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Evidence-Based Oncology™

Research Report

A New Method to Fight Cancer: The Body's Own Immune System

Surabhi Dangi-Garimella, PhD

Michael Kolodziej, MD

In early May, an article reported on an approach undertaken by scientists at the National Cancer Institute (NCI) in which immune cells were isolated from a patient to attack her cancerous cells; the patient was suffering from metastatic cholangiocarcinoma, which had spread from the patient's bile duct to her liver and lungs despite chemotherapy.[1] Following whole-exomic-sequencing, they identified CD4+ T helper cells (T_H1) among the tumor-infiltrating lymphocytes (TILs) of the patient that recognize a mutation in the ERBB2IP protein expressed by the cancerous cells. The patient was initially subjected to an adoptive-cell transfer (ACT) with 25% mutation-specific T_H1 cells, which shrunk the target lesions and stabilized the disease. However, when the disease progressed, the patient was administered >95% mutation-specific T_H1 cells, resulting in tumor regression.[2] Although the patient's tumors have not disappeared, the treatment provides proof of concept that the body's own defense system can be harnessed and reprogrammed to attack a solid tumor.

(continued on page SP339)

Commentary

ASCO's Initiative to Define Value In Cancer Care

Richard L. Schilsky, MD, Chief Medical Officer, ASCO

Richard Schilsky, MD

The American Society of Clinical Oncology (ASCO) is very concerned about the escalating cost of cancer care, and since 2007 has been actively pursuing solutions that address this issue. The unsustainable increase (projected to reach $175 billion per annum by 2020, an increase of 40% from 2010) is the result of:

- an increasing demand for cancer care services (45% new cancer cases estimated by 2030), largely due to aging of the population and due to lifestyle factors
- continued growth of new interventions and treatments without pricing, relative to value.

The overall burden that rising cancer costs place on the national economy translates into enormous strain at the individual level, and may ultimately impede access to lifesaving care. Patients and their families often face crippling expenses during what is already one of the most difficult times in their lives. Furthermore, medical costs are the leading cause of personal bankruptcy, and people with cancer are 3 times more likely to file for bankruptcy than those without cancer.

(continued on page SP341)

Multiple Myeloma

MMRF Efforts Attack the Disease From Every Angle; "Transformation" on the Horizon

Mary K. Caffrey

In 1996, Kathy Giusti was a 37-year-old rising star in the pharmaceutical industry, with a young child. When she learned she had multiple myeloma, the news floored her. Not only did she not resemble the typical profile of someone with this rare blood cancer, but she quickly discovered that treatments for the disease had barely progressed in 40 years.[1]

Neither the projected 3-year life expectancy nor the state of treatment were acceptable to Giusti, and she took action. With her twin sister, Karen, who would become her donor for a life-saving stem-cell transplant, the pair founded the Multiple Myeloma Research Foundation (MMRF).[2] Since 1998 MMRF has raised more than $250 million,[3] and from 2003 to 2007 the foundation helped win FDA approval for 4 drugs that are mainstays of current multiple myeloma therapy: bortezomib, lenalidomide, thalidomide, and doxorubicin.[4] More recently, MMRF offered research support for carfilzomib.[2,4]

By bringing the same principles she learned in her business career to finding treatments for multiple myeloma, Giusti has beaten the odds, in scientific and personal terms. She's lived with the disease for 18 years, and the organization she founded has helped trim approval times for a host of treatments, in turn increasing the average survival from 3 to 8 years.

It's an important time for the foundation and for those who study and treat persons with the disease, said Walter M. Capone, who in December 2013 became MMRF president after several years as chief operating officer. Capone, who came to the organization

(continued on page SP344)

AJMC Panel Asks: Does It Pay to Use Pathways?

WellPoint set off waves with its incentive for oncologists. Our panel discusses what the change could mean (SP347).

Seema Sonnad, PhD, Jennifer Malin, MD, PhD, Peter Paul Yu, MD

Also in this issue...

Adaptive Clinical Trial Design in Oncology

Biomarker-driven adaptive trials personalize treatment and provide improved outcomes (SP320).

James Bolognese, MStat; Jacqueline Hall, PhD

Status in the States: A Look at Cancer Care in New Jersey

In a state where cancer rates are falling but remain relatively high, investments in keeping care closer to home are paying off, with more clinical trials and a new relationship with MD Anderson in South Jersey, shown above (SP332).

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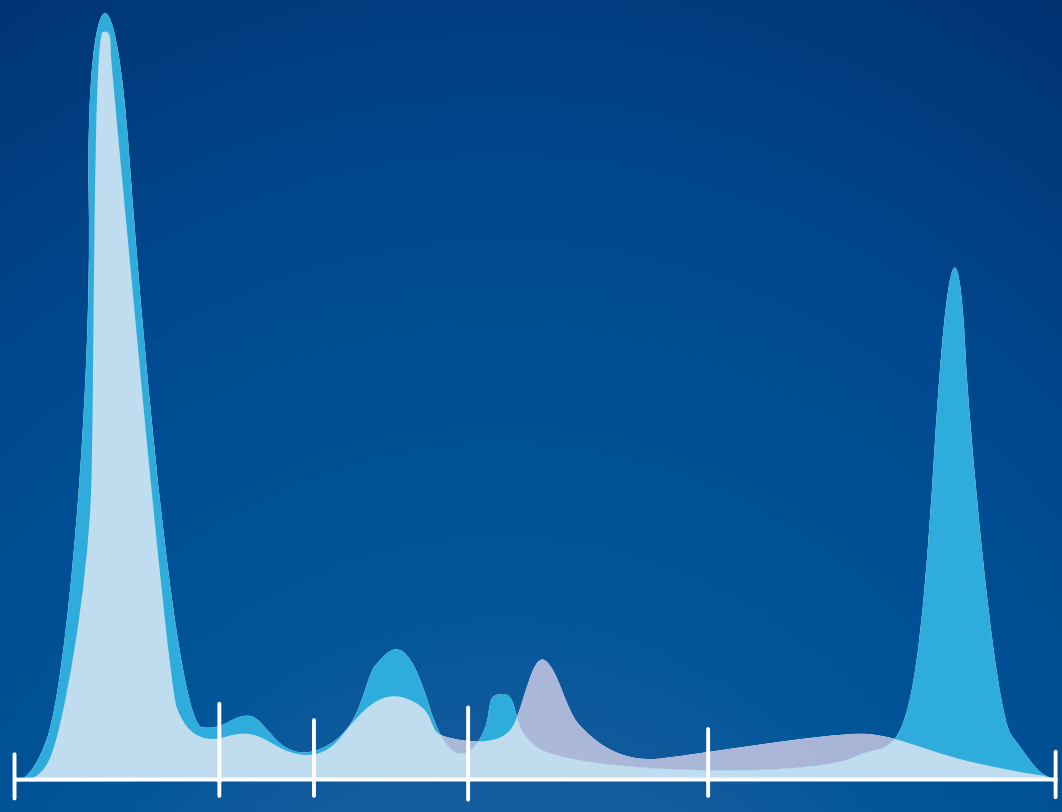

MULTIPLE MYELOMA

NEVER GIVES UP.

BUT NEITHER DO WE.

There is no cure for multiple myeloma. That's why we've dedicated ourselves to three guiding principles: a relentless commitment to scientific advances, a persistent focus on patient needs, and a progressive approach to collaboration.

Celgene has put these beliefs into practice for more than 15 years. And we're not done yet.

Celgene

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IN MBC, ONCOLOGISTS ARE CONSISTENTLY
EXTENDING THE CONTINUUM OF MEANINGFUL CARE[1-3]

With MBC treatment potentially extending to 6 lines and beyond, third-line chemotherapy can still be early in the fight for some patients[2]

MBC=metastatic breast cancer.

Indication

Halaven is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Important Safety Information

Neutropenia

- Monitor complete blood counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days
- Severe neutropenia (ANC <500/mm^3) lasting more than 1 week occurred in 12% (62/503) of patients. Patients with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels
- Grade 3 and Grade 4 neutropenia occurred in 28% and 29%, respectively, of patients who received Halaven. Febrile neutropenia occurred in 5% of patients and two patients (0.4%) died from complications

Peripheral Neuropathy

- Patients should be monitored closely for signs of peripheral motor and sensory neuropathy
- Grade 3 peripheral neuropathy occurred in 8% of patients, and Grade 4 in 0.4% of patients who received Halaven. Delay administration of Halaven until resolution to Grade 2 or less
- Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

Pregnancy Category D

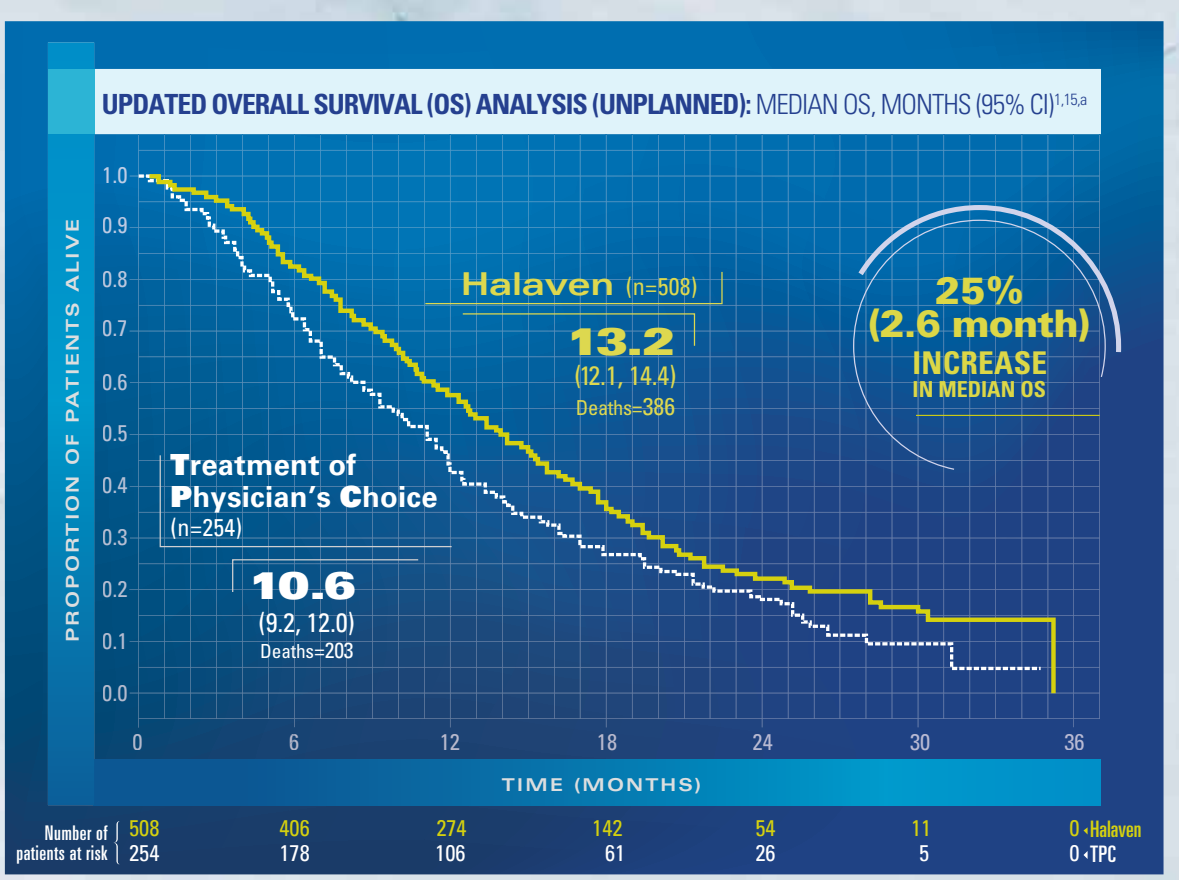
- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias;

GIVE YOUR PATIENTS AN OPPORTUNITY FOR MORE LIFE

The FIRST and ONLY single agent that significantly extended OVERALL SURVIVAL in third-line MBC[7-14]



Results from an updated, unplanned survival analysis of the Phase III, randomized, open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin) (EMBRACE) trial of Halaven versus Treatment of Physician's Choice (TPC) in patients with MBC (N=762), conducted when 77% of events (deaths) had been observed. The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 intravenously for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle, or any single-agent therapy, selected prior to randomization. At baseline, all patients had received ≥2 prior chemotherapeutic regimens for metastatic disease and demonstrated disease progression within 6 months of their last chemotherapeutic regimen. All patients received prior anthracycline- and taxane-based chemotherapy, unless contraindicated. Therapies in the TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [included paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, 10% other chemotherapy), and 3% hormonal therapy.

CI=confidence interval.
[a]Conducted in the intent-to-treat population.

The updated OS analysis was consistent with the primary analysis[7]

- The primary analysis, conducted when ~50% of events (deaths) had been observed, demonstrated a median OS for Halaven vs TPC of 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), hazard ratio=0.81 (95% CI: 0.66, 0.99) (P=0.041)[7,15]

concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities

- Correct hypokalemia or hypomagnesemia prior to initiating Halaven and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome

Hepatic and Renal Impairment

- For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment, a reduction in starting dose is recommended

Most Common Adverse Reactions

- Most common adverse reactions (≥25%) reported in patients receiving Halaven were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%)
- The most common serious adverse reactions reported in patients receiving Halaven were febrile neutropenia (4%) and neutropenia (2%)

References: 1. Dufresne A, et al. *Breast Cancer Res Treat.* 2008;107(2):275-279. **2.** Planchat E, et al. *Breast.* 2011;20(6):574-578. **3.** Ray S, et al. In: *J Clin Oncol.* San Francisco, CA: ASCO Breast Cancer Symposium; 2012. Abstract 116. **4.** Cardoso F, et al. *Ann Oncol.* 2002;13(2):197-207. **5.** Seah DS, et al. Poster presented at: 2012 ASCO Annual Meeting; June 1–5, 2012; Chicago, IL. Abstract 6089. **6.** Lin NU, et al. *Lancet.* 2011;377(9769):878-880. **7.** Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2013. **8.** Saad ED, et al. *J Clin Oncol.* 2010;28(11):1958-1962. **9.** Slamon DJ, et al. *N Engl J Med.* 2001;344(11):783-792. **10.** Geyer CE, et al. *N Engl J Med.* 2006;355(26):2733-2743. **11.** von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006. **12.** Miller K, et al. *N Engl J Med.* 2007;357(26):2666-2676. **13.** Robert NJ, et al. *J Clin Oncol.* 2011;29(10):1252-1260. **14.** Sparano JA, et al. *J Clin Oncol.* 2010;28(20):3256-3263. **15.** Cortes J, et al. *Lancet.* 2011;377(9769):914-923.

Please see accompanying brief summary of Halaven full Prescribing Information.

Visit **www.halaven.com/hcp.aspx**

Halaven®
(eribulin mesylate) Injection
ADVANCING SURVIVAL

HALAVEN® (eribulin mesylate) Injection BRIEF SUMMARY – See package insert for full prescribing information.

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC <1,000/mm^3
  - Platelets <75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1 Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
Platelets <25,000/mm^3	
Platelets <50,000/mm^3 requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC <500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients. Patients with alanine aminotransferase or aspartate aminotransferase >3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin >1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

• Neutropenia • Peripheral neuropathy • QT interval prolongation

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

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

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders[a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]

Table 2 (cont'd)

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a] Based upon laboratory data.

[b] Includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

[c] Not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group: **Eye Disorders:** increased lacrimation; **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth; **General Disorders and Administration Site Conditions:** peripheral edema; **Infections and Infestations:** upper respiratory tract infection; **Metabolism and Nutrition Disorders:** hypokalemia; **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness; **Nervous System Disorders:** dysgeusia, dizziness; **Psychiatric Disorders:** insomnia, depression; **Skin and Subcutaneous Tissue Disorders:** rash.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. 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. **Blood and Lymphatic System Disorders:** lymphopenia; **Gastrointestinal Disorders:** pancreatitis; **Hepatobiliary Disorders:** hepatitis; **Immune System Disorders:** drug hypersensitivity; **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis; **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration; **Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease; **Psychiatric Disorders:** anxiety; **Skin and Subcutaneous Tissue Disorders:** pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

There are no adequate and well-controlled studies with HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. 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 the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area (mg/m^2). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, tongue, stomach and spleen. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.43 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at or above doses of 0.43 times the recommended human dose (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether HALAVEN is excreted into human milk. No studies in humans or animals were conducted to determine if HALAVEN is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk fed infants from HALAVEN, a decision should be made whether to discontinue nursing or to discontinue HALAVEN taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

8.6 Hepatic Impairment

Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

For patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m^2 is recommended for patients with moderate renal impairment. The safety of HALAVEN was not studied in patients with severe renal impairment (CrCl <30 mL/min).

10 OVERDOSAGE

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Hepatic Impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function.

Renal Impairment

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that geometric mean dose-normalized systemic exposure is similar for patients with mild renal impairment (CrCl 50-80 mL/min) relative to patients with normal renal function. However, for patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function.

12.6 Cardiac Electrophysiology

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m^2 of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m^2) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination.
- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN.

Eisai

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.

Patient-Centered Physician Selection: A Necessary First Step for Accountable Care

Brian W. Powers, BA, and Sachin H. Jain, MD, MBA

There is a notable gap in our system-wide efforts to promote accountable, patient-centered care: physician selection. The past decade has borne witness to significant advances in reorienting the processes and experiences of care around patient preferences and values, but the same level of focus has not been directed to helping patients identify the best physician for their needs. Instead, our prevailing approaches to matching patients with physicians remain largely agnostic to variations in patient preferences, tethered to the traditions of peer recommendation and reputation-based referral. Even recent efforts to bring more transparency and consumer choice to healthcare decisions focus primarily on costs and outcomes,[1] and neglect other domains of the patient experience.

This eschews a growing understanding of the divergent priorities many patients have when selecting a physician. Some patients place a premium on clinical reputation and technological advancement, while others are concerned more with measures of quality and value. These preferences are layered on top of additional dimensions as varied as communication style and cultural appropriateness.

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Appreciating and acting on this heterogeneity is essential to improving patient ability to interact with the system and identify clinicians that best fit their needs and preferences. Strengthening the attention to patient preferences in this critical first step of a patient's healthcare experience is critical if patients are going to become engaged partners in their care and form strong therapeutic alliances with their physicians. As accountable care, value-based purchasing, and other new models of care delivery and financing intensify our focus on patient-centered care and longitudinal relationships with physicians, it is necessary to improve the healthcare system's capacity to match patients with physicians who fit their specific needs, preferences, and values.

We draw on the insights from research into patient preferences to propose a framework for understanding and organizing the information necessary to successfully match patients and physicians. Specifically, we outline 5 factors that should be considered when matching patients with physicians.

In this perspective, we draw on the insights from research into patient preferences to propose a framework for understanding and organizing the information necessary to successfully match patients and physicians. Specifically, we outline 5 factors that should be considered when matching patients with physicians, and provide examples of the information and attributes that are important to consider within each factor.

1. Communication and decision making. Communication and decision making anchor the patient-physician relationship, and patient preferences in these areas vary considerably. Physician communication style and the tone of patient interactions, inclusiveness of the patient in decision-making, and attitudes and approaches to uses of clinical evidence are all important variables to consider when selecting a physician. Clinical measures of individual physician performance or survey data from other patients can be important supports to patient choices in this area.

2. Therapeutic approach. For many elective, "preference-sensitive" conditions, the aggressiveness and intensity of treatment vary among physicians.[2] These are precisely the procedures for which patients spend the most time trying to identify the right physician, and it is important that patients understand with clarity the therapeutic options favored by their physician-of-

Table. Five Factors That Mediate the Physician-Patient Relationship: The Preferences of 3 Sample Patients

	Patient A	Patient B	Patient C
Communication and decision making	Defer to physician's best judgment	Shared decision making between physician expertise and patient preferences	Autonomous decision making with limited physician input
Therapeutic approach	Advanced technology and investigational therapies	Complementary and alternative therapies	Less invasive treatment and "watchful waiting"
Social and cultural appropriateness	African American physician	Physician who is fluent in their native language	End-of-life care consistent with their religious beliefs
Cost and value	Minimize total costs (enrolled in an HDHP)	Minimize co-payment	Physician in tier A of their PPO
Practice environment	Integrated primary and specialty care	Patient portal to track conditions and manage appointments	Direct care model with streamlined access

HDHP indicates high-deductible health plan; PPO, preferred provider organization.

"A New And Emerging Concept" in Care

In an interview with *Evidence-Based Oncology*, Sachin H. Jain, MD, MBA, lecturer in healthcare policy at Harvard Medical School, and chief medical information and innovation officer at Merck, said, "Characterizing the physicians and their approaches to practice is quite important." The thought is that the physician and the patient must fit well together, for which efforts must be made in the clinic and by the institution. Citing the example of Memorial Sloan Kettering Cancer Center, Jain said, "The website has information available with regards to an individual physician's practice, the type of patients they see, etc. These are both subjective and objective attributes, but are valuable to patients in physician selection." Jain went on to add that "patient-centered physician selection" is a new and emerging concept that will need a lot more work to be fully implemented.

Although he sees value in using patient liaisons or care navigators in the process, Jain thinks the liaisons are being utilized as "patches between the physician and the patient, since the physicians are always time-crunched. What I'd like to see is a seamless system."

On the role of a patient's family members in the process of physician selection, Jain said that the family "can be very involved in identifying patient preferences." Citing his own family as an example, he noted, "My sense of care is very different from that of my parents. The patient's family, though, can facilitate communication and help the patient's views or goals reach the clinician or the doctor."

The article also alludes to physician awareness of the patient's cultural background. According to Jain, acknowledging that differences exist would be a step in the right direction. "We, as physicians, are not necessarily reflective of everyone, and that needs to be realized. Opportunities exist to enrich our understanding of our patients' individual preferences and needs through conversation. The primary goal, therefore," he concludes, "is communication."

choice. Similarly, a physician's willingness to provide complementary or alternative therapies, along with his or her use of new technologies or investigational drugs and procedures, are important factors of consideration in this area.

3. Social and cultural appropriateness. Patients should be matched with physicians who can deliver care that is consistent with their social, cultural, or religious preferences. For example, patients from historically disadvantaged or marginalized groups are often more comfortable working with physicians with a special aptitude for or interest in working with those groups.[3] Other factors many patients will find important to consider are nationality, ethnicity, or fluency in their preferred language.

4. Cost and value. Economic considerations have a profound effect on healthcare-seeking and -utilization activities.[4] As out-of-pocket deductibles rise and patients increasingly bear the costs of care, appropriate financial data, such as expected or estimated out-of-pocket costs, will be key variables to consider in choosing a physician.

5. Practice environment. The attributes of the system within which a physician practices have a profound impact on a patient's experience with his or her physician. Patients are sensitive to system characteristics such as wait times, the use of patient portals, physician use of electronic health records (EHRs), and the care delivery model in which the physician operates (eg, medical home). Many patients—especially patients with complex illnesses—are especially cognizant of the extent to which clinical interactions across an extended delivery system are coordinated.

This framework is intentionally comprehensive and, in many cases, attributes of clinicians and patients will have relevance across the 5 categories. Patient preference will govern the relative importance of each dimension and its attributes; aligning a patient with the right physician requires information across all of these dimensions. **Table 1** outlines preferences of 3 sample patients to demonstrate the profound heterogeneity that must be considered and managed if patients are to be able to select physicians aligned with their unique needs, preferences, and values. True patient-centeredness will only emerge when we acknowledge this reality and build the tools, systems, and strategies to understand and manage this heterogeneity.

Fortunately, there has been a dramatic influx in the availability of the data needed to populate the various components of this framework. Patient groups and societies sometimes offer direction on choice of provider and therapy. Commercial and government websites such as Physician Compare offer information on patient experience and attributes such as communication style and cultural appropriateness. Commercial insurers are releasing tools that allow patients to receive tailored, real-time estimates of out-of-pocket expenses for different providers. Multi-stakeholder organizations such as the National Committee for Quality Assurance and the Healthcare Information and Management Systems Society have information on system-level factors such as EHR adoption and disease management capabilities. Importantly, certifications from groups like the Joint Commission and data made public by private payers and Medicare can yield information on condition-specific outcomes.

With growing quality, the infrastructure and information exist to move toward a more patient-centered approach to physician selection. But the information is siloed, housed in myriad sources that are hard for patients to navigate and even harder for them to integrate. Helping patients find the right physician requires integrating existing data sources and providing patients with the information they need to select the right physician for their needs. The responsibility for making available these integrated resources will fall on accountable care organizations, physician groups, employers, governments, and patient groups, all of whom share an interest in enabling patients to make sound decisions and begin their healthcare experience by identifying the best physician for their needs. **EBO**

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Reducing Risk and Improving Efficacy of Clinical Trials: the Adaptive Design

Surabhi Dangi-Garimella, PhD

A clinical trial is a massive investment for the drug manufacturer—an investment of time, effort, and funds that are channeled into preclinical research to identify a target and the right molecule for the target. Then, of course, the actual costs of conducting a trial are enormous.

When a molecule fails to achieve the expected end point in phase 3, which according to a recent report happens in 62% of oncology trials,[1] it represents a significant financial and scientific loss, not just for the company but also for the patient who is deprived of a potentially beneficial therapy. Frequently, the trial is successful, but the key to success would be identifying the right patient population or suitable readouts—by using tools such as biomarkers—at predetermined points in a trial. In this scenario, the adaptive clinical trial can prove extremely beneficial.

James Bolognese, MStat

According to an FDA guideline, an adaptive clinical study is one that includes a prospectively planned opportunity to modify one or more specified aspects of the study design and hypothesis based on an analysis of data, usually at the interim period.[2] The traditional fixed trial design—the prevalent and historic design approach—is very restrictive, and can involve a fair bit of guesswork by the trial design team on dose range, patient population, duration and frequency of treatment etc.[3] "In an adaptive trial, instead of driving down a hill with your eyes closed, you open your eyes and adjust the metrics accordingly," said Donald Berry, PhD, professor, Department of Biostatistics at the MD Anderson Cancer Center and owner of Berry Consultants, in an interview with the company Research Insight.[4] Berry has designed more than 500 unique adaptive trials for medical device, biotech, and pharmaceutical companies.[5] The adaptive design allows flexibility—knowledge gained from the accruing data can be analyzed at specific points in a trial, resulting in a smart design, efficient use of resources, and increased precision, although they are a lot more work to create.[4]

What Are the Different Types of Adaptations?

The dynamic adaptations that can be implemented in a trial include modifying/redefining end points, adjusting statistical boundaries, dropping doses and/or drug combinations, adaptive randomization, and identifying patient subpopulations that would benefit from a particular therapy. Data acquired can be immediately analyzed and then used to include or exclude patient subpopulations in a particular trial. Additionally, sample size re-estimation and early termination are other potential advantages of an adaptive design.[5]

James Bolognese, MStat, senior director at Cytel Consulting, said in a telephone interview with *Evidence-Based Oncology*, "Two key criteria that need to be considered when applying an adaptive design are the expected recruitment rate of patients and the time after treatment when a primary end point (like a good biomarker) can be observed. For example, if the end point is mortality at 1 year after treatment, but if recruitment stops at 6 months, then there's a need to identify a biomarker as a surrogate readout at an earlier time point, such as 2 months." However, Bolognese notes that while a large trial without adaptation could be feasible for a big pharmaceutical company seeking to complete a traditional design earlier, a more cost-conscious smaller company might economize by extending the recruitment period to instead run a smaller but longer trial.

Cytel Consulting, a division of Cytel Inc, provides expert advice on innovative clinical program development, with a focus on adaptive trial design, implementation, and regulatory interactions, across a wide range of therapeutic areas. Cytel Inc provides software and clinical research services to improve success rates in the medical drug and device industry.[6]

An instance in which adaptive design helped stop a drug trial early, following observed benefit in phase 3, was the PREVAIL trial for Xtandi (enzalutamide), which is being developed by Medivation/Astellas for metastatic prostate cancer. The premise of the PREVAIL trial was to evaluate the drug as first-line therapy in chemotherapy-naïve men with metastatic prostate cancer who had not responded to androgen-deprivation therapy.[7] Another example is the RESONATE study conducted by Pharmacyclics to compare its drug ibrutinib with the monoclonal antibody ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia. The trial was stopped early in phase 3 after an interim analysis showed improved progression-free survival (PFS) as well as overall survival in patients administered ibrutinib.[8]

Although early trial termination can prove economical, it may not ultimately be in the best interests of patients or even in the best interests of the drug manufacturer, as was observed with the COU-AA-302 study conducted by Johnson & Johnson for Zytiga (abiraterone) in prostate cancer patients.[9] The study was stopped early citing efficiency, but it was not conducted long enough to prove that the drug did indeed provide a survival advantage.

Biomarkers and Personalized Medicine

According to the *Biomarkers Definitions Working Group*, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process, or a pharmacologic response to a therapeutic intervention.[10] A biomarker can be diagnostic, predictive, and potentially usable as a metabolism or outcomes marker.

> *"Including a biomarker can make or break your clinical trial. The value added by including a biomarker in trial design depends on the drug being evaluated and the specific role of the biomarker in the trial, but if done well, can improve the chances of a successful trial."*
>
> —Jacqueline A. Hall, PhD

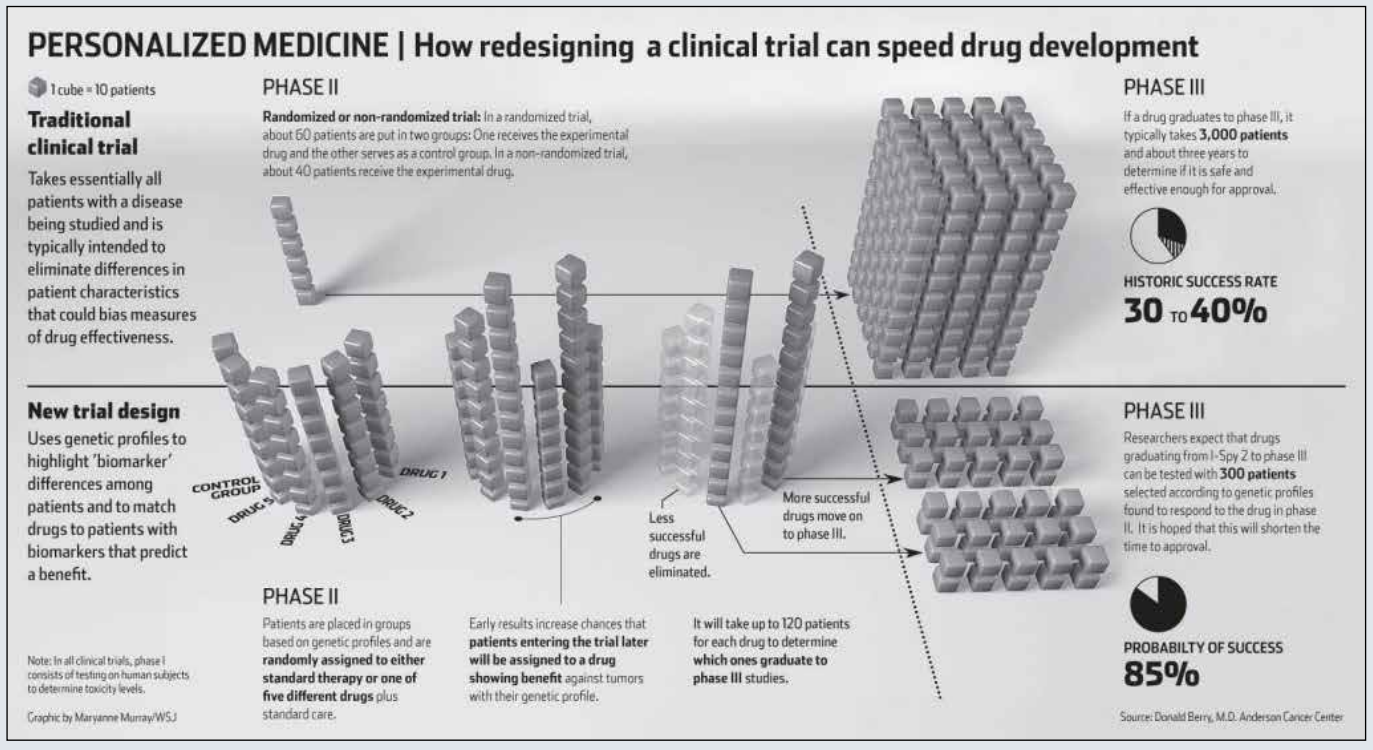
The significance of biomarkers in disease prognosis, treatment, treatment response, and relapse (especially in oncology) is well established. Monitoring a biomarker can validate a particular drug's mechanism of action (MOA) and also identify the patient population most likely to benefit from it.[11] Biomarkers can be significant in establishing a drug's MOA during preclinical development. Subsequently, when the drug is evaluated in clinical trials, the significance of biomarkers in patient selec-

Table. Examples of Adaptive Clinical Trial Designs

Drug	Company	Cancer Type	Biomarker	Target patient population
Veliparib*	AbbVie	Breast cancer	PARP	Triple negative breast cancer
Neratanib*	Puma Biotechnology	Breast cancer	HER2	HER2 negative or amplified or mutated
Nivolumab#	Bristol-Myers Squibb	NSCLC and several other solid and liquid cancers	PD-1	PD-L1 positive

HER2 indicates human epidermal growth factor receptor 2; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.
Sources: *Aptiv Solutions website, http://www.aptivsolutions.com/blog/adaptive-trials/2014/01/i-spy-2-adaptive-trial-returns-promising-results/; #www.clinicaltrials.gov.

Figure. Advantages of an Adaptive Trial Design (case study: I-SPY 2 Trial)



Source: I-SPY 2 innovations: I-SPY 2 Trial. http://www.ispy2trial.org/about/i-spy-2-trial. Accessed May 19, 2014.

tion can grow substantially, especially during phase 2 trials.

Between-patient tumor heterogeneity—mutations in different genes (eg, ER-positive or HER2-positive breast cancer), or different sites of mutations in the same gene (eg, codon 12 vs codon 13 mutations in *KRas* in non-small cell lung cancer)—has long been appreciated, and is primarily responsible for patient selection in clinical trials. Current efforts, though, are aimed at developing methods for accurately identifying patients most likely to respond to treatment and targeting the treatment accordingly.[12]

The *biomarker-strategy design*, a fairly popular trial design among clinicians, is conducted by randomizing patients to a control arm (standard treatment independent of biomarker status) or a biomarker-directed treatment arm. However, if there are data of sufficient quality emphasizing the importance of a particular biomarker, an *enriched trial*, which only recruits patients with the biomarker status, would prove more efficient.[12] The outcome of such a trial would definitely be beneficial to the patient and also to the company sponsoring the trial.

A biomarker can add greatly to the value of a trial, noted Jacqueline A. Hall, PhD, a member of the PathoBiology group at the European Organisation for Research and Treatment of Cancer (EORTC) and author of a recent paper in *Lancet Oncology* on a risk assessment approach to integrating biomarkers in clinical trials, in an e-mail response. "Including a biomarker can make or break your clinical trial. The value added by including a biomarker in trial design depends on the drug being evaluated and the specific role of the biomarker in the trial, but if done well, can improve the chances of a successful trial." She continued, "Adding biomarkers into trials is not always straightforward, and needs to be well managed or it could lead to problems in the conduct of the trial later on." Hall went on to explain that a biomarker could either be an integral part of the trial design—eg, for deciding in which arm of the trial the patient participates—or it could be an "add-on," to be analyzed later in samples collected during the trial. The multiple approaches are associated with different challenges, and thus differently impact trial operations and the patients enrolled. For example, if an experimental biomarker (with limited associated evidence for use) is to be included in a trial, there would be an increased risk of using such a biomarker for patient selection, creating an added complication in trial design.

An overview of the influence of biomarkers in the treatment strategy for lung cancer was recently highlighted in a presentation at the 19th Annual Conference of the National Comprehensive Cancer Network, held March 2014 in Hollywood, Florida.[13] Leora Horn, MD, MSc, assistant professor of medicine at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, presented statistics showing the improved response obtained with the use of targeted therapy, including data that showed an improvement in PFS from 5 months to 8.5 months in EGFR-mutation–positive patients administered EGFR-directed therapy. Additionally, encouraging results were obtained with the PD-1 inhibitor nivolumab in PD-L1–expressing non-small cell lung cancer patients. Survival rates with nivolumab were 42% at 1 year and 24% at 2 years, with limited side effects.[13]

Successful Implementation of Biomarkers in Trials

Incorporating biomarkers into clinical trials is complicated by numerous factors: tumor heterogeneity, subclonal variation, sample handling and processing, assay validity, biomarker validation, bioinformatics, and appropriate trial design. Consequently, the quality of study designs that integrate biomarkers is variable or there may be other logistical challenges that may result in delays or study closures. Relatively few biomarkers, then, stand a chance of clinical application.[14]


Jacqueline A. Hall, PhD

According to Hall, advance planning and a risk mitigation strategy would help safeguard against failures. However, she also recommends regular monitoring of the results "to spot data that may be off." "Including more mature or gold standard biomarkers to fall back on, in parallel with highly exploratory markers, would be one solution. Another option is to choose another design so that the biomarker is used to stratify the statistical analysis rather than for patient recruitment."

How Do You Design an Adaptive Trial?

The *adaptive* design has proved to be a significant cost saving for companies, and one that does not compromise on quality or patient health. The key is to include data analysis while the trial is ongoing, in order to make changes based on patient response to the therapy or therapies. The trial design incorporates flexibility that can fine-tune drug dosage early on, promoting an effective and economical trial. Additionally, since each patient is a resource for making modifications, the adaptive trial could essentially use a much smaller patient population that could still generate suitable data, for additional savings of time and costs.[15]

According to Bolognese, "Specific adaptive designs are utilized for each phase of a clinical development. Dose-escalation studies are used in phase 1, especially in oncology trials, essentially due to drug toxicity issues. Dose-finding design is employed during phase 2 studies, while group sequential and/or sample size re-estimation designs, which allow for patient recruitment increase or interim analysis to stop a trial early, are used in phase 3."

However, adaptive designs present an upfront cost. Says Bolognese, "To evaluate the use or material advantage of an adaptive design over traditional design creates upfront work—more time in advance planning, increased use of resources (including recruiting statisticians and clinicians to help with the design), and increased expenditure. All potential adaptations need to be predefined and the statistical performance characteristics of the adaptive design, if chosen, need to be documented. The goal is to more than offset this increased upfront cost with greater later cost savings."

Aptiv Solutions, a part of the ICON group that provides development solutions to the pharmaceutical and biopharmaceutical industry, recently announced a collaboration with Novartis, Janssen Pharmaceuticals, and Eli Lilly called the ADDPLAN DF Consortium.

Considering the potential risks and benefits associated with integrating biomarkers into phase 2 and 3 clinical onocology trials, experts from 3 global clinical organizations assembled a working committe to provide a new approach for achieving seamless integration of biomarkers into trials.

The goals are to develop statistical methods to design innovative dose-finding clinical trials with an emphasis on adaptive designs, and to develop software based on the data that emerge for the design, planning, and analysis of dose- finding trials.[16]

Drawbacks of the Adaptive Design

Although the adaptive trial design could bring about a substantive change in trial performance, there are some associated negatives. One is that the trial design cannot be easily adapted to a small scale, to evaluate less prevalent cancers, for instance. Additionally, conducting these trials is logistically difficult, especially in a scenario where multiple drugs are to be administered.[17]

In its industry guide for adaptive clinical trial design, the FDA introduced several concerns about the adaptive design, the most important being:

- design, analysis, or conduct flaws that can introduce bias and a Type I error (the false conclusion that the treatment is effective)
- despite control of Type I error, the adaptation process may provide positive study results that are difficult to interpret.[18]

The Regulatory Aspect

According to the guidelines suggested by the FDA and the European Monitoring Agency, trial sponsors that use adaptive designs in late-phase clinical trials should employ external, independent Data Monitoring Committees (DMCs).[19] Says Bolognese, "There could always be a perception of a potential for bias without a DMC external to the study sponsor. So regulatory agencies want that the sponsors be blinded to the results of interim analysis. Unblinded information is made available to the DMCs, who then make their recommendations."

A DMCs typical function is conducting periodic review of interim study results to ensure patient safety, applying decision rules for adaptation, including early stoppage for futility or success, making recommendations for dose-regimen change, and/or sample size adjustment.[19]

Bolognese believes the regulatory agencies are very receptive to adaptive designs for early-phase trials, and are more cautious about late-stage adaptations, since phase 3 trials need a well-understood design and they need to be well controlled with defined statistical properties.

Collaborations to Promote Biomarker Implementation and the Adaptive Design

Several collaborative efforts have been initiated, within the Unites States as well as globally, to promote the integration of biomarkers into clinical trials.

The Cancer Biomarkers Collaborative (CBC) is a product of a partnership between the FDA, the National Cancer Institute, and the American Association for Cancer Research. More than 120 experts from various areas of cancer biomarker research constitute several different CBC committees.[20] The Consortium draws input from national and international experts in academia, diagnostic and pharmaceutical industries, government agencies, regulatory bodies, and patient advocates, with the overall goal of improving cancer treatment.

The Foundation for the National Institutes of Health (NIH) launched the Biomarker Consortium in 2006; it is a public-private biomedical research partnership that includes the NIH, the FDA, CMS, and the Pharmaceutical Research and Manufacturers of America, to name a few members. The objective of this group is to identify, develop, and qualify potential high-impact biomarkers for diagnosis, predicting response, or improving clinical practice. The Consortium also aims to generate information that can aid with regulatory decision making and help the broad scientific community in general.[21]

Considering the potential risks and benefits associated with integrating biomarkers into phase 2 and 3 clinical oncology trials, experts from 3 global clinical trial organizations assembled a working committee to provide a new approach for achieving seamless integration of biomarkers into trials. The working group, which included members from the EORTC PathoBiology group, NCI, and the National Cancer Research Institute, also aimed at providing investigators with useful resources to assist in protocol development of biomarker-driven trials.[14] Together, the panel identified the various challenges associated with biomarker integration into trial design (such as risks to patient safety, operational risks, and risks to biomarker development), and provided recommendations that could help surmount the challenges.[14]

The effort is under way: industry and the FDA are working together to economize the drug development process and to reduce the time-to-approval for new drug entities. The successful incorporation of biomarkers into mainstream trial design, by using means such as companion diagnostic tests, could go a long way toward identifying the right population of patients for a particular drug candidate and also in evaluating patient response to a drug. This could help decide the fate of a drug early on in a trial, instead of waiting to analyze outcomes at the end of phase 3, as is most commonly observed with the traditional study design. **EBO**

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Studies See Value of Prostate Cancer Diagnostic Test, but Will CMS Pay for It?

Mary K. Caffrey

While Myriad Genetics, Inc, touts recent studies on the predictive value of its Prolaris test for prostate cancer, the biggest news may be yet to come: as *Evidence-Based Oncology* went to press, CMS was weighing whether the test merits reimbursement.[1]

Prolaris, which came on the market in 2010,[2] is a 46-gene test designed to gauge the aggressiveness of prostate cancer in individual patients, based on the expression of cell cycle regulator genes. Unlike the prostate-specific antigen (PSA), which offers a snapshot of the cancer on a given day, Prolaris promises a window into the future, assigning a score that increases along with the risk of progression.

Myriad's CMS filing is "the most comprehensive dossier for a molecular diagnostic test ever," said Ronald Rogers, a spokesman for the company. However, as *Evidence-Based Oncology* reported in May, standards of reimbursement for diagnostic tests are still in flux, especially when CMS must pay.[3] Thus, CMS' decision on Prolaris will be watched closely across the diagnostic testing industry.

Evidence-Based Oncology made multiple attempts to seek comment from CMS, but the agency did not respond.

Myriad Presents Results

On May 20, 2014, Myriad presented a new round of results at the annual meeting of the American Urological Association (AUA) in Orlando, Florida. The most important data came from a study of 761 men in the United Kingdom whose cancer was conservatively managed after they were diagnosed by needle biopsy. Patients were followed for an average of 9.5 years, with prostate cancer death as the primary end point. Tumor samples from these patients were later evaluated with the Prolaris test. Results showed that for each 1-unit increase in the Prolaris score, patients' risk of dying from prostate cancer doubled.[4]

"This is the largest study of its kind," said Michael Brawer, MD, vice president of medical affairs for Myriad. Before these results, he said, "There have never been any publications involving patients who were managed conservatively, with death as the end point."

The prospect of better information on how an individual's prostate cancer will act is compelling in light of the controversy in the United States over who should get PSA tests and how often. The AUA was among the groups that pushed back in May 2012, when the US Preventive Services Task Force (USPSTF) issued a recommendation of "D" for PSA tests. USPSTF had responded to concerns about overtesting and high downstream costs from treatment of cancers that posed little risk. However, many were incredulous at the USPSTF rating and said the problem was overtreatment, not screening. As reported in *Evidence-Based Oncology* in February, the journal *Cancer* published results in January that found 72% of the "cost" associated with the PSA test came in the aftermath, not from the test itself.[5]

The AUA responded with its own guidelines to target PSA screening in men aged 55 to 69 years. In March, the National Comprehensive Cancer Network (NCCN) updated its screening criteria, with testing to start as early as age 45 years and repeated at intervals, depending on results and a patient's risk factors.[6] But so far, while some physicians strongly support biomarker use, both AUA and NCCN guidelines are more cautious, with a focus on PSA screening.

Recent updates of AUA guidelines speak to biomarkers generally but not to a Prolaris-type test specifically. The 2013 update on detection of prostate cancer states, "Future studies of the genetic and epigenetic basis of disease development and progression may provide biomarkers and/or panels of biomarkers with improved specificity when compared to PSA. When available, risk assessment tools combining multiple predictors will need to be evaluated in carefully designed trials to be generalizable to the population in which they would be used."[7]

The recently updated guideline on treatment of castration-resistant prostate cancer states, "One of the glaring deficiencies in prostate cancer drug development, by comparison to several other solid tumors, has been the lack of predictive biomarkers to help better personalize therapy. This is especially important if we are to optimize risk/benefit, particularly given that a significant percentage of patients do not benefit or have small benefits from current FDA approved agents."[8]

The NCCN's 2011 task force report on biomarkers offered little enthusiasm for prostate cancer tests.[9] Multiple studies have appeared since then, including reports on Prolaris and ConfirmMDx, a test by MDxHealth designed to avoid repeat biopsies. But payers offer reimbursement based on "clinical utility,"[5] and when prognostic tests are described as an "adjunct" to decision making, coverage may be denied. This happened recently with Blue Cross and Blue Shield of Alabama, which described testing for the *PCA3* biomarker as "investigational."[10]

Comparison to Gleason Score

The 2011 NCCN report said, "In prostate cancer, Gleason score remains the single most prognostic feature of localized cancer. Although many molecular assays have also been found to be associated with prognosis in prostate cancer, none are in broad use, because most offer little to no independent prognostic information over Gleason sum, and thus lack clinical utility."[9]

Myriad's AUA presentations addressed this directly. The company reported results that compare the results of Prolaris with the Gleason score in a study of 230 men who had scores of either 4+3 or 3+4.[4] Gleason scores, which are determined by a pathologist, range from 2 to 10 and represent the sum of 2 evaluations of cancer cells on a scale of 1 to 5. The first number characterizes the appearance of cells in the primary tumor, while the other score describes the secondary pattern in other cancer cells. Sometimes, Gleason scores are "upgraded" based on what pathologists find in a cancerous tissue after a radical prostatectomy.

This study asked how well Prolaris predicted biochemical recurrence (BCR) compared with the Gleason score. There was no difference in BCR based strictly on Gleason score; however, Prolaris more accurately predicted BCR *prior* to upgrading. According to Myriad, this means if the Prolaris test is performed right after a biopsy, the true risk of progression can be known earlier, leading to better initial decisions about treatment.[4]

The Clinical Utility Question

The AUA presentations followed the March publication of the PROCEDE 500 study,[11] which found that 65% of physicians changed their initial treatment plans for prostate cancer patients based on Prolaris results. Of the 305 patients in the study, 122 saw their treatment plans scaled back, while 76 experienced a more aggressive treatment plan after their doctors viewed the results. These findings address "clinical utility," or whether a test makes the difference in guiding treatment decisions. Clinical utility, not validity, is now the benchmark insurers use to decide whether to pay for molecular tests.[5]

Overall, the study reported a 50% reduction in surgical interventions and a 30% reduction in radiation treatment.[10] Myriad's case for CMS reimbursement, which was updated in March, is based largely on these results, which the company says show that the test more than pays for itself by preventing unnecessary care. A press release anticipates a ruling from CMS "by the end of June 2014," but Rogers said the agency is not required to respond to Myriad's filing at that time.[1]

Among clinicians, Prolaris has received high-profile praise from some of the most prolific researchers in prostate cancer, as well as skepticism from others about its value. E. David Crawford, MD, was the lead author on the clinical utility results reported in March,[10] and is head of the Section on Urologic Oncology at the University of Colorado. Crawford called the test "a game changer for urologists, because it adds meaningful new prognostic information in terms of risk assessment."[1]

In the April issue of *Current Medical Research Opinion,* Neal D. Shore, MD, FACS, and director of the Carolina Urologic Research Center, was lead author on an article reporting a survey of urologists who have used the test. Results found that the Prolaris scores differed with expectations 55% of the time.[12] "The data suggest that the test would have the net effect of shifting patients from more aggressive treatment to more conservative treatment," the study said.

But during the AUA meeting in May, leading clinicians not connected with these studies had questions about their significance. Stephen Jones, MD, from the Department of Urology at the Cleveland Clinic, told *Medscape Medical News,* "What is the impact on actual outcomes? We don't know," he said. "The impact on the outcomes is the part that is *not* validated." Jones was among pros-

The median age of patients in the VISTA† trial was 71 years (range: 48-91).

Indication and Important Safety Information for VELCADE® (bortezomib)

INDICATION

VELCADE (bortezomib) is indicated for the treatment of patients with multiple myeloma.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

- **Peripheral neuropathy:** Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- **Hypotension:** Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration.
- **Cardiac toxicity:** Worsening of and development of cardiac failure have occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- **Pulmonary toxicity:** Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.
- **Posterior reversible encephalopathy syndrome:** Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- **Gastrointestinal toxicity:** Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.
- **Thrombocytopenia or Neutropenia:** Monitor complete blood counts regularly throughout treatment.
- **Tumor lysis syndrome:** Closely monitor patients with high tumor burden.
- **Hepatic toxicity:** Monitor hepatic enzymes during treatment.

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

- **Overall survival advantage**
- **Defined length of therapy**
- **Medication cost**

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

VELCADE (bortezomib) combination delivered a >13-month overall survival advantage

- At 5-year median follow-up, VELCADE+MP* provided a median overall survival of 56.4 months vs 43.1 months with MP alone (HR=0.695 [95% CI, 0.57-0.85]; $p<0.05$)†
- At 3-year median follow-up, VELCADE+MP provided an overall survival advantage over MP that was not regained with subsequent therapies

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

- Results achieved using VELCADE twice-weekly followed by weekly dosing for a median of 50 weeks (54 planned)[1]

IF YOU DEFINE VALUE AS MEDICATION COST:

- Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is $1585 per 3.5-mg vial as of July 2014
- When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

- **Embryo-fetal risk:** Women should avoid becoming pregnant while being treated with VELCADE. Advise pregnant women of potential embryo-fetal harm.
- Closely monitor patients receiving VELCADE in combination with strong **CYP3A4 inhibitors**. Avoid concomitant use of strong **CYP3A4 inducers**.

ADVERSE REACTIONS

Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

Please see Brief Summary for VELCADE on the next page of this advertisement.

For Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com.

Reference: 1. Mateos M-V, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol.* 2010;28(13):2259-2266.

*Melphalan+prednisone.

† **VISTA TRIAL:** a randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE administered intravenously in combination with MP vs MP in previously untreated multiple myeloma. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and overall survival. At a prespecified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median 20.7 months with VELCADE+MP vs 15.0 months with MP [$p=0.000002$]), PFS, overall survival, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition. Updated analysis was performed.

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

Brief Summary

INDICATIONS:

VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma. VELCADE for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

CONTRAINDICATIONS:

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS AND PRECAUTIONS:

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain, or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy events was 24% for subcutaneous and 39% for intravenous. Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule. In the VELCADE vs dexamethasone phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension: The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

Cardiac Toxicity: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing, heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the VELCADE group. In the dexamethasone group, the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal. In a clinical trial, the first two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt, comprehensive, diagnostic evaluation is conducted.

Posterior Reversible Encephalopathy Syndrome (PRES): Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, reversible, neurological disorder, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

Gastrointestinal Toxicity: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting, sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

Thrombocytopenia/Neutropenia: VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern, with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice-weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia was related to pretreatment platelet count. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of bleeding (≥Grade 3) was 2% on the VELCADE arm and <1% on the dexamethasone arm. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE. Platelet counts should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE. Gastrointestinal and intracerebral hemorrhage has been reported in association with VELCADE. Transfusions may be considered.

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Hepatic Toxicity: Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited re-challenge information in these patients.

Embryo-fetal: Pregnancy Category D. Women of reproductive potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses.

ADVERSE EVENT DATA:

Safety data from phase 2 and 3 studies of single-agent VELCADE 1.3 mg/m^2/dose administered intravenously twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

In the integrated analysis, the most commonly reported (≥10%) adverse reactions were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathies NEC (38%), thrombocytopenia (32%), vomiting NOS (28%), constipation (25%), pyrexia (21%), anorexia (20%), anemia NOS (18%), headache NOS (15%), neutropenia (15%), rash NOS (13%), paresthesia (13%), dizziness (excl vertigo 11%), and weakness (11%). Eleven percent (11%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%). A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting, and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each), and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (1% each).

In the phase 3 VELCADE+melphalan and prednisone study in previously untreated multiple myeloma, the safety profile of VELCADE administered intravenously in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone. The most commonly reported adverse reactions in this study (VELCADE+melphalan/prednisone vs melphalan/prednisone) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), leukopenia (32% vs 28%), vomiting (26% vs 12%), fatigue (25% vs 14%), lymphopenia (23% vs 15%), constipation (23% vs 4%), anorexia (19% vs 6%), asthenia (16% vs 7%), pyrexia (16% vs 6%), paresthesia (12% vs 1%), herpes zoster (11% vs 3%), rash (11% vs 2%), abdominal pain upper (10% vs 6%), and insomnia (10% vs 6%).

In the phase 3 VELCADE subcutaneous vs intravenous study in relapsed multiple myeloma, safety data were similar between the two treatment groups. The most commonly reported adverse reactions in this study were peripheral neuropathy NEC (37% vs 50%), thrombocytopenia (30% vs 34%), neutropenia (23% vs 27%), neuralgia (23% vs 23%), anemia (19% vs 23%), diarrhea (19% vs 28%), leukopenia (18% vs 20%), nausea (16% vs 14%), pyrexia (12% vs 8%), vomiting (9% vs 11%), asthenia (7% vs 16%), and fatigue (7% vs 15%). The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported SARs were pneumonia and pyrexia (2% each) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (3% each) in the intravenous treatment group.

DRUG INTERACTIONS:

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir). Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients. Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE. St. John's wort *(Hypericum perforatum)* may decrease bortezomib exposure unpredictably and should be avoided. Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients. Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

USE IN SPECIFIC POPULATIONS:

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

Pediatric Use: The safety and effectiveness of VELCADE in children has not been established.

Geriatric Use: No overall differences in safety or effectiveness were observed between patients ≥age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment: The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after the dialysis procedure. For information concerning dosing of melphalan in patients with renal impairment, see manufacturer's prescribing information.

Patients with Hepatic Impairment: The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients.

Patients with Diabetes: During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

Please see full Prescribing Information for VELCADE at VELCADEHCP.com.

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

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Prolaris
(continued from SP247)

tate cancer clinicians who told *Medscape* that the jury is still out on such tests.[13]

Lack of Consensus About Payment

Disagreement among scientists is cited by payers in decision making. The Blue Cross decision in Alabama, for example, cited NCCN's language that biomarkers should not be used as first-line therapy to "increase the specificity" of decisions.[10]

Prolaris costs $3400[2]; a competing test, Oncotype DX, reportedly costs $4000.[11] While some payers have raised alarms about cost, molecular testing companies have told *Evidence-Based Oncology* that without reimbursement, it's difficult to gather the clinical utility data that so many seek.[4] A review article on diagnostic tests by David A. Santori and Daniel W. Chain, which appeared around the time of the AUA meeting, did not mention cost per se, but advised clinicians to evaluate clinical utility and said tests should be "used with caution."[14]

The authors noted that unlike the PSA, which is designed primarily to detect cancer, "The current focus of (prostate cancer) biomarker research is to find markers for aggressive disease. However, there is no consensus on the definition of aggressiveness." The only standard is the NCCN guideline of a Gleason score of 8, although they note that most doctors will view a score of 7 as aggressive.[12] Testing companies, frustrated by inconsistency in reimbursement decisions nationwide, are fighting back. This spring, the California Clinical Laboratory Association sued over Medicare's denial of coverage for several tests.[3]

In an e-mail, Myriad's Rogers said the company believes CMS categories for reimbursement are clear: analytical validity, clinical validity, and clinical utility. However, he said, "The levels of evidence needed to support each of these categories is subjective and open to interpretation, making the process somewhat unpredictable." Myriad believes that well-designed retrospective studies are "appropriate" for demonstrating clinical validity and utility. Others want to see prospective studies, but the company said this is not always practical.

Clinicians may disagree on whether the evidence is in, but even the skeptics say a test such as Prolaris would help doctors and patients. Said Michael Blute, MD, chief of urology at Massachusetts General Hospital, "A test like this is sorely needed."[13] **EBO**

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Technology

Digital Technologies Gain Popularity for Smoking Cessation: Evidence Strongly Supports Some

Milly Dawson, MS, MPH

Interest in digital technologies for smoking cessation is high, among consumers, health plans, employer groups, and public health advocates. Such technologies include text messaging programs, Smartphone apps, social networking platforms, e-mail outreach, and offerings that combine several digital modalities.

If a smoker planning to quit joined a text messaging program, for example, she might receive encouragement and tips in words like these: "Over half the smokers in the United States have quit; if they did, you can too!" At any time, that smoker could text back 1- word alerts, such as "moods" or "cravings," and instantly receive suggestions for coping.[1]

The smoking cessation market is massive. Although US smoking rates have been declining for decades, 18% of Americans still smoked in 2012, according to the Centers for Disease Control and Prevention (CDC). If no Americans smoked, states the CDC, 1 in 5 of all deaths in the United States in a given year would not occur.[2] Worldwide, tobacco use causes more than 5 million deaths annually, more than HIV/AIDS, tuberculosis, and malaria combined. Smoking causes lung cancer, emphysema, bronchitis, and chronic airway obstruction. Smoking-related medical bills and lost productivity annually costs the United States more than $193 billion.[3] For these reasons, interest runs high in effective new ways to foster success among smokers hoping to quit.

Help With a Powerful Multifaceted Addiction

Smokers trying to quit often endure cravings, mood issues, and other withdrawal symptoms. They must also redefine themselves as nonsmokers among friends and relatives with whom they once shared comfortable tobacco rituals, according to Richard Brunswick, MD, author of the guideline-inspired book *Can't Quit? Bullsh*t! You Can Stop Smoking.* Aware of the many hurdles to successful cessation efforts, researchers have been trying to figure out how to put new digital technologies to work for smoking cessation. Expert researchers are at work on digital tools for smoking cessation, as are entrepreneurs with no apparent knowledge of clinically proven approaches.

Says Justin Sims, CEO of Voxiva, "New digital technologies offer potentially important advantages: 1) They can reach people without geographical limits. 2) They can promote interactivity, thus forging new connections between smokers and expert advisors. 3) They provide instant access to information and support around the clock. 4) They may offer cost savings."

Some new efforts, especially those relying on text messages, build upon proven clinical guidelines for smoking cessation. Numerous credible studies support these interactive text messaging services.[4] The text services that have held up well in the literature generally do not work, at least, not as standalones; rather, they advise smokers to also use other well-established approaches: tools such as medications and quitlines. However, other new tools, especially among applications, do not generally refer to established guidelines or advise the use of proven tools.[5]

Payers Seem to Be Holding Back From Coverage for Now

Jan Berger, MD, MJ, and editor-in-chief of *The American Journal of Pharmacy Benefits,*

says that payers welcome the new digital tools for their potential to help "get and keep the attention of the consumer in this very noisy world," modeling successful approaches taken by retailers of consumer goods and services. However, at least 2 major payers do not yet cover these approaches.

A Florida Blue spokesman said in an e-mail response that while clinical "treatments and services are expected to be evidence based," the organization views text and mobile app programs as "member engagement and education tools" that don't go through the rigorous studies that medications go through for coverage. Therefore, Florida Blue members cannot currently expect reimbursement for such digital approaches to smoking cessation.

The program manager for Humana's Chronic Care Strategies, Andrew Renda, MD, MPH, wrote that his company does not currently offer standalone text programs or mobile apps for tobacco cessation. He added that Humana will most likely build these kinds of solutions themselves or partner to create a single comprehensive cessation program, rather than deploy multiple text and mobile app interventions. Humana recently formed a Digital Center of Excellence to explore these kinds of technologies for a range of health services, including tobacco cessation. "Humana will continue to evaluate tobacco cessation technology by evaluating its clinical results and cost-effectiveness," he stated.

Research Support for Certain Text Messaging Programs

A November 2012 Cochrane Review about digital smoking cessation tools found that when compared with control programs, some text messaging programs greatly improved long-term quit rates. The review considered 5 randomized or quasi-randomized studies of mobile phone–based interventions, involving more than 9000 people. The studies included data on continued abstinence at 6 months. Some studies incorporated interactive elements, including polls, while others provided specific messages in response to a person saying they were experiencing cravings. People in the control groups received messages less frequently or heard informational, supportive information over the phone.[4]

Among the 5 studies, the larger, more recent ones showed the biggest improvements in quit rates with the use of digital technologies. Overall, the Cochrane investigators estimated that mobile phone programs almost doubled a smoker's chance of quitting. Only 4% to 5% of smokers in the control group successfully quit for at least 6 months, while 6% to 10% of those in the intervention group did so.[4] Berger noted that these higher rates of sustained abstinence engagement reflected great success in quitting across the age spans—with people in their 50s and 60s embracing text messaging as eagerly as younger people.

In contrast, a 2011 study by Lorien Abroms et al found that smoking cessation apps had "low levels of adherence to key guidelines in the US Public Health Service's 2008 Clinical Guidelines" for smoking cessation. The researchers examined the contents of 47 iPhone cessation apps for sale in the iTunes store during June 2009.[5]

They found that "Few, if any, apps recommended or linked the user to proven treatments such as pharmacotherapy, counseling or a quitline." None strongly followed guidelines that advise a smoker be assessed for willingness to quit, have follow-up, and consider the use of medications and/or counseling.

The apps studied acted primarily as "calculators" (32%), tracking benefits like money saved since quitting. Second-most frequent were "calendars" (28%) that tracked days until and after the quit date. Third came "rationing apps" (11%) that limited the number of cigarettes, and fourth came hypnosis apps (6%). "Other" apps (24%) included some that provided virtual cigarettes to replace actual ones. Five popular apps accounted for 68% of downloads in the study sample. The investigators noted that the most popular apps were the least likely to hold with the guidelines.[5]

Nonetheless, the authors stated that smartphone apps have promise to enhance straight text message offerings. They cited the apps' potential to supplement text messages with games, multimedia such as music videos, e-mail, and social networking sites, and called for future apps to be built around established cessation guidelines.[5]

Evidence-Based Apps, Though Few, Are Emerging

Recognizing the problems with most of the available smoking cessation apps, researchers at the National Cancer Institute (NCI) set out to develop an app that will reflect the latest smoking cessation evidence and will also be rigorously evaluated. This effort yielded QuitPal, an evidence-based app that includes 10 functional areas such as setting a quit date and financial goals and reminders. QuitPal users can track their own daily smoking habits with a calendar. They receive motivational reminders and reports when they reach health milestones. QuitPal also lets users connect with social networks and see personal video messages sent by relatives and friends. On October 12, 2013, QuitPal launched for free in the App Store.[6]

Disparities in smartphone adoption may affect the reach of apps. Smoking is increasingly a class-based issue with lower income people, predominating among smokers.

Encouraged by the evidence supporting the use of text messaging programs, Spanish researchers have also set out to develop an app to help young adults quit, following established guidelines. They published their study protocol in 2013. Plans include recruitment of smokers from 22 primary care centers who will undergo a 6-month guideline-based program that includes the new app. This app will feature a private network for participants and staff as well as entertaining and educational "minigames." The control group will receive "usual care." The outcome of interest will be abstinence at 12 months.[7]

Disparities in smartphone adoption may affect the reach of apps, says Brunswick. He explains, "Smoking is increasingly a class-based issue," with lower-income people predominating among smokers. The book, endorsed by *New York Times* personal health columnist Jane Brody, grew out of his work helping hundreds of patients stop smoking. Meanwhile, according to Pew researchers, smartphone ownership is highest among prosperous, highly educated people, those under the age of 45 years, and non-whites. The Pew survey found that by 2013, a majority of American adults (56%) owned a smartphone.

Companies Offer Varied Digital Tools; Human Coaches Still Have a Role

Agile Health, led by CEO Gary Slagle, offers a text messaging program called Kick Buts. Grounded in current smoking cessation guidelines, Kick Buts was created by University of Auckland researchers who worked with consumer marketers. *The Lancet* published a study strongly supporting the program in 2011.[8]

"We chose text because it lets us offer a simple, understandable, highly interactive dialogue with our users, so we get into the users' heads," says Slagle. Text messaging, he stated, offers a highly standardized, efficient, and low-cost method to reach every mobile phone. However, Slagle cited problems with apps. Among them: apps are not accessible by all mobile phones, and each app must be engineered to work with multiple operating systems on diverse handsets through multiple carriers.

Users of Kick Buts can send back either keywords or spontaneous text messages which prompt targeted replies depending on the need described by the user. Agile's program is not available directly to consumers, but rather to clients such as health plans, employer groups, managed care organizations, hospital systems, and provider groups.

Voxiva, Inc, offers a smoking cessation program called Text2Quit, which the firm developed in partnership with Lorien Abroms of George Washington University. It's a 4-month program planned around a person's quit date, with tracking for a total of 9 months. "It's a multimedia program that combines text, Web, e-mail and mobile webs, with text playing a key role," says CEO Justin Sims. Users find mobile web pages in the texts for more information on specific topics.

Alere Inc has licensed Voxiva's Text2Quit program and integrated it into their telephone- and Web-based smoking cessation services. Alere handles the quitlines for 32 states. "When individuals dial a quitline in many states, they are offered Text2Quit there and then," says Sims. When a person uses Text2Quit, information they text back enters a file, and is also seen by human coaches. People needing human interaction receive it.

With regard to all the new digital approaches, Berger sounds 1 cautionary note, warning that privacy laws and regulations "remain poorly articulated." She points to a notable "lack of clarity" regarding the degree of privacy that must be afforded to personal health information exchanged digitally, such as through text messages.

Where the FDA Stands

In an e-mail response, Jenny Haliski at FDA Office of Media Affairs said that the FDA does not comment on specific products or whether a particular product requires their review. Still, based on content on the FDA website, smoking cessation text programs and apps do not seem to require FDA approval, because they are neither intended for use as accessories to regulated medical devices nor do they transform a mobile platform into a regulated medical device. The FDA en-

courages app developers to contact the FDA as early as possible with any questions about their mobile app, its level of risk, or whether a premarket application is required.[9]

Free Digital Tools Available to Consumers

The US government has interactive text messaging tools available free of charge at several websites, including www.smokefree.gov, www.women.smokefree.gov, and www.teen.smokefree.gov. These sites also provide smokers with no-cost apps such as QuitSTART App, which is available for iOS and Android. The sites now provide brief information on QuitPal, the app described above, which is now under development at the NCI and scheduled for availability in a few weeks. Healthcare providers whose patients may be spending money on commercially available apps with no research basis behind them may want to steer those patients to the free apps offered by the government that were created with proven methods in mind. **EBO**

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Robotic-Assisted Surgery: A Question of Value

Stanton R. Mehr and Marj P. Zimmerman, BSPharm, MS

The arrival of robotics in surgery has been a roller coaster ride, offering another lesson in how technology in healthcare, unlike most industries, faces challenges to show it's better than the status quo.

The use of surgical robotics, especially the well-publicized da Vinci Surgical System, has flourished in the past several years. The name da Vinci is nearly synonymous with the term "robotic-assisted surgery," as it is the overwhelming market leader. As of 2012, more than 2000 of the 1000-pound devices have been sold around the world. Estimates are that da Vinci systems are used in at least 200,000 surgical procedures each year (mostly prostatectomies and hysterectomies).[1] According to Intuitive Surgical, da Vinci's manufacturer, the number of surgeries may have topped 367,000 in 2012.[2]

Many payers are concerned about the expanded use of this technology to "marginally indicated" procedures, based on pressure from the C suite to recoup the costs invested in devices like da Vinci.

However, this roller coaster car may be headed for a long, bone-rattling dip. Today, Intuitive Surgical reports that sales are down, with revenues falling 59% for the first quarter of 2014 compared with that same period in 2013. This drop may be attributable to several things: technical issues and outcomes questions, not to mention high capital (approximately $1.5 million) and maintenance costs (about 10% of the capital costs). This may be a signal of a new wariness among payers and providers regarding the value of robotic-assisted surgery.[3]

Claimed Benefits: Real or Imaginary?

Robotic surgery's promise is straightforward: small incisions and scaled-down surgical movements should mean less damage to surrounding tissue, with improved recovery the result. Yet, evidence to support surgical robotic assistance is tenuous at best.

A recent study from Finland found that when robotic surgery was used in cancer patients who needed hysterectomies, time in the operating room was greater, with patients faring no better that those who had conventional procedures. Furthermore, the cost in Finland was calculated to be at least 50% higher for these patients. These researchers found that when used with patients with benign conditions, the cost of surgical robotic assistance was closer to triple the cost of conventional conditions.[4]

A 2013 investigation by Columbia University researchers found that the use of robot-assisted hysterectomy for benign disorders, among 264,758 women in 441 centers, led to no outcomes benefit, and instead cost $2000 more per procedure compared with conventional laparoscopic hysterectomies.[5] However, the use of this modality jumped 19-fold, from 0.5% to 9.5%, in a span of 4 years. At hospitals with the equipment, robotic-assisted procedures accounted for more than 20% of all hysterectomies performed.

Still, it is thought that robot-assisted laparoscopy has real benefit, particularly in pediatric surgeries and nerve-sparing procedures, where precise suturing, better visualization (3-dimensional view of the area of the affected tissue), and finer movements are high priorities.[6,7] In patients with prostate cancer, a large (>22,000 patients), nonrandomized study found that patients undergoing surgically assisted radical prostatectomies had less frequent positive surgical margins (13.8%) compared with laparoscopic procedures (16.3%) and open surgery (22.8%).[8] Positive surgical margins in prostate cancer are a well-recognized correlate with biochemical reoccurrence.

A study published this year in the *Journal of Clinical Oncology* reviewed records for more than 5900 patients who underwent either open radical prostatectomy (41%) or robot-assisted radical prostatectomy (59%).[9] Data points compared were postoperative complications, blood transfusions, prolonged length of stay, readmissions, additional cancer therapies, and costs of care within the first year. Analyses showed that the 2 groups were similar for odds of overall complications, readmission, and additional cancer therapies. The group undergoing robot-assisted surgery had a higher probability of experiencing genitourinary and miscellaneous medical complications at 30 and 90 days postsurgery (P <.02), but they had a lower risk for requiring a blood transfusion and having a prolonged length of stay (P <.001). Even with these benefits, the expenses at 1 year were greater in this group ($13,394 vs $11,940; P <.001).[9]

A review of literature between 2000 and 2013 indicated that there are benefits associated with robotic prostatectomy, including decreased blood loss, fewer blood transfusions, decreased length of hospital stay and preservation of urinary and sexual function, and other quality-of-life measures that appear to be dependent upon the surgeon's technique.[10] However, costs were significantly less for procedures not employing a robotic surgical system.

These results somewhat conflict with

Figure 1. Da Vinci S System: Patient Cart and Video Screen

Source: Intuitive Surgical Systems.

other studies for safety and length of stay. A study by Hu and colleagues[11] found more complications in the group undergoing robot-assisted surgery. Pierorazio and associates[12] showed a longer length of stay in those undergoing robot-assisted procedures. A review of a sampling of Medicare claims files between August 1, 2008, and December 31, 2008, concluded that similar frequencies of problems with continence and sexual function are experienced by patients undergoing open surgery or robot-assisted prostatectomy surgery.[13]

Adverse Event Reports Cause Concern

The number of adverse events (AEs) associated with the da Vinci Surgical System caused the FDA to take notice. In 2013, the FDA sent a warning letter to Intuitive for underreporting AEs and issued an "urgent medical device recall" for 1300 da Vinci robot arms. A lawsuit was filed in March 2014 by Intuitive's shareholders, claiming that the company underreported AEs and concealed recalls from the FDA.[14]

The number and seriousness of adverse events filed in its Manufacturer and User Facility Experience (MAUDE) database increased by one-third from 2011 to 2012, as the number of robotic procedures jumped 26%, according to Intuitive, da Vinci's manufacturer, in a Securities and Exchange Commission quarterly filing. Reports in the MAUDE database may be filed by the manufacturer, hospitals, clinicians, and patients. Filings can be related to equipment malfunctions that cause no harm to patients, as well as injuries and deaths that may be related to the device or the surgeons operating the device. Unfortunately, data are not available to determine whether there is a correlation among the procedure, facility, patient demographics, disease/morbidity, and/or surgeon.

A 2013 study published in the *Journal for Healthcare Quality* evaluated AEs associated with the use of the da Vinci system over a 12-year period. Cooper and co-workers[15] found a total of 245 AEs that were reported to the FDA, including 71 deaths and 174 events that caused injuries but were not fatal. Researchers from Johns Hopkins were concerned that AEs were underreported, and they termed the process for event reporting "haphazard," calling for improvements in the reporting of these events. The study did not compare AE reporting for robot-assisted surgery with open surgeries of the same type.

Even assuming that AEs associated with robot-assisted surgery are significantly underreported, the frequency would likely amount to a tiny fraction of the total surgeries performed.

Robot-assisted prostatectomy is now more common than the open surgical approach in the United States,[16] although this certainly varies by geographic region and access to the devices. The popularity of the procedure means higher billings for providers who are willing to risk the capital outlay (approximately $1.8 million) and perhaps gain a marketing edge over competing hospitals in a given region.

Where Is the Value of Surgical Robotics?

Payment and reimbursement can be a powerful incentive or disincentive to the growth of robot-assisted procedures. At present, payers do not generally reimburse differently for open surgery, laparoscopic procedures, or robot-assisted surgery. According to the medical director of a regional health plan who participated in a recent survey, "There are no CPT codes for robot-assisted laparoscopic surgeries. This is just another form of laparoscopy. Accordingly, there is no payment differential to the providers for the use of the robot," according to this payer, who asked not to be identified. "Those providers who try to bill with modifier 22 and claim to have a more complicated surgery with the robot are usually denied additional reimbursement. Some of the contracted facilities do have contract rates for robot-assisted surgery; however, as these contracts come up for renewal, the additional enhancement for robot surgery is being eliminated."

Furthermore, many payers are concerned about the expanded use of this technology to "marginally indicated" procedures, based on pressure from the C suite to recoup the costs invested in devices like da Vinci.

Payers are also concerned that any surgeon who does not come out of a training fellowship program where they had "hands-on" experience in using da Vinci would be subject to an unacceptable "learning curve" in actual practice.

Are surgeons and their hospitals focused on getting the latest and greatest technology? Based on the lack of proven improved outcomes, this may be the case, according to the medical director of a national plan who participated in the survey. "I'm the payer representative on our health system's robotics committee. At a recent committee meeting, what struck me was the tone of the surgeons, which I felt was very *gizmo-ish*, if that is a word, in that they were clammering for more access for less-complicated procedures. The general surgeons in our area want to do them for appendectomies and gallbladder removals, and this is being pushed by the manufacturer." This executive added, "There was a 20-minute debate regarding one hospital that just got a new robot-assisted surgery device, who was being sold on converting (to) newest version for only $150,000 more!"

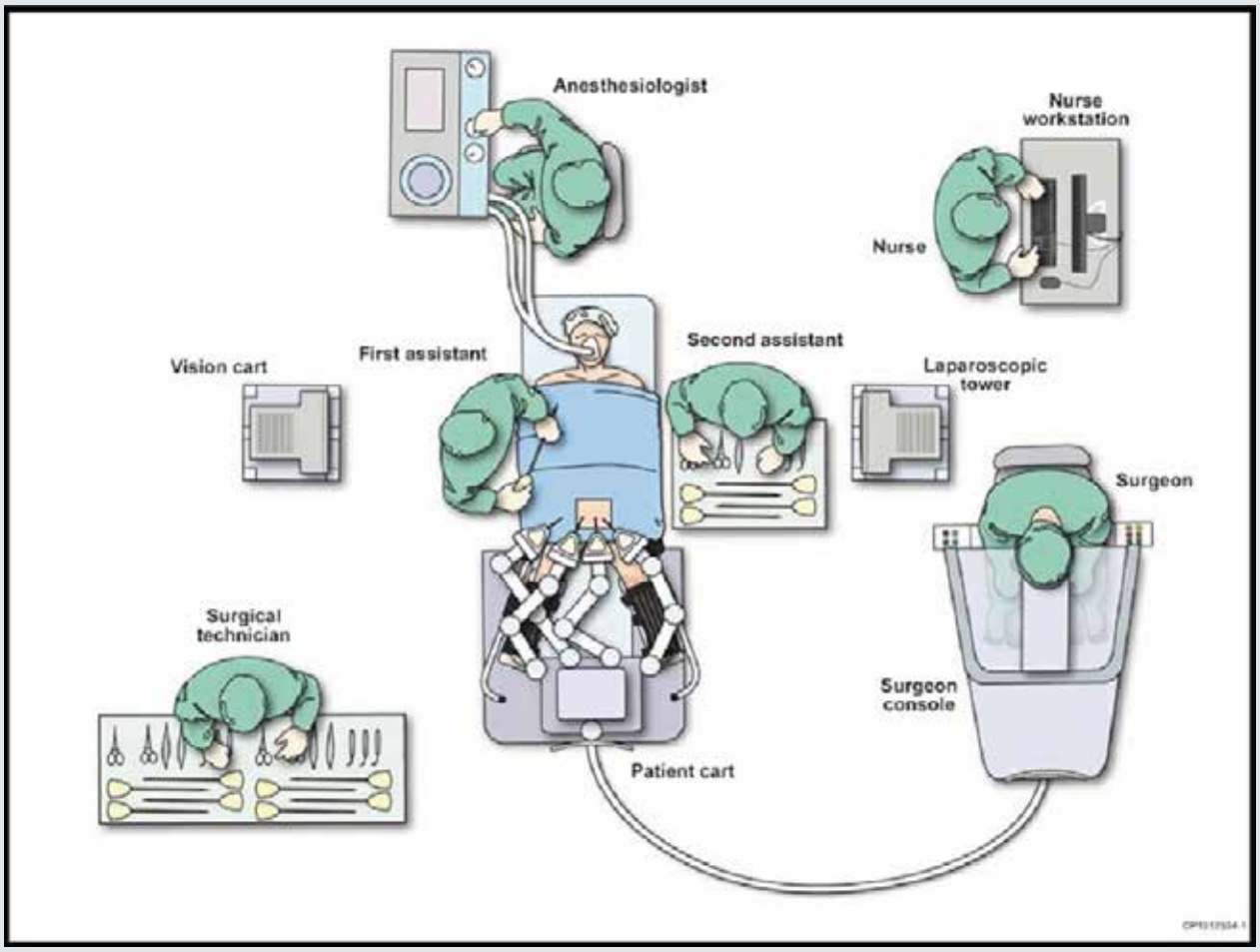
Time in the Operating Room

Most robotic-assisted surgeries, particularly done in centers without a great deal of volume, tend to take significantly more time than conventional procedures. With robotic-assisted surgeries, much of this time is taken in the set-up—preparing the patient, the machinery, and properly positioning the device next to the patient ("docking"). This set-up time also includes camera placement, trochar positioning, and draping the patient.

In a center in Ireland, practitioners recorded the procedure set-up time for hysterectomies, from the first few operations performed to having completed more than 500 consecutive hysterectomies. Setting up the system can take anywhere from 20 to 90 minutes in total, depending again on the user's experience. Furthermore, actual procedures take longer with robotic assistance (of course, depending on the complexity of the surgery), and this is also characterized by a learning curve.

Source: http://www.robotsurgery.ie/clinical-data-from-cork.

Figure 2. Schematic of Operating Room Setup With the Da Vinci System



Source: Higuchi TT, Gettman MT. Robotic instrumentation, personnel and operating room setup. In: L.-M. Su (ed): *Atlas of Robotic Urologic Surgery*: *Current Clinical Urology*. Springer Science+Business Media LLC; 2011.

The amount of training needed on the devices to safely perform the surgeries is also critical. "We've been told about the importance of proctoring and mentoring surgeons on the machines: physicians unfamiliar with the machines will turn a 2-hour prostatectomy into a 6- to 8-hour procedure unless properly trained. And we were told that it probably takes 200 procedures for them to become proficient in robotic prostatectomies." Thus, it seems the healthcare system is paying more, regardless of whether health plans know it. "The cost of operating room and anesthesia for a 6-hour prostatectomy is not noted—it is just paid," said this payer.

A 2012 technology assessment review by the Center for Evidence-Based Policy at the Oregon Health & Science University for the Washington State Health Authority summarized, "Generally there is low to moderate strength of evidence that robotic-assisted procedures are associated with improved outcomes, such as shorter hospital stays, and reduced blood loss and transfusion for several procedures (eg, prostatectomy, hysterectomy, nephrectomy, and cystectomy). Where it has been examined, operative times using robotic assistance are generally longer than for conventional surgeries. There is a general lack of study for patient-centered outcomes (eg, quality of life, longer survival). Many studies are limited by small sample sizes, retrospective nature of data collection and analysis, dissimilar control groups, and inadequate control of potential confounders." The report continued, "Where it was studied, there were data indicating that there is a 'learning curve' for use of robotic equipment and that some outcomes were improved with increasing levels of experience (eg, operative time, length of stay, and complication rates for robotic prostatectomy)."[17]

A Nagging Technological Question

In other industries in the United States, particularly manufacturing, improved technology often results in improved efficiency, better quality, and lower costs. In the healthcare industry, however, it is rare to cite instances where new medical technologies had positive effects on efficiency, quality, and costs. Robotic surgery seems a prime example of the failure of technology in the healthcare industry to improve efficiency and outcomes, at least in prostate surgery. This may not be the case in other types of surgical procedures that requires precise movements. The problem is that evidence is still lacking.

As Debasish Sundi and Misop Han wrote in an editorial18 accompanying the *JCO* article, "Do the results of this study prove superiority or safety of one technique over another? The simple answer is no." **EBO**

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In New Jersey, Focus in Fight Against Cancer Changes, and Care Comes Closer to Home

Mary K. Caffrey

If one thinks "cancer" and "New Jersey," the images that come to mind might be those that have long defined the state: plumes of smoke along the Turnpike, acres of oil refineries, or fleets of trucks spewing exhaust.

Howard Kaufman, MD, FACS
Rutgers CINJ photo

An actual map of cancer incidence reveals something else. For starters, most of the cancer occurs in South Jersey (**Figure**), where cornfields have given way to retirement communities. As for images that evoke emerging threats, think sun and sand, not smokestacks.

In line with the recent warning from Acting US Surgeon General Boris D. Lushniak,[1] rising rates of melanoma in counties along the famous 126-mile shoreline have drawn attention from both state health officials and leading researchers.[2] In summer months, the NJ Department of Health (DOH) sends teams right on to the beaches, both to educate sun worshippers and to screen for early cases of skin cancer, according to spokeswoman Dawn Thomas.

New Jersey's cancer threats are similar to the rest of the nation's; the difference is the degree (**Table 1**). While overall cancer rates have fallen over the past 20 years, the state still ranked seventh in cancer incidence in 2011 with 49,080 cases, according to the American Cancer Society.[3]

That report stated the "big 4"—lung, prostate, breast, and colorectal cancer—still account for most of the state's cancers; 52% of all cancer incidence and 49% of all cancer deaths. Lung cancer, with most cases caused by smoking, is the single biggest killer, accounting for 4100 of the state's 16,370 cancer deaths in 2011.[4] Rising rates of melanoma among the young and overall higher rates of thyroid cancer, which may or may not be explained by better detection,[4,5] are also part of New Jersey's complicated cancer story, which is one of great strides on some fronts and frustration in others.

If New Jersey once sat in the shadow of New York City and Philadelphia, it doesn't act that way anymore. In the wake of Lushniak's warning, the home page for the Cancer Institute of New Jersey (CINJ) was overhauled to highlight the "Call to Action" on melanoma, featuring both the work of CINJ behavioral scientist Eliot Coups, PhD, and of Howard L. Kaufman, MD, FACS, associate director of clinical science, who had just presented important phase 3 results using talimogene laherparepvec to treat melanoma at the American Society of Clinical Oncology in Chicago.[6]

To be sure, New Jersey has come a long way from the 1970s, when it had the highest cancer rates in the country[2,3] and a hard-to-treat case almost certainly meant crossing a river to one of its neighboring cities for treatment. Today, cancer rates among African American men have fallen and disparities between whites and minorities are narrower than in many other states.[3,47] Best of all, a state known for its bruising politics has achieved a bipartisan consensus that cancer patients should not have to travel out of state for care. Against a backdrop of state budget cuts and a recession that was deeply felt, cancer care for many has come closer to home, with governors and legislators from both parties overseeing significant investments in infrastructure.

A $139 million medical school to serve South Jersey, discussed for decades, opened in Camden in 2012.[8] Next door is the $100 million MD Anderson Cancer Center at Cooper, which opened in October 2013, transforming both a section of a beleaguered city and care itself.[9]

Generosa Grana, MD

More hard-won was a 2012 law, brokered by Republican Governor Chris Christie and Democratic Senate President Stephen Sweeney, who comes from Gloucester County in South Jersey, that restructured New Jersey's higher education assets.[10] Leaders of the major research institutions say this step is finally dismantling the silo effect that for decades prevented research entities from collaborating as fully as they might have and from taking full advantage of their close proximity to leading pharmaceutical manufacturers.

Research today emanates from CINJ, a National Cancer Institute-designated center based in New Brunswick, NJ, that became part of Rutgers University in 2013 and had 476 active clinical trials last year, according to spokeswoman Michele Fisher.[10] Eight medical centers across the state enjoy major partnerships with CINJ, and even more have relationships. In South Jersey, the hub for cancer care is Camden, NJ, where a year-old collaboration between Cooper Medical School at Rowan University and the world-famous MD Anderson Cancer Center is ramping up; spokeswoman Wendy Marano reports that between October 2013 and June 2014, the center experienced 18% growth in patient volumes across all areas, including an 11% increase in complex cancer cases. The medical school itself is still very new, having accepted its first class in 2012 (third- and fourth-year medical students from Robert Wood Johnson Medical School had previously trained at Cooper).[9]

At both CINJ in New Brunswick and MD Anderson at Cooper, leading oncologists report that the old pattern of New Jersey patients automatically going out of state for cancer care is quickly ebbing. In some cases, they say, cancer patients cross the Delaware or Hudson rivers *into* New Jersey to receive care. Marano said between October 2013 and June 2014, MD Anderson at Cooper experienced a 30% increase in cases from outside the traditional service area, including cases from Pennsylvania.

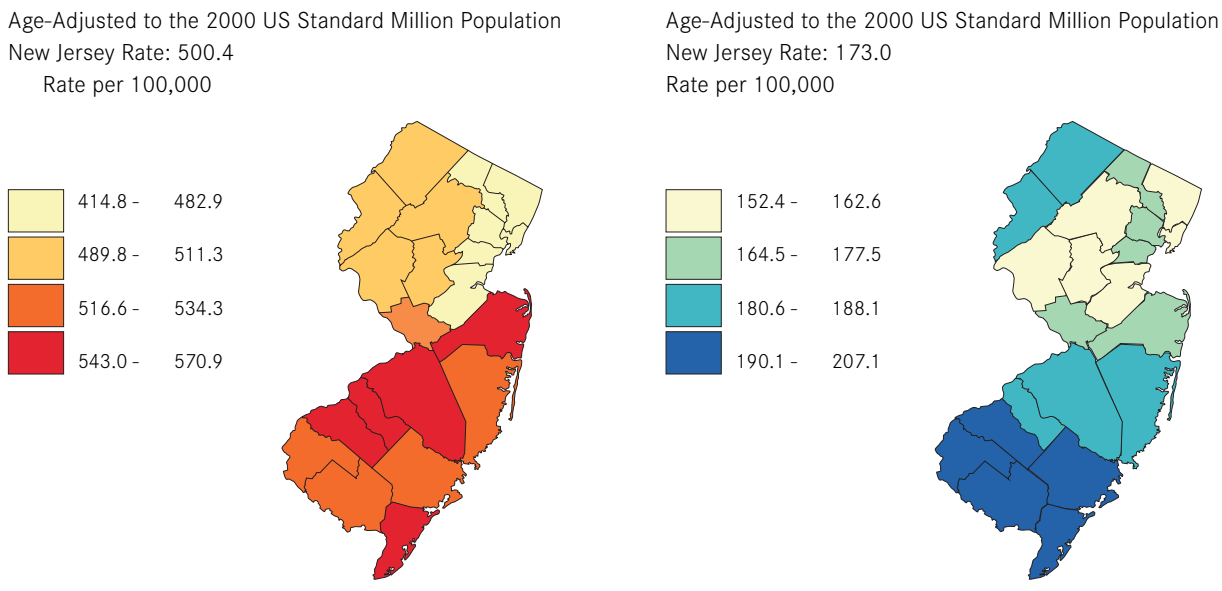
Amid these good signs, however, is a lingering undercurrent: the state's ongoing financial distress. For more than 20 years, multiple governors have patched over or ignored the growing unfunded retirement obligations for New Jersey's public employees. This spring, another revenue shortfall caused Gov. Chris Christie to propose cutting $1 million from the New Jersey Commission on Cancer Research and $10 million from CINJ.[11] In April, Christie blamed the cost of public employee pensions for the proposed cut.[12] Although the Legislature restored all the funding for budget for the fiscal year that began July 1, 2014,[13] New Jersey's ongoing challenge of how to meet the cost of retirement obligations to public employees threat-

Table 1. NJ Cancer Rates

Cancer Type	NJ Incidence	NJ Deaths	US Incidence	US Deaths
Prostate (Male)	144.5	53.9	126.1	60.5
Breast (Female)	124.7	23.2	119.2	22.1
Lung	54.9	42.2	62	47.7
Colorectal	42	16	40.6	15.6
Melanoma	21		19.2	
Thyroid	18.1		13.5	

All rates per 100,000 of population for 2010. Source: CDC.
Melanoma and thyroid cancers were not among top 10 sources of cancer deaths.

Figure. Age-Adjusted Cancer Incidence Rates and Mortality Rates in New Jersey, All Sites, 2007-2010, by County



Source: NJ Cancer Registry.

en every part of the budget, including cancer research, which has widespread support.

Overlooked in the budget debate is the fact that not a dime that New Jersey receives from the 1998 Master Settlement Agreement (MSA) with the 4 largest tobacco companies goes to combat smoking.[14] Like 17 other states, New Jersey took the payout from the agreement upfront, and sold bonds that are paid off as settlement dollars arrive, a process called securitization. Unlike some states, New Jersey did not carve out settlement funds for smoking cessation.[15] Instead, New Jersey uses $2.2 million in federal dollars for cancer screening and prevention; Generosa Grana, MD, director of MD Anderson at Cooper, had strong praise for the state health department efforts, which DOH's Thomas said are based in all 21 counties.

"We are catching cancer at an earlier stage," Grana said, attributing this to 3 factors:

- sustained public education efforts, including attention from the media
- better screening and detection services, including broader access
- more access to genetic testing services, and a recognition of the role that testing and genetic counseling play in overall survival.

As with other parts of New Jersey's cancer story, the onset of the Affordable Care Act (ACA) has been a mixed bag. While some patients who previously lacked insurance now have it, CINJ's Kaufman said some patients insured by the exchanges who have tried to get a test or scan out of state had trouble doing so (**Table 2**).

Table 2. How Many Became Insured Under the Afforadable Care Act?

Number determined eligible to enroll	**301,965**
Number determined eligible for financial assistance	**193,286**
Number determined eligible for Medicaid/ CHIP	**179,775**
Number of enrollees as of April 19, 2014	**161,775**

Source: State Marketplace statistics. Kaiser Family Foundation website. http://kff.org/health-reform/state-indicator/state-marketplace-statistics/. Updated May 1, 2014. Accessed August 14. 2014

Fighting Cancer in New Jersey

The state's environmental history is strongly connected to cancer's footprint here, but just how much has been the subject of debate for decades. Concerns about air and water pollution, and about toxins in landfills in a state where people are abundant and open space increasingly scarce, have driven state planning and environmental policies since the 1980s. New Jersey remains home to one of a handful of cancer clusters tracked by the CDC: the area around Toms River, NJ, where local concerns over possible connections between childhood leukemia and waste from Ciba-Geigy arose in 1996.[16]

But Grana said studies of connections between environmental causes and cancer have not pinpointed a single factor. By contrast, she said, higher rates of smoking in South Jersey undoubtedly contribute to higher cancer rates in those counties, along with the older demographics of the population. Overall, only 16.8% of New Jersey adults over the age of 18 years smoked in 2011, according to the CDC,[17] but Grana said rates are higher in South Jersey, and this is reflected in lung cancer statistics. She said, however, that treatment for lung cancer is improving: CDC figures reflect that of the 4 major cancers, only lung cancer rates are lower than national averages (**Table 1**).

The state's cancer prevention efforts flow through NJ Cancer Control and Early Detection (NJ CEED) program, which operates through the state's counties to provide education, outreach, and screening for breast, cervical, prostate, and colorectal cancer, according to Thomas. She said in the fiscal year that ended June 30, 2014, the program screened 24,700 women for breast, cervical, and colorectal cancer, as well as 847 men for prostate cancer. Ten task forces that cover 2 counties apiece operate statewide (including 1 through MD Anderson at Cooper). In a state that has long valued local control, this dissemination of screening services matters.

Evelyn Robles-Rodriguez, RN, MSN, APN-C, AOCN, who is the director of Oncology Outreach Programs at MD Anderson at Cooper, offered an example of the kind of program NJ CEED funds. Robles-Rodriguez received a call from an Indian temple in a nearby suburb a decade ago informing her that women at the temple weren't being screened for cancers, and she was able to get funds for a screening program and a translator to ensure "culturally competent" services. On the very first visit, 38 women were screened, and today that clinic sees women at the temple once a month.

Another effort addresses the needs of Vietnamese women living in Camden, many of whom work as nail technicians throughout the area. A nurse practitioner at the hospital has just received funding to examine data from these 2 initiatives, "to see what inroads we have made," Robles-Rodriguez said.

Could New Jersey do more? Cancer control advocates succeeded in getting the legislature to ban minors under the age of 17 years from using commercial tanning beds, after the infamous case of the "tanning Mom," whose 5-year-old showed up at school with burns.[18] Most of the 2013 recommendations from the American Cancer Society advocate getting more money aimed at the war against tobacco.[4] A February 2014 report by another national group, the Campaign for Tobacco-Free Kids, criticized several states for the gaps between what they collect in tobacco taxes and MSA funds and what they spend on smoking cessation. In that report, New Jersey was listed with $947.2 million in overall tobacco-related revenue for fiscal year 2014. Instead of spending the CDC-recommended amount of $103.3 million on tobacco prevention, New Jersey was spending zero, according to the group.[14]

A spokesman for the NJ Department of Treasury, Christopher Santarelli, said in an e-mail that $391.5 million in cigarette tax revenues are deposited "for general state use." Currently, 76% of the MSA funds are used to pay bondholders and the rest goes to the Treasury; Santarelli said that this use is consistent with the purpose of the MSA, which is

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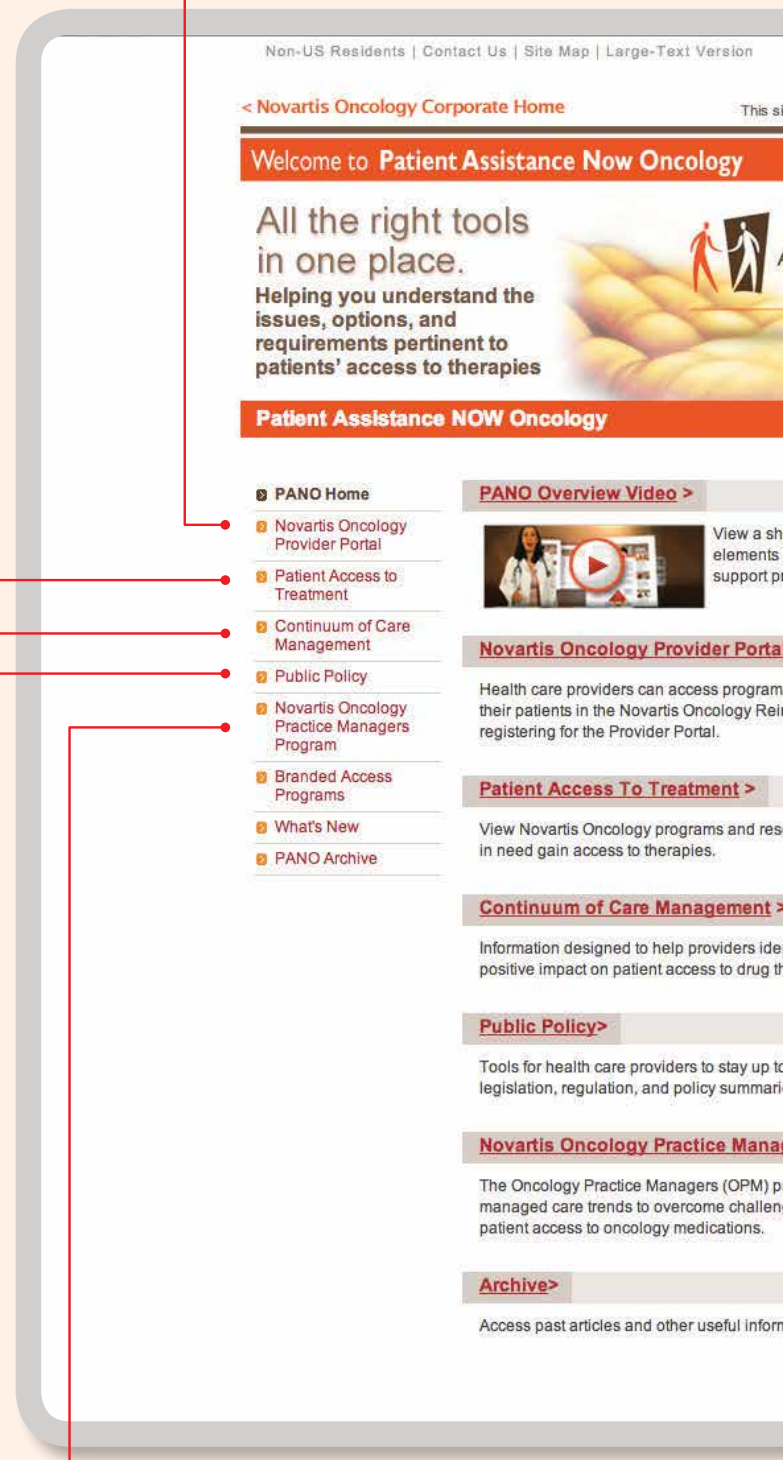

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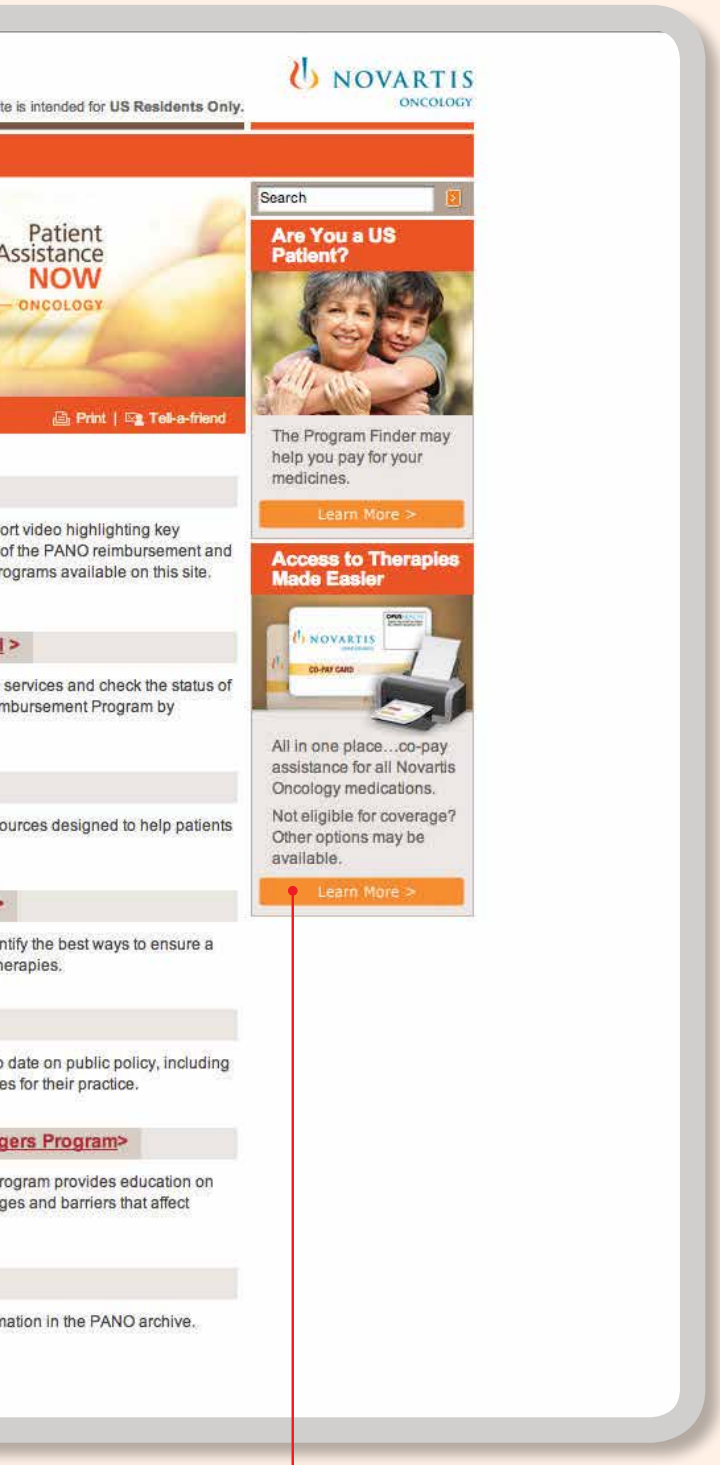

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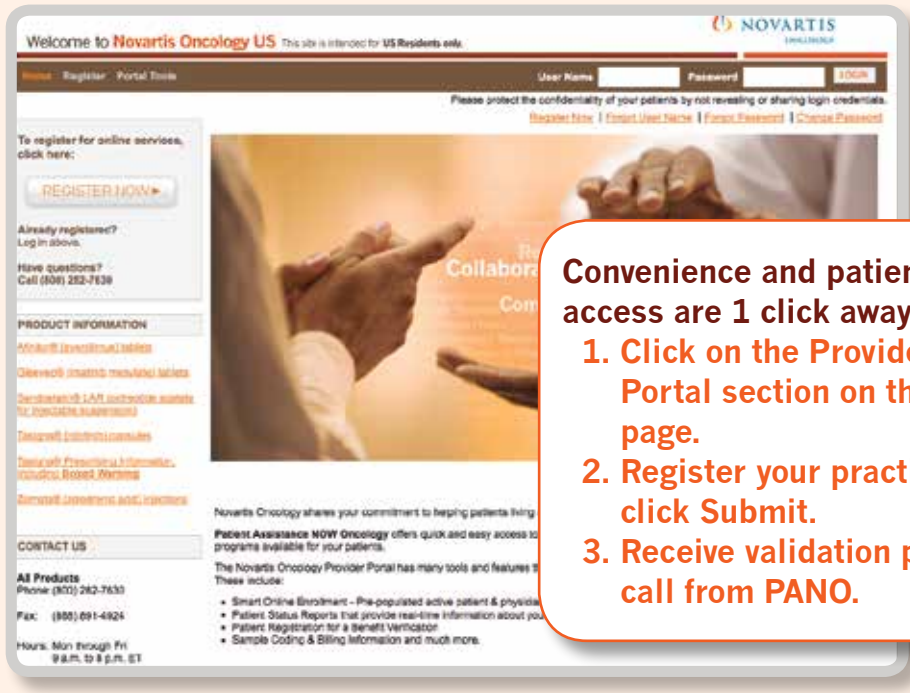

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A Glimpse Into Managed Care of Diagnostics

Mary K. Caffrey

Leaders at New Jersey's major academic research institutions are enthusiastic about the role that genetics and precision medicine will play in cancer care. However, which genetic and diagnostic tests gain ground in the market may not be up to oncologists and researchers.

This summer, Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ) removed Myriad Genetics from its network, becoming the first major carrier to change network status, according to Myriad spokesman Ronald Rogers. Instead, Horizon will coordinate all genetic testing through its in-house laboratory, LabCorp, which has formed a specialty testing group, Integrated Genetics.[1] In December, less than 6 months after the US Supreme Court ruling that ended Myriad's monopoly on BRCA testing,[2] Integrated Genetics announced a new national BRCA testing suite called BRCAssure.[3]

Thomas Vincz, a spokesman for Horizon BCBSNJ, said in an e-mail to *Evidence-Based Oncology* that Horizon's longstanding relationship with LabCorp will allow its members to pay less for services by using an in-network provider, and that, "Horizon believes LabCorp's BRCA testing is equivalent to testing by Myriad Genetics."

Myriad, meanwhile, during its fourth-quarter earnings call August 12, 2014, strongly maintained the position that its testing quality and customer service are superior to competitors, based on the experience gained from testing 1.3 million patients. Elsewhere in the market, Myriad has reached relationships with other insurers, notably UnitedHealthcare, to offer its myRisk test to patients.[4] But in New Jersey, the Horizon decision is both a financial and policy blow. Not only does Horizon BCBSNJ have 54% market share and 592,630 enrollees,[5] but Horizon is a longtime administrator of the self-funded State Health Benefits Program, which covers thousands of public employees and retirees and, this being New Jersey, many lawmakers themselves.[6]

Of note, Horizon's relationship with LabCorp does not extend to all tests that LabCorp administers. In January, LabCorp announced the launch of Prosigna, the breast cancer prognostic gene assay from NanoString, which has FDA clearance.[7] According to Vincz, Horizon still considers Prosigna an "investigational" assay, and consistent with national policy for the Blues affiliates, it is "not currently a covered benefit for Horizon BCBSNJ members."

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to repay states for the cost of tobacco-related illnesses.

"Would it be ideal to have more money?" Grana asked rhetorically. It would always be better to have more, but she and Robles-Rodriguez sounded hopeful about how far they have come, using funds from multiple public and private sources. Said Grana, "The governor's Office on Cancer Prevention and Control has done a great job of building the infrastructure we have."

At CINJ, Getting the Right Therapies to Patients

The annual retreat on cancer research, co-sponsored by CINJ and the Commission on Cancer Research (CCR), came on May 21, 2014, at the height of the effort to restore millions in research dollars to the state budget. It was a display of contrasts, which at the time were quite serious. At the check-in table, a CCR commissioner hawked the familiar "Conquer Cancer" license plates while grumbling about Christie's proposed cuts to research. Meanwhile, keynote speaker Arnold J. Levine, PhD, formerly of Princeton and Rockefeller Universities and today a professor at Rutgers Robert Wood Johnson Medical School, treated medical students to a high-level talk on his decades of work with p53-knockout mice, which has revolutionized the study of how cancer develops.

The breadth of studies at New Jersey's research retreat was impressive: posters featured everything from preclinical studies on agents to treat pancreatic cancer, to studies of breast cancer among women veterans at the East Orange Veterans' Administration hospital. With 134 clinical trials in various phases, the East Orange VA is yet another important source of cancer research.

At a session designed for the public, medical oncologist Janice Mehnert, MD, a Rutgers graduate, covered the rising incidence of melanoma along with CINJ's ability to deliver newer immunotherapies to treat it through clinical trials. Mehnert was among those sounding the alarm about the dangers of too much sun. "Many of my patients come from Monmouth and Ocean counties," she said.

In a later interview, CINJ's Kaufman said getting the best, new therapies to cancer patients is among the institute's main goals. "The division of clinical science is dedicated to identifying the most promising new drugs in development, to looking at new technology, in terms of diagnosis as well as treatment, and to fostering that translation into getting these things to the patient," Kaufman said.

Bringing CINJ into Rutgers, he said, has allowed better integration with the research units that do basic science; for example, the chemistry department has faculty that work on drug development, but in the past lacked the connections to get their work into clinical trials.

"We're also trying to develop much stronger relationships with Newark, which has a different population of patients and different types of cancer," Kaufman said. Both Rutgers and the state medical school have long had a presence in Newark, and the integration will open doors for more clinical trials at multiple sites that attract both larger numbers and a more diverse patient population.

Already, Kaufman said, CINJ is expanding its precision medicine program; the program has treated an initial 100 patients and is in the process of treating 500 patients. Of the first 100, Kaufman said, "40% had a change in clinical management based on information identified in genomic analysis."

For South Jersey, a School of Its Own

Arguments for giving South Jersey its own medical school and cancer center have been around for years. The population is growing. The demographics tilt toward seniors, who don't want to travel far for care. Putting new medical facilities in Camden would provide jobs and economic development the city desperately needs. But most of all, the case makes sense medically. All one has to do is look at a map.

The southernmost counties that make up the area MD Anderson at Cooper serves have higher rates of cancer incidence and mortality than the rest of the state, according to CDC data. Higher smoking rates and demographics account for most of this, Grana said.

A visit to MD Anderson at Cooper reveals a hospital built from scratch with customers in mind. A wide driveway designed for easy pickups and drop-offs gives way to an airy entrance, and the facility features ample room for families and a healing garden. Patients receiving infusions can do so together or in private rooms. There's no more hurrying to multiple appointments on different floors; instead, the doctors take turns visiting the patient in a state-of-the-art "pod."

The relationship between MD Anderson and the medical school is close, with the cancer center's physicians serving on the Cooper Medical School faculty, according to Grana. She said members of the incoming class were admitted based on both academics and their embrace of Cooper's service ethic, for the purpose of "populating South Jersey with physicians who are well-trained and committed to the mission of the school."

Cooper's third class is highly competitive, according to data supplied by John McGeehan, MD, associate dean for student affairs and admissions. Some 5200 applicants vied for 72 spots in the class of 2018, and 53 members of the incoming class are from New Jersey.

Bringing the MD Anderson name and relationship to Cooper was no small feat, Grana said. Three factors that made MD Anderson interested were Cooper's "completely employed physician model," an existing infrastructure that supported clinical research and strong community outreach for

Patients at MD Anderson at Cooper in Camden, NJ, are treated with newly designed "pods;" doctors from different specialties come to the patients instead of patients traveling throughout the facility.
Photo is courtesy of MD Anderson at Cooper

cancer prevention and control, Grana said. After initial meetings took place, a 6-month due diligence period followed during which MD Anderson reviewed "every aspect" of Cooper's program, she said. The agreement was signed in September 2013, and the new facility opened a month later.

There's plenty of back-and-forth travel between Houston and Camden; faculty from the 2 sites sit on each other's tumor boards and take part in numerous committees that cover everything from health information technology to patience experiences.

Outreach is expanding, too. Robles-Rodriguez is seeing her role grow into new prevention and survivorship programs, which will be measured more than ever under the ACA. Cooper's historic role as the provider for those without insurance is allowing the hospital to take the cancer screening data on patients who now have coverage, and deliver it to new patient-centered medical homes. For those who have survived cancer, group sessions are allowing those who have had similar diseases to support one another as they work with Cooper to get nutrition information and develop a treatment plan, a new ACA mandate.

During 17 years at Cooper, Robles-Rodriguez has seen plenty of change, and she sounds optimistic. Years ago, patients fighting breast cancer "only had a handful of medications," she said. "Now we have an arsenal of weapons. That has made a big difference, especially for those with more aggressive disease."

More and more people are hearing the message, she said, "The earlier you detect the cancer, the higher your chances of surviving the disease." **EBO**

A doctor visits with patients receiving chemotherapy at MD Anderson at Cooper. Patients have the option of receiving treatment together or in private rooms.
Photo is courtesy of MD Anderson at Cooper

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FDA Moves to Regulate Thousands of Diagnostic Tests

Mary K. Caffrey

Thousands of tests that give doctors guidance on how to treat cancer or other progressive, chronic illnesses will face FDA scrutiny for the first time, according to a July 31, 2014, announcement from FDA Commissioner Margaret A. Hamburg, MD.

The FDA issued final guidance on its clearance policies for companion diagnostics, which are used in cancer treatment to identify those patients who may benefit from a specific therapy. These tests, often based on genetics, are frequently developed in tandem with the therapy and were already subject to FDA clearance.[1]

Margaret Hamburg, MD

The agency had also exercised oversight of all direct-to-consumer tests as well as those whose reliability had to be guaranteed across multiple laboratories, such as those in hospitals. What's new is the FDA's movement into the realm of laboratory developed tests, known as LDTs, which are designed, manufactured and used within a single laboratory; tests are performed with a patient's blood or tissue samples.[1]

"Ensuring that doctors and patients have access to safe, accurate and reliable diagnostic tests to help guide treatment decisions is a priority for the FDA," Hamburg said in a statement. "Inaccurate test results could cause patients to seek unnecessary treatment or delay and sometimes forgo treatment altogether. Today's action demonstrates the agency's commitment to personalized medicine, which depends on accurate and reliable tests to get the right treatment to the right patient."[1]

The number of tests that could be affected by FDA's action could be as high as 11,000, and the number of labs involved as high as 2000.[2] Forthcoming guidance documents will spell out how manufacturers will provide information about their LDTs, which they can continue to sell and perform pending new rules. For now, the FDA will not move to regulate LDTs for rare diseases and certain tests for which there is no FDA-cleared option.

FDA's move is not a surprise, as the agency has had its eye on the industry for some time. FDA issued a report in October 2013, "Paving the Way for Personalized Medicine,"[3] outlining its possible role in nurturing molecular diagnostics. Some industry experts like Bruce Quinn, MD, PhD, of Foley Hoag LLP, have highlighted the contrast between the FDA's view of the potential of molecular diagnostics compared with CMS,[4] which is being sued by the California Clinical Laboratory Association over reimbursement disputes with Medicare contractors.[5]

The agency has also been pressed by some members of Congress to close the regulatory gap exposed by the sharp rise in genetic and molecular testing, particularly in cancer care. US Rep. Louise M. Slaughter, a New York Democrat who is a microbiologist, hailed the FDA's move, which came just over a year after she wrote to the Office of Management and Budget calling on the agency to exercise its authority to bring "transparency and accountability" to the field. "Diagnostic testing is an incredible medical breakthrough that holds the key to personalized medicine, but patients can only realize the benefits of diagnostic testing if the tests are safe and effective," Slaughter said in a statement.[6]

In her June 2013 letter, Slaughter noted that LDTs outside FDA oversight not only lack pre-market approval, but also are not subject to any post-market surveillance or recalls, despite their "interchangeable" nature in clinical settings. The current system, she said, offers "little transparency for patients or even doctors regarding what test has been used."[6]

There has been debate within the testing industry whether more FDA oversight helps or hurts. While regulation would bring higher costs to enter the market, some believe it could pave the way for fewer reimbursement disputes with insurers and, especially, with CMS.

One testing company contacted by *Evidence-Based Oncology* said officials would review FDA's plan before reacting. In an e-mailed statement, Myriad Genetics said the company "looks forward to collaborating with policymakers and stakeholders to provide input and focus on the future of the US regulatory process for LDTs."

> *"Many industry participants are watching closely to see how payers react to the Prosigna assay in terms of setting both medical policy and establishing reimbursement. It will be important for them to see that the investment in FDA clearance is worthwhile if others are to follow in our footsteps."*
>
> **—Brad Gray**
> CEO, NanoString

Myriad, which has a reimbursement application pending with CMS for its Prolaris prostate cancer test (**see page SP323**), also said in its statement, "Myriad has a strong track record of scientific excellence that includes conducting numerous clinical studies in support of the analytical and clinical validity of our diagnostic tests."

Nanostring CEO Brad Gray said a risk-based system of regulation could work as long as the reimbursement process recognized its value. He discussed the clearance process that Nanostring's Prosigna breast cancer assay went through, which Gray said "required multiple clinical and analytical validation studies run to the FDA's exacting standards across thousands of samples. We believe that the results are impressive, with the Prosigna assay outperforming the leading Laboratory Developed Test, Oncotype Dx, in a 1,000+ patient comparative effectiveness study." (Gray cited a study that appeared in the *Journal of Clinical Oncology*.[7])

"As a result, we believe the key to making the system work will be recognition by payers of the substantial time and investment required to meet the FDA requirements," Gray continued. "Many industry participants are watching closely to see how payers react to the Prosigna assay in terms of setting both medical policy and establishing reimbursement. It will be important for them to see that the investment in FDA clearance is worthwhile if others are to follow in our footsteps."

Gray noted that already, a large national payer has started offering Nanostring reimbursement for Prosigna. **EBO**

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Harnessing the Immune System
(continued from cover)

Table. Immunotherapies: Current and Prospective

Drug	Company	Clinical Stage	Tumor Type
BIFUNCTIONAL ANTIBODIES			
Catumaxomab (Removab)	Neovii Biotech	Phase 2	Gastric cancer, ovarian cancer
MT110 (Solitomab)	Amgen Research	Phase 1	Solid tumors
TF2	Immunomedics Inc	Phase 1/2	Medullary thyroid carcinoma, recurrent HER2-negative breast cancer
Anti-GD2	St. Jude Children's Research Hospital	Recruiting/phase 1	Neuroblastoma, melanoma, osteosarcoma, Ewing sarcoma
CANCER VACCINES			
Sipuleucel-T (Provenge)	Dendreon Corp	Approved	Metastatic castration-resistant prostate cancer
Allogenic GM-CSF-secreting breast cancer vaccine	Sidney Kimmel Comprehensive Cancer Center	Phase 2	Breast neoplasms
GVAX	Cell Genesys	Phase 1/2	Prostate cancer
PVX-410	OncoPep Inc	Phase 1	Smoldering multiple myeloma
IMMUNE CHECKPOINT INHIBITORS			
Ipilimumab (Yervoy), anti-CTLA-4 antibody	Bristol-Myers Squibb	Approved	Unresectable/metastatic melanoma
Nivolumab, anti-PD-1 antibody	Bristol-Myers Squibb	Phase 3	Unresectable/metastatic melanoma, non-squamous NSCLC
		Phase 1/2	Recurrent and metastatic colon cancer
Pidilizumab (CT-011), anti-PD-1 antibody	CureTech Ltd	Phase 1/2	Multiple myeloma
	Georgia Regents University	Phase 2	Resected pancreatic cancer
MK-3475, PD-1 inhibitor	Merck	Phase 1	Renal cell carcinoma
		Phase 1/2	NSCLC
MPDL3280A, anti-PD-L1 antibody	Genentech	Phase 1	Neoplasms

GM-CSF indicates granulocyte-macrophage colony-stimulating factor; NSCLC, non-small cell lung cancer. Source: www.clinicaltrials.gov.

Early Success With Leukemia and Melanoma

This approach has previously been used in treating patients suffering from leukemia and melanoma. Physicians at Memorial Sloan Kettering Cancer Center in New York treated 5 patients with relapsed B-cell acute lymphoblastic leukemia (B-ALL) with their own genetically modified T cells that expressed a CD19-specific CAR receptor.[3] Although tumors in all 5 patients were rapidly eradicated, 2 patients died—1 from a blood clot and 1 in whom the cancer relapsed. However, 3 of the survivors received subsequent bone marrow transplants and have a good prognosis. The group recently published results from another study, this time with 16 patients with relapsed or refractory B-ALL who were treated with autologous T cells expressing CAR. The complete response rate was 88% among the 16 patients, most of whom subsequently received stem cell transplants. The group now plans to conduct a multicenter phase 2 study with the therapy.[4]

In 2012, the National Cancer Institute published a report on the success of ACT in melanoma patients.[5] Three separate trials treated 93 melanoma patients with their own TILs, which had been grown out in the laboratory, along with the cytokine interleukin-2 (IL-2). Of the 93 patients, the tumor was completely eradicated (complete response) in 20, and 19 remained tumor-free for more than 5 years; some stayed tumor-free more than 8 years. Significant tumor shrinkage was observed in 52 patients. A similar trial at The University of Texas MD Anderson Cancer Center found that 25 of 50 patients had partial or complete tumor responses.

However, according to Michael Kolodjiez, MD, national medical director for oncology strategies at Aetna, although these treatments are very promising, they'd be difficult to adopt in the clinic. In an interview with *Evidence-Based Oncology*, Kolodjiez said, "CAR T cell therapies are complicated, their administration is complicated—consider what happened with Provenge. It's definitely exciting therapy, but adopting it in the clinic can be challenging."

ACT: Adverse Effects

The treatment is coupled with certain issues and side effects, as most cancer therapies are. The required lymphodepletion prior to the treatment, as well as the IL-2 administration, are associated with toxicity. A predicted consequence of rapid and potent antitumor immunity is the development of a generalized proinflammatory immune state. Furthermore, infusion of the large amount of T cells can generate an immune response, the cytokine release syndrome (CRS), that could potentially be fatal.[5,6] CRS has been reported to occur several days to weeks after infusion of T cells. Additionally, both tumor lysis syndrome and macrophage activation syndrome have also been reported with the treatment.[6] Efforts are ongoing to improve upon some of these procedural side effects of the therapy.

Artificial Immune Cells Join the Battle

A research group at the Institute for Cell Engineering at the Johns Hopkins University School of Medicine, led by Jonathan Schneck, MD, PhD, has developed an innovative technique to attack a tumor: nanoscale artificial antigen-presenting cells (aAPCs). A graduate student in Schneck's laboratory observed that treating the aAPCs with a magnetic field resulted in a clustering of T cells to which the aAPCs bind. Subsequently, naïve T cells were functionalized, which made the active T cells even more active. In turn, the normal immune response increased significantly. When injected into mice that were growing skin tumors, mice treated with nano aAPCs and then treated with a magnetic field presented significantly smaller tumors and longer survival compared with the control untreated mice.[7]

Schneck has pioneered a start-up, NexImmune, based on these nanoparticles; the company has trademarked the process as Artificial IMmune (AIM) Technology.[8] The company claims that AIM aAPCs can be precisely engineered to orchestrate a polarized immune attack on the patient's tumor. The immune cells can be readily designed and are not susceptible to suppression by T_{reg} cells.

Refining the Traditional Approach

Traditionally, immunotherapy approaches can be classified into: *monoclonal antibodies*, *cancer vaccines*, and *nonspecific immunotherapies*.

Monoclonal antibodies reflect a more specific/targeted approach, since the antibody can be precisely targeted to a tumor-specific antigen.[9] The current approach to improving the efficacy and safety of antibody treatment is the use of bispecific and even trispecific antibodies, combining parts of 2 (bi) or 3 (tri) antibodies together. A market research report released late last year identified several pharmaceutical companies (Roche, AbbVie, Pfizer, Sanofi, Amgen, Merck, and others) with ongoing phase 1 and 2 trials for bispecific antibodies.[10] Meanwhile, a trifunctional antibody developed by TRION Pharma, Removab (catumaxomab), received approval in the European Union for the treatment of malignant ascites and is undergoing clinical trials in the United States (**Table**).

Cancer vaccines were developed with the goal of boosting the immune system to attack cancer cells, quite unlike the traditional vaccines administered to prevent infectious diseases. Cancer vaccines can include entire cancer cells, parts of cells, or just the antigens.

A more personalized approach involves using a patient's own immune cells and sensitizing them to the tumor cells in the laboratory to create a vaccine.[11] An example of an FDA-approved cancer vaccine is sipuleucel-T (Provenge) for advanced prostate cancer (**Table**).

The nonspecific immunotherapy approaches include injecting cytokines, such as IL-2, interferons, and GM-CSF, into the body. Cytokines, produced by immune cells, regulate the growth and activity of other immune cells and blood cells, and can be administered either alone or concomitant with chemotherapy.[11]

Immune checkpoint inhibitors (both chemical inhibitors and monoclonal antibodies) are currently receiving much attention. Immune checkpoints are a part of the body's defense system that prevents immune cells from attacking "self." Cancer cells, however, use these checkpoints to circumvent an attack by the immune system, and drugs targeting these checkpoints have gained huge strides in the clinic. Some of the immune checkpoint proteins being targeted include cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and programmed death-ligand 1 (PD-L1). CTLA-4, expressed on the surface of T cells, keeps T cells from attacking other cells in the body. Cancer cells use this to their advantage to prevent an immune attack. Ipilimumab is a monoclonal antibody that binds to and inhibits CTLA-4 (**Table**). Although approved for melanoma, it is now being evaluated in combination with other antibodies and chemotherapy in the treatment of numerous other cancers. PD-1 is expressed more often in T cells in inflamed tissues and tumors, where binding of the ligand PD-L1 prevents an immune response.[11] Cancer cells have been found to overexpress PD-L1 and efforts are ongoing to develop an antibody that effectively blocks PD-1 (**Table**).

Said Kolodjiez, "There's a lot coming out with the new checkpoint therapies, and although it's very exciting, it's still too early. Policy decisions regarding such novel therapies are not made (at Aetna) until the FDA has approved them. Additionally, we at Aetna also try to harmonize with the NCCN (National Comprehensive Cancer Network) treatment guidelines." He added that Aetna has an evidence section led by the senior medical director, which helps draft company policies on coverage by amalgamating FDA approval, NCCN guidelines, and of course the available evidence on the drug or treatment. Initially, coverage will reflect the FDA label indications, which he said are the strongest indications based on evidence. "Expansion of coverage will take into consideration the NCCN recommendations. Once the drug is commercially available, it's very important to ensure that the right person gets the right treatment."

The Managed Markets

Early this year, *The American Journal of Managed Care* convened a panel discussion that brought together clinicians and payers to address the impact of the increased use of immunotherapy drugs in treating cancer in a managed care setting.[12] The panelists agreed that immunotherapy, especially the newer checkpoint inhibitors, offer a promising approach in oncology. The drugs are currently being employed in refractory/relapsed patients, but the panel members expressed hope that immunotherapy would soon be used in curative and adjuvant settings.

Added Kolodjiez, "The sequence of therapies is important, but that's not very clear yet. We need evidence for determining the sequence of administration of drugs. For example, consider melanoma: you have ipilimumab, B-RAF inhibitors, and the PD-1/PD-L1 inhibitors." The FDA label could provide recommendations, but he suspects it will not.

The novel approach by researchers at the NCI and at Memorial Sloan Kettering is still at an early stage and considered "experimental" by insurance companies. Aetna's policy bulletin states that ACT, using TILs or IL-2–treated lymphokine-activated killer cells, is classified as experimental and investigational therapy since there is not yet sufficient evidence that it is more beneficial than IL-2 alone.[13] Cancer vaccines, specifically for melanoma and ovarian cancer, are also considered experimental therapy due to insufficient evidence of safety and effectiveness.[14] Based on the available information for the drug, ipilimumab is considered necessary for malignant melanomas but experimental and investigational for all other cancers.[15]

Labeled as the "Breakthrough of the Year" in 2013 by *Science* magazine,[16] immunotherapy holds immense promise as an effective treatment—but an expensive one. If expert predictions hold true, employer-sponsored insurance plans have to brace for a big hit, because it is estimated that immunotherapy drugs—expected to treat nearly 60% of all cancers—will cost $35 billion per year within 10 years.[17] Payers, of course, are developing models and algorithms—including reimbursement incentives, guideline-based coverage, pharmacist medication consults, and early intervention—to help reduce the cost of treatment with these specialty drugs.[17]

> ***"The cost discussion surfaces when the magnitude of benefit is small. For treatments that provide greater benefit, there isn't even a discussion."***
> **—Michael Kolodjiez, MD**

When asked about determining the "value" of a particular treatment, Koldjiez said there are 2 important things that need consideration: "What is the outcome in terms of survival benefit, and the magnitude of the outcome in terms of symptom relief? Consider the PD-1/PD-L1 inhibitors as an example. Some patients have an extremely durable response and don't need any more treatment for a long time, and the associated toxicities are minimal. But this is an exception and not a rule. In case of renal cell carcinoma patients, these inhibitors have proved extremely toxic and their effect does not last too long." If a treatment is beneficial, says Koldjiez, the cost does not matter. The cost discussion, according to Kolodjiez, surfaces when the magnitude of benefit is small (a few weeks or months vs years). For treatments that provide greater benefit, there isn't even a discussion.

Although the debate continues, an even-minded approach remains essential. Open conversation among patients, providers, payers, and the pharmaceutical industry will be what ultimately defines "value": be it that of the drug or, more importantly, the patient's life. **EBO**

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ASCO Value Initiative
(continued from cover)

It's important to remember that cost is only 1 component of what really is a question about the "value" of cancer care. Value is defined by more than cost—it includes the clinical outcomes patients can expect from any specific treatment regimen, as well as consideration of costs and side effects. The overall value of care reflects the benefits in quality and quantity of life gained against the physical, emotional, and financial costs of medical intervention.

Figure. ASCO's Value Initiative

ASCO has launched a strategic new value initiative to:

- obtain optimal outcomes at lowest cost
- develop a framework or methodology to assess the relative value of treatment options based on:
  - clinical benefit
  - toxicity
  - cost

ASCO believes that medical decision making must be the result of informed discussions between patients and their physicians in the context of the local care delivery system—with the patient's preferences and goals at the center. ASCO's Board of Directors is developing the value framework to help physicians and patients determine the most appropriate evidence-based high-quality treatment option, considering the patient's clinical status, preferences, and personal and family needs. To achieve the broadest consensus, ASCO plans to solicit input from:

ASCO believes that medical decision making must be the result of informed discussions between patients and their physicians in the context of the local care delivery system—with patient's preferences and goals at the center.

- ASCO members and other oncology providers
- the pharmaceutical industry
- the insurance industry
- patients and patient advocacy groups. **EBO**

Conference Coverage: ASCO 2014

How Do You Establish Value in Cancer Care?

Surabhi Dangi-Garimella, PhD

While the incidence of cancer increases, survival rates continue to improve for even the deadliest of cancers thanks to the ongoing development of novel and targeted therapies. However, innovations in cancer diagnosis and treatment are associated with high cost. Cancer therapy constitutes nearly 11% of the total healthcare budget, and the number continues to trend upward.[1] The National Cancer Institute estimated the costs of cancer therapy at $124.6 billion in 2010, a number projected to touch $207 billion in 2020.[2] With an aging population and improved insurance coverage, that figure will almost surely stay on the rise. The result: patients and providers are very often restricted from choosing the highest quality treatment option due to the burden of associated costs.


Diane Blum, MSW, FASCO

The problems and possible solutions were the focus of an opening-day Extended Education Session at the 50th annual meeting of the American Society of Clinical Oncology (ASCO), held in Chicago from May 30 through June 3, 2014. The session—titled "Can We Find Common Ground? Stakeholder Perspectives on Value in Cancer Care"—began with remarks from session chair Neal J. Meropol, MD, of Case Comprehensive Cancer Center, Case Western Reserve University. Meropol recently coauthored an article on best practice approaches for designing decision-support tools.[3] The article described the rigorous development process and initial feedback of the PRE-ACT (Preparatory Education About Clinical Trials) Web-based intervention, designed to improve preparation for decision making in cancer clinical trials.

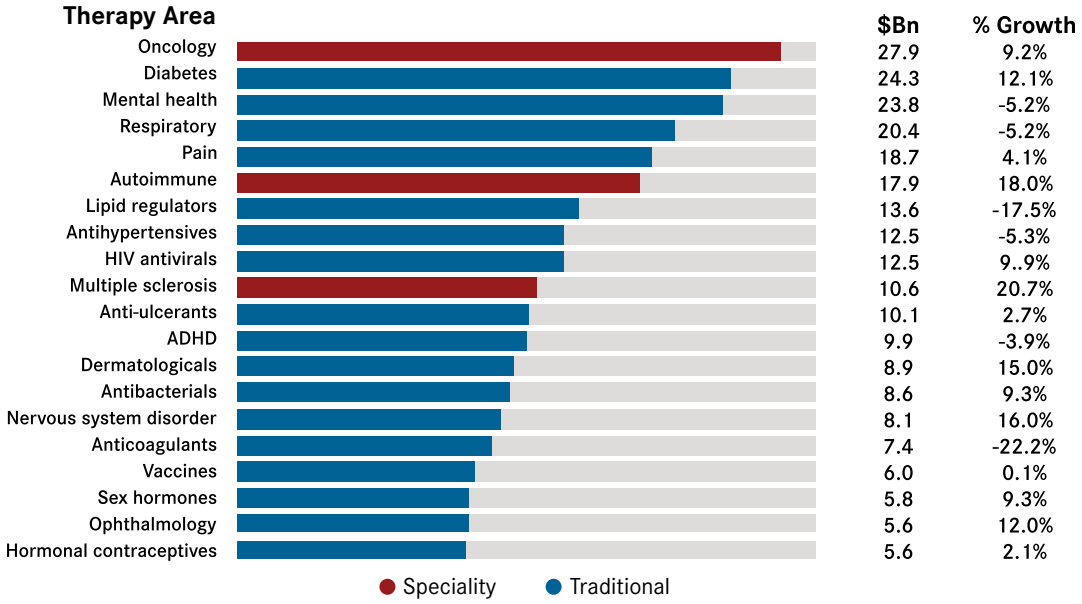

Neal J. Meropol, MD

In his talk, "Value in Cancer Care: What's the Problem?", Meropol defined value as the ratio of benefit over cost. Benefit, he said, is a combination of survival, progression, quality of life, and avoidance of toxicity, while cost is determined by biomarkers, the therapy received, therapy avoided, management of toxicity, and other indirect costs. "Value versus cost-effectiveness is the elephant in the room," he said.

Meropol laid out the problems currently facing the United States:

- Drug approvals based on "safety and efficacy," without cost

Figure 1. Drug Spending in Leading Therapeutic Areas in 2013



- The top 5 classes in 2013 were oncology ($27.9Bn), antidiabetes ($24.3Bn), mental health ($23.8Bn), respiratory agents ($20.4Bn), and pain (18.7Bn).
- Absolute spending growth gains were highest for autoimmune, antidiabetes, and oncology.
- Spending growth was highest in multiple sclerosis, autoimmune, and nervous system disorders.
- Three specialty classes (MS, autoimmune, and oncology) contributed $6.9Bn, or 68% of total growth.
- Spending in 2 therapy areas, anticoagulants and lipid regulators, declined more than 15% due to patent expiries.
- Four of the top 10 therapy areas had declines in spending in 2013, all declining more than 5%.

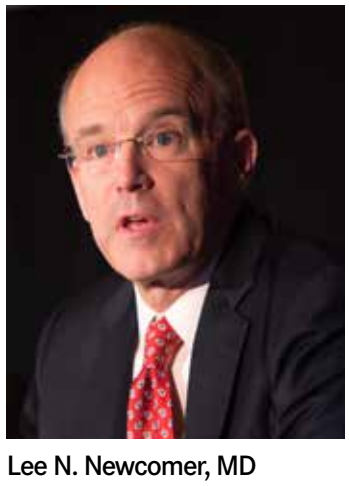
Bn indicates billion; MS, multiple sclerosis. Source: Medicine use and shifting costs of healthcare–a review of the use of medicines in the United States in 2013. IMS Institute for Healthcare Informatics website. http://bit.ly/1qcrzlk. Published April 2014.

considerations
- Producer sets the price for new innovation
- Payers cannot negotiate cost
- Consumers cannot be choosers
- Financial protection, historically offered by insurance, is eroding as cost burden shifts to the patient

"The current system is unsustainable, as it prevents access to high-quality cancer care," said Meropol. However, he pointed out that economic recession, increased cost sharing, payment reductions to providers, increased provider efficiency, and slowed innovation have somewhat moderated healthcare spending. An uptick in spending growth is anticipated, however, as the economy improves and insurance coverage improves, enabling the aging population to increase healthcare spending.

Oncology drug expenditures lead the way in spending among the various therapeutic areas. In this country, $27.9 billion was spent on oncology drugs in 2013, representing an annual increase of 9.2%, according to a recent IMS Institute for Healthcare Informatics study (**Figure 1**). High cost of care can increase disparities in care and patient outcomes, exacerbated by steep co-pays, tiered formularies, the part D donut hole in Medicare, and oncology drug shortages. The result? Patients delay consultations and treatment, and limit or alter their treatment, to the detriment of their health. Hospitals also reduce their spending on charity care.

"The stakeholders need to work together," concluded Meropol, "to find solutions, drive policy, and achieve reform."


Lee N. Newcomer, MD

Next, Lowell E. Schnipper, MD, presented "Defining Value: An ASCO Initiative," to offer insight into ASCO's strategic initiative to define value in cancer care. Schnipper, chief of hematology/oncology at Beth Israel Deaconess Medical Center in Boston and the chair of ASCO's Value in Cancer Care Task Force,[4] spoke about unsustainable trends in the United States: Medicare, he postulated, is a major reason for deficit projections, in addition to cancer costs, which are rising by 15% to 18% annually. Schnipper encouraged the oncologists in the audience to discuss the financial implications of therapy with their patients, asserting that patient-centered care, both financial and health outcomes based, should be a key element when defining value of care.

The main threats to value in healthcare, Schnipper said, include unwarranted variation in quality and outcome; harm to patients; wastefulness of resources and failure to maximize value; health inequalities and inequities; and failure to prevent disease.

A major value initiative introduced by ASCO, the Quality Oncology Practice Initiative (QOPI),[5] aims to remedy these ills by evolving a transparent, clinically driven method for defining and assessing the relative value of cancer care options and finding a balance among clinical benefit, toxicity, and cost. The objective of the task force behind QOPI is to afford providers with the necessary skills and tools to meet those goals, and to give patients ready access to essential information, including how to cope with co-pays that are potentially bankrupting.

"We are not caring about the dollars spent, but rather how well we are caring for the patient. Patient-centric is the best way to go," concluded Schnipper.

Representing "The Patient Perspective," as her talk was titled, was Diane Blum, MSW, FASCO, a former executive director at CancerCare, an organization that provides emotional and financial support to cancer patients and their families.[6]

Blum defined value in various terms. Her favorite was crafted by Scott Ramsey, MD, PhD, of the Fred Hutchinson Cancer Research Center in Seattle: An intervention in cancer care can be described as having value if patients, their families, physicians, and health insurers all agree that the benefits afforded by the intervention are sufficient to support the total sum of resources expended for its use.

"Value is a dynamic process—hopes and expectations change through the continuum of illness and must be assessed regularly, said Blum. "Perception changes from cure to palliation. Value rests not just in clinical response, but also in trying."

How do you help the patient assess value? ASCO's Choosing Wisely campaign aids the process, said Blum. Encouraging ongoing conversation between physician and patient, as well as a shared decision-making process, are usually very beneficial as well.

Lee N. Newcomer, MD, MHA, senior vice president of oncology, genetics, and women's health at UnitedHealthcare, spoke next, providing a payer viewpoint on the increasing cost of diagnosing and treating cancer patients. Newcomer recently published his perspective on innovative payment models and measurements in cancer care, in which he introduced the models being evaluated by payer and physician groups for cost-effective care.[1] These include (1) pay-for-performance (P4P)

programs that reward physicians for meeting prespecified goals, (2) bundles or episode payments, and (3) capitation.[1]

Newcomer emphasized the fact that currently, health insurance premiums equal 50% of the average household income, and by year 2033, they are estimated to surpass the average household income (**Figure 2**).

Gregory P. Rossi, PhD

Addressing insurance benefit design issues, Newcomer said that benefits are not cancer specific, value-based insurance design is hard to implement, and that the site of service distorts benefit. He further added that the value-based insurance (VBI) plan is trying to create a differential between high-value and low-value services.

Noting that barriers to VBI include access to an external, independent source of measurement lto define value, Newcomer pointed out that the Value in Cancer Care Task Force, spearheaded by ASCO, is working to surmount this obstacle. Emphasizing that consumer literacy is extremely important, Newcomer said that value-based programs compel consumers to digest a lot of information that can be overwhelming, especially when survival decisions are in question. Although demarcating boundaries is extremely difficult, it's drawing those lines that will help establish value. The most difficult option to choose, he said, would be not to pay at all. For example, the payer could say: no PET surveillance post therapy, no PSA testing for men with less than a 10-year life expectancy, or no targeted therapy without a predictive biomarker.

"Resources are limited, so using high-value resources and/or eliminating resources with limited or no value is the need of the day," said Newcomer. These decisions, he concluded, are unavoidable.

Speaking next and representing the pharmaceutical industry was Gregory P. Rossi, PhD, vice president of payer evidence at AstraZeneca UK, who oversees coverage and reimbursement submissions and is responsible for outcomes studies as well as fulfilling payer evidence requirements.[7] In "Industry Perspective: Drug Development, Costs, and Return on Investment," Rossi discussed the costs of innovation, research and development (R&D) investment decisions, value-based pricing, and patient affordability. He characterized himself as a proponent of collaboration between research communities and patient communities to advance cancer treatment, he said.

What drives innovation costs and decisions about investments? Rossi noted that success rates in pharmaceutical drug development are about 5%, driving costs per new molecular entity to $3 billion (1 molecule per year for every $3 billion spent). Technical risk, time, and market assumptions all impact investment decisions. Obviously, Rossi noted, treatments directed at small patient populations require higher drug prices to gain returns.

A related issue: value-based pricing. The last 17 oncology drugs approved in the United States offered, on average, 3 months of improvement in survival, but the average monthly cost of each drug, said Rossi, was $65,000. Can this be deemed beneficial? Rossi opined that the National Institute for Health and Care Excellence in the United Kingdom would definitely say "No!" Rossi explained that cost- effectiveness and the willingness-to-pay threshold are very difficult matters, and suggested developing innovative means to evaluate the cost-benefit ratio of new drugs.

"Patient affordability is obviously a big issue," said Rossi. "It is inappropriate to tax the patients with high copays. The pharmaceutical industry has set up assistance programs, but this bandage is not sufficient to fix the current broken system."

Rossi concluded with a slide on ways to find common ground. To confront the burden of illness and the complexity of cancer, he proposed maintaining R&D investment to help discover new targets and develop novel technologies. For cancer-related reimbursement issues, he had 3 suggestions:

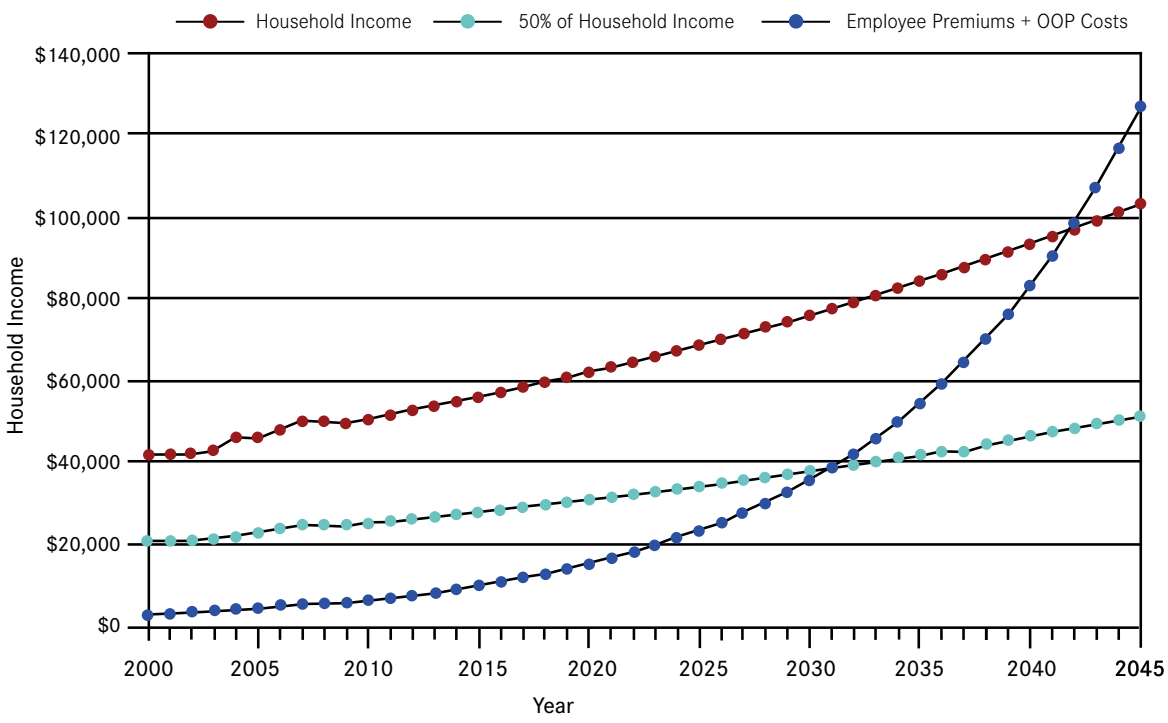
- Maintain reward for meaningful innovation
- Develop a payment process based on indication and clinical pathway adherence
- Continue to refine insurance benefits to reduce the financial risk for patients

Lowell E. Schnipper, MD

The insightful session concluded with "How Should Oncologists Become Value-Based Providers?", presented by Ezekiel J. Emanuel, MD, PhD, vice provost for Global Initiatives and chair of the Department of Medical Ethics and Health Policy at the University of Pennsylvania's Perelman School of Medicine. Said Emanuel: "Let's be honest: it is about cost. We are concerned about value, but we are also concerned about cost. Let's all be honest as a community about where the real cost of cancer care is."

Emanuel—also an oncologist—alleged that expensive treatments are being prescribed despite the availability of cheaper treatment options. The obligation of an oncologist, he said, is to avoid unnecessary testing—when therapeutically equivalent treatment is available, prescribe the cheaper one. Additionally, oncologists should exclude options that do not add value. "This is not a victimless crime—to choose the expensive treatments when cheaper alternates are available," Emanuel said. "I do think we have common ground, but we can't reach it without payment reform and taking steps to choose value-based options." **EBO**

Figure 2. Projected Annual Insurance Cost for a Family Relative to the Average Household Income (United States)



OOP indicates out-of-pocket. Source: Young RA, DeVoe JE. Who will have health insurance in the future? an updated projection. *Ann Fam Med.* 2012;10(2):156-162.

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Multiple Myeloma

MMRF Efforts
(continued from cover)

after years in the pharmaceutical sector, said he expects the next few years to resemble the shift he witnessed from 1996 to 1998 in HIV treatment, with the arrival of both new drugs—protease inhibitors and non-nucleoside analogue inhibitors—and new viral load detection tests.

The ability to both detect HIV more accurately and attack it through multiple channels, Capone said, ended the disease's status as a certain death sentence. By 2012, HIV qualified as a "chronic condition" under the Affordable Care Act.[5]

Multiple myeloma treatment is headed in the same direction, he said. "This couldn't be a more exciting time…the advances that are going on are going to be quite significant and transformational," Capone reported.

Although the declaration of a "cure" for multiple myeloma is well in the future, doctors are much closer to finding one than when the MMRF started. Researchers still don't completely understand what sets the disease in motion, but they know that in a healthy person a delicate balance properly regulates the transition of B lymphocytes into plasma cells as they leave the bone marrow. When the immune system is damaged, this process produces oncogenes instead. Healthy blood cells get crowded out, causing a host of health problems such as fatigue, kidney damage, and calcium deposits. The skeletal system is compromised, and multiple myeloma patients may suffer broken bones from no obvious cause.

Table 1.

Prolaris Score	10-year death rate, %
<0.0	7
0.0-1.0	15
1.1-2.0	36
>2.0	59

Source: Myriad Genetics, May 21, 2014. Summary of data presented at AUA Annual Meeting, Orlando, Florida.

Table 2.

Approved by FDA for Multiple Myeloma	Year
zoledronic acid	2002
bortezomib	2003
thalidomide	2005
lenalidomide	2005
doxorubicin	2006
carfilzomib	2012
pomalidomide	2013

Source: Multiple Myeloma Research Foundation, 2014.

The MMRF sees progress in how multiple myeloma has expanded its presence on the scientific agenda. Advances have taken center stage at recent meetings of the American Society of Hematology[4] (ASH) and the National Comprehensive Cancer Network (NCCN). At NCCN's spring meeting, Kenneth C. Anderson, MD, director of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute, and chair of the steering committee for the MMRF's scientific arm, the Multiple Myeloma Research Consortium, proudly told his colleagues, "I want you to get excited about the future…we think we're about to get a monoclonal antibody or two."[5]

A central feature of multiple myeloma, and a challenge of treatment, is how the disease behaves differently from patient to patient. Even in a given person, it must be attacked on multiple fronts. Thus, the MMRF supports research into many different types of drugs, while also spearheading the science that examines myeloma's genetic underpinnings.

In the necessary diversity of approaches, "It's like an investment portfolio," said Capone.

Drawing on the HIV comparison, he foresees breakthroughs in both the diagnostic and therapeutic areas: next-generation sequencing and circulating tumor cell detection strategies, as well as whole new classes of drugs. There are elotuzumab and daratumumab, the antibodies that Anderson referenced at NCCN. Capone also sees promise in the histone deacetylase inhibitors, which are being studied in combination with bortezomib and dexamethasone in patients with relapsed myeloma.[6]


Walter M. Capone

> *"The advances that are going on are going to be quite significant and transformational."*
>
> **—Walter M. Capone,**
> MMRF President and CEO

Capone also pointed to Millennium's late phase 3 trials on what would be the first oral proteasome inhibitor. Results presented at ASH 2013 in New Orleans showed a combined complete response and very good partial response rate of 76% (46/62), and a 94% overall response rate (58/62 ≥ partial response.)[7]

The Genetic Foundations

MMRF's most ambitious project to date may be its CoMMpass Study, an effort to track 1000 multiple myeloma patients for at least 5 years each.[8] Patients enrolled in the study will provide a tissue sample when they are newly diagnosed, and then provide additional samples each time their disease relapses. The goal is to examine how each patient's molecular profile affects the progression of the cancer, with the hope of not only tailoring treatment for that individual patient but also developing an increasingly rich database, one that will propel the discovery of more effective targeted therapies with each passing year.

CoMMpass patients come from a variety of treatment settings, and its data are open to clinicians and researchers. All this is by design, Capone said, to facilitate clinical trials and to aid treatment for patients far from academic research centers. When asked if MMRF had a position on whether pharmaceutical or diagnostic testing companies should share patients' genetic data, Capone strongly supported making data available for all researchers:

"I've got a particularly strong emotional and practical position," he said. "It's the patients' data," and, thus, does not belong to any one company.

"The fact that industry in its various forms might to try optimize it, well, that's only wonderful if it's for the patients' benefit. When that becomes secondary and subordinated, that's a fundamental problem. And that's why we put the data on a public portal."

MMRF's efforts in genomics predate the 2011 launch of the CoMMpass study. In 2005, the foundation started its Multiple Myeloma Genomics Initiative, which gathered 250 tissue samples for study.[9] Those efforts bore fruit in March 2011 with the publication of an article in *Nature*.[10] Researchers examining the first batch of tumor genomes collected by the MMRF observed mutations of the kinase *BRAF* in 4% of the patients, suggesting that *BRAF* inhibitors should be studied in multiple myeloma patients in clinical trials.[10]

As a result, new therapies that have been highly successful in treating metastatic melanoma patients—vemurafenib, trametinib, and dabrafenib—are now at various trial stages for multiple myeloma patients with *BRAF* V600E and V600K mutations.[11-14]

Is Screening in the Future?

The diversity or heterogeneity of mul-

tiple myeloma means that what works in one patient might fail in another. As Giusti discovered shortly after she was diagnosed, that's what kept pharmaceutical companies from investing in multiple myeloma for so long.

The rise of genomic research is the game changer. It offers the ability to build clinical trials around therapies that have already worked in other cancers, or to include multiple myeloma patients in trials for new therapies aimed at a particular mutation seen in many cancers. This is already happening with the *BRAF* mutations. But as this strategy unfolds, it will mean attacking the disease on many fronts. That will mean many drugs. And that could get very expensive.

Kathy Guisti

A panel convened recently by *The American Journal of Managed Care* (**see related story, below**) discussed the cost implications for payers as multiple myeloma patients live longer with the disease. One clinician, Jack Goldberg, MD, of Penn Presbyterian Medical Center in Philadelphia, said it was essential to get better at treating the disease earlier. Not everyone agreed that screening for multiple myeloma made sense, since it might not be treated right away, causing patients undue stress.

Capone, however, sees a future for screening among persons older than 60 years. Screening could become routine, just as colonoscopies and prostate-specific antigen (PSA) tests have, he said. Identifying biomarkers for multiple myeloma, and certainly catching more cases at the "smoldering" stage, while figuring out ways to prevent full-blown disease, makes tremendous sense.

"From an intervention standpoint, therapies that involve the priming of, or strengthening of, the immune system to identify and mitigate aberrant cell development offer the best benefit for patients," Capone said. "It's much less expensive to treat it early." **EBO**

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AJMC Panel: Advances in Multiple Myeloma Therapy Extend Survival for Patients, Raising Cost Concerns

Written by Mary K. Caffrey

Produced by Nicole Beagin

It's a concern that only comes when cancer therapy succeeds: as the length of survival for the typical multiple myeloma patient has nearly tripled, the number of patients living with the disease has also increased.[1] Today, this blood cancer that was once a blip on the radar screen for insurers is slowly catching their attention as the cost of care increases, both for individual patients and gradually, across payment systems.

The American Journal of Managed Care recently convened a panel that included clinicians and representatives from the payer community and the Multiple Myeloma Research Foundation (MMRF). The group discussed the rapid advances in diagnosis and treatment of the disease. But as patients are living longer and therapy regimens become more complex, the cost of care is rising for this still relatively uncommon blood cancer.

Joining moderator and *AJMC* co-editor-in-chief **Michael Chernew, PhD,** were **Shaji K. Kumar, MD**, professor of medicine, Mayo Clinic; **Jack Goldberg, MD,** clinical professor of medicine, Penn Presbyterian Medical Center; **Gene Reeder, RPh, PhD**, director, Managed Care Networks, Xcenda; and **Anne Quinn Young, MPH,** vice president, Development and Strategic Partnerships, MMRF.

According to the MMRF, about 24,000 new patients will be diagnosed in the United States in 2014.[2] Over the past 2 decades, advances in therapy and the use of stem cell transplants have revolutionized care and increased average survival from 3 years to about 8 years, according to Kenneth Anderson, MD, director of the Jerome Lipper Multiple Myeloma Center at Dana Farber Cancer Institute, who in March gave the multiple myeloma update at the 19th annual con-

The evolution of multiple myeloma from hard-to-treat blood cancer to a chronic disease means that it will likely become expensive for payers as patients live longer, Goldberg said, although this may be offset by more years of productivity and quality of life.

ference of the National Comprehensive Cancer Network (NCCN).[3,4]

Screening and Diagnosis

Chernew asked how diagnosis of multiple myeloma has changed, and what the optimal practice would be for early screening. Kumar said routine screening of everyone over a certain age was impractical, as it would identify persons for whom there were no therapeutic options, and "would only contribute to anxiety."


Michael Chernew, PhD

That said, there is a group for whom the disease should be identified well before the onset of the "CRAB" criteria: elevated calcium levels, renal failure, anemia, and bone failure. "At that point it may be too late," Kumar said. Techniques such as examining circulating tumor cells, while not new, are becoming more precise in their prognostic value. The challenge is finding the optimal way to identify patients with myeloma early. For years, advances in treatment of multiple myeloma stalled because of the very nature of the disease, which presents differently from patient to patient and thus was not a good candidate for investment by the pharmaceutical sector. But the advancement of genomics, in which researchers identify the mutations that cause the varieties of myeloma, is allowing multiple myeloma patients to join clinical trials of therapies aimed at mutations that occur across multiple cancers.


Gene Reeder, RPh, PhD

Potentially quite fruitful is the CoMMpass Study, an effort by the MMRF that Anne Quinn Young discussed. CoMMpass seeks to gather tissue from 1000 patients at diagnosis and at each time the patient experience a relapse. The effort, Young said, will yield data about 3 kinds of sequencing: whole genome, exome, and RNA. Hopefully, "this will help give us a better understanding of the natural history of the disease and give us some clues to better precision medicine approaches," she said.

Getting an early diagnosis does not mean a patient must be treated, Goldberg said. "It means better outcomes," he said. Even if treatment is not immediate, patients can make lifestyle changes such as eating healthier foods and avoiding alcohol. Finding the fine line in "smoldering" myeloma—the optimal time, after diagnosis but before symptoms appear, when treatment should start—remains the challenge.

While Goldberg is hopeful that biomarkers may someday help pinpoint that line, thus far some biomarkers under study "are not ready for prime time. "It may take years, he said, "before these experimental markers are going to be able to tell us what the future will be."

A Revolution in Treatment

Kumar explained that treatment advances have 2 pathways: changes due to new therapies, and changes due to better understanding of multiple myeloma's biology.

New drugs such as bortezomib and thalidomide have already changed the treatment landscape for the disease. Excitement is building because there aren't just several new drug classes. As at NCCN in March, Kumar spoke animatedly about the clinical trials involving monoclonal antibodies (elotuzumab and daratumumab).


Shaji K. Kumar, MD

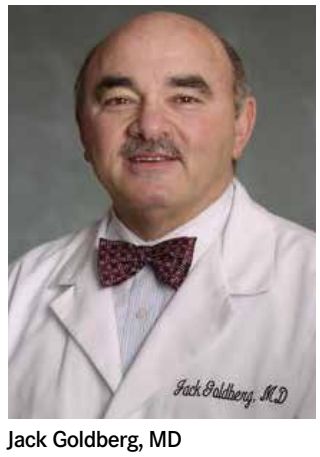
"The second half of the story is the changing understanding of the science," Kumar said. In the past, the approach to therapy was "hit and run," but today, clinicians know that "the bottom line is that patients need a couple of years' worth of therapy, or even more. This is dictated by the underlying biology," he said, as myeloma must be treated chronically to keep it under control.

That is possible, Goldberg said, because the newer drugs are much less toxic than their predecessors. Longer treatment periods achieve a "deeper" response, and "That's where the benefit has been seen the most," he said.


Anne Quinn Young, MPH

A simple truth, he said, is that to treat a patient with cancer, "You've got to be able to deliver the drug." If the side effects are so awful that the patient can't tolerate them, then the therapy has limited value.

The challenges today, Goldberg said, often involve dosing, and how to use the growing number of options in combination. The concept of "minimum residual disease" or MRD, is also new to myeloma, because until recently, patients never got to that point, he said.


Jack Goldberg, MD

Concerns for Payers

The evolution of multiple myeloma from hard-to-treat blood cancer to a chronic disease means that it will likely become expensive for payers as patients live longer, Goldberg said, although this may be offset by more years of productivity and quality of life. Kumar noted that some drugs that treat the disease will soon come off patent, which will mitigate costs somewhat. But the clinicians explained that the complexity of the disease and its heterogeneity means that treatment will always be very individualized, and that many patients will be on multiple drugs at once.

Both Goldberg and Kumar said that thus far, insurers have largely not balked at paying for multiple myeloma therapies, with the possible exception of oral therapies. But they said that could change as monoclonal antibodies near approval, and the variety of available options increases again.

"The insurer market is concerned about all these things," said Reeder. While it's clear that patients have benefited, he said, payers will likely reach a point of determining which patients will benefit from which therapy, and establishing a "stopping rule" to handle requests to repeat therapies that have already failed.

Young said one outcome of the CoMMpass study will be its guidance for precision medicine. It will show which patients can be helped with drugs that are off-patent, as well as which patients only need perhaps 2 drugs.

The most important task, the panelists agreed, will be making improvements in tackling myeloma at the outset. Said Goldberg, "We have to figure out how to do the best job in the beginning." **EBO**

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AJMC Panel Asks: Does it Pay to Use Pathways?

Written by Mary K. Caffrey

Produced by Nicole Beagin

Clinical care pathways in oncology have been discussed for some time as a strategy for controlling healthcare costs. These "road maps" guide the treatment protocol depending on how the disease progresses. Pathways have supporters and opponents, but they are gaining notice: WellPoint announced a $350 per patient per month incentive on May 27, 2014, in *The Wall Street Journal*[1] during the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

Peter Paul Yu, MD

WellPoint's pathways initiative began in 6 states on July 1, 2014. With that effort set to begin, *The American Journal of Managed Care* convened a panel, with voices from the payer and provider realms, to discuss how pathways are changing cancer care. **Seema Sonnad, PhD**, associate editor and director of Health Services Research at The Value Institute at Christiana Care Health System, led the discussion.

Joining Sonnad were ASCO President **Peter Paul Yu, MD**, who is director of cancer research at Palo Alto Medical Foundation; **Jennifer Malin, MD, PhD,** medical director for Oncology Care Management, WellPoint; **Chadi Nabhan, MD, FACP**, associate professor of medicine, hematology and oncology section, and medical director, Clinical Outpatient Cancer Center, University of Chicago; and **I.W. Tischler, MD**, national medical director, oncology, Cigna.

Jennifer Malin, MD, PhD

When the president of ASCO says that healthcare spending is "unaffordable" and "unsustainable," it's little surprise that both insurers and leading physicians are looking for ways to bend the cost curve. In cancer care, clinical pathways are gaining ground among payers and some providers, although how well they will work and how much they will save remains unknown.

"We have an unaffordable, unsustainable healthcare system," Yu said at the start of the discussion, describing the challenge that confronts cancer care. With an aging population, the prospect of more cancer patients, and new, expensive drugs to treat them, how does the system allocate limited resources? "We need to get a handle on the rising costs of care," he said.

What are pathways? Nabhan said there's a "gray area" between clinical guidelines, such as those developed by the National Comprehensive Cancer Network and ASCO, and pathways, which account for real-world situations like side effects, and, of course, the cost of therapy. Not all pathways are alike, the panelists agreed; some direct toward a "single best treatment," while others offer 3 to 4 options. And, once a patient progresses past second- or third-line therapy, the judgment of the oncologist starts to replace the protocols. Pathways are still a new concept, and several speakers credited US Oncology with both pioneering the concept and publishing data from the experience.

Pathways differ from guidelines in that they confront cost, a factor that physicians historically avoided; it was not considered ethical to do so. But with the rising costs of cancer care, and the out-of-pocket expenses patients face, doctors and health plans have little choice. The new term "financial toxicity" refers to the effect that these burdens have on patients, and their families, as they undergo treatment. Yu and Tischler agreed that oncologists had to be good stewards of this realm. "This is going to enhance the patient experience," Tischler said. "We are really stewards not only of our individual patients, but of the population as well."

Pathways seek to reduce the variability out of the system, not only to

WellPoint Initiative May Challenge Some Practices

Mary K. Caffrey

Ted Okon

The insurer WellPoint made news in late May when it promised to pay $350 per month per patient to those oncologists who adhered to its cancer care clinical pathways.[1] While the use of pathways is not new, this particular incentive appears to be a game changer, albeit one that not all think is a good idea.

Smaller oncology practices, which already face competitive disadvantages under healthcare reform, will struggle if they must keep track of multiple pathways for different insurers, said Ted Okon, executive director of the Community Oncology Alliance. "The idea that each payer has a different pathway is not sustainable; it's totally unworkable," he said. Okon told *Evidence-Based Oncology* he was aware of a practice that now has 5 different pathways it must track; WellPoint's program alone includes protocols for breast, lung, and colorectal cancer.

The WellPoint program, which began July 1, 2014, in Kentucky, Indiana, Missouri, Wisconsin, Ohio, and Georgia, will expand nationwide throughout 2015.[1] The initiative follows the release of studies over the past 2 years that show pathways can help reduce costs without harming the quality of care. In May 2013, *Evidence-Based Oncology* published a study by Cardinal Health Specialty Solutions, with Bruce A. Feinberg, DO, as the lead author, that showed an oncology pathways program could trim cancer care costs by 15% and reduce hospital admissions by 7%.[2] More recently, UnitedHealth announced results from a 3-year pilot study involving 810 patients that produced a 34% reduction in cancer care costs. The study was published in the *Journal of Oncology Practice*.[3,4]

But because pathways seek to narrow treatment options beyond guidelines published by the National Comprehensive Cancer Network, the prospect of every health plan having its own protocols for reimbursement has unsettled some oncologists, especially those outside major hospital systems. Community oncologists lack the infrastructure to juggle multiple pathways protocols, Okon said, and he warned that this trend could be "another nail in the coffin" of community care. Meanwhile, other studies show that cancer drug costs, which are a prime target of savings in pathways, soar if the patient is treated in a hospital or hospital-owned clinic instead of a community practice.[5]

"I understand WellPoint's drive toward trying to get a handle on costs," Okon said. However, he said, "Pathways are not a panacea. They are a tool." If too much judgment is taken from individual physicians, "It's a slippery slope to a regimented formulary."

Okon warned that with the onset of the Affordable Care Act, there are multiple pressures on community oncologists. Because many newly insured selected the lower-cost silver or bronze plans, pressure will mount to use narrow networks and formularies to control the costs of care. "We've only seen the tip of the iceberg," he said. **EBO**

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WellPoint Hopes a Name Change Will Ensure a New Tide of Consumers

Surabhi Dangi-Garimella, PhD

With a consumer-focused approach, the second-largest healthcare provider in the United States has announced plans to change its corporate name to Anthem, Inc, the company it merged with a decade ago.[1] The merger in 2004 between Anthem Inc and WellPoint Health Networks Inc created the giant conglomerate that is WellPoint Inc.[2]

In the press release making the announcement, Joseph Swedish, president and CEO of WellPoint said, "As consumer engagement is heightened, we recognize that brand–an indicator of trust and a predictor of willingness to engage–is going to be of increasing importance. We believe it is important to call ourselves by the name that people know best–Anthem. Changing the corporate brand to Anthem is an important expression of our commitment to serve as a trusted partner in health."[1]

Following the merger, WellPoint used the Anthem brand to cover 14 of its Blue-plan states, while the WellPoint name was used in investor materials and social media activities.[3] Following implementation of the Affordable Care Act, insurance marketplaces (exchanges) were created across states, which saw a tremendous rise in WellPoint's enrollment numbers early this year. "There's been a major pivot to a more consumer-focused approach. The Anthem brand is better-recognized among consumers, and we're not going to swim upstream any longer," said Swedish in an interview with the *Wall Street Journal*.[3] **EBO**

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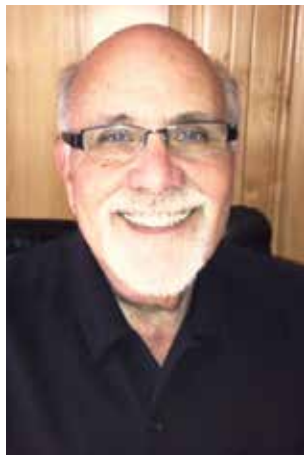
control cost, although that is a goal, but also to improve care by bringing more focus to evidence-based guidelines, panel members agreed. That said, pathway compliance will never be 100%, nor should it be; each patient is different, and pathways must provide enough leeway for clinicians to tailor treatment toward individual needs and responses to treatment. The panelists agreed that about 80% compliance to predetermined pathways could be expected.

Yu called for improvements in technology, and better integration of electronic health records with pathways, which he said would allow oncologists to record why they deviate from pathways. This could lead to more frequent updates and improvements in care.

What will make pathways successful? Payer and provider representatives on the panel agreed that "buy in" from treating clinicians was crucial. "You have to have people believe that it's a transparent process of pathway development that they respect and feel they had a voice in," Yu said. Whether institutions use pathways developed by an outside vendor or build them in-house, it's essential to have representation from "across the spectrum of academic and community medicine" of care, he said. "That helps build trust into the decisions," said Yu. He believes that the medical literature doesn't always reflect the reality on the ground, and providers can bring that reality into pathway design.

Malin said WellPoint considered using an outside vendor for its pathways but ended up using in-house expertise, consisting of oncologists and pharmacists, who developed the protocols in a process not unlike that used to place therapies on a formulary. Internal teams of oncologists and pharmacists put together summaries based on efficacy, quality of life, and cost. The external advisory group members came from community and academic oncology practices, including National Cancer Institute–designated institutions, she said. WellPoint's pathways are available through an online portal, and forms of feedback come both weekly and quarterly, Malin said.



I.W. Tischler, MD

The essential element of WellPoint's program is that it offers rewards, not penalties, Malin said. If providers deviate from the pathway, which is anticipated, "They will still get reimbursed," she said. "But if they are on the pathway, (they are eligible for) additional reimbursement for treatment planning and care coordination."

Yu said incentives are preferable to penalties at this stage, since pathways are new. "You're trying to change people's thinking in a positive manner," he said.

> *"Our pathway is about rewarding quality care. We're not going to exclude something from the pathway simply because it's more costly. Pathways, like the rest of clinical medicine, is an iterative process—a groundbreaking therapy that is going to change the care for a large percentage of patients with particular tumor type—that would need to be put in the pathway right away."*
>
> **—Jennifer Malin, MD, PhD**

What about the most expensive drugs? Malin said that while WellPoint's pathways plan aims to bend the cost curve, it will not keep cutting-edge therapies away from patients if the evidence shows they save lives.

Chadi Nabhan, MD, FACP

"Our pathway is about rewarding quality care," she said. "We're not going to exclude something from the pathway simply because it's more costly. Pathways, like the rest of clinical medicine, is an iterative process—a groundbreaking therapy that is going to change the care for a large percentage of patients with a particular tumor type—that would need to be put in the pathway right away." By contrast, a therapy that would only affect a small share of patients would be added more slowly; for other therapies, as evidence accumulates, a therapy may have better or worse toxicity or effectiveness, and thus may be added or dropped, Malin said.

Among the challenges, and opportunities, of pathways is the fact that the evidence needed to include therapies in practice might be based on different criteria than in a clinical trial. More emphasis might be placed on toxicity and other side effects, or on "value," which involves survival-versus-cost calculations, and that's where judgments get complicated.

"You can't exclude an expensive drug just because it's expensive," Nabhan said. His main concern is that it can take time to gather evidence to determine the value of a new therapy; what is the right amount of time to include a drug in the pathway?

Yu emphasized that pathways must be dynamic, living vehicles that are constantly revised to include new findings. This is where better integration with technology will be critical, he said: if a regimen that was well-followed suddenly falls out of compliance with the pathway, it would be an indication that there's a new study that should be reflected in a pathway update.

As Nabhan noted, "We don't have a metric to decide, 'What is the cost of one life saved for how long?' We really don't—that is the elephant in the room—it's critical to address at some point." **EBO**

Reference

1. Mathews AW. Insurer push to rein in cancer spending. *The Wall Street Journal.* http://online.wsj.com/articles/insurer-to-reward-cancer-doctors-for-adhering-to-regimens-1401220033. Published May 27, 2014. Accessed July 2, 2014.

GRANIX™
(TBO-FILGRASTIM)
Injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
GRANIX™ (tbo-filgrastim) Injection, for subcutaneous use

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome (ARDS)

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

5.3 Allergic Reactions

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

5.4 Use in Patients with Sickle Cell Disease

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

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

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

Leukocytosis

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

6.2 Immunogenicity

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-filgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In the embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC_{0-24}) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No case of overdose has been reported.

TEVA Oncology

Manufactured by:
Sicor Biotech UAB
Vilnius, Lithuania
U.S. License No. 1803

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Product of Israel
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This brief summary is based on TBO-003 GRANIX full Prescribing Information.

GRANIX™
(TBO-FILGRASTIM)
Injection

Take a bite out of G-CSF acquisition costs*

GRANIX™ is another option in short-acting G-CSF therapy

GRANIX™ is an option for hospitals and payers to consider when determining health system budgets

- **FDA approved through the rigorous BLA† process**
- **Teva's short-acting G-CSF was first introduced in Europe in 2008 and is available in 42 countries‡[1]**
- **GRANIX J Code: J 1446-Injection, tbo-filgrastim, 5 micrograms, effective January 1, 2014**

†Biologics License Application.

‡As of February 2014.

*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

Indication

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

Important Safety Information

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

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

For more information, visit GRANIXhcp.com.

Reference: 1. Data on file. Teva Pharmaceuticals: Filgrastim MA Approvals Worldwide. February 2014.

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