLETTA

MITCHELL

LEVY

PELLINI

At the Emerging Issues and Opportunities in Health Information Technology Policy Summit hosted by the National Comprehensive Cancer Network, on June 27, 2016, an afternoon panel discussed the role of technology and its importance in promoting dissemination of data. Sharing information, the panelists agreed, can help create a learning system that can improve patient outcomes.

Anthony V. Coletta, MD, MBA, executive vice president and chief executive officer of Tandigm Health, a joint venture by Independence Blue Cross and Health Care Partners, said that culture change is a disruptive innovation. "Payers have to be a part of the process," Coletta argued, "They cannot remain on the periphery."

"It is important to provide access [to health IT platforms] for community practitioners," said Michael Pellini, MD, chief executive officer of Foundation Medicine. He pointed out that several tools are currently being developed to do so.

Edith Mitchell, MD, a medical oncologist at Sidney Kimmel Cancer Center at Jefferson Health in Philadelphia, explained that one of the objectives of Cancer Moonshot[1] is to simplify trial design and participation. "As a part of Cancer Moonshot, trial design will be simplified, with patients in those specific communities finding access to these trial programs, to allow quicker and efficient validation of these trials. Additionally, breaking down the silos between the various parts of the government" can provide a tremendous push to the project, Mitchell stated.

"Biomarker-driven studies, such as the NCI-MATCH trial,[2] can provide early information on a patient's tumor genetic make-up," according to Mia A. Levy, MD, PhD, who heads Cancer Health Informatics and Strategy at the Vanderbilt Ingram Cancer Center. This, she believes, will provide a much-needed push toward better personalized care and help rapid learning. "We need this accessible to [patients] around the entire country, unlike right now where it is accessible only in certain geographical pockets." Levy also indicated that reimbursement for diagnostic testing is another barrier, since not all health plans offer coverage. "The testing needs to be paid for," she said.

"When we can get this data into the right framework, and when testing becomes more common and accessible, it would be interesting to see whether and how this data can inform care decisions," said Allen Roeseler, a senior vice president at NantHealth, one of the sister companies floated by Patrick Soon-Shiong, the pioneer of Cancer Moonshot 2020.[3]

Levy pointed out that clinicians could be overwhelmed with the tsunami of data that they need to collate, and "average clinics may not be adept at handling that amount of information. We need systems or tools that can assimilate and interpret this data to have an impact on clinical decisions," she said.

The real-time bearing of these platforms and tools cannot be disregarded. "We now have the ability to determine if treatment is effective in a couple of weeks, as opposed to waiting for 10 weeks," said Mitchell. "So, not only can trials finish sooner, but more importantly, we can change the course of treatment for an individual patient if it's not effective."

"We have collaborated to develop a knowledgebase for cancer and merged it with an individual patient's clinical information to make this a clinical decision support tool."

—MIA LEVY, MD, PHD

With Cancer Moonshot, "rather than looking at 1 therapy or technology, we are simultaneously evaluating multiple treatments—so we are breaking silos," Mitchell added.

Pellini indicated that Foundation Medicine has "not followed the Myriad model because we want those 80% [of] patients in the community to have the ability to know that they have access to their information in the community clinics they visit. That's not possible if we hold on to that data." According to Pellini, anything above and beyond what the technology captures can be turned into proprietary information.

"We have collaborated to develop a knowledgebase for cancer and merged it with an individual patient's clinical information to make this a clinical decision support tool," said Levy, describing the platform that Vanderbilt has developed in house.

NantHealth, Roeseler said, has created eviti,[4] which is currently being used by a large number of oncologists and includes individual genetic profiles. He emphasized that a part of understanding clinical utility of these platforms is speaking to the end users, the clinicians.

Transparency, eliminating silos, and making data readily accessible to those who can use it for the best outcomes was Pellini's takeaway message. "We need to decentralize the generation of information to improve access to drugs. Additionally, we can reach out to academic centers to decentralize input from these research centers. Technology and data allows us that opportunity," he said.

Levy stressed the importance of biomarker-driven research early on in clinical trials to improve efficiency and save time. "We need tools to expand clinical trial access and improve recruitment," she added, drawing attention to the extremely low rate of adult oncology clinical trial enrollment. **EBO**

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PRODUCED BY NICOLE BEAGIN AND LAURA JOSZT

Dr Tricia Neuman Talks About Letting Medicare Negotiate Drug Prices

Presidential candidates Hillary Clinton and Donald Trump have both called for Medicare to be able to negotiate drug prices. What has prevented such a policy from being implemented?

This is an idea that has been kicked around for a long time. People in Washington and elsewhere have been talking about the government doing more to negotiate lower drug costs, specifically leveraging lower drug costs for people on Medicare. Honestly, people have been talking about it for at least a decade.

There are a lot of issues that are involved in this sort of broad idea, however. How would this happen? For example, would this be for all drugs that are covered by Medicare? would it be for a subset of drugs? And I think at this point it is sort of a general feeling that something should be done about drug spending, but we won't know the impact until these policies get better defined.

In the past, the Congressional Budget Office looked at this idea of government negotiations and their view is that it might have a negligible effect on spending unless the proposal has real teeth. Which is to say, the government would set a formulary, the government would decide what the cost-sharing would be, and most importantly the government would be willing to walk away from the table if they couldn't get a better drug price from the pharmaceutical companies.

So, this is a big idea, and I think the question is: what are the specifics underneath this broad idea? Of course there are big political forces and major stakeholders engaged in this debate, which is why it hasn't happened so far.

Dr Albert Tzeel Discusses the Benefits of Increased Risk Arrangements

How have increased risk arrangements changed the way providers are working together?

It's interesting. When we put providers at risk, a lot of them move on a path to risk. So I guess I should back track and say that it's not just someone takes risk at the beginning and they don't know what to do with it. I mean, we certainly work with them to try to get them on a path to risk so that they understand what it entails so whether that's just strictly upside for doing the appropriate things when it comes to performance, to eventually being able to accept full risk for the care of that particular member.

Now, how does it change in terms of how providers can collaborate? I think there's more accountability between providers. Primary care physicians, they want communication from the specialty care physicians. They want communication from the hospitalists. They want communications from the health plan. They've always been called the quarterback of the member's care plan, and they are, but they want accountability from other providers who are involved in that member's care because of the fact that they are on the hook for that member's care.

What I've seen, and we have a lot of providers that are at risk in my particular market, but from what I've seen they still want to do the right thing for the member, but they want to make sure everyone else is doing the right thing and communicating that back so they can all be on the same page, because that's the only way everyone together can do the right thing for the member and improve health [outcomes].

Dr Steven Pearson: No Silver Bullet to Constrain Drug Prices

What policies can be implemented to help constrain drug prices going forward?

Well, there's a growing menu of policy considerations on the table and they range from Medicare negotiating prices itself to states somehow pegging the prices that they will pay to the best price paid to the VA system; there are lots of considerations around having drug companies make more transparent the costs that they incur when bringing a drug to market. All of these are going to be debated, I think, over the coming months because they all may play some role, but they will require extensive consideration because there's no silver bullet.

Nothing is going to solve this problem because there will always be a tension, to some extent, between the resources that we have to spend on health, our desire to maintain broad access to important new medications, and the resources or the incentives that we want to create for future innovation. So within the set of policies that could possibly address that tension, we think that using a value-based price approach is going to be a core part, especially if Medicare negotiates because it will need some standard for understanding what a fair or sensible price is.

If we're going to use incentives in the market system, both carrots and sticks for pharmaceutical companies, to encourage them around pricing there has to be some sense of what a fair or sensible price is. So, our goal is to help provide, in an independent and transparent way, some benchmark that triggers people to think more broadly about what the policy mechanisms would be for really, really transforming the system so that value is at the center.

Improve Medicare Policy to Remove Barriers to Bone Marrow and Cord Blood Transplants

(CONTINUED FROM COVER)

represent the only hope for a cure for these patients,[3] the United States Congress created the C.W. Bill Young Cell Transplantation Program,[4] which provides for a a national registry of adult volunteer donors and publicly available cord blood units. Today, nearly 10,000 Americans search this registry for a match each day (our unpublished data). To a significant extent, the national registry has solved the problem of providing a mechanism to identify willing donors, and with help from Congress, this registry continues to grow to meet the needs of a diverse population. It currently lists more than 13.5 million adult volunteer marrow donors and 225,000 cord blood units. When factoring in international relationships, the donor base includes approximately 27 million potential marrow donors and 680,000 cord blood units across the globe.[5] Be The Match can access all of these HPC sources on behalf of a patient seeking help.

Since 2005, the registry has increased donor diversity, including significant growth in the number of African American, Asian, and Hispanic donors. Today, half of the registry's donors have diverse ancestry, greatly improving the odds of finding a match for patients with various ethnic backgrounds.

The importance of a registry like Be The Match cannot be overstated, addressing the need of the 70% of patients who lack an adequate marrow donor within their immediate families. For this reason, I have dedicated much of my professional career to Be The Match, operated by the National Marrow Donor Program (NMDP). Since its inception nearly 30 years ago, Be The Match has facilitated over 75,0000 transplants—65,000 in the last 15 years.[6]

OBTAINING MEDICARE COVERAGE

As we find ways to connect patients with donors, we are breaking down once intractable obstacles to care. However, even as walls come down, there are new challenges to overcome. Currently, Medicare policy is a formidable impediment for older Americans seeking access to transplantation..

While bone marrow and cord blood transplants are used to treat nearly 70 conditions, Medicare only officially covers a few of these indications. Specifically, it covers transplants for:

1. Leukemia, leukemia in remission, or aplastic anemia
2. Severe combined immunodeficiency disease and Wiskott-Aldrich syndrome
3. Myelodysplastic syndromes pursuant to Coverage with Evidence Development (CED), which requires data collection of a Medicare-approved, prospective clinical study.

In January 2016, CMS agreed to cover transplantation to treat multiple myeloma, myelofibrosis, and sickle cell disease through the CED mechanism.[7] Currently, Medicare determines whether to expand coverage on an indication-specific basis. Lacking a national coverage decsision, coverage may still be possible on a regional basis, but this is seldom the case. If Medicare decides not to cover the cost of the transplant, the patient and his or her provider is required to pay the full cost of transplant. As a result, patients are placed between a rock and a hard place; if they opt for a potentially lifesaving procedure, they put themselves at risk of financial ruin. And many transplant centers are reluctant to consider a transplant if the funding source is uncertain (**TABLE**).

It is important to note that Medicare coverage policy differs greatly from commercial and managed care plans, which cover virtually all indications. The divergence makes little sense, considering:

1. The median age of diagnosis for diseases such as acute myeloid leukemia is 67 years, according to the National Cancer Institute.[8] This means that just as individuals reach the age when they are most likely to need treatment, they are covered by a payer that makes facilitating access very difficult.
2. Medicare beneficiaries already receive nearly 16% of the stem cell transplants facilitated by NMDP/Be The Match, and they are the most rapidly growing age segment for transplant. It is, therefore, quite clear that older Americans are interested in pursuing treatment of these diseases.
3. Reduced-intensity preparative chemotherapy regimens have made it possible for older patients to tolerate a transplant and experience successful outcomes.
4. Federal employees have access to transplantation for a wide range of indications through their health insurance benefits.

As the nation's Medicare population continues to grow and, hence, the number of transplants for the elderly continues to rise, more vulnerable Americans will be put at risk due to limited Medicare coverage.

Payment Gaps

Limited coverage is an undeniable issue, especially for those over the age of 65 years. However, the problem is further accentuated by CMS payment policy, which reimburses significantly below the transplantation's actual cost. The federal reimbursement rate for bone-marrow transplants is currently 47% below the procedure's true cost. As a result, hospitals performing marrow transplants for Medicare patients report average losses of nearly $40,000 per transplant.

This gap is evidenced by an analysis of the 2014 MedPAR database looking at 1 item of cost: the acquisition of cells for an unrelated donor or cord blood transplant. The following Table shows the Medicare Inpatient Prospective Payment System (IPPS) rates for each diagnosis-related group, and the average costs of cell acquisition. Depending on the cell source selected, the Medicare payment leaves little or no funds to cover other costs incurred during the inpatient stay.

State-level data, which can vary considerably, show that in some areas, the current rates often do not even cover the costs of cell acquisition, let alone supplementary costs incurred by the hospital for this procedure. In California, for example, providers are already $5001 over the Medicare rate once they acquire bone marrow (our unpublished data). In Rhode Island, providers are an incredible $21,540 over the current rate if they acquire cord blood as the source of cells for a transplant (our unpublished data). As a result of such financial realities, hospitals across the country are contemplating whether they can continue to offer transplant services to Medicare patients. To put it simply, the existing inadequate reimbursement rates have created yet another barrier limiting access to this life-saving therapy.

Following the Solid Organ Reimbursement Model

The most direct way to eliminate this barrier is to reimburse these cellular transplants in the same manner as solid organs. In particular, the model for reimbursing living kidney donors and other solid organs could be adapted to the cellular transplant model. In both instances, the same set of services are necessary to qualify the donation, such as donor evaluation, cell collection, transportation of the cells to the donor, and medical follow-up of the donor post transplant.

For all types of solid organ acquisitions, Medicare provides a pass-through for acquisition costs outside of the IPPS rate to ensure that hospitals are adequately compensated for acquisition expenses. Adopting the solid organ reimbursement

Just as individuals reach the age when they are most likely to need treatment, they are covered by a payer that makes facilitating access very difficult.

ABOUT THE AUTHOR

JEFFREY W. CHELL, MD

Dr Chell is the chief executive officer of the National Marrow Donor Program and Be The Match.

Address for correspondence
Jeffrey W. Chell, MD
Chief Executive Officer
National Marrow Donor Program
500 N 5th St.
Minneapolis, MN 55401-1206

jchell@nmdp.org

As the nation's Medicare population continues to grow and the number of transplants for the elderly continues to rise, more vulnerable Americans will be put at risk due to limited Medicare coverage.

TABLE. Medicare Inpatient Prospective Payment System Rates for Each Diagnosis-Related Group

Medicare rate	Average cost of bone marrow/ PBSC in United States	Remaining amount of Medicare rate	Average cost of cord blood in United States	Remaining amount of Medicare rate
Inpatient $62,245	$46,653	$15,592	$65,927	($3682)
Outpatient $3045	$46,653	($43,608)	$65,927	($62,882)

PBSC indicates peripheral blood stem cell.

model for bone marrow and cord blood would create parity across Medicare transplant policies and reduce the role of cost in limiting access for beneficiaries.

Eventually, barriers to accessing lifesaving HPC transplants can be overcome. The infrastructure is in place to grow the registry and match donors and cord blood units with patients in need. We now need CMS to update its policies and eliminate reimbursement as a barrier to access for Medicare beneficiaries. This policy change will have an enormous positive impact on patients, with a relatively small impact on Medicare spending. As a physician and an advocate, the evidence is clear: it's time for a change. **EBO**

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ABOUT THE AUTHOR

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Proton Therapy

STEVEN J. FRANK, MD

Dr Frank, is medical director of the MD Anderson Proton Therapy Center, and associate professor, Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center.

Address for correspondence
Steven J. Frank, MD
Medical Director, Proton Therapy Center–Houston
Associate Professor and Director of Advanced Technologies, Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center, Unit 1422, 1400 Pressler St.
Houston, TX 77030-4008

sjfrank@mdanderson.org

PROVIDER PERSPECTIVE

Proton Therapy Eliminates Unnecessary Radiation Exposure and Is Medically Necessary

(CONTINUED FROM COVER)

outcomes is tempered by having an established treatment plan, but suddenly, your insurance company slams on the brakes. With no reasonable explanation, you discover that your health insurance will not cover proton therapy. Or, worse yet, the company says the treatment—despite the guidance of an informed group of the world's leading oncologists—is not "medically necessary" and is deemed experimental." The fear, disappointment, and frustration are indescribable—now, your focus must shift from preparing for a life-changing battle against cancer to fighting your own insurance company.

Now picture the same scenario from the doctor's perspective—something I experience time, and again. As a physician, I am frustrated when insurance companies respond with indifference toward what our oncology team, the experts in state-of-the-art cancer care, have considered, reviewed, and recommended. Not only are my patients denied care that is critical to fighting their cancer, but now I must take time away from other patients to get on the phone and start lobbying with the insurance company on my patients' behalf. For each individual patient denied coverage, I explain our medical team's cancer care management plan to the insurance company and the published data that support our decision. Insurance company representatives usually have little, if any, experience with oncology, let alone highly advanced forms of radiation or proton therapy. Consequently, patients' access to cancer treatment is often limited by insurance panels that do not understand proton therapy or have expertise in the field of radiation oncology. During the so-called "peer-to-peer" review of each patient's case, these panels simply quote their insurance company's medical policy and move the case to another step in the complicated, multilayered, and lengthy appeals process. Most patients do not have the time, knowledge, or inclination to navigate the insurance process on their own, to lobby on their own behalf to prove that the treatment recommended for them is indeed medically necessary.

WHO DEFINES "MEDICAL NECESSITY?"

Each insurance company's medical policy tends to have a unique definition of "medical necessity," and this is the heart of the problem for patients and doctors alike. Patients, physicians, and policy makers seem unaware that the definition of "medical necessity" is not standardized and can be changed at the discretion of each insurance company to suit their own medical policies. This definition is critical; if the cancer treatment recommended by the oncology team does not fit within the policy definition of "medical necessity," then the recommended treatment will be considered "experimental and investigational" and will not be covered by the insurance company. The burden of assuming the financial risk for treatment thus is shifted from the insurance company to the patient during the very moment they are diagnosed with cancer.

So what does "medically necessary" really mean? In real-

ity, it is impossible to tell, because the evidence used by insurance companies not only varies widely, but also changes often. Why should insurance companies—whose financial incentives direct them toward cost savings—be dictating what is medically necessary for cancer treatment?

Physicians have experienced inconsistency in the labeling of "medically necessary" procedures for years. However, our colleagues from The University of Texas MD Anderson Cancer Center and the Boston University School of Medicine have now reinforced anecdotal evidence of the effectiveness of proton therapy with facts. In a study recently published in the *International Journal of Particle Therapy*,[1] we found that insurance coverage of proton beam therapy in the State of Texas varied not only among payers, but also for the type of cancer. Even more concerning, a previous decision to cover proton therapy for prostate cancer was reversed and proton therapy was determined to be "not medically necessary" after the removal of key published references from the payer's updated medical policy.

The solution to this part of the problem is clear: we need a consistent definition of "medical necessity" and uniform coverage that ensures patient access to proton therapy when that therapy is recommended by multidisciplinary medical teams.

Still more frustrating in the ongoing arguments over proton therapy is evidence showing that coverage of proton therapy could actually *reduce* healthcare costs. The episodic cost of care can be reduced when proton therapy decreases the amount of radiation to parts of the body that are not affected by the cancer by eliminating or reducing the severity of treatment-induced acute and long-term side effects and by reducing the risk of secondary cancers. One such study showed that hospital stays were longer for patients with esophageal cancer treated with older techniques (mean length of stay 13.2 days after conventional 3-dimensional radiation therapy, 11.6 days for intensity-modulated radiation therapy, and 9.3 days for proton therapy).[2] Using advanced radiation therapy technologies like proton therapy can reduce postoperative complications and shorten hospital stays, which reduces healthcare costs.

PROVIDER–PAYER COLLABORATION

There are pockets of hope for expanding access to proton therapy for treating cancer. In Texas, a new pilot program between The University of Texas System's employee benefit program, Blue Cross Blue Shield of Texas, and The University of Texas MD Anderson Cancer Center allows proton therapy to be covered for employees of The University of Texas and their families for cancer of the head and neck, esophagus, breast, and lung, as well as for patients participating in clinical trials of proton therapy. This pilot program is an example of how insurers and employers can work together to develop better cancer coverage policies and to demonstrate the value of proton therapy. Over the next year, the program will not only serve patients, but also enable clinicians and researchers to collect and share information about proton therapy and its costs, which will help to make the case that broader coverage should be extended to other states and healthcare systems. By starting small and serving patients in the MD Anderson community in Texas, we can set an example for others across the United States.

Cancer touches thousands of lives each year in a truly indiscriminate way. However, we should not be arbitrary in the way we combat the disease and define medical necessity. If we wish to defeat cancer once and for all, all parties—both doctors and insurers—must finally unite in support of best practices such as proton therapy. Let's start now and be advocates for all patients with cancer. **EBO**

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PATIENT ADVOCACY

Finding Solutions for Cancer Patients: *The American Cancer Society's Health Insurance Assistance Service*

(CONTINUED FROM COVER)

initiated in 2005, was designed to help patients learn more about available health insurance options. HIAS offers cancer patients under age 65 a free resource that connects them with health insurance specialists who work to address their needs. HIAS specialists gather detailed information from the patient such as cancer type, treatment protocol, insurance status, and work to help them navigate through their insurance issues. Currently, HIAS provides health insurance information and resources to more than 3300 patients per year.

Prior to the implementation of the Affordable Care Act, HIAS primarily addressed issues faced by uninsured patients. Today, HIAS is approached by a growing number of individuals who are underinsured. Cost sharing has become a significant issue and cancer patients are often confronted with high deductibles, co-pays, additional costs for out-of-network care, and coinsurance. These are serious financial challenges for a cancer patient, and can place them at significant risk of not being able to afford their much needed healthcare. Many patients are financially vulnerable and their cancer diagnosis and treatment can impede their ability to work, while some cancer patients lose their jobs altogether.[1]

Between 2004 and 2014, OOP costs for covered workers grew 77%.[2] Cancer patients generally have high OOP expenses, and patients may pay $4000 to $5000 out of pocket per year for their cancer care.[3] Of those expenses, typically one-third are attributed to prescription drug costs, one-third for physician fees, outpatient procedures and other ambulatory care costs, and lastly, one-third to inpatient care and related costs.[3] HIAS

ABOUT THE AUTHORS

KATHERINE SHARPE, MTS

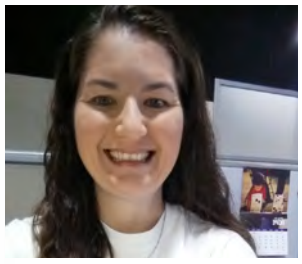
Ms Sharpe is senior vice president, Patient and Caregiver Support, American Cancer Society.

Address for correspondence
Katherine Sharpe
American Cancer Society
250 Williams Street
Atlanta, GA 30303

Katherine.sharpe@cancer.org

MELISSA FELLERS

Ms Fellers is senior consultant, American Cancer Society.



MANDI BATTAGLIA SEILER

Ms Seiler is team supervisor, Health Insurance Assistance Service, American Cancer Society.

TABLE 1. Issues Presented by Cancer Patients and Their Caregivers

ISSUE	AFRICAN AMERICAN (n = 498)	CAUCASIAN (n = 1393)	HISPANIC/LATINO (n = 425)
Cannot access specialized cancer care	45.60%	43.40%	58.8%
Cash up front before treatment begins	2.01%	5.10%	1.88%
Diagnosis delayed because patient was uninsured/underinsured	16.87%	19.81%	20.47%
Health deteriorating because care is inaccessible	6.02%	5.74%	8.00%

TABLE 2. Solutions Identified by HIAS for Cancer Patients and Their Caregivers

SOLUTION	AFRICAN AMERICAN (n = 498)	CAUCASIAN (n = 1393)	HISPANIC/LATINO (n = 425)
Assistance from state/county indigent programs, community health center, or hospital charity care	33.9%	32.1%	34.6%
Drug manufacturer assistance program	7.2%	8.0%	5.6%
Insurance premium assistance programs	4.6%	5.6%	2.8%
Patient Advocate Foundation	39.4%	44.9%	35.8%
Veterans health benefits, including Tricare, VA, TAMP	1.8%	1.4%	1.2%

TAMP indicates Transitional Assistance Management Program; VA, Veterans Affairs.

works to identify programs and services to help patients and their caregivers find resources to help them pay for their care and complete the treatment in a timely fashion. Yet many patients continue to fall through the cracks, as many of the programs and resources are inadequate in addressing the patient's financial needs.

HIAS: PROVIDING OPTIONS

In 2015, 3378 patients benefitted from the services of the staff at HIAS, 2747 of whom had multiple issues that they discussed with HIAS staff. These issues ranged from an inability to access specialized cancer care or being unable to afford coverage. In **TABLE 1**, we illustrate common patient issues and the percentage of patients broken down by race, that illustrates some of the challenges faced by patients in accessing timely cancer care.

The 2 leading issues—the inability to access specialized cancer care, and the inability to pay for coverage—are significant barriers to care for these patients. A patient who cannot access a specific cancer treatment will often apply for charity care from the healthcare system. Often, patients have to forego care if they are uninsured, but if they are underinsured, they normally have to go through an appeals process.

The ability to resolve these issues is somewhat limited by the resources available to cancer patients and their caregivers. HIAS specialists work with the patient and their caregiver to identify resources to help them access the care that they need. Those who contact HIAS are asked a series of questions about their insurance needs, employment status, income level, current/former insurance status, and diagnosis. Subsequently, a health insurance specialist will research and provide information about the insurance options that are most appropriate for the patient.

The health insurance specialists receive state-of-the-art training to enable them to provide guidance for general and state-specific insurance needs. Specialists provide information regarding a variety of health insurance issues, federal laws, and state-specific laws and programs. However, in many cases, although coverage options were identified for the patient, they did not completely address patient needs. For others, no insurance option was available to solve the patients' issue. As a result, HIAS staff work with patients to guide them to noninsurance resources (such as hospital charity care programs) to assist with getting medical care. In **TABLE 2**, we have highlighted some of the noninsurance resources that HIAS utilizes to help patients access the care they need following their cancer diagnosis.

COLLABORATION WITH THE PATIENT ADVOCATE FOUNDATION

Patients often find the insurance system difficult to navigate and a burden they cannot bear, particularly given the impact of cancer on their lives. In addition, many patients face issues with insurance adequacy, availability, and affordability that leave them without appropriate treatment, or burden them with insurmountable healthcare-related debt. Access to information on insurance resources can ensure these patients are exploring all options available to them. Yet for far too many, there are either inadequate or unaffordable insurance resources that present access to care issues.

Data consistently show that cancer patients, around the country, face substantial barriers to care including the major barriers described earlier in this article (IOM, 2008). Even those individuals who can find a way to pay for care often have to choose between financial stability and receiving the entire course of therapy.

As illustrated in **TABLE 2**, a majority of patients that contact HIAS are referred to the Patient Advocate Foundation (PAF) for further assistance with their financial needs. ACS and PAF established a strategic collaboration in 2009, giving millions of patients and their families, quick access to timely cancer information and specialized resources. Furthermore, this collaboration significantly extends our ability to provide case management services to patients and their families experiencing financial or legal issues. This provides desperately needed assistance to cancer patients who are in danger of losing their jobs or their healthcare coverage, or who have other situations that might impact access to care. PAF offers assistance to patients with specific issues that they may encounter with their insurer, employer and/or creditor regarding insurance, job retention, and debt-crisis matters relative to their diagnosis of life-threatening or debilitating diseases. Professional case managers and attorneys, specializing in mediation, negotiation, and education, advocate on behalf of patients experiencing issues with access to care, job retention, and debt crisis.

The collaboration with PAF has resulted in millions of dollars of debt relief for patients and their caregivers through

charitable contributions, write-offs, correcting coding and billing errors, and overturning insurance denials. However, there are opportunities to reduce the number of individuals who have to manage issues with high cost sharing, including information regarding insurance options and coverage, as well as policy efforts that seek ways to control healthcare costs.

PUBLIC POLICY INITIATIVES TO RAISE AWARENESS

As noted in a workshop conducted by the Institute of Medicine (now called the Health and Medicine Division), on the costs of cancer care, many patients enroll in a silver plan, which results in an estimated $10,000 in OOP costs for a family of 4 with an income of $47,000.[1] It is imperative that patients be at the center of decision making about their treatment including the costs of care and the coverage their insurance provides. In order to accomplish this, patients must be equipped with clear, accurate, and up-to-date information about their cancer diagnosis, treatment options, and insurance options and coverage. When faced with making decisions about insurance coverage, individuals often select plans that seem affordable upfront, and this often results in coverage that emerges as being expensive due to high deductibles and other cost-sharing issues. Better education and information regarding insurance coverage is critical to ensure adequate understanding of coverage policies.

Public policy can play a significant role in the fight against cancer. Lawmakers and policy makers, across the country, consider legislative proposals and policies that could help people with cancer. As the Society's nonpartisan advocacy affiliate, the American Cancer Society's Cancer Action Network (ACS CAN) encourages elected officials, candidates, and policy makers to make cancer a top national priority. ACS CAN works to improve access to quality, affordable healthcare so no one is forced to choose between their life and their lifesavings to get the care they need.

As part of those efforts, ACS CAN continues to monitor innovative models of cancer care to better understand their impact on cancer patients and their families. The ACA has supported the development of 3 key payment and delivery reforms that can play an important role in enhancing the quality of care delivered to cancer patients—accountable care organizations, patient-centered medical homes, and bundled payments—that share common elements directed at fostering coordinated, patient-centered care for patients with complex, chronic illnesses such as cancer. For the typical cancer patient who frequently experiences a variety of challenges navigating the US healthcare system, these new delivery models demonstrate the potential to improve the quality of cancer care. Given an aging population and the high proportion of our economic resources already devoted to healthcare,[4] it is critical that we continue efforts to improve cancer care for all. **EBO**

Cost sharing has become a significant issue and cancer patients are often confronted with high deductibles, copays, additional costs for out-of-network care, and coinsurance.

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