Bridging the gap between payer and provider perspectives

May 2014
Volume 20
Special Issue 7

THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based Oncology™

Technology

The Role of Bioinformatics in Oncology Drug Development—and Precision Medicine

Surabhi Dangi-Garimella, PhD

Oncology drug development, a burgeoning therapeutic field for pharmaceutical companies, is also extremely time consuming and expensive. Navigating a single drug moiety through the tedious process of preclinical studies, clinical trials, and of course the FDA's approval process is a net investment of 12 to 15 years and over a billion dollars.[1] This, added to the failure rates of clinical trials (5 of the top 10 clinical trial failures in 2013 were of drugs for cancer indications[2]) makes it imperative that the discovery and development process be streamlined to be cost-effective and timely.

Arathi Krishnakumar, PhD

GenBank, an all-inclusive, open-source database initiated by the National Center for Biotechnology Information (NCBI), has a very important role to play in this process. GenBank includes nucleotide sequences for more than 280,000 species and the supporting bibliographies, with submissions from individual laboratories as well as large-scale sequencing projects. Addi-

(continued on page SP225)

Commentary

Choosing a BRCA Genetic Testing Laboratory: A Patient-Centric and Ethical Call to Action for Clinicians and Payers

Ellen T. Matloff, MS,[1] Rachel E. Barnett, MS,[1] and Robert Nussbaum, MD[2]

[1]Yale Cancer Genetic Counseling, Yale Cancer Center, Yale School of Medicine
[2]Division of Medical Genetics, University of California, San Francisco School of Medicine

Genetic testing laboratories are using aggressive and manipulative tactics to capture market share in the BRCA testing market. Clinicians and payers are encouraged to utilize patient-centric criteria, including open access to data, to make decisions about genetic testing laboratories.

Ellen T. Matloff, MS

The past 12 months in the world of cancer genetic counseling have been more notable, perhaps, than the past 12 years combined. In May 2013, Hollywood icon Angelina Jolie went public with her BRCA1+ status, thrusting the field of cancer genetic testing and counseling into the spotlight and increasing referral rates to clinics by as much as 40% (E. T. Matloff, MS, oral communication, July 2013).[1] One month later, the US Supreme Court unanimously ruled against the validity of patents that lay claim to genomic DNA in Association for Molecular Pathology v Myriad Genetics, Inc.[2] Within hours, multiple laboratories began offering more comprehensive genetic testing for the hereditary breast and ovarian cancer genes BRCA1 and BRCA2, and at half the cost. The battle for the multi-million-dollar BRCA testing market had begun.

(continued on page SP229)

Paying for Diagnostics

When Science Outpaces Payers: Reimbursement in Molecular Diagnostics

Mary K. Caffrey

For several years, the future of cancer care has revolved around "personalized medicine." This process leverages all that can be learned about a patient's tumor from genetic or protein characteristics, and treats the cancer with a therapy or cocktail that matches the tumor's profile, based on clinical trials.

The development of highly sophisticated tests, which pair cancers with custom treatments, has become its own scientific frontier. Scientists and companies pushing these edges say when targeted therapy succeeds, it's worth every dollar spent, not only in lives saved but in costs avoided—on expensive chemotherapies that would not have worked, or hospital costs from avoidable side effects, or both.[1]

"Personalized medicine can change the trajectory costs in our healthcare system," said Mark Capone, president of Myriad Genetic Laboratories. Based on his meetings with payers, he believes they are seeing the value.

But not everyone agrees. Many see the industry at a crossroads, with reimbursement issues at the center. The future of molecular diagnostics is both entwined in the broader discussion of paying America's healthcare tab and its own separate beast, for reimbursement issues present a steep scientific and regulatory challenge. Almost everyone who spoke with *Evidence-Based Oncology* predicted an industry shakeout would occur. Some promising small companies will join large ones, while others will disappear. (An example: Myriad Genetics' acquisition of Crescendo Bioscience, and its rheumatoid arthritis test, for $270 million.[2])

(continued on page SP230)

Higano Carroll Purcell

AJMC.com

Partner of Center For Value Based Medicine®

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

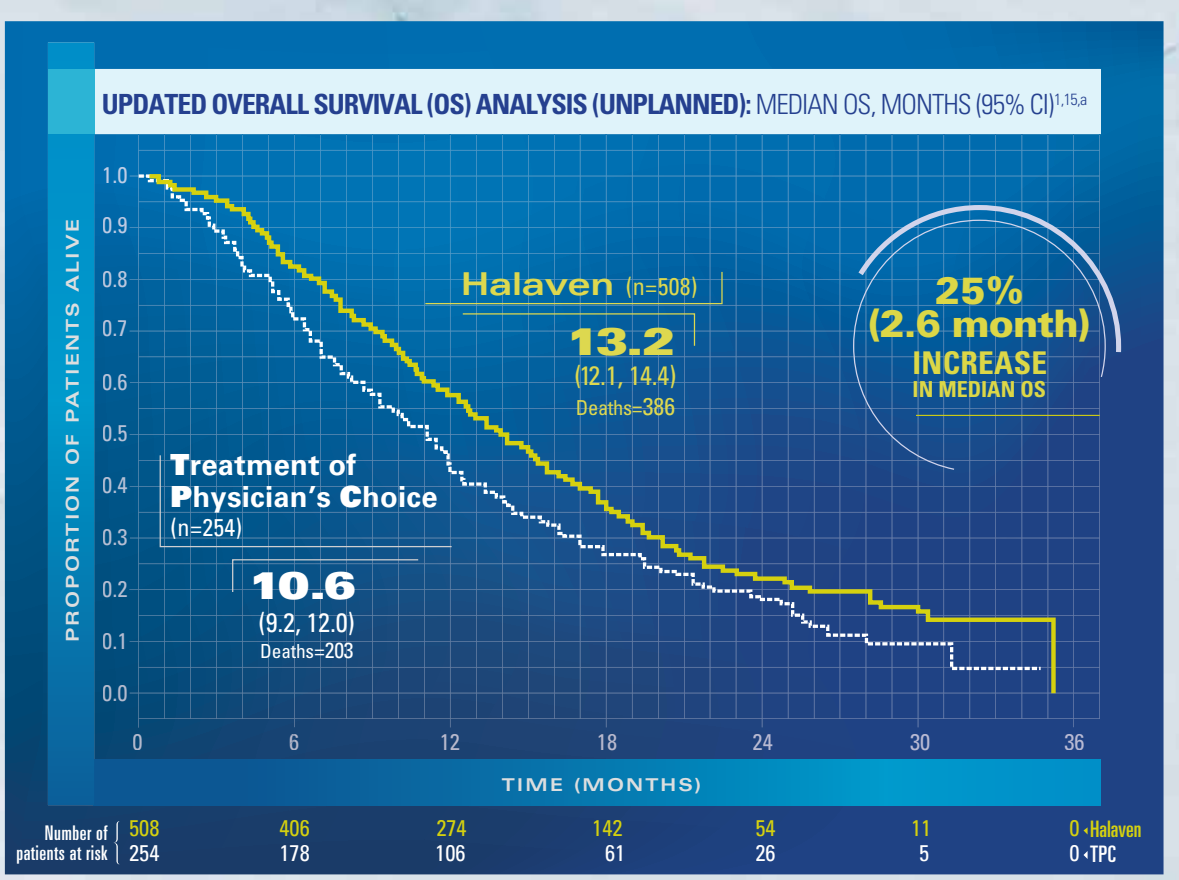
- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

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

The American Journal of Managed Care ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 666 Plainsboro Rd, Bldg. 300, Plainsboro, NJ 08536.

Scan here to visit ajmc.com

We are very excited to present to you the third issue of *Evidence-Based Oncology* for the year 2014.

We offer commentaries on 2 very significant developments in the healthcare world. The first, written by Troyen A. Brennan, MD, MPH, chief medical officer at CVS Caremark, provides insight into CVS's decision early this year to stop selling tobacco products in its stores nationwide by October 2014. "As a company of 26,000 pharmacists, nurse practitioners, and physician assistants who provide trusted advice to 5 million customers each day, selling tobacco products contradicts our core commitment to healthcare and our growing role as an integral part of the healthcare system," writes Brennan.

The other commentary that sits right on the cover is a collaborative opinion piece by Ellen Matloff, MS, Rachel E. Barnett, MS (both of Yale Cancer Genetics), and Robert Nussbaum, MD (UCSF Division of Genetic Medicine), which highlights certain ethical issues that have emerged following a decision by the US Supreme Court against Myriad Genetics last year, preventing the patenting of genomic DNA. A story on the reimbursement regulatory process between CMS and manufacturers (such as Myriad) of molecular diagnostic/companion diagnostic tests—a big boost to personalized medicine—complements the commentary.

The commentary on the cover highlights ethical issues that have emerged following the Supreme Court's decision against Myriad last year; it is complemented by a story on the reimbursement negotiations between CMS and diagnostics companies.

The issue also includes several articles evaluating the influence of technology on drug development, diagnostics, and healthcare management.

The first of the technology articles on the cover highlights the importance of taxpayer-supported databases such as GenBank and their immense impact on drug development. This open-access database, a platform on which scientists share gene sequences and associated findings, is also the foundation for the development of *personalized/precision medicine*. A later-stage application, of course, is the *adaptive* clinical trial design, wherein predetermined end points (based on certain biomarkers) provide the flexibility to alter regimens or halt trials early, thereby ensuring improved outcomes.

The second technology article draws attention to the extraordinary influence of information technology platforms in healthcare—from phone apps to hospital networks. According to Nicolaus Henke, director at McKinsey & Company, "Why is Big Data emerging in healthcare now? There are really 3 reasons. We have so much more captured, machine-readable data available to us than we did just a few years ago. The second reason is that it's much cheaper and easier to link these data. The third reason is a big imperative to understand population health better… it's important both for outcomes and costs."Additionally, there's in-depth coverage of the National Comprehensive Cancer Network's 19th annual conference, *Advancing the Standard of Cancer Care*, held in Hollywood, Florida, with updates on cancer guidelines. The increased risk of cancer in obese individuals and the recent strides in stem cell research form the rest of the package.

Stay tuned for coverage of the 50th annual ASCO meeting to be held in Chicago, May 30 to June 3, 2014; and as always, check for updates on www.ajmc.com.

Sincerely,

Brian Haug
President, *The American Journal of Managed Care*

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.

Everolimus in Elderly Hormone-Receptor–Positive Advanced Breast Cancer Patients

Funding: Novartis Pharmaceuticals Corporation

Data discussed in this letter were presented at the 2012 American Society of Clinical Oncology Annual Meeting; June 1-5, 2012; Chicago, IL (Abstracts 551 and 559); and at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX (Poster P6-04-02).

Everolimus in Elderly Hormone-Receptor–Positive Breast Cancer Patients

To the Editors:

I read with great interest the article entitled "Breast Cancer: Will Treatment Costs Outpace Effectiveness?" by MP Zimmerman et al, published in the December 2012 issue (Volume 18, Special Issue 5, SP200-SP202) of *The American Journal of Managed Care*. In response to the authors' discussion regarding the potential for treatment costs to outpace effectiveness in breast cancer, I would like to provide clarification, specifically with respect to the effectiveness of everolimus combined with exemestane to treat patients older than 65 years.

The authors accurately reported the overall results from BOLERO-2, a phase III trial (N = 724) with everolimus, a mammalian target of rapamycin (mTOR) inhibitor, in postmenopausal women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) that was refractory to nonsteroidal aromatase inhibitors (NSAIs). Results of this trial show that treatment with everolimus plus exemestane improved progression-free survival (PFS) by 4.6 months, from 3.2 months with exemestane alone to 7.8 months with the combination therapy (local assessment, hazard ratio: 0.45; 95% CI: 0.38-0.54; P <0.0001).[1] Although overall survival at the time of interim analysis was not mature, results at the median 18-month follow-up assessment showed that fewer deaths occurred among patients treated with everolimus plus exemestane compared with those treated with exemestane alone (25.4% vs 32.2%).[1]

Exploratory subgroup analysis of the BOLERO-2 trial at a median 18-month follow-up visit showed that for patients younger than 65 years and patients 65 years and older, improvements in PFS, overall response rate (ORR), and clinical benefit rate (CBR) were observed with everolimus + exemestane versus placebo + exemestane (**Table 1**).[2] Additionally for patients younger than 70 years and 70 years and older, improvements in PFS ORR and CBR were observed with everolimus + exemestane versus placebo + exemestane (**Table 1**). The safety profile of EVE + EXE in elderly patients with advanced BC was consistent with the known overall profile of each agent.[2]

In conclusion, contrary to the claim put forth by Zimmerman et al, results from the BOLERO-2 trial show that patients younger than 65 years and those 65 years and older with HR+ HER2– BC have the potential to benefit from treatment with everolimus + exemestane. Currently, everolimus, in combination with exemestane, remains the only mTOR inhibitor approved by the FDA for managing patients with HR+ HER2– BC that is refractory to NSAI therapy.

Table. Efficacy Measures of the BOLERO-2 Study by Age[2]

	<65 years		≥65 years	
	Everolimus + Exemestane (n = 290)	Placebo + Exemestane (n = 159)	Everolimus + Exemestane (n = 195)	Placebo + Exemestane (n = 80)
PFS	8.31	2.92	6.83	4.01
HR (95% CI)	0.38 (0.30-0.47)		0.59 (0.43-0.80)	
ORR	15%	0%	8%	5%
CBR	58%	24%	41%	31%
	<70 years		**≥70 years**	
	Everolimus + Exemestane (n = 364)	Placebo + Exemestane (n = 196)	Everolimus + Exemestane (n = 121)	Placebo + Exemestane (n = 43)
PFS	8.11	4.01	6.77	1.51
HR (95% CI)	0.44 (0.36-0.54)		0.45 (0.30-0.68)	
ORR	14%	<1%	9%	7%
CBR	57%	27%	36%	23%

CBR indicates clinical benefit rate; HR, hazard ratio; ORR, overall response rate; PFS, progressive free survival

References

1. Piccart M, Baselga J, Noguchi S et al. Final progression-free survival analysis of BOLERO-2: a phase III trial of everolimus for postmenopausal women with advanced breast cancer. Presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX.

2. Pritchard KI, Burris HA, Rugo HS et al. Safety of everolimus for women over 65 years of age with advanced breast cancer (BC): 18-month follow-up of BOLERO-2 2012. Presented at the 2012 American Society of Clinical Oncology Annual Meeting; June 1-5, 2012; Chicago, IL.

Author Disclosures: Dr Rogerio reports employment with Novartis Pharmaceuticals Corporation, which funded this study.

Authorship Information: Concept and design; acquisition of data; critical revision of the manuscript for important intellectual content.

Address correspondence to: Jaqueline Rogerio, MD, Senior Medical Director, Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936. E-mail: jaqueline.rogerio@novartis.com.

Reply From the Authors

Thank you for your somewhat belated comments on our article, "Breast Cancer: Will Treatment Costs Outpace Effectiveness?", published in the December 2012 issue (Volume 18, Special Issue 5, SP200-SP202) of *The American Journal of Managed Care*. The information presented in the article from the BOLERO-2 study was acquired from information cited in the abstract by Martine J. Piccart-Gebhart, et al, presented at the June 2012 American Society of Clinical Oncology meeting and the press release from the FDA on July 23, 2012, announcing that it had approved everolimus.[1,2] The information available at the time showed that everolimus had an overall positive effect when used in combination therapy for breast cancer. These 2 references did not contain any efficacy results stratified by age.

Additional subgroup analysis is quite often performed after initial results of trials are presented. These subgroup analyses many times identify efficacy and safety information that is valuable to clinicians in treating and managing their patients. Thank you for providing further valuable information that will assist clinicians in determining optimal therapy for their patients.

Marj P. Zimmerman
Stanton R. Mehr

References

1. Piccart-Gebhart MJ, Noguchi S, Pritchard KI, et al. Everolimus for postmenopausal women with advanced breast cancer: updated results of the BOLERO-2 phase III trial. *J Clin Oncol.* 2012;30:abstract 559.

2. Drugs: everolimus. FDA website. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm313008.htm. Published July 23, 2012. Accessed September 12, 2012.

Stem Cells Create a Therapeutic Niche

Surabhi Dangi-Garimella, PhD

Stem cell therapy has gained increasing traction in various therapeutic areas, from cancer to diabetes to ocular regeneration. Although the use of embryonic stem cells is controversial, remarkable research in the field of adult induced pluripotent stem cells (iPSCs) has highlighted the tremendous potential of this unique treatment in development and regeneration. Additionally, understanding how stem cells function would improve our insight into various diseases—to fathom "what went wrong."

Globally, patients are actively being recruited to participate in clinical trials of these regenerative therapies. A biotechnology company, Advanced Cell Technology, is testing human embryonic stem cell (hESC)-derived retinal cells for 2 different eye diseases: Stargardt's macular dystrophy,[1] which is a form of juvenile macular degeneration, and age-related macular degeneration.[2] These are primarily phase 1 and 2 safety and efficacy trials, and a preliminary report published in early 2012 did not observe any safety issues with the therapy.[3] Hematopoietic stem cells (HSCs), isolated from the bone marrow or umbilical cord blood, have been widely used to treat blood cancers and other blood disorders for a while now. Osiris Therapeutics, based out of Columbia, Maryland, is currently conducting phase 2 trials using human mesenchymal stem cells (MSCs) to repair heart tissue following a heart attack, repair lung tissue in chronic obstructive pulmonary disease patients, and protect pancreatic beta cells in patients with newly diagnosed type 1 diabetes mellitus.[4]

While bone marrow transplants for numerous blood disorders, including cancer, have been covered by insurance policies for some time now, stem cell therapies are increasingly gaining attention with improved and less ethically challenging procedures being developed from adult stem cells.

The Basics

Stem cells, during early stages of development (in infants and children), have the unique potential to develop into any cell type, a property defined as "pluripotency". Additionally, stem cells, even in adults, have "regenerative" potential, which helps them replenish damaged tissues and organs. These cells present distinct behavior depending on their site or location in the body, and they respond to specific environmental cues. For example, stem cells in the gut and HSCs regularly divide to repair and replenish worn-out tissues, while stem cells in organs like the pancreas or the heart divide only under specific conditions.[5]

Distinct from other cell types, stem cells have the ability to undergo cell division and replicate, even after dormancy. Additionally, following specific cues, they can be prompted to differentiate into tissue- or organ-specific cells with special functions.[5] Although every human organ (except nerve cells) can undergo repair by stem cells, the process dwindles with age, or is quite inactive in some organs and tissues.[6] Most of the current research, independent of the therapeutic area, is geared toward understanding the stimuli that activate/reactivate stem cells to allow for age- or disease-related tissue damage.

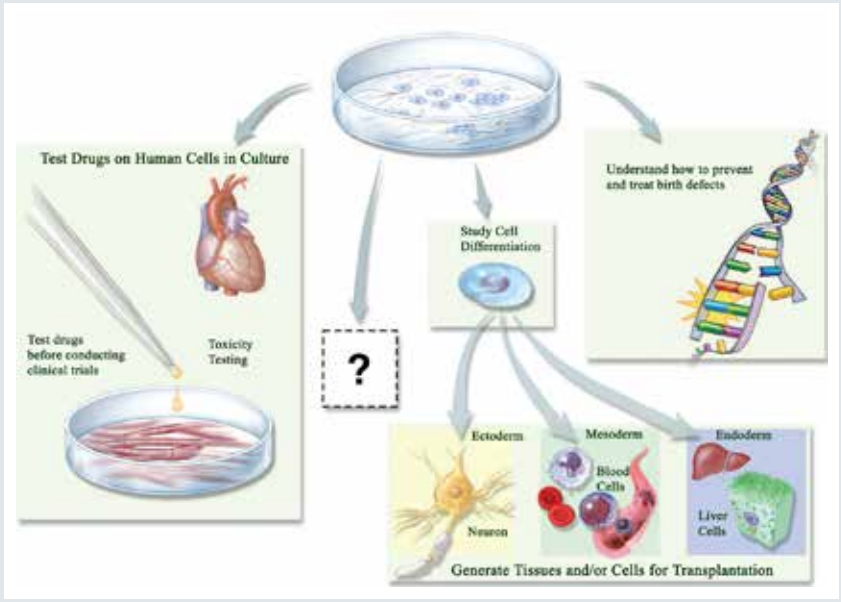
CSCs have made it easier to explain resistance, recurrence, and minimal residual disease.

Types of Stem Cells

The human body is primarily the source of 2 types of stem cells: *embryonic stem cells* and *adult* or *somatic stem cells*. hESCs are derived from embryos that remain unused following in vitro fertilization, following the informed consent of the donor.[5] These cells need specific signals to differentiate to the required cell type, but they run the risk of developing into a tumor if injected directly.[7] Thus, in addition to the associated ethical issues, tumor formation and transplant rejection are some of the barriers faced with hESCs.[8]

The use of adult stem cells, such as HSCs, does not involve any ethical issues, and when obtained from the recipient, the cells are not susceptible to immune rejection. An adult stem cell—an undifferentiated cell that exists among differentiated cells in a tissue or organ—is capable of generating the cell types of the tissue in which it resides, and maybe unipotent or multipotent. The field is burgeoning, and there is tremendous excitement among researchers to use adult stem cells in therapy.

Figure 1. The Tremendous Potential Offered by Stem Cell Research[10]



While HSCs have long been used in stem cell transplants, MSCs (non-HSCs) can generate cartilage, bone, and fat cells to form blood and fibrous connective tissue (**Figure 1**).[5]

Exciting, albeit controversial, results of human cloning were recently published in the journal *Cell Stem Cell* following collaborative research conducted by scientists at the CHA Stem Cell Institute in Seoul, Korea, the Research Institute for Stem Cell Research (a part of the CHA Health Systems), and the company Advanced Cell Technology. The scientists "reprogrammed" an egg cell by removing its DNA and replacing it with nuclei from 2 adult donors aged 35 years and 75 years. The experimental procedures could successfully generate 2 karyotypically normal diploid ESC lines. This technique had previously been developed, but with infant/fetal donor cells, which, unlike adult cells, are not associated with age-related changes such as shortened telomerases and oxidative DNA damage.[9]

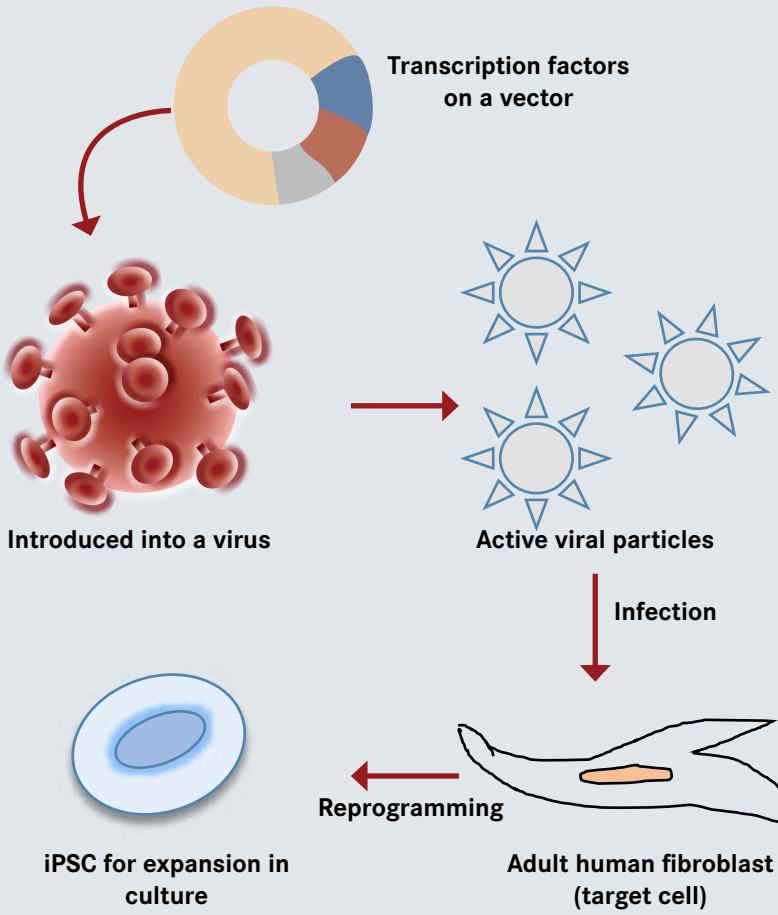
Jun Takahashi, MD, PhD

iPSCs

Extracting and then maintaining adult stem cells in the laboratory is extremely difficult, as they have a limited capacity to divide in culture.[5] The discovery of the "transdifferentiation" process of adult stem cells, wherein adult stem cells are subjected to certain differentiation techniques to generate cell types different from the predicted types, was therefore very exciting.[8] Taking the process a step further, researchers in Japan developed a technique to reprogram normal adult cells into stem cells, called induced pluripotent stem cells (iPSCs), by the forced introduction of a set of transcription factors into the cells.[10] These transcription factors (different combinations of Oct4, Sox2, Klf4, c-Myc, Nanog, Lin28) regulate important steps in early embryonic development and force the adult somatic cells into an embryonic stem cell–like state. This technique has essentially revolutionized the field of regenerative medicine; the patient himself could now be an unlimited source of immune-matched pluripotent cells.[11]

As promising as the therapy sounds, it is riddled with its own problems. It has always been known that the genes that regulate developmental pathways also regulate cancer, and are especially potent when expressed in combination. Therefore, researchers have trimmed the initial group of 4 transcription factors down to 2, with the aim of simultaneously treating the cells with various chemicals to boost reprograming efficiency. Additionally,

Figure 2. Generation of iPSCs From Adult Somatic Cells



iPSCs indicates induced pluripotent stem cells.
Adapted from: *Regenerative Medicine*. Department of Health and Human Services. http://stemcells.nih.gov/info/scireport/Pages/2006report.aspx. Published August 2006. Accessed April 4 2014.

the use of either lentiviruses or retroviruses (**Figure 2**) to introduce the genes into the host cell can result in uncontrolled effects of viral integration. Current efforts are directed toward reprograming cells without viruses or using more efficient integration techniques.[11]

Applications of iPSCs

iPSCs offer tremendous potential in understanding disease, developing drug candidates, and regenerative medicine. Disease-specific iPSCs are being developed to treat Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, and ALS/Lou Gehrig's disease.[11] Researchers at the RIKEN Center for Developmental Biology in Japan have piloted the first set of studies to evaluate iPSCs in humans. In August 2013, patient recruitment was initiated to evaluate the safety and efficacy of iPSC-derived retinal pigment epithelium (RPE) cells in patients with age-related macular degeneration.[12] The premise for using iPSCs is the fact that the current remedies for the disease prevent further damage without promoting any repair.

A new iPSC transplantation therapy will also be evaluated for safety in patients with Parkinson's disease. Jun Takahashi, MD, PhD, and his colleagues at the Kyoto University's Center for iPS Cell Research and Application have successfully developed a technique to generate dopamine-producing nerve cells from patient-derived iPSCs for transplantation into the patient's brain, an attempt at regenerating the damaged dopaminergic neurons.[13] When contacted by e-mail, Takahashi responded that they are currently conducting preclinical studies, the results from which will be submitted for approval prior to initiating clinical trials.

In a novel approach, researchers at the RIKEN Research Center for Allergy and Immunology reported the generation of cancer-specific killer T cells from iPSCs. The human body has a natural ability to produce tumor-specific cytotoxic T lymphocytes, which when activated are effective but not sufficient to cure the patient, due to their short lifespan. To tackle this problem, the scientists reprogrammed T cells into iPSCs, which were further manipulated to differentiate into mature T cells. Although the tools are ready, they have not yet been tested in vitro or in vivo for their cancer cell–killing potential.[14]

Targeting Cancer Stem Cells

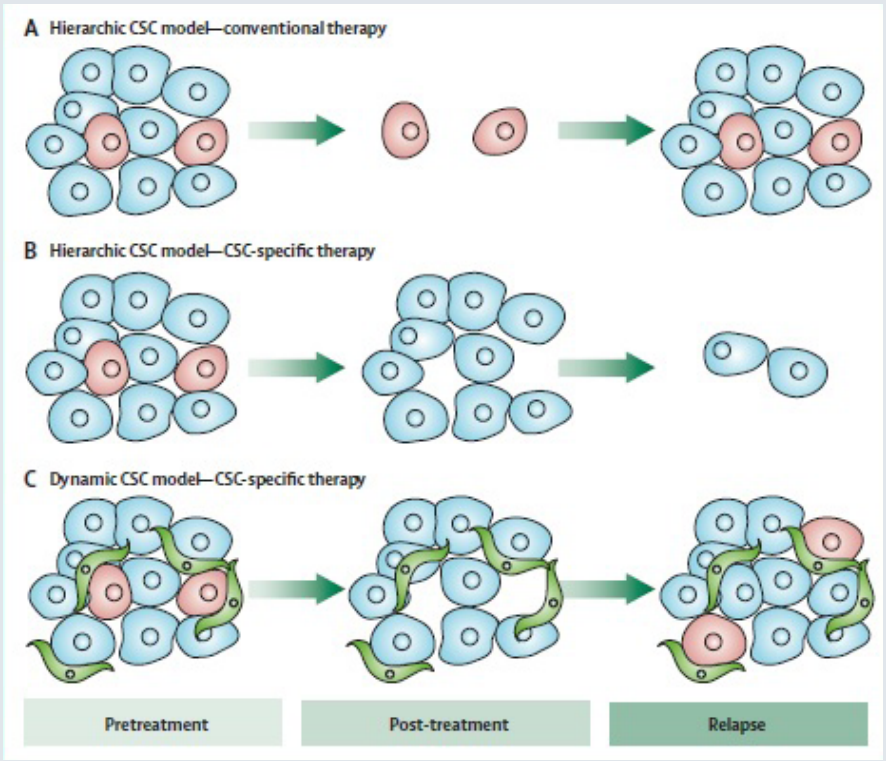
The concept of a cancer stem cell (CSC) has been around for quite some time; scientists found it easier to explain the problems of resistance, recurrence, and minimal residual disease in cancer by acknowledging that these types of cells do exist.

A CSC is defined by its ability to regenerate an entire tumor and is explained by either a stochastic model (every cancer cell can become a CSC) or the hierarchical model (which identifies CSCs as an independent entity within a tumor).[15] Recently, the dynamic CSC model has been gaining hold, which proposes that the differentiated cancer cells can reacquire CSC features following environmental cues (**Figure 3**).[16] Either way, the persistent problem faced in cancer treatment is the elimination of these cells. The cells that survive gather mutations as they evolve, especially after exposure to drugs, and develop increasing resistance. Additionally, the entire region becomes more fluid—creating a stem cell "niche"—due to crosstalk with the tumor microenvironment that further promotes tumor maintenance.[15]

When asked to comment on the importance of CSCs in malignancy and resistance, Robert Weinberg, PhD, Daniel K. Ludwig Professor for Cancer Research in the Department of Biology at the Massachusetts Institute of Technology and a founding member of the Whitehead Institute for Biomedical Research, said in an e-mail, "There is increasing evidence that carcinoma cells that have undergone an epithelial-mesenchymal transition (EMT) are more aggressive clinically, sources of metastasis, and poised to enter into the CSC state, which by definition confers on them tumor-initiating powers. Presumably such powers are critical for disseminated cancer cells to serve as the founders of new metastatic colonies. Moreover, CSCs appear to be generally more resistant to a variety of currently employed chemotherapeutics, making them sources of residual disease following initial treatment in the oncology clinic and thus sources of clinical relapse."

In response to whether he thought that the stromal cells that constitute the tumor milieu might be differentiated CSCs that feed back and promote the aggressiveness of the disease, Weinberg, who also serves as the chairperson on the scientific advisory board of the biopharmaceutical company Verastem, said, "Since carcinoma cells that have undergone EMT take on many of the attributes of the mesenchymal cells in the adjacent recruited host stroma, they may take on many of the attributes of naturally arising stromal cells; however it remains unclear whether these mesenchymally converted carcinoma cells contribute significantly to

Figure 3. The CSC Resistance Model[15]



A. Cancer stem cells (CSCs, red) are more resistant to conventional therapies than differentiated cells (blue). The surviving CSCs following treatment repopulate the tumor with their clones, resulting in relapse.
B. CSC ablation should result in reduced proliferation and malignancy.
C. Differentiated cells can rebound and acquire CSC features following environmental cues and signaling by stromal cells (green), resulting in relapse when treatment is halted.

Table. CSC-Targeting Drugs Under Development

Drug	Indication	Stage	Company
VS-6063 (FAK inhibitor)	KRAS mutant NSCLC	Phase 2	Verastem
	Mesothelioma	Phase 2	
	Ovarian cancer	Phase 1/1b	
VS-4718 (FAK inhibitor)	Metastatic non-hematological malignancies	Phase 1/1b	
VS-5584 (PI3K and mTOR1/2 inhibitor)	Solid tumors and lymphomas	Phase 1/1b	Verastem
SL-401 (recombinant human IL-3)	AML	Phase 1	Stemline
	BPDCN	Phase 2	
SL-701 (vaccine)	Recurrent glioblastoma multiforme	Phase 1/2	Stemline
Demcizumab (anti-DLL-4 antibody)	NSCLC	Phase 1b	OncoMed
Demcizumab (+ gemcitabine +/- abraxane)	Pancreatic cancer	Phase 1	OncoMed
Demcizumab (+ taxol)	Ovarian, primary peritoneal, fallopian tube	Phase 1	OncoMed
OMR-59R5	Pancreatic cancer	Phase 1b/2	OncoMed
	SCLC	Phase 1b/3	

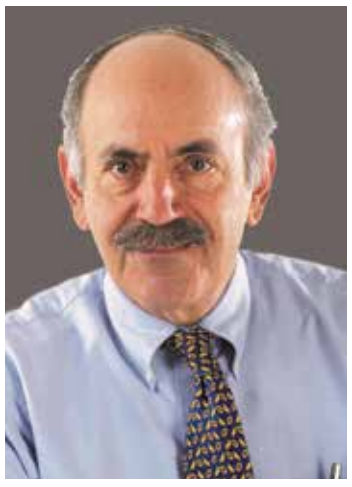
AML indicates acute myeloid leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CSCs, cancer stem cells; DLL-4, delta-like ligand 4; FAK, focal adhesion kinase; IL-3, interlukin-3; mTOR, mammalian target of Rapamycin; NSCLC, non-small cell lung cancer; PI3K, phosphatidyl inositol-3 kinase; SCLC, small cell lung cancer.
Sources: www.clinicaltrials.gov; Verastem website. http://www.verastem.com/products/. Accessed April 16, 2014; Stemline website. http://www.stemline.com/clinicalPrograms.asp. Accessed April 16, 2014; OncoMed website. http://www.oncomed.com/Pipeline.html. Accessed April 16, 2014.

the overall cellularity of the stroma."

Interfering with the innate survival signals in CSCs, as well as the survival signals that are transmitted to CSCs from the tumor environment, seems the most likely path to follow to eliminate these culprits. This approach has proved to work in preclinical animal models and is being applied to humans as well. Companies such as Verastem, Stemline, and OncoMed are developing drugs that would specifically target the CSC population in various tumors (**Table**).

Healthcare Coverage

Is regenerative medicine covered? Payers such as Humana, Blue Cross and Blue Shield, Aetna, and UnitedHealth definitely have policies in place for HSC and bone marrow transplants, a procedure that has been in use for a long time now for patients with blood disorders. However, companies that have developed, or are in the process of developing, regenerative therapies, face hurdles with not just the FDA, but also reimbursement.



Robert Weinberg, PhD

The company Advanced BioHealing developed *Dermagraft*, a product that consists of allogenic human fibroblasts, to aid with wound closures in diabetic foot ulcers. In 2011, the company was acquired by Shire Pharmaceuticals, which immediately initiated the task of improving the reimbursement profile for *Dermagraft* and put 2 new procedure codes in place for the product.[17]

Provenge, an autologous dendritic cell therapy manufactured by Dendreon for the treatment of advanced prostate cancer, also faced stumbling blocks, initially for FDA approval. Subsequently, the CMS did not provide an automatic coverage for this expensive treatment ($93,000 for 3 doses) following the approval, but rather reviewed the payment process first before approving it after a year. Medicare coverage was absolutely essential for this drug, since 75% of the target population was Medicare eligible (65 years or older). Thus the combination of the price and the large number of patients that would be eligible for this treatment was the premise for Medicare's extended review.[18,19]

According to a brief released by the Alliance for Regenerative Medicine, an advocacy organization that creates a common platform for commercial, academic, and not-for-profit institutions, Medicare requires that the regenerative therapy should fall within a defined Medicare benefit and the parameters of one of these segments to qualify for payment. Medicaid relies more on managed care and strict formularies, while private health plans may primarily be concerned with whether the therapy falls under the medical benefit or prescription drug benefit. FDA approval is necessary but no longer sufficient for reimbursement.[20]

Defining the bottom line for the high-cost coverage of regenerative medicine requires answering the same question that must be asked in considering expensive treatments such as Sovaldi and Olysio (hepatitis C). Although the upfront cost of treatment is very high, if the therapy proves to have *breakthrough* effects, it could help avoid long-term treatment costs, especially for chronic conditions. In order for insurance companies to cover these therapies, stem cell therapy would need to prove a substantial advantage over preexisting and relatively inexpensive treatment options. **EBO**

References

1. Sub-retinal transplantation of hESC derived RPE (MA09-hRPE) cells in patients with Stargardts macular dystrophy. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01345006?term=ACT+and+human+embryonic&rank=1. Accessed April 4, 2014.

2. Safety and tolerability of sub-retinal transplantation of hESC derived RPE (MA09-hRPE) cells in patients with advanced dry age related macular degeneration (Dry AMD). ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01344993?term=ACT+and+human+embryonic&rank=2. Accessed April 4, 2014.

3. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720.

4. Stem cells and diseases. National Institutes of Health website. http://stemcells.nih.gov/info/pages/health.aspx. Accessed April 4, 2014.

5. Stem cell basics. National Institutes of Health website. http://stemcells.nih.gov/info/basics/Pages/Default.aspx. Accessed April 3, 2014.

6. Stem cells and cancer. Ludwig Center for Cancer Stem Cell Research and Medicine website. http://ludwigcenter.stanford.edu/overview/. Accessed April 14, 2014.

7. Types of stem cells. GE Healthcare Life Sciences website. http://www.gelifesciences.com/webapp/wcs/stores/servlet/catalog/en/GELifeSciences-us/applications/types-of-stem-cells/. Accessed April 14, 2014.

8. Cha HJ, Hwang ES. Current status of biology, bioengineering, and therapeutic potential of stem cells. *Arch Pharm Res*. 2012;35(2):193-196.

9. Chung YG, Eum JH, Lee JE, et al. Human somatic cell nuclear transfer using adult cells [published online April 17, 2014]. *Cell Stem Cell*. doi:http://dx.doi.org/10.1016/j.stem.2014.03.015.

10. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. *Nature*. 2007;448(7151):313-317.

11. Regenerative medicine. Department of Health and Human Services. http://stemcells.nih.gov/info/scireport/Pages/2006report.aspx. Published August 2006. Accessed April 4 2014.

12. Pilot clinical study into iPS cell therapy for eye disease starts in Japan [press release]. RIKEN; July 30, 2013. http://www.riken.jp/en/pr/press/2013/20130730_1/. Accessed April 4, 2013.

13. Geji K. Scientists to test iPS cells for Parkinson's disease therapy. The Asahi Shimbun. http://ajw.asahi.com/article/behind_news/social_affairs/AJ201306070062. Published June 7, 2013. Accessed April 15, 2013.

14. Vizcardo R, Masuda K, Yamada D, et al. Regeneration of human tumor antigen-specific T cells from iPSCs derived from mature CD8+ T cells. *Cell Stem Cell*. 2013;12(1):31-36.

15. Filipovic A, Stebbing J, Giamas G. Cancer stem cells—therapeutic targeting or therapy? *Lancet Oncol*. 2013;14(7):579-580.

16. Vermeulen L, de Sousa e Melo F, Richel DJ, Medema JP. The developing cancer stem-cell model: clinical challenges and opportunities. *Lancet Oncol*. 2012;13(2):e83-e89.

17. Schaffer C, Littman N. Why planning your payment strategy is critical in early product development. California Institute for Regenerative Medicine website. http://cirmresearch.blogspot.com/2013/06/cirm-webinar-why-planning-your-payment.html. Published June 17, 2013. Accessed April 17, 2014.

18. Larkin C. Dendreon wins final Medicare coverage decision on prostate cancer drug. Bloomberg website. http://www.bloomberg.com/news/2011-06-30/dendreon-wins-final-medicare-coverage-decision-on-prostate-cancer-drug.html. Published June 30, 2011. Accessed April 17, 2014.

19. Maziarz R, Driscoll D. Hematopoietic stem cell transplantation and implications for cell therapy reimbursement. *Cell Stem Cell*. 2011;8:609-612.

20. Alliance for Regenerative Medicine. Alliance for Regenerative Medicine reimbursement portfolio. http://www.cirm.ca.gov/sites/default/files/files/agenda/ARM_Reimbursement_Portfolio_Oct_2013_0.pdf. Accessed April 17, 2014.

Cheap and Easy-To-Use Diagnostic Tests to Detect Disease Biomarkers, Including Cancer

Surabhi Dangi-Garimella, PhD

A new paper diagnostic test for cancer? That is what engineers at the Massachusetts Institute of Technology (MIT) have developed—a simple, low-cost, noninvasive paper test that can improve diagnosis rates and hasten treatment.[1] The test, which essentially works like a pregnancy test, may have the potential to determine if a patient has cancer—within minutes.

Developed by Sangeeta Bhatia, MD, PhD, director of the laboratory for multiscale regenerative technologies at MIT, the technology is based on nanoparticles that interact with proteases (proteins, known to be overexpressed in numerous tumors, that can cleave peptide bonds), which can release hundreds of biomarkers that can be detected in the patient's urine. Bhatia's group designed nanoparticles conjugated to ligand-encoded reporters through protease-sensitive peptide substrates. The ligand on the nanoparticles is targeted to reach the disease site, be it solid tumors or blood clots or other sites, where upregulated proteases cleave the peptide substrates and release the reporters that are excreted in the urine. The urine can be tested either by a paper lateral flow assay or a sandwich enzyme-linked immunosorbent assay.[2] This diagnostic platform, claim the authors, can be applied in any disease setting without expensive equipment or trained medical personnel, and may allow low-cost diagnosis of disease at the point of care in resource-limited settings.

The novel aspect of Bhatia's work is designing the exogenous nanoparticle biomarkers; companion point-of-care (POC) diagnostic paper strips were originally invented through a collaborative effort between researchers at Harvard University and the University of Sao Paulo. Driven by the need to develop easy-to-use diagnostics in the developing world, based on the World Health Organization's ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment free, and deliverable to end-users) criteria, the microfluidic paper-based analytical devices (*m*PADs) were developed as a new class of POC diagnostic.[3] Urinalysis assays using *m*PADs proved that the platform was ideal for ASSURED diagnostics.

Diagnostics For All (DFA), a company based in Cambridge, Massachusetts, has licensed out this patterned paper


Sangeeta Bhatia, MD, PhD

technology that was developed by the Harvard research group, with the aim of developing POC diagnostics for the developing world.[4] Currently, the company is working on the following diagnostic tests:

- Liver function tests (to monitor patients on antiretroviral therapies)
- Rapid immunity assessment (to monitor efficacy of vaccination against tetanus and measles; funded by the Bill and Melinda Gates Foundation)
- Child nutrition monitoring (funded by the Bill and Melinda Gates Foundation)
- Nucleic acid detection to diagnose *Brucella abortus*

When contacted by e-mail, DFA informed *Evidence-Based Oncology* that it is not currently developing any oncology diagnostic test.

Although Bhatia's *PNAS* paper describes using the platform to detect colorectal cancer and thrombosis, diseases associated with an abundance of active proteases, the applications are enormous. These studies were conducted in a mouse model; in order to guide the results to the next level and study patient populations, Bhatia aims to develop a business plan for a start-up based on a Technological Innovation grant that the group received to commercialize the technology and conduct clinical trials.[1] The research group is also working on developing an implantable nanoparticle formulation that could aid long-term monitoring.

The engineering of low-cost and rapid assays to detect cancer has been on the rise. Mechanical engineers at the University of Washington, working in collaboration with a pathologist in the school of medicine, have developed a device that can help diagnose pancreatic cancer earlier and faster by avoiding the time-consuming manual labor associated with processing biopsy tissue samples. The microfluidic gadget (simply a modified petri dish with Teflon tubes) uses fluid transport to perform the basic steps of processing a biopsy sample. This device is expected to automate and streamline the manual process that a pathologist follows to help diagnose a biopsy sample. Another advantage is that this technology would allow for 3-dimensional imaging, unlike the current technique followed by pathologists which only allows 2-dimensional imaging, providing a much more detailed and complete view of the tumor.[5]

VOC Diagnostics, a start-up company that is the brainchild of business school students at the University of Louisville, Kentucky, is developing a lung cancer diagnostic test that has the easiest sample collection technique: the patient simply breathes into a bag. The air from the sealed bag is then released over a diagnostic microchip called VitaLung, also developed at the University of Louisville, which then detects volatile organic compounds in a person's breath. The results from the patient sample are then compared against the molecular profile (biomarkers) of lung cancer to make a diagnosis. VOC Diagnostics initiated efficacy trials at the beginning of 2013, and early results showed 90% accuracy.[6]

The American Lung Association recommends an annual low-dose computed tomography (LDCT) screen in individuals with a high risk for the disease, such as current or former smokers.[7] Although beneficial in high-risk individuals, an exhaustive review published in the *Journal of the American Medical Association* evaluating the effect of LDCT on lung cancer mortality screening concluded that the screen could potentially be harmful, as it cannot distinguish between benign and cancerous tumors. Therefore, additional imaging to confirm potentially benign nodules increases the patient's exposure to radiation, while surgeries undertaken to excise benign nodules can result in complications.[8] Considering these complications, VitaLung is safer and was definitely found to be accurate based on preliminary results.

The currently prevalent tests for cancer diagnosis, including computed tomography, magnetic resonance imaging, and positron-emission tomography, require not just specialized instruments, but also highly trained staff to conduct the examination and then to interpret the reports. The entire process is therefore time consuming as well as expensive. Innovative ideas being developed by academicians in partnership with venture capitalists or the pharmaceutical industry could simplify the process and also prove economical. **EBO**

References

1. Trafton A. A paper diagnostic for cancer. Massachusetts Institute of Technology website. http://web.mit.edu/newsoffice/2014/a-paper-diagnostic-for-cancer-0224.html. Published February 24, 2014. Accessed March 28, 2013.

2. Warren AD, Kwong GA, Wood DK, Lin KY, Bhatia SN. Point-of-care diagnostics for noncommunicable diseases using synthetic urinary biomarkers and paper microfluidics. *PNAS*. 2014;111(10):3671-3676.

3. Martinez AW, Phillips ST, Whitesides GM, Carrilho E. Diagnostics for the developing world: microfluidic paper-based analytical devices. *Anal Chem*. 2010;82:3-10.

4. Diagnostics For All website. http://www.dfa.org/projects/projects-overview.php. Accessed March 31, 2014.

5. Ma M. Credit card-sized device could analyze biopsy, help diagnose pancreatic cancer in minutes. University of Washington website. http://www.washington.edu/news/2014/02/06/credit-card-sized-device-could-analyze-biopsy-help-diagnose-pancreatic-cancer-in-minutes/. Published February 6, 2014. Accessed March 31, 2014.

6. Combs V. Biomarker test could make screening for lung cancer cheap and easy. Medcity News website. http://medcitynews.com/2013/02/biomarker-test-could-make-screening-for-lung-cancer-cheap-and-easy/. Published February 27, 2013. Accessed April 1, 2014.

7. New lung cancer screening assessment tool. American Lung Association website. http://www.lung.org/about-us/our-impact/top-stories/new-lung-cancer-screening.html. Published October 30, 2013. Accessed April 1, 2014.

8. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA*. 2012;307(22):2418-2429.

Photo credit: Bryce Vickmark

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 $1568 per 3.5-mg vial as of January 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

V-12-0306a 1/14

The Big Data Revolution: From Drug Development to Better Health Outcomes?

Andrew Smith

Normal analysis of discreet health data, like blood pressure and cholesterol, identified 5000 patients at risk of developing congestive heart failure.

Automated analysis of doctors' notes and other unstructured information from Carilion Clinic's 8 hospitals turned up 3500 more.[1]

Early treatment should prevent many of those extra cases from ever developing and save the communities of western Virginia hundreds of lives and millions of dollars.

Such efforts to avert the chronic diseases that kill the majority of Americans and consume the majority of their healthcare dollars rank among the most promising medical applications for "Big Data" analysis.

But there are countless others.

An unbelievably large amount of medically useful information is available for study—a century of published studies, decades of insurance claims—and that stock expands every time a doctor completes an electronic medical record or a runner dons a heart-rate monitor.

Software that can find, interpret, and analyze it all may eventually revolutionize healthcare.

A McKinsey & Company analysis, for example, predicts such programs will soon save at least $300 billion a year in American healthcare spending—and possibly much more.[2]

"Why is Big Data emerging in healthcare now? There are really 3 reasons," said McKinsey director Nicolaus Henke. "The first is availability. We have so much more captured, machine-readable data available to us than we did just a few years ago. The second reason is that it's much cheaper and easier to link these data. The third reason is a big imperative to understand population health better…it's important both for outcomes and costs."

Indeed, even with all the limitations in both data and software, would-be innovators are already finding significant ways to use the existing data to improve patient health.

The most famous applications to date lie in taking some of the data that modern life automatically generates about individual activity and reusing it to benefit that individual.

Smartphone applications that tap GPS and clock functionality to track runs have millions of users. Diet applications that use phone cameras and Internet connectivity to help users track what they eat have even more.

Medical practices are using similar tools to help patients.

Billing records have always recorded when patients come in for Papanicolaou tests (Pap smears), but now software sold to gynecologists can automatically look through those records, infer which patients are overdue for another Pap smear, and send reminders to those patients.[3]

Such programs can also look through medical records to see which women began receiving the sequence of shots needed for Human Pappilomavirus vaccination and call them to remind them about the next shot.[3]

Applications like that, which use relevant data from each individual to help that same individual, may provide substantial health benefits, but experts see even more promise in tools that use both individual data and collective data, such as the tools that IBM used to predict congestive heart failure (CHF) at Carilion.

Ed Macko

"Traditional models use a handful of medical measurements to predict CHF," said Ed Macko, IBM's chief technology officer for healthcare & life sciences.

"Our systems—after scanning not only structured data but also free-written material from doctors' notes, journals, and other sources—found dozens of relevant factors, including stuff that has rarely been considered before, like whether the patient has a job or someone at home that can provide care during illness."

Such deep analysis allowed IBM's technology to identify 70% more at-risk patients than traditional tools, all while maintaining an estimated 85% accuracy rate that matches prior standards.

And each passing month increases both the number of patients identified and the accuracy of the prediction.

IBM has plenty of competitors, big and small, that want to use Big Data to improve healthcare. The McKinsey report estimates that 200 new companies have already entered the space. Older companies, universities, government agencies, and other nonprofits are also getting into the act.

Erica Mobley

Much of their work resembles the project at Carilion. It seeks to predict which people will become chronically ill—be it from CHF, diabetes, chronic obstructive pulmonary disease, drug addiction, or a handful of other problems—and prevent the downward spiral.

"It makes sense to focus here because a relatively small number of very ill people account for a huge percentage of both the suffering and the cost," said Erica Mobley, senior manager at a hospital-monitoring nonprofit called The Leapfrog Group.

"Hospital systems have also focused on using Big Data to expand and improve upon data-driven decision making," said Mobley, who noted that the real analytical pioneers among hospitals tend to be self-insuring university systems that can get a full picture of patients by using complete medical records, drug records, and insurance records.

The University of Pittsburgh Medical Center, for example, announced in 2012 that it was working with outside companies to create an enterprise data warehouse that would draw on more than 200 data sources to provide doctors with individualized care recommendations for particular patients.[4]

"Ever more data, sometimes right down to the genetic level, give hospitals the ability to help staff determine the correct decision in ever more specific situations. These data-driven decisions replace instinct or gut feeling, which studies have generally shown to be little better than raw guesswork."

Big Data is also helping groups like Leapfrog improve their hospital rankings.

When Leapfrog was founded in 2000, hospitals reported so little data on safety that sophisticated analysis was unnecessary. Now, thanks to efforts by Leapfrog and other groups to increase transparency, patients can compare hospitals on issues as specific as the likelihood that the doctors will leave something inside them after surgery or that the staff will give them the wrong type of blood.

To help patients understand how to value all those extra data, Leapfrog (which still wants way more data) now uses sophisticated analytics to weigh the different factors and compile a single letter grade for each facility.

Government agencies have also begun using Big Data to improve healthcare.

The FDA has launched a number of projects that mine and analyze data, including a program called Mini-Sentinel that automatically combs medical databases for signs of drug safety issues that were not detected before approval.

The numbers involved are vast. An FDA report from January revealed that as of July 2012, the Mini-Sentinel system had already collected records of some 3.8 billion medical visits and 3.5 billion dispensations of medication for 160 million Americans.[5]

For all those records, however, questions remain about the reliability of the analysis performed by the current system. A research letter published in January's edition of the *Journal of the American Medical Association*, for example, noted that traditional studies comparing the bleeding risk of warfarin (Coumadin) and dabigatran (Pradaxa) have all found substantially more risk with dabigatran, while Mini-Sentinel found more with warfarin.[6]

Looking forward, the FDA reportedly plans to expand its automatic monitoring system to read sources like Facebook and Twitter for signs of drug safety issues.[7]

Similar techniques have already demonstrated some usefulness. Google, for example, has demonstrated that it can often spot a regional outbreak of flu earlier than health authorities simply by noting the prevalence of flu-related Web searches.

Researchers at Stanford and Columbia, moreover, were able to find a drug interaction the FDA had missed—the tendency of paroxetine (Paxil) and pravastatin (Pravachol) to raise blood sugar when used together—by analyzing tens of millions of search queries.[8]

The most famous applications lie in taking some of the data that modern life automatically generates and reusing it to benefit the individual.

Amid its efforts to use Big Data to monitor the safety of marketed drugs, the FDA also hopes its collection of drug trial information can help it develop software to better predict the behavior of experimental drugs in the human body.

Agency officials are using their vast archives of data to help build physiologically based pharmacokinetic models to predict drug absorption. Such models may spot potential problems with new drugs and improve the FDA's ability to evaluate them.[9]

Of course, the FDA's mountain of trial data could prove useful to many health-related analyses, so the agency plans to throw much of it open to outside researchers. FDA officials have launched a resource called the Janus Clinical Trials Repository, designed not only to release terabytes of information but also to make it user friendly.[10]

The FDA is also tapping outside organizations for help.

It funded a Center for Excellence in Regulatory Science and Innovation (CERSI) at the University of Maryland to help it use Big Data (and many other tools) to modernize and improve the review and evaluation of drugs and medical devices.[11]

The CERSI's work on Big Data and healthcare, which includes a recent conference on the subject, nicely complements other efforts by Maryland to collect and harness records, efforts like its Research HARBOR (Helping Advance Research By Organizing Resources) project.[12]

"Assembling databases in useful ways has been very hard work. Claims databases lack the detail that researchers want. Medical records are only just going electronic—and even the electronic records we have are often incomplete and sometimes inaccurate," said Eleanor M. Perfetto, PhD, MS, professor of pharmaceutical health services research at the University of Maryland's School of Pharmacy.

"Still, while there is much work to be done, not only with traditional data sources but also completely new ones such as social media, we are making progress."

Indeed, researchers can access data from insurers such as UnitedHealthcare, government entities such as the United Kingdom's National Health Service, or the companies that make electronic medical record software. There are also data sellers like Humedica that try to link data from several sources to give researchers more holistic views of patient health.

Such data have many uses, but the most valuable, commercially speaking, may be the development of new treatments.

Many device and drug makers think Big Data can significantly improve the success rates of their laboratories and help them bring drugs to market faster, and more of them. Their projects vary widely. Some are monitoring social media, analyzing what people say about their products, and considering that feedback in new designs. Others are using archived medical records to determine the characteristics of target populations and thus improve enrollment criteria for drug trials.

Most of these projects have yet to advance beyond pilot programs and other early-stage initiatives.

The same could be said about virtually all efforts to better healthcare with Big Data. The successes of these efforts, while sometimes impressive, have generally been limited in scope, and many obstacles will hinder attempts to expand them to the system as a whole.

Patient data, as Perfetto said, is sometimes wrong, often sketchy, and almost always stored in dozens of different databases that must be accessed separately, if they can be accessed at all. Territorialism, privacy concerns, and other issues will hinder adequate data assembly. What's more, computer software suffers real limitations in its ability to interpret and analyze the available material.

Big Data failures still outnumber successes, and some very easy sounding analyses still lie outside the realm of possibility.

That said, each week brings news of another promising application for data-parsing software, applications such as ones that help drug development by "reading up" on the nearly endless supply of peer-reviewed articles that have been published over decades of time.

No one person—no team of people—could ever read all the relevant studies before choosing a drug target or a promising design, but programmers are "teaching" their computers to understand subject areas such as biology and chemistry and to "read" far more research than humans ever could.

One research hospital, in collaboration with IBM, used software IBM to analyze decades' worth of literature about p53, a protein involved in both normal cell growth and many types of cancer. Using information in those papers about kinases that are known to act on p53, the software created a general understanding of p53-kinase interaction. It then made a list of other proteins mentioned in the literature that were probably kinases that would interact with p53.

Most of the computer's predictions proved accurate.

"This software isn't going to cure cancer yet, but it did make significant new discoveries about a very heavily studied protein, and there is a significant possibility that some of these proteins could be medically useful," said Ying Chen, a research staff member from IBM's Watson Group.

"This technology is ready to make real contributions."

References

1. IBM predictive analytics to detect patients at risk for heart failure [press release]. Armonk, NY: IBM Newsroom; February 19, 2014. http://www-03.ibm.com/press/us/en/pressrelease/43231.wss. Accessed April 30, 2014.

2. Kayyali B, Knott D, Van Kuiken S. The big data revolution in US healthcare: accelerating value and innovation. McKinsey & Company website. http://www.mckinsey.com/insights/health_systems_and_services/the_big-data_revolution_in_us_health_care. Published April 2013. Accessed April 30, 2014.

3. Tracey JK. Big Data and the research HARBOR. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/TracyNotes.pdf. Accessed April 30, 2014.

4. UPMC fosters 'personalized medicine' with $100 million investment in sophisticated data warehouse and analytics [press release]. Pittsburgh, PA: University of Pittsburgh Medical Center; October 1, 2012. http://www.upmc.com/media/newsreleases/2012/Pages/upmc-personalized-medicine-investment.aspx. Accessed April 30, 2014.

5. Mini-Sentinel Data Score. Mini-Sentinel Distributed Database Year 3 Summary Report. Mini-Sentinel website. http://www.mini-sentinel.org/work_products/Data_Activities/Mini-Sentinel_Year-3-Distributed-Database-Summary-Report.pdf. Published July 2012. Accessed April 30, 2014.

6. Sipahi I, Celik S, Tozun N. A comparison of results of the US Food and Drug Administration's Mini-Sentinel program with randomized clinical trials: the case of gastrointestinal tract bleeding with dabigatran. JAMA Intern Med. 2014;174(1):150-151.

7. Karlin S. Adverse events in social media: FDA expects Signal Detection Revolution. The Pink Sheet. http://www.pharmamedtechbi.com/publications/the-pink-sheet/76/4/adverse-events-in-social-media-fda-expects-signal-detection-revolution. Published January 27, 2014. Accessed April 30, 2014.

8. Markhoff J. Unreported side effects of drugs found using data, study finds. *The New York Times.* March 7, 2013. http://www.nytimes.com/2013/03/07/science/unreported-side-effects-of-drugs-found-using-internet-data-study-finds.html. Accessed April 30, 2014.

9. Florian J. FDA use of Big Data in modeling and simulations. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/FlorianNotes.pdf. Accessed April 30, 2014.

10. Rosario L. Janus Clinical Trials repository: an update and insights into future directions. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/RosarioNotes.pdf/. Accessed April 30, 2014.

11. Center of Excellence in Regulatory Science and Innovation website. University of Maryland. http://cersi.umd.edu/. Accessed April 30, 2014.

12. Clinical and Translational Sciences Institute website. University of Maryland. http://medschool.umaryland.edu/ctsi/harbor.asp. Accessed April 30, 2014.

National Comprehensive Cancer Network

19th Annual Conference In Advancing the Standards of Cancer Care

Guidelines Updates

At the 19th Annual Conference of the National Comprehensive Cancer Network (NCCN), held March 12-15, 2014, experts reviewed research and presented updates to the NCCN Clinical Practice Guidelines in Oncology. The conference also featured a roundtable discussion on how the early months of implementing the Affordable Care Act are affecting the delivery of cancer care. Beyond treatment for cancer, NCCN issued updates to last year's survivorship guidelines as well as new recommendations in the realm of cancer screening.

For complete NCCN guidelines, create a profile and visit: http://www.nccn.org/professionals/default.aspx.
For the August 2013 NCCN Bone Health Task Force Report, visit: http://www.nccn.org/JNCCN/supplements/PDF/bone_health_cancer_care_tf.pdf.

NCCN Panel Asks What ACA Means to Cancer Care Delivery

Mary K. Caffrey

As the deadline for the first open enrollment under the Affordable Care Act (ACA) approached, a panel of experts gathered March 14, 2014, at the 19th Annual Conference of the National Comprehensive Cancer Network (NCCN) in Hollywood, Florida, to discuss how the early days of healthcare reform were affecting the delivery of cancer care. Almost no one had anticipated that a late surge would take enrollment on state and federal exchanges past 7 million over the next 2 weeks. But all predicted that no matter what the final tally, change was on the way.

Cliff Goodman, PhD, opened the discussion by asking how the early days of the ACA are affecting cancer care delivery, or if that can yet be determined.

"So where are we now?" Goodman asked. "How in particular is it affecting cancer care?" He asked the 2 payer representatives on the panel, Michael Kolodziej, MD, of Aetna, and Lee H. Newcomer, MD, MHA, of UnitedHealthcare, to weigh in on where cancer care ranks in overall spending in their plans. Both said it takes up 11% percent of overall spending, and Newcomer commented that for UnitedHealthcare, cancer care is a growing piece, as the insurer is a large Medicare provider and also administers many self-insured plans for businesses.

Cliff Goodman, PhD

Michael Kolodziej, MD

"Who is walking through the door now who is different?" Goodman asked. W. Thomas Purcell, MD, MBA, of the University of Colorado Cancer Center, said the nature of "narrow network" exchange means that as an academic medical center, his facility has historically dealt with many indigent patients, and many of those issues remain. Some of the newly insured are showing up with the same diseases, but new issues: It turns out being underinsured can pose as big a challenge as being uninsured. Many lower-income Americans, having not been insured, are selecting the lowest priced option available, the bronze plan, which come with huge out-of-pocket costs in cancer care, as Kolodziej and Newcomer discussed.

"One big issue we don't have a handle on are the large copays," on the bronze plans, Purcell said. "We are thinking strategically how to help them pay for these large out-of-pocket expenses."

While several panelists said it was a little early to have a full grasp of how the ACA would affect cancer care, there was some sense that older, sicker patients were among the first to enroll.

Liz Fowler, PhD, JD, who previously worked for both the White House and the Senate Finance Committee to help pass the ACA, said this mirrors an earlier experience with a bridge program launched in 2010. When people who have been denied care have opportunities to enroll, they move quickly to do so. Christian G. Downs, JD, MHA, agreed. "We've seen cancer patients who have jumped right in. We probably have addressed some of the pent-up demand."

Goodman asked if there were any early data to report about enrollment selection. John C. Winkelmannn, MD, said at this stage, there are more anecdotes than data, including a study that suggests that the political divisions that have surrounded the ACA extend into personal decisions about paying a penalty for not having a policy: Winkelmann reported results that said 15% of uninsured Democrats would rather pay a penalty than enroll, but that share rose to 45% of uninsured Republicans.

Lee Newcomer, MD, MHA

Goodman noted that with the technical problems of the rollout and continuing uncertainty, it appears plans are going to have to set premiums for another year without having a complete year's worth of data. "Actuaries don't like uncertainty," he said.

Both Newcomer and Kolodziej said payers would manage as best they could, with Kolodziej adding, "Independent of what the law is, reform in oncology was going to happen." And he remained positive about the expansion of healthcare generally, despite the bumps. Patients who have not had access to care are gaining access. Fowler, the veteran of crafting the healthcare law, said there are ways to make course corrections for risk if the numbers of young enrollees fall short of projections. Downs concurred that patience is necessary.

"We are going to need to give it more time. It's not something that's going to be done in 1 year," he said.

Newcomer echoed Kolodziej's sentiment about the positive aspects of seeing coverage reach more Americans. But the technical challenges with the websites and the policy reversals have created unanticipated costs his company has had to absorb. "It's

W. Thomas Purcell, MD, MBA


Liz Fowler, PhD, JD


Christian G. Downs, JD, MHA

been an extremely expensive product to roll out," he said. "That said, getting to the point of usability will be a good thing for consumers."

When asked what he sees in his practice, Mohammed S. Ogaily, MD, said patients still have trouble signing up for coverage. "We are delighted to see the opportunity (for patients) to get coverage, but process is slow."

Purcell said the changing nature of narrow networks makes it imperative that providers increase the ability to discuss financial issues with cancer patients. Said Goodman, "So, we need to expend more resources to provide patient navigation?"

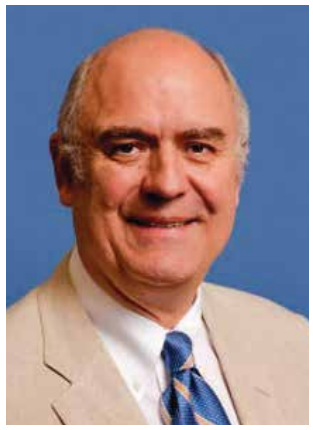
He then turned the discussion to payment models, including accountable care organizations (ACOs) and oncology medical homes, asking whether the panelists were seeing the emergence of these models as called for under the law.

"There's some concern about providers going too quickly into models they don't totally understand," said Downs. The new models will work in some places but not in others, he said. Said Ogaily, "The oncology medical home—it is logically difficult to do, and there is not a lot of enthusiasm."

Even a large academic center like Colorado finds the going slow, Purcell said. But he thinks there are "some savvy practitioners" who will find a way to make new models work. Goodman then turned the economic discussion form the practice level to the big picture: how does the ACA affect the financial outlook?

"It's been an extremely expensive product to roll out. That said, getting to the point of usability will be a good thing for consumers."
—Lee Newcomer, MD, MHA

Newcomer, of UnitedHealthcare, said the ACA is shifting financial pressure off government programs and on to private plans, which is having spillover effects. The uncertainty doctors and hospitals feel, which is triggering the rounds of hospital purchases of practices, is having a direct effect


John C. Winkelmann, MD


Mohammed S. Ogaily, MD

on what his company pays for cancer drugs. "We are seeing a 10-fold increase in the price of a drug if a hospital acquires a practice."

Asked Goodman, given UnitedHealthcare's size, isn't a discount possible? "We are huge nationally, but not locally. In any given town, I'm not the biggest provider." To which Goodman said to Fowler, "Is this what you had in mind?"

He then asked if the consolidations would ultimately affect drug pricing to the point where it affected demand for the products Johnson & Johnson makes and sells. Fowler said she doesn't see effects on the research side, but there is concern about what happens when drugs go to market: how affordable will they be?

Goodman then took the discussion to a more practical level: with an aging population projected to produce more cancer cases, who will provide the care? Winkelmann quoted sobering data from the American Society of Clinical Oncology and the American Society of Hematology: a survey nearly 5000 practitioners found that 20 to 25% of those in clinical practice planned to retire in the next 5 years.

Purcell said oncology faces a rising tide of "increasing volume, decreasing ability to make a margin, and resistance to change." As a physician leader, he said, "I'm trying to create a platform to say, 'we cannot wait or the tsunami to come.' Healthcare reform will bring winners and losers, but it must be managed to ensure there are enough providers, including physician extenders such as physician assistants and specially trained nurses, to meet demand in cancer care."

Kolodziej wondered if critical issues like survivorship were best handled directly by oncologists, or whether others would perform those tasks better at a lower cost. Downs worried more about competing for a limited pool of these specialty workers.

Goodman ended the session with a question: "What's missing?" Winkelmann said healthcare reform needs more explicit information on protected patient reimbursement during clinical trials. Newcomer wants to see more done with medical necessity clauses to reduce waste and give payers the ability to take cost into account.

Said Purcell, "We have to become experts in improvement science." **EBO**

Understanding Which Therapy Comes First in Treating Castration-Resistant Prostate Cancer

Mary K. Caffrey

The title of the talk by Celestia S. Higano, MD, "New Developments in the Treatment of Hormone Refractory Prostate Cancer," was notable in the use of a term that has been replaced over the past decade with "castration resistant." It was a change that Higano, of the Fred Hutchison Cancer Research Center in Seattle, Washington, admits she did not support at the time.

But she acknowledged March 15, 2014, in presenting therapy options for these harder-to-treat patients, that "refractory" really no longer applies, and that made for a challenging and interesting session at the National Comprehensive Cancer Network's (NCCN's) 19th Annual Conference: Advancing the Standard of Cancer Care, held in Hollywood, Florida.

Higano presented a chart showing standard-of-care options for metastatic castration-resistant prostate cancer (mCRPC), which featured 9 different therapies across columns for patients at various points, from those with symptoms to those without, and for those who have already received docetaxel. Of the 6 therapies with level 1 evidence for survival benefits, only docetaxel itself had been approved "in the last 4 years," she noted. (The others are sipuleucel-T, abiraterone, enzalutamide, radium 223, and cabazitaxel.)

With so many new therapies available, Higano said the question becomes, "How do I decide what treatment is best in a given situation?" It comes down to what the patient presents: Are there symptoms? If so, what are they? How fast is the disease progressing? Is there any presence of lung, liver, nodal, or soft tissue disease?

Higano sought to break up the usual "pathway" chart oncologists often see and get down to basics: there are therapies for mCRPC patients without symptoms (immunotherapy and hormonal therapy, perhaps docetaxel), for those with symptoms (radium 223 is an option), and for those who have had docetaxel (cabazitaxel was listed as the first option).

More so than some of the NCCN presenters, she put forth highly challenging cases and treatment choices, and then reviewed the scattered responses with some strong feedback. A key moment occurred regarding the immunotherapy sipuleucel-T, at which time Higano sought to take on concerns about cost. "I would argue there are plenty of other therapies that are just as expensive," she said.

Higano thinks the new sequencing and combination data will give oncologists better information to use when making decisions about treatments in the future.

Higano suggested that immunotherapy involves a different process and thus requires a different way of thinking about costs and benefits, especially since the effects do not take hold immediately. To her, the evidence is clear: In the 2010 study published in the *New England Journal of Medicine*, at 3 years, the median survival benefit was 4.1 months and, more importantly, there was 22% relative reduction in the risk of death over the 3-year period.[1] (Higano was a coauthor of the study.) "Subsequent trials have confirmed the data, and with milder toxicities and a shorter period to the first use of pain medication, there are clear benefits," she said.

When should immunotherapy be used? Higano recommended early in course of mCRPC, before second-line hormonal treatments, corticosteroid use with chemotherapy, and abiraterone. At this stage, patients are less likely to have symptoms or rapid progression or to experience liver metastases.

If immunotherapy is used, Higano recommends baseline imaging to assess pain and monthly follow-up to monitor the patient. Patient education about the differences in how the treatment works is important, she said.

Two hormonal therapies, abiraterone and enzalutamide, are also indicated for mCRPC in patients without symptoms. While abiraterone appears to show less time to chemotherapy than enzalutamide from the placebo arm of the phase 3 study (8.4 vs 17 months), Higano said it is very important to note that the abiraterone trial included prednisone in the placebo arm, while the enzalutamide trial did not. "Prednisone, even by itself, is an active agent. That could have increased the difference between 2 two arms," she said.

Celestia S. Higano, MD

In discussing radium 223, Higano emphasized it is indicated only when patients have shown symptoms. It is a calcium mimic and targets bone metastases; thus, she predicts that skeletal-related events will become an end point in upcoming studies. While it can only be handled and administered by a specialist in nuclear medicine, there are no restrictions on the patient coming into contact with others. It should not be combined with docetaxel. "That is too toxic," she said.

In discussing cabazitaxel, Higano offered what she labeled "practical" advice: reduce the initial dose to 20 mg/m^2, use growth factor in all high-risk patients, and understand that a lack of pain progression does not mean a lack of clinical benefit.

The choices are challenging, to be sure, but Higano said that new sequencing and combination data will give oncologists better information to use when making decisions about treatment in the future. **EBO**

Guideline Update, January 2014:

- Radium-223 dichloride is a first-in-class radiopharmaceutical that recently received approval for the treatment of patients with symptomatic bone metastases and no known visceral disease. It received a category[1] recommendation as both a first-line and second-line option.
- The prostate cancer panel also revised recommendations on the choice of intermittent or continuous androgen deprivation therapy based on recent phase III clinical data comparing the 2 strategies in the nonmetastatic and metastatic settings.

Source: Journal of the National Comprehensive Cancer Network

Reference

1. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;29363(5): 411-422.

New NCCN Prostate Cancer Screening Guidelines Aim for Middle Ground

Mary K. Caffrey

On March 14, 2014, new prostate cancer screening guidelines that seek to balance overtreatment concerns with the need to preserve gains in curbing prostate cancer mortality were unveiled at the National Comprehensive Cancer Network's 19th Annual Conference, Advancing the Standard of Cancer Care, held in Hollywood, Florida.

Peter R. Carroll, MD, MPH, said the new guidelines, which call for starting screening as early as age 45 years and continuing it past age 70 years for patients in good health and without other comorbidities, would reduce overdetection by as much as 45%.

For 2 years, prostate cancer screening has been among the most contentious issues in cancer prevention. Since the development of the prostate-specific antigen (PSA) test, specialists promoted

Peter R. Carroll, MD, MPH

Controversy over PSA testing will ebb as molecular profiling helps resolve ambiguities of treat or watch-and-wait among moderate-risk patients.

the screening tool among men and succeeded in trimming the prostate cancer mortality rate by 45% in the United States—a drop so steep it accounted for 20% of the overall drop in cancer mortality in men since 1930. An unqualified success, right?

Not according to the US Preventive Services Task Force (USPSTF), which in May 2012 stunned urologists and the cancer prevention community in general when it gave the PSA test a rating of D, saying that the benefits did not outweigh the harms. All that screening had led to overtreatment, the USPSTF said. The entity's rulemakings are significant—only ratings of B or higher ensure reimbursement from Medicare and Medicaid, and

insurers often follow suit.

"We achieved a 45% reduction in mortality in prostate cancer in the United States, in contrast with an increase worldwide," Carroll said. "Yet, the USPSTF gives it a D.

"How did we arrive here?"

Both Carroll and his co-presenter, statistician Andrew J. Vickers, PhD, of Memorial Sloan Kettering Cancer Center, said the USPSTF had some fundamental misunderstandings about the studies it relied upon in making its decision; Vickers in particular said the 2 studies, from the United States and Europe, were very different and numbers from each should not have been consolidated. But Carroll did agree with the USPSTF on 1 point: too much screening can lead to overtreatment.

The American Cancer Society did not agree with the USPSTF; the American Urological Association responded with its own guidelines that targeted screening for men aged 55 to 69 years, although it was vague on when biopsies should occur.

That left the NCCN in a tough spot: the group dedicated to setting standards of care had weighed in on the matter just prior to the USPSTF edict in 2012 with a call for guidelines that Carroll described yesterday as "screen early, screen often, biopsy many."

Carroll, who is professor and chair of the University of California, San Francisco Department of Urology, said the new guidelines will address the concerns of overtreatment as well as those of professional groups that want to preserve the use of PSA screenings. He said that the changes were being revised right up to the last minute; unlike other new material presented at the conference, these newsworthy guidelines were not included along with other electronic material provided to meeting attendees.

Carroll summarized the new criteria as follows:

- They define a target population based on more recent random controlled trials.
- They seek testing that starts at age 45 to 50 years, with a single PSA test; later testing will be in selective patients based on risk factors.
- Testing will be less frequent.

Guideline Update, January 2014:

- Revisions seek balance between USPSTF recommendation of D for the use of prostate-specific antigen (PSA) testing and aggressive, repeated screening.
- Defines target population based on recent randomized controlled trials.
- Family history and physical exams, with first baseline PSA test between ages 45 and 49 years. A digital rectal exam (DRE) should follow for those with elevated serum PSA.
- Based on initial results, only high-risk patients (PSA >1 ng/mL) need repeat testing at intervals of 1 to 2 years. If DRE is normal and PSA is equal or less than 1 ng/mL), do not test again until age 50 years.
- From age 50 to 70 years, testing at 1 to 2 year intervals, assuming a normal DRE result, PSA <3 ng/mL, and no other biopsy indications.
- Revises indications for biopsy. Use of prostae-specific antigen velocity (PSAV) at low PSA removed as explicit indication for biopsy.
- Testing after age 70 years only indicated in very healthy men with few to no comorbidities.

- Indications for biopsy are more explicit and will occur with caution: this is the biggest change in the guidelines. Only "highly suspicious" digital exams will be indicated for biopsy.
- PSA velocity, by itself, will not be a reason for biopsy.

Data from will be published soon in support of these new criteria, Carroll said. He and Vickers agreed that the controversy over PSA testing will ebb as molecular profiling helps resolve ambiguities around those moderate-risk patients, for whom it has been a tougher call whether treatment or "watchful waiting" makes more sense. **EBO**

Denlinger Discusses Posttreatment Surveillance for Cancer Survivors

Mary K. Caffrey

Crystal Denlinger, MD, keeps expanding her expertise in "survivorship." The Fox Chase Cancer Center physician almost didn't make it to the National Comprehensive Cancer Network's 19th Annual Conference in Hollywood, Florida, after her evening flight from Philadelphia to Fort Lauderdale, Florida, crashed on the runway just after takeoff on March 13, 2014.[1]

Crystal Denlinger, MD

Undaunted, Denlinger boarded a later flight and arrived in Florida after midnight, on March 14, 2014, in time to rest before her presentation with Terry S. Langbaum, MAS, of Johns Hopkins. The pair discussed what patients and providers should know about surveillance after the initial wave of cancer care ends.

Langbaum, a cancer center administrator who has had Hodgkin's disease, and Denlinger, a medical oncologist and specialist in gastric cancer, opened the discussion by laying out a common misconception: patients who have survived cancer assume that good follow-up care means lots of tests and scans. But, as Denlinger showed, the evidence says that isn't so.

Her presentation, "Optimal Post-Treatment Surveillance: Is More Really Better?" addressed a topic that challenges not only patients and their physicians, but also payers and accountable care organizations (ACOs) as we move toward a national healthcare system, searching for better quality at a lower cost. First, Denlinger opened her "less is more" argument with a few realities: most recurrences are picked up by symptoms, not scans or exams; the risk of recurrence is greatest within the first 5 years of diagnosis; and a cure with treatment after a recurrence is unlikely in most cancers, although palliative care can extend life and bring better quality.

Guideline Update, January 2014:

The NCCN Guidelines Committee on Survivorship is issuing updates in the following areas:

- The algorithm for treatment of anxiety and depression is being revised.
- The algorithm for treatment of male sexual function is being revised.
- The algorithm for recommendations for exercise is being revised.
- The algorithm for recommendations for immunizations and infections is being revised.

While there are arguments in favor of active surveillance with multiple tests, there are also downsides, especially as cancer patients live longer, Denlinger said. Exposures to too much radiation and procedures carry their own risks, burden patients with added costs and anxiety, and can get in the way of more productive elements of survivorship care, such as making positive lifestyle changes. Concerns about the cumulative effect of too much imaging were borne out in a 2009 study. Over 22 years, a cohort of 31,462 US patients were studied, and it was determined that repeated computed tomography (CT) exposure adds to baseline cancer risk; while most patients accrued low radiation-induced cancer risks, a small subgroup of 7% had higher risks due to the cumulative effects of repeat CT imaging.[2]

"A CT scan is not as benign as one might have thought," Denlinger said. "The evidence shows there is a subset facing a cancer risk just from the radiation (of the

tests)." What's more, CMS is starting to limit the number of lifetime scans a person may have to reduce these dangers, she said.

If testing occurs, it should be meaningful. Denlinger offered some parameters:

- The interval between tests, and the duration of testing, should align with the maximal recurrence risk and tumor history.
- Testing should be directed at the sites where recurrence is most likely.
- Testing should have high predictive value.
- Don't test except if there is a therapy available for a cure, to prolong life, or to provide relief of symptoms.
- Test if there is an increased risk of a secondary malignancy, based on shared risk, but do so knowing the complications of therapy.

Denlinger then went through a variety of studies and scenarios across breast, colorectal (CRC), lung, gastric, prostate, and ovarian cancers, indicating where surveillance would be most beneficial. It turns out that of the major cancers, recent evidence shows CRC survivors benefit the most from regular carcinoembryonic antigen testing, with CT at 12- to 18-month intervals.[3]

Surveillance after lung cancer is controversial and the subject of mixed results, Denlinger said, in part because 50% of cancer recurrence for these patients occurs outside the lung. The USPSTF last year called for lung cancer screenings for older smokers and former smokers meeting certain criteria before cancer hits. Denlinger said the most important "survivorship" issue for lung cancer patients who are smokers is to make sure they quit.

Denlinger acknowledged that the "less is more" approach will require some adjustments, but it's essential. "Survivors are living longer. Many, many survivors are living past that 5-year mark. We are potentially doing them harm. It's going to take some mind-set changing," she said. **EBO**

References

1. Mulcahy N. Oncologist survives plane crash, gives NCCN talk. Medscape Multispecialty. March 14, 2014. http://www.medscape.com/viewarticle/822040.

2. Sodickson A, Baeyans PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology*. 2009;251:175-184.

3. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA*. 2014;311(3):263-270.

More Enthusiasm for Newer Melanoma Therapies

Mary K. Caffrey

In his talk, "Melanoma Guideline Update: New Agents and Opportunities for Treatment," John A. Thompson, MD, of the Fred Hutchinson Cancer Research Center in Seattle, Washington, first displayed the preferred list of treatments for advanced or metastatic melanoma: ipilimumab, vemurafenib, dabrafenib, dabrafenib plus trametinib, high-dose interleukin-2, and the drugs-to-come in the category: "clinical trials."

John A. Thompson, MD

Then, Thompson told the gathering at the National Comprehensive Cancer Network's (NCCN's) 19th annual conference—Advancing the Standard of Cancer Care—that "Enthusiasm for older cytotoxic agents is waning very quickly," a nod to the significant advances that have been made very recently—just in the past 3 years—including results presented last June at the annual meeting of the American Society of Clinical Oncology.

Thompson spoke March 13, 2014, on the opening day of the NCCN conference in Hollywood, Florida.

Advances in metastatic melanoma treatments offer more hope than ever in this once-deadly disease. Treatment advances have not come without some rethinking of what constitutes progress, however, as the newer therapies work differently, and the pattern of delayed response has required some adjusting for everyone involved. "We have to be patient and wait for the response," Thompson said.

Since the pair of studies that led to the approval of ipilimumab in the Uni ted States in 2011, the therapy has been watched closely, especially since not all patients react to the drug the same way. And now that some time has elapsed since approval, and more results are in, there's more that can be shared with patients about what to expect from the therapy, with regard both to outcomes and to side effects.

Ipilimumab is now being used as part of a combination therapy, and it is far from the only modern option.

"We have to be careful about toxicities," Thompson said. Just as response to therapy itself can vary, so can the side effects. "There can be a wide variation when they appear, but usually it's about the second dose at about 3 weeks." A wallet card can inform a caregiver or healthcare provider about what to expect, Thompson said.

Ipilimumab is now being used as part of combination therapy, and it is far from the only modern option. Thompson put his audience through multiple case scenarios, asking them to suggest treatment options, and the answers were scattered. An interesting slide came late in the presentation, when Thompson showed results from Ribas et al, a 2012 article in *Clinical Cancer Research*,[1] which seemed to show more robust results early on for targeted therapies in melanoma, but better long-term results for immunotherapy.

What does Thompson see ahead in immunotherapy and targeted therapy for melanoma? In immunotherapy, he sees progress in (1) new immune checkpoint inhibitors, such as anti-PD-1s; (2) T-cell therapy, including cells with engineered immune-receptors; (3) lymphokins such as IL-15 and IL-21, alone or in combination with vaccines or checkpoint inhibitors; and (4) receptor-directed cytokines.

In targeted therapy, look for (1) "molecularly targeted" agents, such as MEK inhibitors; (2) studies of the mechanisms of acquired resistance to targeted agents; and (3) combinations of targeted agents with immunomodulators, which regulate the skin's immune response. **EBO**

Guideline Update, March 2014:

- Based on recent FDA approval, the combination of dabrafenib plus trametinib was added to the list of preferred systemic therapy options for advanced or metastatic melanoma. The combination of dabrafenib and trametinib was associated with progression-free survival compared with dabrafenib monotherapy in a phase I/II trial; however, improvement in overall survival has not been demonstrated. Combination therapy may be associated with less cutaneous toxicity than monotherapy.
- Single-agent trametinib is not indicated for the treatment of patients who have experienced progression of disease on prior *BRAF* inhibitor therapy. Single-agent trametinib can be used for the treatment of BRAF-mutated melanoma in patients who are intolerant of single-agent *BRAF* inhibitors.

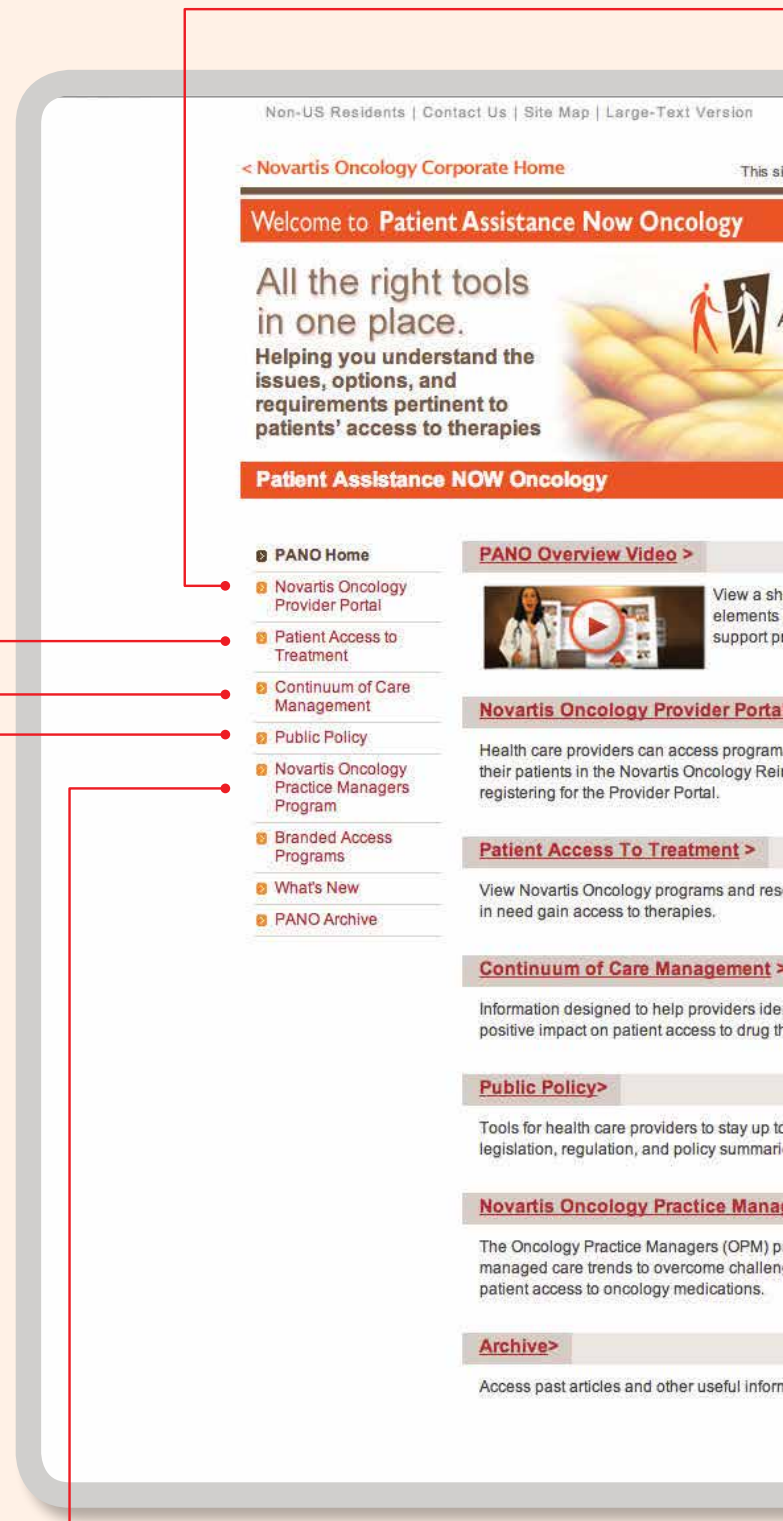
Reference

1. Ribas A, Hersey P, Middleton MR, et al. New challenges in endpoints for drug development in advances melanoma. *Clin Cancer Res.* 2012;18:336-341.

Patient Assistance NO

All the Right Tools in One Place

The Novartis Oncology Patient Assistance NOW Oncology (PANO) website makes it easy with all-in-one convenience providing simplicity, efficiency, and streamlined access for you, your patients, and your oncology practice managers (OPMs).



Patient Access to Treatment

A link to our central hub of patient access resources, where you will find tools for insurance verification, assistance with identifying alternate sources of coverage/funding that may assist with patient costs, assistance for low-income and uninsured patients, and more.

Continuum of Care Management

Information designed to help your practice identify the best way to ensure a positive impact on patient access to drug therapies.

Public Policy

Links to information about the ever-changing landscape of health care reform, reform requirements, Medicare, and drug purchasing options.

Novartis' Oncology Practice Managers Program

A link to a program for OPMs that provides education and tools

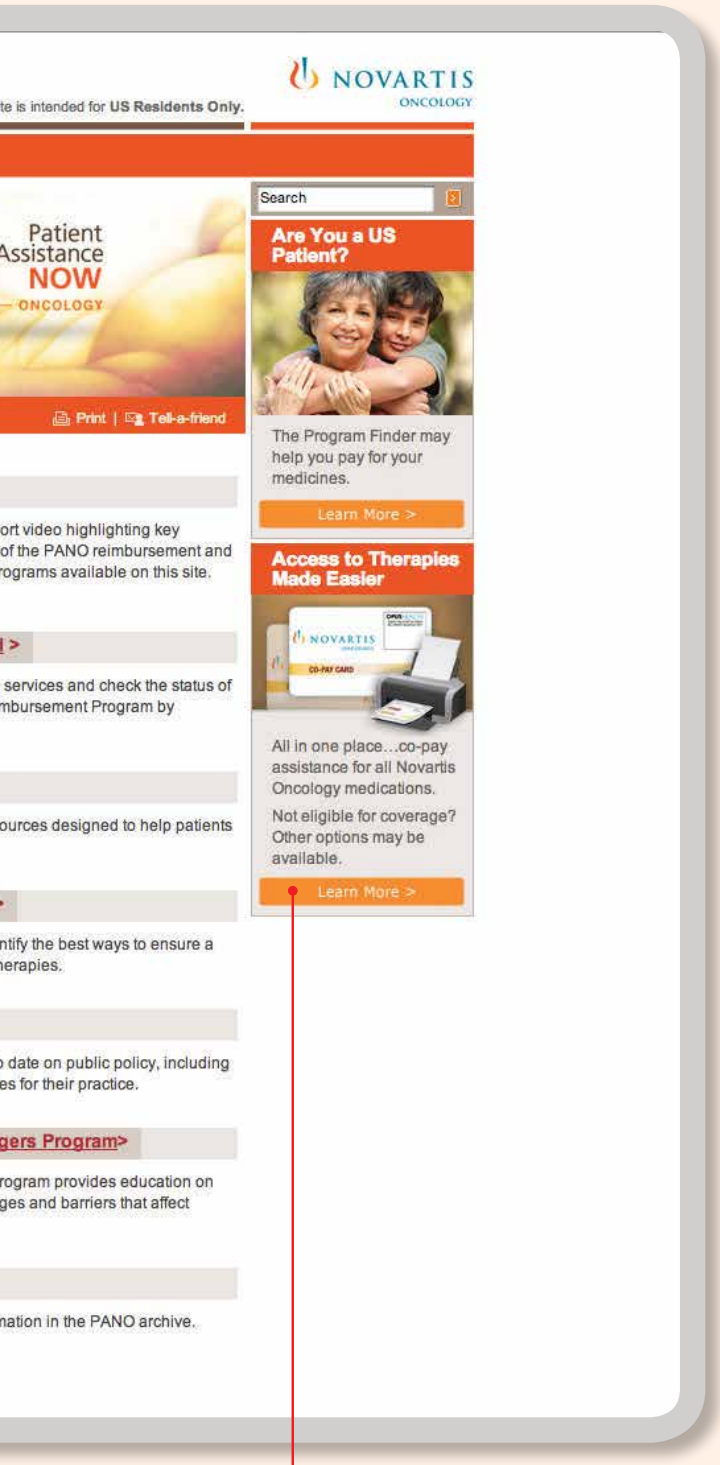
- Health care trends
- Overcoming challenges and barriers that impact patient access
- Link to e-slide library

NOVARTIS ONCOLOGY

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

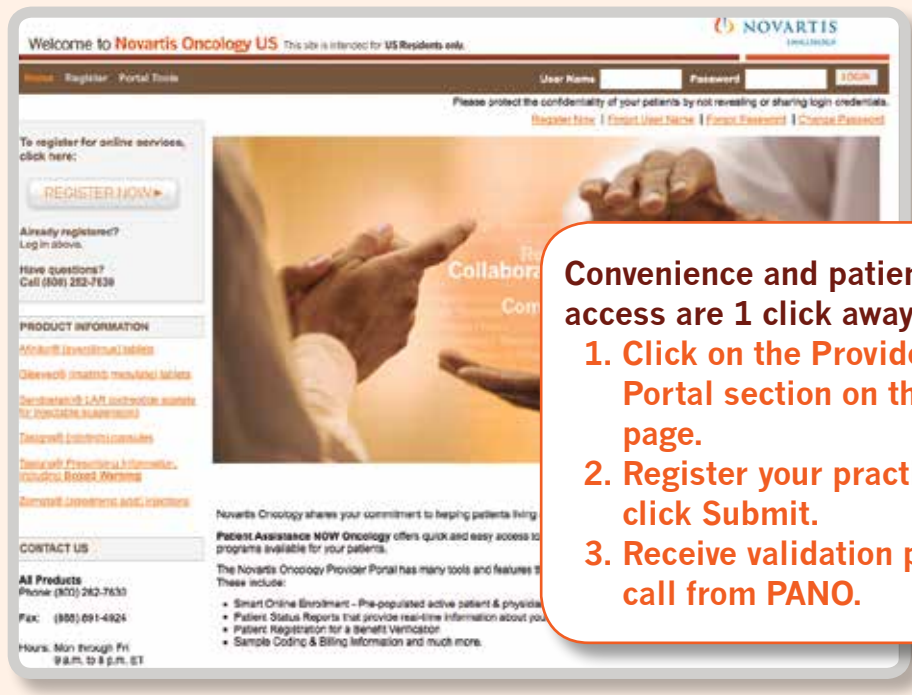
PAN-1087341

W Oncology **Mapped!**®



Helping Make Access to Therapies Easier

Find pertinent information about available Novartis Oncology brand-specific patient access and reimbursement programs to help support your patients.



Novartis Oncology Provider Portal

- Enroll a new patient or check the status of a current patient
- Organize patient reports tailored to meet your needs
- See a listing of all your patients as soon as you enter the portal
- Get immediate alerts that highlight important tasks and events to expedite patient treatment
- Download forms
- Click on a patient's name to instantly display that patient's information
- Attach a document to a patient's electronic file (as easy as adding an attachment to an e-mail)
- Manage your individual user profile and easily change your contact information

Patient Assistance NOW Oncology
www.OncologyAccessNow.com

Patient Assistance NOW Oncology Hotline:
1-800-282-7630

Patient Assistance NOW ONCOLOGY

AJMC Managed Markets Network

Mutations That Drive Lung Cancer Also Driving Frontiers of Treatment

Mary K. Caffrey

A more individualized view of what drives the onset of non-small cell lung cancer (NSCLC) is raising treatment hopes as new therapies emerge and enter development, said Leora Horn, MD, MSc, of the Vanderbilt-Ingram Cancer Center, who presented an overview March 14, 2014, at the National Comprehensive Cancer Network's (NCCN's) 19th Annual Conference: Advancing the Standard of Cancer Care, held in Hollywood, Florida.

Once upon a time, asking what kind of lung cancer a patient had would yield 1 of 4 answers: large cell carcinoma, small cell carcinoma, squamous cell carcinoma, or adenocarcinoma; this last type afflicts both smokers and nonsmokers but has become more common among smokers in recent decades.[1]

Leora Horn, MD, MSc

That limited view meant limited treatment, even though lung cancer causes more deaths than any other type in the United States.[1] Today, however, oncologists are gaining a greater understanding of what sets cancer in motion at the molecular level; nearly a dozen mutations, notably *KRAS* and *EGFR*, are now known to account for about half of lung cancer cases.

For years, lung cancer waited for a game changer. As Horn showed with results from the ECOG 1594, and in other studies, multiple comparative combinations were producing few differences in survival, although there were differences in toxicity and cost.[2] Horn noted the 2010 results of the AVAiL trial, which found no overall survival (OS) benefit for patients taking bevacizumab, a monoclonal antibody, with chemotherapy, compared with those taking chemotherapy alone.

Results published in October 2013 by the American Society of Clinical Oncology[3] did show a small difference in progression-free survival (PFS) between patients taking pemetrexed with a combination of bevacizumab and carboplatin (median PFS = 6.04 months) compared with those taking paclitaxel and the bevacizumab/carboplatin combo (median PFS = 5.5 months). Greater differences were seen in OS, which were 12.55 months for the pemetrexed arm compared with 13.4 months for the paclitaxel arm.

Enter biomarkers and targeted therapy, and the differences begin to grow. Horn showed a series of results comparing gefitinib with traditional chemotherapy combinations for patients with EGFR-positive mutation, and the outcomes were stark. A roundup of studies comparing targeted therapies with traditional regimens typically had differences in PFS of 5 months, with 1 study involving erlotinib reporting a difference of 8.5 months.

What's coming in immunotherapy may raise even more optimism. There's increased understanding of PD-1, as well as its ligand PD-L1 and their role in NSCLC.

What's coming in immunotherapy may raise even more optimism. There is increased understanding of PD-1, as well as its ligand PD-L1, and their roles in NSCLC; PD-L1 is overrepresented in both adenocarcinoma and in squamous cell lung cancer, which are most common among smokers. Immunotherapy targets T-cell activity, which is regulated by a balance of costimulatory and inhibitory signals known as checkpoints. The body's self-regulation through these checkpoints enables it to respond to infections and prevent tumor progression, as well as prevent autoimmune-type responses.

Nivolumab, a PD-1 inhibitor, is an investigational therapy that has received attention since a 2012 article in the *New England Journal of Medicine*[4] reported on its effects on patients across multiple cancers, including NSCLC. It gained further notice from ASCO in 2013 and at the World Conference on Lung Cancer in October 2013. Survival rates at 1 year with nivolumab were 42% and reached 24% at 2 years, according to the median 20.3-month follow-up.[5] Horn also reviewed the side effects, which were relatively limited in the NSCLC cohort.

In current trials, nivolumab is being tested against chemotherapy as second line in PD-L1–positive NSCLC patients, and nivolumab is being tested with and without ipilimumab in small-cell lung cancer. There are 25 trials involving the drug; besides NSCLC, there are phase 3 trials involving melanoma and renal cell carcinoma.[5]

An anti-PD-L1 monoclonal antibody, MPDL3280A, is currently under study in combination with bevacizumab and chemotherapy; like nivolumab, it is being studied for other cancers. A related agent is being studied as a second-line therapy in combination with docetaxel. **EBO**

Guideline Update, February 2014:

RISK ASSESSMENT
- Smoking history (past or present) and second-hand smoke exposure
- Radon exposure
- Occupational exposure
- Cancer history
- Family and disease history, including lung cancer, chronic obstructive pulmonary disease, pulmonary fibrosis
- Absence of symptoms or signs of lung cancer

RISK STATUS

A patient is HIGH RISK if:
- Age 55-74 years and...
- At least 30 pack-years (equivalent of 1 pack a day for a year; or 2 packs a day for 15 years)
- Smoking cessation of <15 years (category 1)

Or:
- At least 50 years old and...
- At least 20 pack-year smoking history and...
- 1 additional risk factor, other than second-hand smoke

A patient is MODERATE RISK if:
- At least 50 years old and...
- At least 20 pack-year smoking history or second-hand smoke exposure
- No other risk factors

A patient is LOW RISK if:
- Less than 50 years old and/or
- Less than 20 pack-year smoking history

SCREENING is recommended in *HIGH-RISK* patients. ROUTINE SCREENING is NOT RECOMMENDED in *MODERATE RISK* and *LOW-RISK* patients.

SCREENING MODALITY

BASELINE CT (LDCT)
- If lung nodules found on LDCT, see EVALUATION GUIDELINES.
- If no lung nodules found, continue annual LDCT for 2 years if high-risk (category 1); consider annual LDCT until patient no longer eligible
- Evaluate findings for follow-up for diseases other than lung cancer.

References

1. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014. http://www.surgeongeneral.gov/initiatives/tobacco.

2. Phase 3 randomized trials comparing platinum-containing doublets for advanced NSCLC. Medscape Multispecialty. http://www.medscape.org/viewarticle/500190_3. Accessed March 16, 2014.

3. Patel JD, Socinski MA, Garon ME et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer [published online October 21, 2013]. *JCO*.

4. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Eng J Med*. 2012;366(26):2455-2465.

5. Inman S. Nivolumab survival benefit extended in updated NSCLC results. OncLive. http://www.onclive.com/web-exclusives/Nivolumab-Survival-Benefit-Endures-in-Updated-NSCLC-Results. Published October 28, 2013. Accessed March 16, 2014.

Promising News in Treating Multiple Myeloma

Mary K. Caffrey

Advances in treating multiple myeloma have transformed the field over the past decade, giving clinicians more effective therapy options for newly diagnosed patients who are candidates for stem cell transplant and those who are not.

But the best may be yet to come, with 2 promising monoclonal antibodies on the horizon, according to Kenneth C. Anderson, MD, of the Dana-Farber Cancer Institute. Anderson discussed treatment advances on March 15, 2014, at the National Comprehensive Cancer Network's (NCCN's) 19th Annual Conference: Advancing the Standard of Cancer Care, held in Hollywood, Florida.

Kenneth C. Anderson, MD

Anderson said the 9 new approvals for multiple myeloma from the FDA have prolonged median survival for patients 2 to 3 years, with most patients now living 5 to 7 years with the disease. "In spite of all this, we still need novel agents," he said, before sharing his optimism about therapies in the pipeline.

The addition of bortezomib has rewritten NCCN guidelines in recent years, and the 2014 version Anderson shared features the proteasome inhibitor in various combinations with immunomodulatory drugs in 5 of the 6 preferred regimens for patients who are transplant candidates.

Positive results on bortezomib-based regimens continue to come in; Anderson reviewed data presented at the American Society of Hematology (ASH) meeting in New Orleans in December 2013, which he said show that the treatment consistently improves progression-free survival by an average of 9 months, as well as overall survival, with a median of 84 months reached.[1]

For patients ineligible for transplant, a new standard of care has emerged, Anderson said. Based on the results of the FIRST trial presented at ASH in December, lenalidomide and low-dose dexamethasone (len-dex) has been moved into the NCCN guidelines. At a massive, standing-room–only plenary session, Thierry Facon, MD, presented results showing a 28% better survival rate for patients in the trial than for patients taking the previous standard of melphalan, prednisone, and thalidomide (MPT).[2]

Anderson emphasized the real-world practicality that Facon noted at ASH[1]: the FIRST trial (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) involved a large group of relatively older patients, much closer to the group that will be developing multiple myeloma as the population ages.

Thierry Facon, MD

But for all the good news, said Anderson, multiple myeloma remains incurable. New approaches, he suggested, are needed to treat and ultimately prevent relapse. "I want to get you excited about the future," Anderson said. "We think we're finally going to get a monoclonal antibody or two."

The bright spots are elotuzumab, which is currently in phase III trials but has shown very promising results in combination with len-dex, and daratumumab, which in June 2013 became the first single-agent monoclonal antibody to receive FDA breakthrough status for relapsed and refractory multiple myeloma.[3]

Anderson's final point may be the most exciting of all: It's not just the newly diagnosed patients who are benefitting from the advances, but patients who have relapsed as well. Incorporation of novel therapies at all stages of disease is further improving patient outcomes, he said. **EBO**

Guideline Update, February 2014:

- The table for smoldering (asymptomatic) myeloma was modified to include: IgG ≥3 g/dL; IgA >1 g/dL or Bence-Jones protein >1 g/24 hours.
- The understanding of Smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics including IgG levels of >3 dg/L, IgA of >2 g/dL, or urinary Bence-Jones protein of >1 g/24 hours, or abnormal free light chain ratios, have an increased risk of progression to active (symptomatic) myeloma. It is also increasingly recognized that the classical definition of smoldering myeloma using certain tests such as plain x-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as "asymptomatic" to having "active disease" are under way.
- Post autologous stem cell transplant, response, or stable disease
  - Retrospective studies suggest a 2-to-3-year minimum length of remission for consideration of a second autologous stem cell transplant for salvage therapy (category 2B).
- Maintenance therapy, other regimens was modified to include:
  - Bortezomib plus prednisone (category 2B)
  - Bortezomib plus thalidomide (category 2B)

References

1. Sonneveld P, Scheid C, van der Holt B, et al. Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma: extended follow-up of the HOVON-65/GMMG-HD4 trial. [ASH Abstract 404]. *Blood*. 2013;122(21).

2. Caffrey MK. When less is more: results herald "paradigm shift" in treating newly diagnosed multiple myeloma patients. *Am J Manag Care*. 2014;20(SP2):SP51.

3. McCall B. Daratumumab response high and durable in multiple myeloma. Medscape. http://www.medscape.com/viewarticle/806458. Published June 18, 2013. Accessed March 16, 2014.

Sorting Through Screening Protocols for Colorectal Cancer

Mary K. Caffrey

Who should receive genetic counseling and screening for colorectal cancer (CRC)? And how early should annual colonoscopies happen once those at risk are identified? These are important questions with equally important and complex answers.

Heather Hampel, MS, CGC, of the Ohio State University Comprehensive Cancer Center, took those questions on in an information-packed hour at the 19th annual conference of the National Comprehensive Cancer Network (NCCN)—Advancing the Standard of Cancer Care. Hampel spoke March 13, 2014, as the conference opened in Hollywood, Florida.

Questions about genetic testing for CRC start with "need": The origin of 10% to 30% of CRC is familial, while 65% to 85% is sporadic,[1] with another 1% caused by familial adenomatous polyposis and 3% by hereditary nonpolyposis colorectal cancer or Lynch Syndrome (LS). When a family risk is known, proper counseling and screening can identify those CRC patients who need different treatment options, as well as identify family members who may be at risk for other cancers associated with LS.

Genetic counseling is important, however, as Hampel would explain. Families are not as large as they once were, so it may not be as easy to detect a family history of CRC. On the plus side, wider use of colonoscopy is detecting polyps and cancers earlier, when the disease is more treatable, than was the case in previous generations. The presence of LS in the family makes all the difference in terms of the approach to screening and possible prophylactic options, as CRC is not the only LS-linked cancer that family members face—others include ovarian, urinary tract, and even skin cancer.

When LS is present in the family, depending on the mutation, colonoscopy should begin as early as age 20 years and occur every 1 to 2 years for those family members who carry the mutations. Colonoscopies could move up to as early as 5 years prior to the earliest known colon cancer in the family.

There is no clear evidence for some other forms of screenings, including endometrial sampling, transvaginal ultrasound, and esophagoscopy

Guideline Update, January 2014:

- Cowden syndrome and Li-Fraumei syndrome added as examples of high-risk syndromes.
- Colonoscopy with polyps
  - Recent studies have demonstrated that fecal immunohistochemical testing (FIT) is more sensitive than guaiac-based testing.
  - Other screening modalities such as double contrast barium enema should be reserved for those who are not able to undergo colonoscopy, or if colonoscopy is technically incomplete.
- Low-risk adenomatous polyps
  - If repeat colonoscopy within 5 years is negative, colonoscopy should be repeated every 10 years.
  - Other factors in determining intervals may include the results of the prior examinations and the presence of comorbid conditions. Generally, the results of the first 2 screening examinations may predict the patient's overall colon cancer risk.
- Increased risk based on personal history of CRC
  - Testing by MSI and IHC was included.
- Increased risk based on positive family history
  - Criteria eliminated:
    - ≥2 second-degree relatives with CRC at any age.
    - 1 second-degree relative and ≥2 third-degree relatives with CRC at any age.
    - Grandparent aged >50 years with CRC
    - Aunt/uncle aged >50 years with CRC or 3 third-degree relatives with CRC at any age.
  - If the patient has 1 second-degree relative with CRC aged <50 years or a first-degree relative with advanced adenoma(s), the follow-up screening was advised to be repeated as per colonoscopy findings.
  - Multiple (2 or more) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.
- Quality indicators for colonoscopy are emphasized as an important part of the fidelity of findings.
- Screening
  - Stool-based
    - Annual stool occult blood testing should not be performed if colonoscopy is used as a screening measure in an average-risk patient.
  - FIT
    - Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.
  - A link was included for AGA standards for gastroenterologists for performing and interpreting diagnostic CT colonography.

- **High-risk syndromes**
  - **Lynch Syndrome (LS)**
    - In patients identified as carriers of a mutation in *MLH1*, *MSH2*, *MSH6*, or *PMS2*, genetic testing for at-risk family members was recommended.
    - Surveillance for *MLH1* and *MSH2* mutation carriers
      - There are data to suggest that aspirin may decrease the risk of colon cancer in LS; however, at this time the data are not sufficiently robust to make a recommendation for aspirin's standard use.
      - There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer for LS. Selected individuals, families, or those of Asian descent may consider EGD with extended duodenoscopy.
      - Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified, preventing recommendation of screening.
      - There have been suggestions that there is an increased risk of breast cancer in LS patients, but limited data prevent recommendation of screening.
    - Surveillance recommendations were added for *MSH6* and *PMS2* mutation carriers.
    - The table for cancer risks associated with *MSH6* and *PMS2* mutations has been updated.
  - ***APC*** and ***MUTYH*** genetic testing criteria, testing strategies, and treatment/surveillance have been updated.
  - **Familial adenomatous polyposis/AFAP**
    - Germline *APC* mutation was added in the phenotype.
    - A clinical diagnosis of FAP is made when >100 polyps are present at a young age; however, genetic testing of *APC* and *MUTYH* is important to differentiate FAP from MAP or colonic polyposis of unknown etiology. Identification of a germline *APC* mutation confirms the diagnosis of FAP.
    - There is currently no consensus on what constitutes a clinical diagnosis of AFAP. AFAP is considered when >10 to <100 adenomas are present, and confirmed when an *APC* mutation is identified. Genetic testing of *APC* and *MUTYH* is important to differentiate AFAP from MAP or colonic polyposis of unknown etiology.
  - **Familial adenomatous polyposis/FAP**
    - Surveillance
      - The use of chemoprevention is to facilitate management of the remaining rectum post surgery. There are no FDA-approved medications for this indication at present. While there are data to suggest that sulindac is the most potent polyp regression medication, it is not known if the decrease in polyp burden decreases cancer risk.
      - For gastric cancer, non-funding gland polyps should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically but have high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy.
    - *APC* gene testing is recommended for familial mutation.
  - **Attenuated familial adenomatous polyposis**
    - Earlier surgical intervention is recommended in noncompliant patients.
    - *APC* gene testing recommended for familial mutation.
  - **Colonic adenomatous polyposis of unknown etiology**
    - Recommendations for management/surveillance for disease of unknown etiology included.

gastroscopy duodenoscopy with extended duodenoscopy, but Hampel said that clinicians could consider the latter, starting between age 30 and 35 years. Urinalysis could be considered also, starting between age 25 and 30 years. The most important element, of course, is getting a good family history starting at age 25 years.

Hampel said that despite the challenges LS may present, there is good news: the cost for genetic panels and tumor screening has come down. Tumor screening costs about $500, and the cost for all LS mutations using Sanger Sequencing is about $4550. Next-generation seq uencing costs are lower, ranging between about $2700 and $4000 for 14 to 20 CRC genes per panel. The technology is better, which is why the cost is lower, but it does take somewhat longer than it once did to get results. Hampel said this is a cost-effective option for families in which more than 1 gene is involved.


Heather Hampel, MS, CGC

Fears that families had in the past about getting genetic tests have eased with the passage of the Genetic Information Nondiscrimination Act, which offers protection in health coverage and employment based on results of genetic tests. However, Hampel warned that the same is not true in life insurance, disability, and long-term care coverage, and she encouraged those attending the NCCN session to counsel patients to have these forms of coverage in place before proceeding with genetic testing. **EBO**

Reference

1. Burt RW. Familial risk and colorectal cancer. *Gastroeterol Clin North Am.* 1996;25(4):793-803.

Protecting Bone Health During Cancer Care

Mary K. Caffrey

Life-saving therapies that halt cancer can take a toll on the skeletal system, leaving survivors with bone loss or more serious injuries such as broken wrists, ribs, or hips. Watchful attention, screening, and therapy are needed to prevent these outcomes.

Azeez Farooki, MD, an endocrinologist and specialist in cancer-induced bone loss at Memorial Sloan Kettering Cancer Center, presented the findings of the National Comprehensive Cancer Network's (NCCN's) Bone Health Task Force on March 13, 2014, at the group's 19th annual conference—Advancing the Standard of Cancer Care—held in Hollywood, Florida.

Avoiding fractures starts with screening, and Farooki said bone mineral density (BMD) assessments for osteoporosis are recommended in all postmenopausal women 65 years and older, regardless of risk factors, and in all men starting at age 70 years.

Men and women aged 50 to 70 years should receive BMD tests if they have certain risk factors, such as previous fractures, glucocorticoid therapy, parental history of hip fracture, low body weight, excessive alcohol use, or rheumatoid arthritis, or if they are current smokers or have chronic obstructive pulmonary disease. Other risks are premature menopause, malabsorption, chronic liver disease, hypogonadism, and inflammatory bowel disease.

Bone loss with age is normal, Farooki explained, but certain cancer treatments speed up the process more than others. He shared a slide comparing normal bone loss in men at the low end with that of men following various types of cancer treatments. The greatest loss occurred, though, among women experiencing premature menopause and secondary chemotherapy.

While it is common to associate bone loss with women and menopause, Farooki explained that men are also at risk for bone loss and skeletal injury. He noted that while men experience one-third of hip fractures, they experience higher levels of mortality from hip fractures than women: 37.5%, compared with 28.2% in women.

So what to do? Bone health maintenance involves strategies in scans and treatment, including preventive treatment. Farooki went through a number of recommendations.

In early-stage breast cancer, the use of adjuvant bisphosphonates to reduce recurrence and improve survival is currently considered investigational, though there are some promising data so far in the "low estrogen" state.


Azeez Farooki, MD

In prostate cancer, no bisphosphonate has shown benefit for bone metastasis prevention. Denosumab has been shown to delay the onset of bone metastases in castration-resistant prostate cancer, although the clinical significance has yet to be determined.

Farooki said the NCCN does not recommend the use of osteoclast-targeted therapy for prevention of bone metastases in prostate cancer. He also reviewed the use of antiresorptives—which can help with both the prevention of bone loss generally, and aid in treatment of bone metastases and myeloma—in the prevention of fractures and in the easing of bone pain.

Calcium intake goal should be 1200 mg per day, but work with a nutritionist may be needed, because if supplements are used in excess, patients can be at risk for developing kidney stones. There are similar recommendations with vitamin D—it is a dietary necessity, but food is a better source, and there is such a thing as too much vitamin D.

Some caveats: estrogen is preferred for young women with premature menopause and non–estrogen-dependent cancer. Raloxifene use with an aromatase inhibitor is not advisable. And denosumab is the only drug recommended for men on androgen deprivation therapy that has solid fracture prevention data.

In response to questions, Farooki said he does recommend that patients work with physical therapists to improve bone strength to prevent fractures, and balance to prevent falls, which can lead to fractures. **EBO**

Guideline Update, August 2013 Task Force Report:

- **Atypical Femoral Fractures.** After 3 to 5 years of potent antiresorptive therapy (bisphosphonate or denosumab), or after cancer therapy posing a risk for bone loss is stopped, reassess fracture risk and consider a drug holiday or discontinuation.
- **Calcium Intake.** 1200 mg per day from food sources and supplements, recognizing that too much calcium from supplements can increase risk for kidney stones.
- **Radium 223.** This treatment of prostate cancer (see Prostate Treatment guideline) was approved by the FDA for use in men with advanced prostate cancer who have symptomatic bone metastases.

Breast Cancer

Guideline Update, February 2014:

- A pertuzumab-containing regimen may be administered preoperatively to patients with ≥T2 or ≥N1, HER2-positive early-stage breast cancer.
- Paclitaxel plus trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.
- A pertuzumab-containing regimen may be administered preoperatively in patients with ≥T2 or ≥N1, HER2-positive early-stage breast cancer. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.
- The following dosing schedule was added: Paclitaxel plus trastuzumab
  - Paclitaxel 80 mg/m^2 IV weekly for 12 weeks, with
  - Trastuzumab 4 mg/kg IV with first dose of paclitaxel, followed by
  - Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complement 1 year of trastuzumab treatment.
  - Cardiac monitoring at baseline, 3, 6, and 9 months.

Gallbladder Cancer

Guideline Update, January 2014:

- The choice of treatment modality may depend on extent/location of disease and institutional capabilities
- Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with lymph-node–positive disease.

Non-Hodgkin's Lymphomas

Guideline Update, January 2014:

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

- Diagnosis, essential
  - CLL diagnosis requires presence of monoclonal B lymphocytes ≥5 × 10^9/L in peripheral blood.
  - Clonality of B cells should be confirmed by flow cytometry.
  - Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers: kappa/lambda, CD19, CD20, CD5, CD23, CD10; if flow is used for diagnosis, also include cytospin for cyclin D1 or FISH for t(11;14); t(11q:v).
  - SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes ≤5 × 10^9/L in peripheral blood.
  - SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy.
- Diagnosis, informative for prognostic/therapy determination
  - Cells of same phenotype maybe seen in reactive lymph nodes; therefore diagnosis of SLL should only be made when effacement of lymph node architecture is seen.
- Frail patient, significant comorbidity:
  - Obinituzumab plus chlorambucil was added.
  - Chlorambucil plus/minus rituximab was changed to rituximab plus chlorambucil and chlorambucil was added as a monotherapy.
- CLL without del (11q) or del (17p):
  - First-line therapy, patients aged ≥70 years, or younger patients with comorbidities
    - Obinutuzumab plus chlorambucil was added
    - Chlorambucil plus/minus rituximab was changed to rituximab plus chlorambucil and chlorambucil was added as a monotherapy.
    - Alemtuzumab was removed.
    - Lenalidomide was removed.
  - Patients aged <70 years, or older patients with significant comorbidities
    - Obinutuzumab plus chlorambucil was added.
  - Relapsed/refractory therapy, short response for patients aged ≥70 years
    - Ibrutinib was added.
    - Chlorambucil plus/minus rituximab was changed to rituximab plus chlorambucil.
  - Relapsed/refractory therapy, short response for patients aged <70 years, or older patients without significant comorbidities
    - Ibrutinib was added.
    - R-HyperCVAD was removed.
    - Does-adjusted EPOCH-R was removed.
- CLL with del (11q):
  - First-line therapy
    - Obinutuzumab plus chlorambucil was added.
  - Relapsed/refractory therapy
    - Ibrutinib was added.
    - R-HyperCVAD was removed.
  - First-line therapy, patients aged ≥70 years, or younger patients with comorbidities
    - Obinutuzumab plus chlorambucil was added.
    - Chlorambucil plus/minus rituximab was changed to rituximab plus chlorambucil and chlorambucil was added as a monotherapy.
    - Alemtuzumab was removed.
    - Lenalidomide was removed.
  - Patients aged <70 years, or older patients with significant comorbidities
    - Obinutuzumab plus chlorambucil was added.
  - Relapsed/refractory therapy, short response for patients aged ≥70 years
    - Ibrutinib was added.
    - Chlorambucil plus/minus rituximab was changed to rituximab plus chlorambucil.
  - Relapsed/refractory therapy, short response for patients aged <70 years, or older patients without significant comorbidities
    - Ibrutinib was added.
    - R-HyperCVAD was removed.
    - Does-adjusted EPOCH-R was removed.

(continued on SP219)

Non-Hodgkin's Lymphomas
(continued from SP218)

Follicular lymphoma
- Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious of transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy.
- For stage 2 bulky, 3, 4:
  - PET-CT scan was recommended before initial therapy.
  - After initial response, PET-CT (preferred) or CT scan was recommended to evaluate for response status.
    - A PET-positive PR is associated with a shortened PFS; however, additional treatment at this juncture has not been shown to change outcome.
- Histologic transformation to diffuse large B-cell lymphoma
  - For minimal or no prior chemotherapy
    - BCEL-C as first-line therapy.
    - PET-CT scan (preferred) or CT-scan were recommended following treatment with chemotherapy plus rituximab plus/minus RT.
- For pathologic evaluation of histologic transformation, FISH for BCL2 rearrangement [t(14:18)] and MYC rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
- First-line therapy:
  - Bendamustine plus rituximab changed from category 2A to category 1 recommendation.
- First-line consolidation or extended dosing:
  - If initially treated with single-agent rituximab consolidation with rituximab 375 mg/m^2 1 dose every 8 weeks for 4 doses.
- For patients with locally bulky or locally symptomatic disease, consider ISRT 4-30 Gy plus or minus additional systemic therapy.
- First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine plus rituximab has not been studied
-

Gastric MALT lymphoma
- Diagnosis, useful under certain circumstances
  - Molecular analysis to detect antigen receptor rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation is present.
- Locally advanced diseaes is more likely in patients with gastric MALT lymphoma with t(11;18), which is less likely to respond to antibiotics
- If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary.
- t(11;18) is a predictor for lack of tumor response (5%) to antibiotics. Antibiotics are used in these patients to eradicate *H pylori* infection. These patients should be considered for alternative therapy of the lymphoma. t(11;18) is a marker for all stages gastric MALT lymphomas that will not respond to *H pylori* eradication.

Mantle cell lymphoma
- Therapies removed:
  - CVP plus rituximab.
  - Dose-adjusted EPOCH plus rituximab.
- Therapies added:
  - Ibrutinib.

Diffuse large B-cell lymphoma
- Diagnsosis
  - MYC was added to the essential IHC panel
  - Molecular analysis to detect: antigen receptor gene rearrangements; CCND1; BCL2; BCL6; MYC rearrangements by FISH or IHC, was removed.
- For stage 3 and 4
  - CT scan should be repeated only as clinically indicated.
  - After end-of-treatment restaging with a complete response, "Consider RT to initially bulky disease" was changed to a category 2A recommendation.
- Other treatment options:
- Treatment regimens include:
  - RCHOP x6 cycles plus RT
  - Dose-adjusted EPOCH-R plus rituximab, ×6 to 8 cycles; for persistent focal disease, RT can be added.
  - RCHOP x4 cycles followed by ICE ×3 cycles plus or minus RT.

Burkitt lymphoma
- Cytogenetics plus/minus FISH: t(8;14) or variants and MYC were recommended as essential diagnostic tests.

AIDS-related B-cell lymphoma
- CD30 for PEL was added to additional immunohistochemical studies to establish lymphoma subtype.
- In patients on active antiretrovirals being treated with a rituximab-based regimens, low CD4 count (<100/mL) may be associated with decreased response and survival outcomes; CD4 count <50/mL has been associated with increased treatment-related deaths.

Primary cutaneous B-cell lymphoma
- If adequate material is available, flow cytometry or PCT can be useful to diagnose B-cell clonality.

Peripheral T-cell lymphoma
- Additional immunohistochemical studies were recommended to establish lymphoma subtype: F1, TCR-CUM1, CD279/PD1, CXCL-13.
- Induction therapy
  - Treatment recommendations for all stages of PTCL, NOS; ALCL, ALK–; AITL. EATL have been combined and the follow-up therapy for stage 1, 2 low/low-intermediate disease has been eliminated.
  - For multiagent chemotherapy, the number of cycles have been reduced from 8 to 6.
  - Radiation dose of 30 to 40 Gy was considered appropriate.
- First-line therapy
  - CHOP followed by IVE alternating with intermediate-dose methotrexate was recommended only in patients with EATL.
  - For transplant candidates as well as non-candidates, Brentuximab vedotin for CD30+ PTCL was added.

CVS Caremark Quits for Good: Our Decision to Stop Selling Tobacco Products

Troyen A. Brennan, MD, MPH, Chief Medical Officer, CVS Caremark

The statistics related to the negative health and financial impacts of tobacco use have been cited numerous times, but they remain staggering each time you see them:

- 42 million people in the United States continue to smoke and 16 million current and former smokers have smoking-related illnesses[1];
- More than 480,000 deaths occur each year in the United States as a result of smoking[1];
- Tobacco use costs $132 billion in direct medical costs and $157 billion in lost productivity.[1]

What these numbers make abundantly clear is that, despite 4 decades of concerted tobacco control efforts, finding ways to reduce the morbidity and mortality associated with tobacco use is one of the most important public health challenges we face as a nation.

On February 5, 2014, CVS Caremark announced that our company will stop selling cigarettes and other tobacco products at all CVS/pharmacy stores across the country—that's more than 7600 stores—by October of this year. As the first national pharmacy chain to make such a commitment, we came to this decision because we believe the sale of tobacco products in our stores poses a paradox that is at odds with our role as a healthcare company and contradicts our purpose of helping people on their path to better health.

Over the past 40 years, a variety of policies have helped reduce the prevalence of cigarette smoking, including increases in tobacco taxation, legislation to create smoke-free public areas, and growing support for smoking cessation. In 1965, 43% of US adults smoked cigarettes, compared with 18% of US adults today.[2] Despite this progress, in the past decade the rate of reduction in smoking prevalence has stalled, suggesting that new approaches and interventions are needed.

Recently, public health advocates have been turning toward programs designed to make smoking less socially acceptable. The rationale for this approach is that increasing the stigma of tobacco use and reducing the social acceptability associated with smoking could result in fewer people smoking and an increase in the number of smokers who attempt to quit. One example of this approach includes the launch of 3 large-scale, national, mass media campaigns in 2014 by the CDC, the FDA, and the Legacy Foundation for Health. Another example is the ban on smoking in outdoor public spaces in New York City.

Studies have also demonstrated a clear relationship between tobacco use and the geographic density of stores that sell cigarettes.[3] This research supports the concept that access to cigarettes can play a role in reducing tobacco use. At CVS Caremark we believe that combining reduced access to cigarettes with policy changes at the state and federal level, and efforts to make tobacco use less socially acceptable, could help further reduce tobacco use and its resulting negative health and financial consequences.

Troyen A. Brennan, MD, MPH

For CVS Caremark, removing cigarettes and other tobacco products from our CVS/pharmacy locations is a concrete way we can help reduce access and make these products less readily available. As a company of 26,000 pharmacists, nurse practitioners, and physician assistants who provide trusted advice to 5 million customers each day, selling tobacco products contradicts our core commitment to healthcare and our growing role as an integral part of the healthcare system. As pharmacies are becoming more and more involved in chronic disease management and counseling, we find ourselves faced with a conundrum. How can we provide support and counseling to patients who have high blood pressure, high cholesterol, and diabetes—all conditions that are exacerbated by smoking—and then turn around and sell them cigarettes? Clearly, tobacco products have no place in a setting where healthcare is delivered. When we think about where we expect to be in the future as a healthcare company, it is clear that removing tobacco products from our stores is the right thing to do.

CVS Caremark is not alone in recognizing the paradox of selling cigarettes and tobacco products at pharmacies that are supposed to be focused on healthcare. Back in 2010, the American Pharmacists Association urged pharmacies to discontinue the sale of tobacco products and urged state pharmacy boards to stop issuing and renewing licenses for pharmacies that sell these products.[4] The American Medical Association has passed a resolution opposing the sale of tobacco products in pharmacies, and calls to ban tobacco sales in pharmacies have also come from the American Heart Association, the American Cancer Society, and the American Lung Association (ALA). Even cities in California and Massachusetts, particularly San Francisco and Boston, have banned the sale of tobacco products in pharmacies,[5] and efforts to institute statewide prohibitions are on.

Our decision to stop selling tobacco products at CVS pharmacy locations may not cause the majority of people to stop smoking; smokers will most likely simply go somewhere else to buy their cigarettes. But if other retailers that are focused on healthcare recognize this paradox and follow our lead, tobacco products will become much more difficult to obtain. And, perhaps this will reinforce the social unacceptability of tobacco use, as people begin to realize that pharmacies no longer sell tobacco products because it is not conducive to the promotion of health and well-being that these institutions stand for.

We think this concept is catching on. Shortly after we made our announcement, 8 senators—led by Senate Health, Education, Labor and Pensions Committee Chairman Tom Harkin (D-IA)—sent a letter to the CEOs of Rite-Aid, Walgreens, and the National Association of Chain Drug Stores (NACDS) urging them to follow our example. In the letter, the senators said, "By reducing the availability of cigarettes and other tobacco products and increasing access to tobacco cessation products, [you, as a company,] have the power to further foster the health and wellness of [your] customers and send a critical message to all Americans—and especially children—about the dangers of tobacco use." In addition, a few weeks later, 26 of the nation's leading public health and medical organizations—ranging from the American Academy of Pediatrics to the American Public Health Association—issued an open letter citing our decision and calling on other drugstores and retailers to also end the sale of tobacco products. These actions reinforce the odd juxtaposition inherent in selling tobacco products in a retail location that promotes health and wellness, and recognize the potential impact of reducing easy access to tobacco products.

Although surveys show that 7 out of 10 smokers say they want to quit, we do recognize that quitting smoking is not an easy task. As a result, in tandem with our decision to stop selling tobacco products, CVS Caremark is also making a pledge to actively help Americans quit smoking. This spring we will launch a robust national smoking cessation program that will encompass the assets of our full enterprise as a retail pharmacy, retail clinic provider, and pharmacy benefit manager, because research shows that quitting smoking has proven health benefits. According to the ALA, as soon as 12 hours after quitting smoking, carbon monoxide level in the bloodstream returns to normal; 2 to 3 months after quitting, the risk of heart attack begins to drop and lung function begins to improve; 1 year after quitting, the added risk of coronary heart disease is half that of a smoker; and 5 to 15 years after quitting, the risk of stroke is reduced to that of a nonsmoker.[6] Our goal is to reduce easy access to cigarettes, help those people who want to quit smoking do so, and help people along their path to better health. **EBO**

References

1. The Health Consequences of Smoking: 50 Years of Progress. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

2. Frieden TR. Tobacco control progress and potential. *JAMA*. 2014;311(2):133-134.

3. Pearce J, Hiscock R, Moon G, Barnett R. The neighourhood effects of geographical access to tobacco retailers on individual smoking behaviour. *J Epidemiol Community Health*. 2009;63(1):69-77.

4. American Pharmacists Association. Report of the 2010 APhA House of Delegates: discontinuation of the sale of tobacco products in pharmacies and facilities that include pharmacies. *J Am Pharm Assoc*. 2010;50(4):471.

5. Katz MH. Banning tobacco sales in pharmacies: the right prescription. *JAMA*. 2008;300(12):1451-1453.

6. American Lung Association. Benefits of Quitting. http://www.lung.org/stop-smoking/how-to-quit/why-quit/benefits-of-quitting/.

MYRIAD®

Innovation that changes lives.

Myriad Genetic Laboratories is a leading molecular diagnostic company dedicated to making a difference in patients' lives through an understanding of the role genes play in human disease. We answer the most pressing questions for patients and their healthcare providers regarding disease.

Questions asked by patients and their healthcare providers:	Myriad's portfolio of products that bring the answers:
Will I? Predictive Medicine	MYRIAD myRisk™ Enabling better planning by assessing an individual's risk of developing disease later in life.
Do I? Diagnostic Medicine	MYRIAD myPath™ Enhancing diagnosis by determining the likelihood of disease presence.
Should I? Prognostic Medicine	MYRIAD myPlan™ Empowering decision-making by assessing the risk of disease progression, recurrence and mortality.
With what? Therapy Selection	MYRIAD myChoice™ Informing treatment by assessing the efficacy and risks of various options.

To find out more about how we are changing the way we view disease, visit our booth #2039 at ASCO.

Myriad Genetic Laboratories, Inc.
320 Wakara Way, Salt Lake City, UT 84108
800-469-7423 | Fax: (801)-584-3615 | **www.Myriad.com**

The Double Whammy of the Obesity Epidemic: Increased Susceptibility to Cancer

Surabhi Dangi-Garimella, PhD

Cancer. When we first think of the disease, genetics and environmental factors spring to mind. However, obesity, the other epidemic that faces the United States, has also been associated with an increased risk of numerous cancers (**Figure 1**). A National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data study classified 4% of new cancer cases in men and 7% in women in 2007 to be a result of obesity.[1]

Although the actual percentages of cases varied for different cancers, endometrial and esophageal cancers had the highest numbers. According to the study, even a small reduction (1%) in the body mass index (BMI) of every adult could reduce the incidence of new cancer cases by about 100,000.[1] Interestingly, although associated with an increased risk of developing such malignancies as colorectal cancer, esophageal adenocarcinoma, cancers of the gallbladder, pancreas, liver, kidney, and thyroid, non-Hodgkin lymphoma, multiple myeloma, ovarian cancer, and prostate cancer, the development of a few cancers including lung cancer, premenopausal breast cancer, and esophageal squamous cell carcinoma have been inversely associated with obesity.[2]

Not only are obese patients at an increased risk of developing malignancies, they have also been found to be at a significantly greater risk of dying due to the malignancy. A prospective study published back in 2003 on a large cohort (more than 900,000 adults) demonstrated that among heavy patients, with a BMI of at least 40 kg/m^2, death from cancer was 52% higher among men and 62% higher among women compared with their corresponding "normal-weight" controls. These results, determined based on a 16-year follow-up period, identified the cancers carrying the highest risk of obesity-associated cancer death as liver and pancreatic cancer in men and uterine, kidney, and cervical cancer in women.[3]

Two studies that drive in the nail on the link between obesity and cancer were conducted in Sweden and in the United States. The Swedish prospective study evaluated the outcomes of bariatric surgery in 2010 patients compared with 2036 controls, after a median follow-up of 10.9 years, and identified a 40% reduction in cancer incidence.[4] A retrospective study conducted in a single clinic in Utah that compared 7925 patients who had undergone bariatric surgery with 7925 matched controls during a follow-up period of 7.1 years revealed a 60% decrease in cancer mortality associated with bariatric surgery.[5]

Acknowledging the rise in evidence for obesity as a risk factor for cancer and other diseases, payers have recognized that a healthy body weight can reduce the incidence and complications of various diseases, which in turn would reduce medical costs and improve productivity.

Figure 1. Association Between Obesity and Cancer

Mechanism of the Increased Risk

Research delving into the molecular basis for the increased association of obesity with cancer risks has provided several leads. These include molecules such as estrogen, insulin, insulin-like growth factor-1, and adipokines (**Figure 2**). Additionally, chronic low-level inflammation, oxidative stress, and altered microbiomes are risk factors for cancer observed in obese individuals.[1,5]

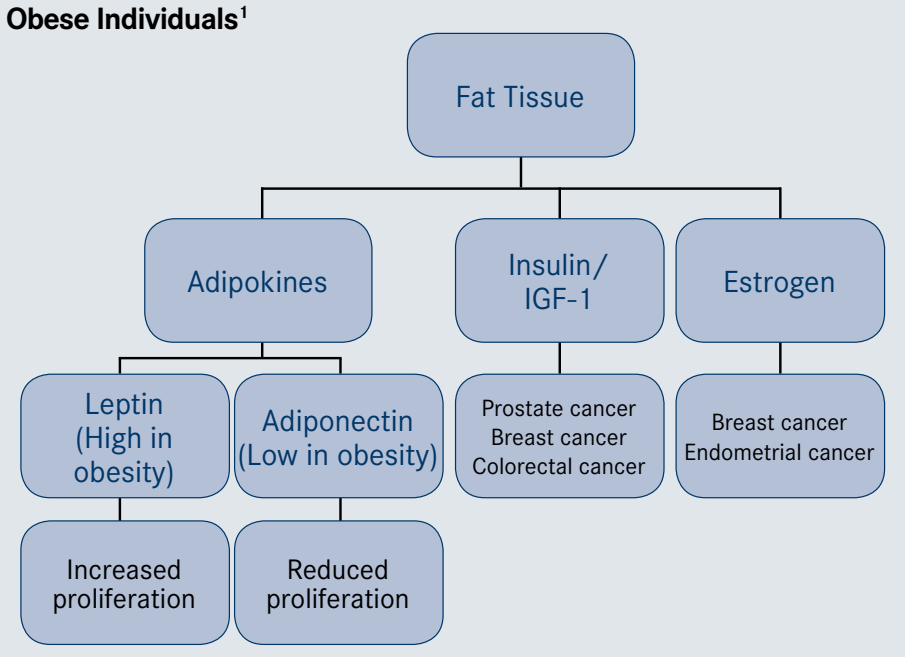
Breast cancer

Overweight and obese women who have not been exposed to hormone therapy develop a modest risk of postmenopausal breast cancer for estrogen and progesterone receptor–expressing tumors due to an increased level of estrogen production, but are at a reduced risk of premenopausal breast cancer. Following menopause, the ovaries stop estrogen production and the fat tissue becomes the primary source of the hormone. Obese women, with more fat tissue, have higher estrogen levels, resulting in a rapid growth of estrogen-responsive tumors.[1]

A study recently presented by researchers from the German Breast Group, Neu-Isenburg, Germany, at the 9th European Breast Cancer Conference held in Glasgow, Scotland, reported that a high BMI is an adverse determinant of survival without recurrence or metastasis. However, the study, conducted in 11,000 patients with early breast cancer treated with neoadjuvant therapy, reported that HER2-positive patients did not have obesity as a risk factor. Another issue raised by the study is that obese patients were observed to have received a lower dose of chemotherapy due to a dose cap resulting from a fear of overdosing. But this could result in a lower quality of chemotherapy in that population, which could stem a relapse.[6]

At the molecular level, a link between high caloric intake and altered breast cancer gene 1 (*BRCA1*) transcription has been discovered. *BRCA1* plays a very important role in DNA repair, cell cycle regulation, and transcriptional regulation, and mutations or altered expression of

Figure 2. Molecular Mechanisms of the Increased Risk of Cancer in Obese Individuals[1]



IGF-1 indicates insulin-like growth factor–1.

the protein have been shown to be detrimental to the cell, leading to increased proliferation, chromosomal instability, and tumorigenesis. The transcriptional corepressor C-terminal–binding proteins (*CtBP1* and *CtBP2*) are a part of the transcriptional machinery that binds to the *BRCA1* promoter and represses expression of the gene. High caloric intake and obesity were found to disrupt the NAD^+/NADH ratio, resulting in increased *CtBP* activity and subsequently a reduced expression of *BRCA1*.[7]


Edmund Pezalla, MD, MPH

Colorectal cancer

Studies conducted in Europe have identified obesity as the root cause of 11% of colorectal cancer cases. Obese men seem particularly at risk, with studies showing that obesity is associated with a 30% to 70% increased risk of colon cancer in men.[8]

A high dietary glycemic load, a known risk factor for obesity, was found to be significantly associated with an increased risk of recurrence and mortality in stage 3 colon cancer patients.[9] The prospective, observational study was conducted in 1011 stage 3 colon cancer patients receiving adjuvant chemotherapy. The patients reported their dietary consumption during, and 6 months after, participation in the chemotherapy trial, and the impact of their glycemic load, glycemic index, fructose, and carbohydrate intake on cancer recurrence and mortality was evaluated. Significantly, the increased risk of recurrence and death with higher dietary glycemic load and total carbohydrate was primarily observed in overweight and obese patients.

A recently published study in the journal *Cell Metabolism*, by scientists at the National Institute of Environmental Health Sciences, identified an important role of the gene *NAG-1*, known to protect against colon cancer, in preventing weight gain in mice fed a high-fat diet. The scientists generated mice that expressed human *NAG-1*, while the control mice did not. When fed the same high-fat diet, the *NAG-1*–expressing mice stayed lean while the controls grew plump. Further, cells isolated from the colon of the obese mice showed altered patterns of histone acetylation, a sign of cancer progression.[10]

Pancreatic cancer

BMI has also been identified as a risk factor for pancreatic adenocarcinoma (PAC), the 13th-most common cancer and the 8th-leading cause of cancer-related death in the world. Overweight or obese individuals were observed to have an increased risk of PAC, and an earlier age of onset. Further, overweight or obese older patients were also at an increased risk of dying due to the disease.[11]

Genetic factors that regulate obesity have also been found associated with PAC. *NR5A2* plays an important role in lipid and glucose metabolism, improving glucose uptake, and regulating cholesterol transport, and a significant association between *NR5A2* gene variants and a decreased risk of pancreatic cancer has been identified.[12]

The Healthcare Aspect

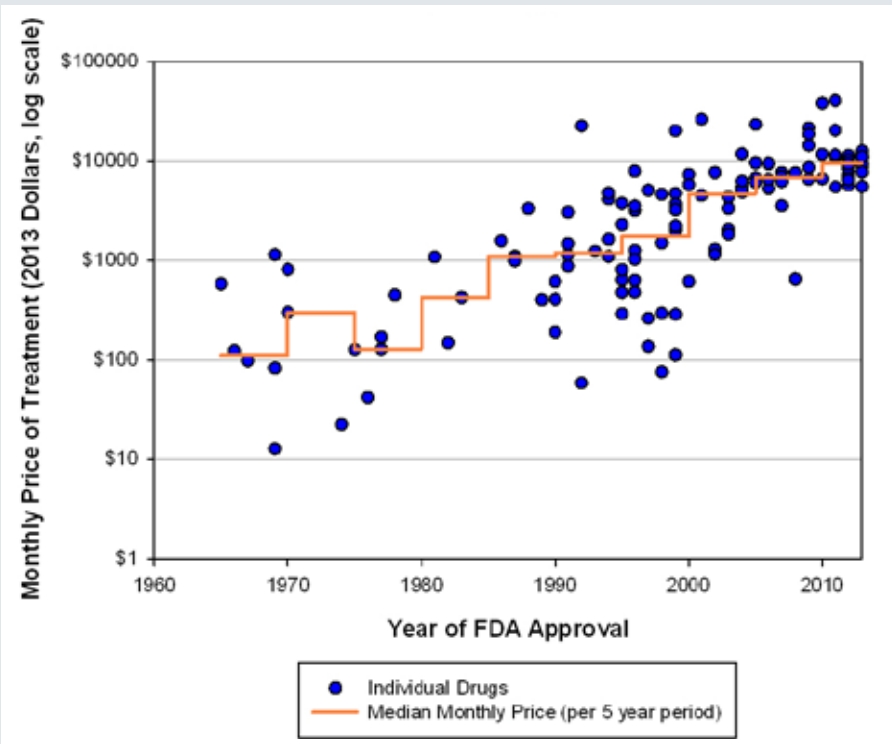
Although Medicaid programs in most states and Medicare do not cover weight loss drugs,[13] screening and counseling for obesity are covered by Medicare.[14] Further, most private insurance companies will be forced to cover their patients' weight loss efforts thanks to the Affordable Care Act.[14]

Early this year, Aetna announced the launch of a program to assess the influence of weight loss and other lifestyle improvement tools to lower medical costs, improve health outcomes, and increase workplace productivity. The agenda includes a pilot program geared for self-insured plan sponsors to evaluate 2 FDA-approved (in 2012) prescription weight loss drugs, Belviq and Qsymia, among high-risk members. Results from this pilot are expected by the end of 2014.[15]

When contacted for comment, Edmund Pezalla, MD, MPH, national medical director for pharmacy policy and strategy at Aetna, said in an e-mail response: "Yes, there are epidemiologic data to suggest that obesity increases the risk of cancer. We don't know if treating obesity will reduce that risk (ie, by the time you treat, has something changed in the patient's biology?). We are not promising or counting on reducing cancer risk as a return on our program." He went on to say, "Our program will not go on long enough or with enough patients to determine the reduction in risk from weight loss for many important factors, but from the existing literature we do expect to see some results:

- Short term: reduced use of medications and other improvements in the control of diabetes, high blood pressure, and cholesterol;
- Medium term: reduction in need for bariatric surgery and treatment of some other weight related disorders like gastroesophageal reflux; and
- Long term (and beyond the scope of our projects): reduction in patients progressing to diabetes, cardiac events, and other weight-related problems like need for joint replacement."

Figure 3. Monthly and Median Cost of Cancer Drugs at the Time of FDA Approval Based on Medicare Reimbursement Rates



Organizational Efforts to Combat Obesity as a Risk Factor for Cancer

The Obesity Society, based in Silver Spring, Maryland, is actively working at combating obesity, with the aim of confronting the associated comorbidities, including cancer. The society launched the *Treat Obesity Seriously* campaign last year to educate policy makers on the need to recognize obesity as a serious condition and provide clinicians with useful diagnostic tools.[16] The society also serves as a platform to promote collaborations among members to boost cancer-obesity research at the molecular, clinical, and epidemiological levels, and to communicate the resulting information to professional and lay audiences.[17]

This could prove an important step in obesity prevention efforts, especially with evidence of the associated disease risks in obese individuals, including but not limited to chronic conditions such as diabetes, cardiovascular disease, and cancer. Especially for cancer, improvements in research strategies, such as the development of biologicals, have seen a rapid increase in drug prices as well as the associated treatment costs (**Figure 3**). It's a bubble that is rapidly expanding and could burst anytime. With this realization, redirecting efforts to prevent disease onset and regulating the associated risk factors is of the essence. **EBO**

References

1. Obesity and cancer risk (fact sheet). National Cancer Institute website. http://www.cancer.gov/cancertopics/factsheet/Risk/obesity. Accessed April 17, 2014.

2. Berger NA. Obesity and cancer pathogenesis. *Ann NY Acad Sci*. 2014;1311:57-76.

3. Calle EE, Rodriguez C, Walker-Thurmond W, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625-1638.

4. Sjöström L1, Gummesson A, Sjöström CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol*. 2009;10:653-662.

5. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357:753-761.

6. Obesity and diabetes have adverse effects on outcomes across different tumour types and should be taken into account when planning breast cancer treatment. European Cancer Organisation website. http://www.ecco-org.eu/Global/News/EBCC9-PR/2014/03/Fontanella-Obesity-and-diabetes-have-adverse-effects-on-outcomes-across-different-tumour.aspx. Published March 20, 2014. Accessed April 15, 2014.

7. Di L, Fernandez AG, De Siervi A, Longo DL, Gardner K. Transcriptional regulation of *BRCA1* expression by a metabolic switch. *Nat Struct Mol Biol*. 2010;17:1406-1413.
8. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut*. 2013;62(6):933-947.
9. Meyerhardt JA, Sato K, Niedzwiecki D, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Natl Cancer Inst*. 2012;104(22):1702-1711.
10. Li R, Grimm SA, Chrysovergis, K, et al. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. *Cell Metab*. 2014;19(4):702-711.
11. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA*. 2009;301:2553-2562.
12. Tang H, Dong X, Hassan M, Abbruzzese JL, Li D. Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20:779-792.
13. Koven S. Diet drugs work: why don't doctors prescribe them? *The New Yorker* website. http://www.newyorker.com/online/blogs/elements/2013/12/diet-drugs-work-why-wont-doctors-prescribe-them.html. Published December 4, 2013. Accessed April 23, 2014.
14. Hellmich N. Screening and counseling for obesity is covered under a preventive services benefit of the Affordable Care Act, but what health plans offer patients varies. *USA Today* website. http://www.usatoday.com/story/news/nation/2013/07/04/obesity-disease-insurance-coverage/2447217/. Published July 4, 2013. Accessed April 23, 2014.
15. Aetna promotes personalized weight-loss options [press release]. Hartford, CT: Aetna; January 14, 2014. http://newshub.aetna.com/press-release/products-and-services/aetna-promotes-personalized-weight-loss-options. Accessed April 22, 2014.
16. Treat obesity seriously encourages treatment of obesity as a serious health condition [press release]. Silver Spring, MD: The Obesity Society; May 9, 2013. http://www.obesity.org/news-center/treat-obesity-seriously-encourages-treatment-of-obesity-as-a-serious-health-condition-may-9-2013.htm. Accessed April 23, 2014.
17. Obesity and cancer. The Obesity Society website. http://www.obesity.org/about-us/obesity-a-cancer.htm. Accessed April 23, 2014.
18. Cost of cancer drugs. Memorial Sloan Kettering Cancer Center website. http://www.mskcc.org/research/health-policy-outcomes/cost-drugs. Accessed April 23, 2014.

FDA Update

Roche Molecular Diagnostic's cobas HPV Test Approved by the FDA

Surabhi Dangi-Garimella, PhD

A test that can detect the DNA of the human papilloma virus (HPV), to confirm the need for cervical cancer screening in women 25 years and older, has gained the FDA's support as a primary screening test. This test, developed by Roche Molecular Diagnostics, can also provide information on the patient's risk of developing cervical cancer in the future.[1]

According to the company website, the HPV test, which utilizes a sample of cervical cells, can simultaneously detect 14 high-risk HPV subtypes and can provide specific genotyping information for HPV types 16 and 18 in a single analysis by polymerase chain reaction (PCR).[2]

Women who test positive for HPV 16 or HPV 18, based on the results of the test, are further advised to undergo colposcopy, while women who test positive for 1 or more of the other 12 high-risk HPV types are recommended to undergo a Papanicolaou (Pap) test to confirm a need for colposcopy. Additionally, the FDA recommends that providers view the results of the cobas HPV test in conjunction with patient screening history, risk factors, and professional guidelines on cervical cancer detection.[1]

Initially approved in 2011 as a follow-up to a Pap test, the current approval allows using cobas as a co-test or a primary cervical cancer screening test, without altering the current practice guidelines. Data provided by the company for the current approval included a study of more than 40,000 women 25 years and older undergoing routine cervical exams. Women who had a positive Pap test or whose cervical cells screened positive for HPV, as well as a subset of women whose Pap and HPV tests were both negative, underwent a colposcopy and cervical tissue biopsy. Biopsy results were compared with the Pap and cobas HPV test results. Following a 3-year follow-up on women who underwent colposcopy, the cobas HPV test was deemed safe and effective for its new indication for use.[1]

According to the CDC, deaths due to cervical cancer have significantly decreased as a result of regular Pap tests, which can detect precancerous cervical cells. Despite the progress, the latest statistic shows that 11,818 women in the United States were diagnosed with cervical cancer in 2010 and 3939 women died of the disease that year.[3] **EBO**

Reference
1. FDA approves first human papillomavirus test for primary cervical cancer screening [press release]. Silver Spring, MD: FDA; April 24, 2014. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm. Accessed April 30, 2014.
2. cobas HPV test. Roche Molecular Diagnostics website. http://molecular.roche.com/assays/Pages/cobasHPVTest.aspx. Accessed May 1, 2014.
3. Cervical cancer statistics. CDC website. http://www.cdc.gov/cancer/cervical/statistics/. Accessed April 30, 2014.

Fast Track for Prima Biomed's CVac Clinical Trial Development Program

Surabhi Dangi-Garimella, PhD

Prima Biomed's clinical program called CVac, to improve overall survival in relapsed patients with platinum sensitive epithelial ovarian cancer in their second cycle of remission, has been granted a Fast Track Designation by the FDA. The company, based in Australia, would like to bring this treatment option to patients in the United States soon. The Fast Track status for CVac follows an "Orphan Drug Designation" that was conferred in September 2010 by the FDA, soon after the European Medicine Agency granted CVac an "Orphan Medicinal Product Designation."[1]

According to company CEO Matthew Lehman, "This designation is an important milestone for Prima. The FDA decision is in recognition of the serious nature of ovarian cancer and the clear unmet medical need to develop new treatments for relapsed platinum-sensitive ovarian cancer in remission. Building from our CAN-003 trial data, which indicated an improvement in progression-free survival in this patient population, we look forward to accelerating our recently commenced CAN-004-B trial to establish OS advantages of CVAc as soon as possible."[1]

The CAN-003 trial, which evaluated patients in remission, found that CVac was well tolerated with no serious adverse events, while most of the non-serious adverse events were mild and transient. Additionally, there was no evident humoral response following CVac administration. Significantly improved progression-free survival (PFS) was observed only in patients administered CVac who were in second remission, compared to the controls; for patients in first remission, there was no observed difference in PFS between the CVac and control groups.

CVac is a biological formulation aimed to provide a personalized treatment option for ovarian cancer patients. Customized as per the patient, the technology involves isolating the patient's own immune precursor cells from the blood (leukapheresis) and then growing them out in the laboratory following separation of the dendritic cells. The cells are treated in vitro with a specific form of the protein mucin 1. Following intradermal administration in the patient, CVac activates T cells to recognize and destroy tumor cells that express that particular form of mucin 1.[3] **EBO**

References
1. Prima Biomed's CVac granted Fast Track Designation by FDA [press release]. Sydney, Australia: Prima BioMed; May 9, 2014. http://www.primabiomed.com.au/media/pdf/2014/09_05_14_announcement.pdf.
2. Clinical Development. Prima BioMed website. http://www.primabiomed.com.au/trial/clinical_developement.php. Accessed May 9, 2014.
3. CVac. Prima BioMed website. http://www.primabiomed.com.au/products/cvac.php. Accessed May 9, 2014.

Bioinformatics
(continued from cover)

tionally, sequences from issued patents are submitted by the US Patent and Trademark Office.[3] Despite the open access to this database, researchers all over the world have actively contributed to building up the resource, realizing the vast potential of this knowledge-sharing database. The information either goes to GenBank or is submitted through its European counterpart, the European Bioinformatics Institute (EBI), or its Japanese counterpart, the DNA Data Bank of Japan (DDJB).[4] All the leading journals need researchers to submit their sequences to GenBank and cite the corresponding access number in the published article. The new sequences can be directly submitted to EBI, DDJB, or GenBank, and the 3 databases are synchronized daily for easy access to all the information on all 3 databases. The data are virtually in real time, with minimal delay in access to the latest data, free of cost.

Other commonly used nucleotide databases include the European Molecular Biology Laboratory (EMBL; EBI is run by EMBL), SwissProt, PROSITE, and Human Genome Database (GDB).[5] Taken together, these databases are essentially a *bioinformatics* tool that helps integrate biological information with computational software. The information gained can be applied to understand disease etiology (in terms of mutations in genes and proteins) and individual variables, and ultimately aid drug development.

According to the National Institutes of Health Biomedical Information Science and Technology Initiative, bioinformatics is defined as "research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral, or health data, including those to acquire, store, organize, archive, analyze, or visualize such data."[6]

Development of GenBank

Initially called the Los Alamos Sequence Database, this resource was conceptualized in 1979 by Walter Goad, a nuclear physicist and a pioneer in bioinformatics at Los Alamos National Laboratory (LANL).[7] GenBank followed in 1982 with funding from the National Institutes of Health, the National Science Foundation, and the Departments of Energy and Defense. LANL collaborated with various bioinformatics and technology companies for sequence data management and to promote open access communications. By 1992, GenBank transitioned to being managed by the National Center for Biotechnology information (NCBI).[8]

Submissions to the database include original mRNA sequences, prokaryotic and eukaryotic genes, rRNA, viral sequences, transposons, microsatellite sequences, pseudogenes, cloning vectors, noncoding RNAs, and microbial genome sequences. Following a submission (using the Web-based BankIt or Sequin programs), the GenBank staff reviews the documents for originality and then assigns an accession number to the sequence, followed by quality assurance checks (vector contamination, adequate translation of coding regions, correct taxonomy, correct bibliographic citation) and release to the public database.[3,8]

How Are Researchers Utilizing This Database?

BLAST (Basic Local Alignment Search Tool) software, a product of GenBank, allows for querying sequence similarities by directly entering their sequence of interest, without the need for the gene name or its synonyms.[4] An orphan (unknown) or de novo nucleotide sequence, which may have been cloned in a laboratory, can gain perspective following a BLAST search and a match with another, better-characterized sequence in the database. Further, by adding restrictions to the BLAST search, only specific regions of the genome (such as gene-coding regions) can be examined instead of the 3 billion bases.[4] BLAST can also translate a DNA sequence to a protein, which can then be used to search a protein database.

BLAST, which was developed at NCBI, works only with big chunks of nucleotide sequences, and not with shorter reads, according to Santosh Mishra, PhD, director of bioinformatics and co-director of the Collaborative Genomics Center at the Vaccine and Gene Therapy Institute (VGTI) of Florida. Mishra, who worked as a postdoctoral research associate with Goad at LANL, was actively involved in developing GenBank. His work contributed to the generation of the "flat file" format, and he also worked on improving the query-response time of the search engine. Additionally, he initiated the "feature table" in GenBank—the documentation within that helps GenBank, EMBL, and DDJB exchange data on a daily basis.

According to Mishra, the STAR aligner, developed at Cold Spring Harbor, works better with reference sequences, while Trinity, developed at the Broad Institute in Cambridge, Massachusetts, is useful for de novo sequences. (The Broad Institute made news last month with its work on identifying gene mutations that prevent diabetes in adults who have known risk factors, such as obesity.)

Advantages and Disadvantages of the GenBank Platform

The biggest single advantage of GenBank is the open-access format, which allows for a centralized repository in a uniform format. The tremendous amount of data generated by laboratories (such as from microarrays and microRNA arrays) cannot be published in a research article. However, the data, tagged and uploaded on GenBank, can be linked to the journals' websites and the links can be provided in the print versions of the articles as well.[4]

On the flip side, the biggest advantage of being an open-access platform is also the biggest disadvantage of the software. There's always the probability of scientists registering faulty genetic sequences on the website, which will not be caught unless they are peer reviewed. Despite the incorporation of several quality control mechanisms into the system, reuse of the data by other scientists alone can help discover glitches in the existing data. Additionally, GenBank encourages its users to submit feedback and update records, which unfortunately is not a very proactive process.[4]

Bioinformatics and Pharmacogenomics in Drug Discovery/Development

Accelerating the drug development process saves costs for the pharmaceutical industry, especially with the way the industry functions today. The company that discovers or invents a new chemical entity, which could metamorphose into a new drug candidate, can squeeze the maximum profit out of the drug before the patent expires and competitors catch on. Essentially, companies jump at every opportunity to accelerate any aspect of the discovery/development process. Resources like the GenBank and EBI are data mines that can speed up the entire process in the following ways:

Target identification

Drug candidates can be identified (following a high-throughput screen of chemical libraries) and developed only after a "druggable target" is discovered for a disease condition. Typically, about 1 in 1000 synthesized compounds will progress to the clinic, and only 1 in 10 drugs undergoing clinical trials reaches the market.[9] Optimizing/validating a target is essential due to the prohibitively high cost of conducting trials, and the potential targets for drug discovery are increasing exponentially.[10] By mining and storing information from huge data sets, like the human genome sequence, the nucleotide sequence of the target proteins has become readily available, as has the potential to identify new targets. This can exponentially increase the content of the drug pipelines of pharmaceutical companies.[10]

According to Arathi Krishnakumar, PhD, a protein biochemist and a senior research investigator with the department of Exploratory Biology and Genomics, Bristol-Myers Squibb (BMS), "For compounds that have no obvious targets from a typical phenotypic screening, proteomics offers tools for target identification or target deconvolution. Monitoring the global phosphorylation status of proteins that are downstream of tyrosine kinase inhibitors—also termed phosphoproteomics—is a very attractive tool that can also be used for target as well as biomarker identification. These events can be used as reporters (biomarkers) for specific upstream kinase(s)."

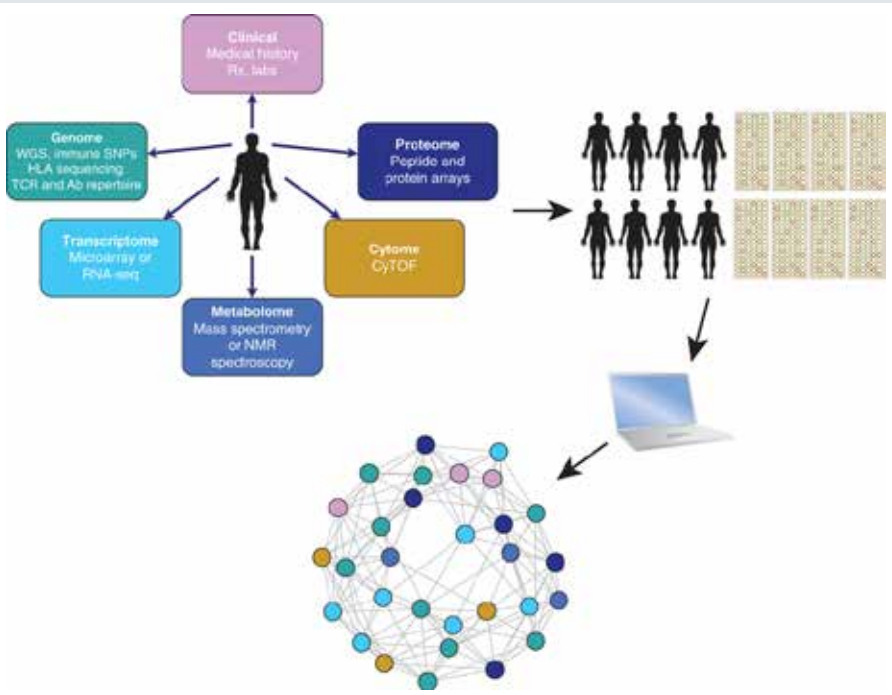
Companies such as N-of-One are developing analyzers coupled with software that can provide molecular interpretation of next-generation sequencing data.

Target validation

Establishing a robust association between a likely target and the disease, to confirm that target modulation translates into a beneficial therapeutic outcome, would not only validate the drug development process but also help absorb the risks associated with clinical trial failure of the molecule being developed.[10]

Says Krishnakumar, "Target validation is typically done with knock-out or knock-down of the proposed target using RNAi and then monitoring the disease phenotype in relevant cellular models. Proteomics tools are also highly valuable in monitoring specific events on proteins like post translational modifications, including phosphorylation, methylation, oxidation, etc, new product generation, degradation products, protein-protein interaction, etc, all of

Figure 1. Integrating Bioinformatics With Biology for Precision Medicine



Source: *Nature Immunol*. 2014,15:118-127.

which could be direct or indirect consequences of target activation or engagement."

Cost reduction

The drug development process is not just lengthy (product development can take 10 to 15 years[9]), but is prohibitively expensive as well. Averaging $140 million in the 1970s, the cost of developing a drug was estimated at a whopping $1.2 billion in the early 2000s,[11] and a recent *Forbes* analysis estimated the cost at $5 billion.[12]

Worth noting is that the final cost of any drug, which includes the total costs from discovery to approval, includes the cost of absorbing all the clinical trial failures.[10] Clearly, bioinformatics tools improve the efficiency of target discovery and validation processes, reduce the time spent on the discovery phase, and make the entire process more cost-effective.

Mishra believes GenBank is a good starting point in the drug discovery process. When a new sequence (of known or unknown function) is identified/isolated in the laboratory, a GenBank search will help identify homologues (human or in other organisms) with a 70% to 80% match. Functional studies would then ensue, along with cell and tissue distribution studies.

Industry Partnerships

With the value of personalized medication gaining acceptance, the study of *pharmacogenomics* (genetic variants that determine a person's drug response; one size does not fit all) is extremely helpful to tailor the optimal drug, dose, and treatment options for a patient to improve efficacy as well as avoid adverse events (AEs).[10] According to the Agency for Healthcare Research and Quality of the HHS, AEs annually result in more than 770,000 injuries and deaths and may cost up to $5.6 million per hospital.[13]

To this end, EMBL-EBI is actively involved in industry partnerships (the partnerships were initiated in 1996), which include Astellas, Merck Serono, AstraZeneca, Novartis, GlaxoSmithKline, BMS, and several others.[14] With the high-throughput data that research and development (R&D) activities generate, open-source software and informatics developed by organizations like the GenBank and EBI could greatly improve efficiency and reduce the cost of drug discovery and development.

Translational Bioinformatics and Precision Medicine

Healthcare today is primarily symptom driven, and intervention usually occurs late in the pathological process, when the treatment may not be as effective. Identifying predisease states that could provide a window into the forthcoming risk of developing a disease, identifying reliable markers, and developing useful therapies would be the key to managing disease treatment[15]—not just to improve efficiency but also to reduce healthcare costs, which it is estimated will steadily increase and by 2022 account for 19.9% of the gross domestic product (GDP).[16]

With *precision medicine* or *personalized medicine*, molecular profiles generated from a patient's genomic (coupled with other "-omics" such as epigenomics, proteomics, and metabolomics) information could help accurately drive the diagnostic, prognostic, and therapeutic plans, tailored to the patient's physiological status. Predictive models can also be developed for different biological contexts, such as disease, populations, and tissues.[15] However, the deluge of data generated by bioinformatics tools requires a framework to regulate, compile, and interpret the information. Most importantly, the key stakeholders (government, research industry, biological community, pharmaceutical industry, insurance companies, patient groups, and regulatory bodies[17]) that would drive the widespread acceptance and implementation of precision medicine need to be brought up to speed with the enormous progress made in the field and the promise it brings. There would also be a revolutionary change in the approach to conducting clinical trials—the phase 3 studies conducted in the target population could focus on a more select patient group, which could improve both clinical and economic efficacy.[17]

At BMS, Krishnakumar's group actively provides support to clinical trials by developing assays for clinical samples. When it comes to administration of biologics such as antibodies, individual variations such as expression levels of various proteins and their affinity for an antibody essentiate dose-titration in order to *personalize* treatment to improve efficacy.

The developing field of *translational bioinformatics* creates a platform to bring all the data together, which can then be used to generate a treatment plan personalized to a patient (**Figure**). It has been defined as "the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data into proactive, predictive, preventative, and participatory health."[15] The primary goal of translational bioinformatics is to connect the dots and develop disease networks that can be used as predictive models. In other words, *harmonization* of the data from different sources (genome, proteome, transcriptome, metabolome, and patient's pathological data) could help in making better-informed treatment decisions.

Within medical R&D, a commonly held belief is that cures for diseases could be found residing within existing data, if only the data could be made to give up their secrets.[18] The current status of the scientific, medical, and healthcare fields is that experts in each field have set their minds on developing the best technologies; unfortunately, the technologies are compartmentalized and they work in parallel. The great need, which has been recognized and implemented in limited areas, is to create platforms where the data can be merged to produce meaningful outcomes.

The adaptive trial design includes interim analysis points that would allow researchers to alter the trial based on earlier trial participants.

Data Integration Platforms to Boost Evidence-Based Decisions

Implementing these huge changes would necessitate that physicians and providers be more adept at interpreting molecular data, which essentially requires improved education models that include relevant courses during graduate training. Also, development of software that can interpret the data would provide a tremendous advantage to researchers, clinicians, scientists, pathologists, and maybe patients as well.

To this end, companies such as N-of-One are developing analyzers coupled with software that can provide molecular interpretation of next-generation sequencing data. The company recently announced the launch of Variant Interpreter™, a cloud-based application, on Illumina's BaseSpace Apps (applications store for genomic analysis).[19] The app allows oncologists, pathologists, and researchers to access relevant biological and clinical information related to the tumor profile generated following sequencing. Additionally, the user can request a molecular interpretation of a variant or multiple variants in a tumor

and receive a customized interpretive road map linking the variant data to scientific knowledge on it. With a plan for future expansion, the software currently includes 30 cancer-associated genes.[19]

An application developed by Remedy Informatics, TIMe, boosts the process further. TIMe merges data, registries, applications, analyses, and any other relevant content. TIMe promises to enable faster, more informed decisions in clinical practice, research, and business operations. It also is expected to improve treatment effectiveness, quality of care, and patient outcomes.[20]

The MD Anderson cancer center is working in collaboration with IBM, using the IBM Watson computing system to enable clinicians to reveal relevant research and patient data from the cancer center's rich databases. The Oncology Expert Advisor, a product of this collaboration, will integrate clinical and research data to help physicians develop, observe, and fine-tune treatment plans for the patients, and also help them anticipate adverse events that may occur through the treatment period.[21]

Table. Approved Targeted Therapies in Cancer

Molecular target	Drug	Cancer
Estrogen receptor	Tamoxifen (Nolvadex), toremifene (Fareston), fulvestrant (Faslodex)	Breast cancer
Multiple tyrosine kinases	Imatinib mesylate (Gleevec)	Gastrointestinal stromal tumor, leukemia, and others
	Dasatinib (Sprycel)	CML, ALL
	Nilotinib (Tasigna), bosutinib (Bosulif)	CML
HER-2 receptor	Trastuzumab (Herceptin)	Breast cancer, gastric cancer
	Pertuzumab (Perjeta)	Metastatic breast cancer not treated with chemotherapy or HER-2–directed therapy
	Lapatinib (Tykerb)	Advanced/metastatic breast cancer
EGFR	Gefitinib (Iressa)	NSCLC
	Erlotinib (Tarceva)	NSCLC, pancreatic cancer
	Cetuximab (Erbitux)	Head and neck cancer, colorectal cancer
	Panitumumab (Vectibix)	Metastatic colon cancer
mTOR	Temsirolimus (Torisel)	Advanced renal cell carcinoma
	Everolimus (Afinitor)	Advanced kidney cancer, advanced breast cancer, pancreatic neuroendocrine tumors
BRAF V600E	Vemurafenib (Zelboraf)	Inoperable/metastatic melanoma
Proteasome	Bortezomib (Velcade)	Multiple myeloma, mantle cell lymphoma
	Carfilzomib (Kyprolis)	
VEGF	Bevacizumab (Avastin)	Glioblastoma, NSCLC, metastatic colorectal cancer, metastatic kidney cancer
	Ziv-aflibercept (Zaltrap)	Metastatic colorectal cancer
	Sorafenib (Nexavar)	Advanced renal cell cancer, hepatocellular cancer
Immune targets		
CD20	Rituximab (Rituxan)	B-cell non-Hodgkin lymphoma, CLL
	Ofatumumab (Arzerra)	CLL resistant to fludarabine and alemtuzumab
CD52	Alemtuzumab (Campath)	B-cell CLL
CTLA-4	Ipilimumab (Yervoy)	Unresectable or metastatic melanoma

Other targeted therapies such as cancer vaccines and gene therapy are currently in clinical trials.
ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor.
Source: Targeted cancer therapies. National Cancer Institute website. http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted. Accessed March 26, 2014.

Applications of Translational Bioinformatics

Once the genomic and/or proteomic data have been generated, what next? How are providers employing these data to their advantage and to guide treatment? Several reports on clinical studies are being successfully conducted on the foundation of precision as well as evidence-based medicine.

A study published in the *New England Journal of Medicine* highlighted the importance of using panitumumab (Vectibix; Amgen Inc) in combination with traditional chemotherapy only in those patients with metastatic colorectal cancer (mCRC) who do not have RAS mutations. The study found that the subset of mCRC patients who expressed wild-type RAS demonstrated improvements in progression-free as well as overall survival upon the inclusion of panitumumab in their treatment regimen.[22] The protein *KRAS* functions downstream of the epidermal growth factor receptor (*EGFR*). Mutations in the *KRAS* gene entail receptor-independent functioning of the protein, so using panitumumab, which is an *EGFR* antagonist, would be completely fruitless in this context. Thus, prior knowledge of the patient's genomic status helped in selecting the right cohort for successfully using this drug.

Proteomics has led to the development of a molecular diagnostic tool to detect precancerous cysts in the pancreas.[23] Although computed tomography (CT) and magnetic resonance imaging (MRI) can detect cysts, identifying the ones that can develop into cancer is difficult. An important issue faced with pancreatic cancer is that the patient is indication-free as the tumors initially develop, and disease symptoms appear only following tumor metastasis to distant organs, at which stage the disease is usually difficult to treat. This has resulted in a poor prognosis of pancreatic cancer. Scientists at the Sahlgrenska Academy in Sweden have developed a method to identify precancerous cysts by detecting mucins in the cystic fluid as biomarkers. Following evaluation, the diagnostic tool could accurately predict the nature of the cysts examined with 97% accuracy. Additionally, the researchers tested existing tumors and could determine which tumors have developed into cancers with 90% certainty.

Bioinformatics studies have also yielded microRNAs, which are small (~22 nucleotides), noncoding RNA molecules that can repress the transcription of messenger RNA (mRNA) or promote its degradation, thereby silencing gene expression.[24] Initially thought of as "junk" sequences on the DNA since they are non-coding nucleotides, miRNAs (about 24,521 listed in miRBase, a database maintained by the University of Manchester[25]) have now found their place in clinical trials as biomarkers (cancer,[26] multiple sclerosis,[27] psoriasis[28]) and are also being developed as "drugs" by companies like Mirna Therapeutics Inc.[29]

The "Adaptive" Clinical Trial Design

The "omic" revolution has also had a tremendous impact on clinical trial design. The FDA definition of an adaptive clinical study is "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data from subjects in the study."[30] The trial design includes interim analysis points that would allow researchers to alter the trial (treatment dose or schedule, randomization) based on results from earlier study participants. Two of the 20 ongoing adaptive trials recently published positive results.

The *i-SPY 2* trial launched in 2010 in patients with newly diagnosed, locally advanced breast cancer was designed to screen 12 cancer drugs from multiple pharmaceutical companies, by adding each individual drug to a standard neoadjuvant chemotherapy. Adapta-

tion was based on examining the transcriptional profile of the patient's tumor right when enrolled in the trial, evaluating the responses following treatment, and comparing them against the responses to the same treatment of previous patients with a similar genetic tumor signature. Based on the results, the patients would be randomized to various trial arms. Two of the 12 drugs in the trial, veliparib (AbbVie) and neratinib (Puma Biotechnology), proved promising in 2 different breast cancer subtypes.[1]

J. Craig Venter, PhD

The *BATTLE* trial, ongoing at the MD Anderson Cancer Center, is evaluating the effectiveness of multiple drugs on multiple mutations in a single cancer type: non-small cell lung cancer (NSCLC). Only 40% of the patients in the first phase of the study were evaluated for biomarkers and assigned to 4 treatment arms. In the second phase of the trial, the remaining 60% of patients were evaluated for their biomarker status and then assigned to treatments following an assessment of the responses from patients with a similar tumor profile in the first phase. The result: the trial reported encouraging clinical activity in the sorafenib-treated cohort harboring a wild-type epidermal growth factor receptor (EGFR).[1]

Genetic Testing to Determine Disease Susceptibility

Another aspect of bioinformatics is genetic testing, which along with risk assessment is rapidly being streamlined into mainstream oncology practices, especially with the recommendations provided by the US Preventive Services Task Force.[31] Genetic counseling has become the standard of care for patients with a personal or family history of breast, ovarian, or colon cancer, while genetic testing is appropriate for some patients with pancreatic, renal, skin, or thyroid cancers as well as with some rare cancer syndromes.[32]

Then you have J. Craig Venter, PhD, a biologist and entrepreneur, who competed with the Human Genome Project to sequence the human genome and who recently announced the launch of a new company, Human Longevity. The company plans to sequence 40,000 human genomes per year to gain insights into the molecular causes of aging and age-associated diseases such as cancer and heart disease.[33]

The Healthcare Equation

Insurance companies are rapidly adapting to this changing scene of "big data" in their own right. Back in 2011, Aetna announced a partnership with the Center for Biomedical Informatics at Harvard Medical School with the aim of improving the quality and affordability of healthcare (healthcare informatics). The researchers at Harvard aimed to:

- Evaluate the outcomes of various treatments for specific conditions based on quality and cost
- Determine factors that predict adherence for chronic diseases
- Study how claims data and clinical data, available through electronic health records, can best be used to predict outcomes
- Improve the ability to predict adverse events through a proactive study of claims and clinical data.[34]

The possibilities are enormous, with application in all disease fields. Translational bioinformatics integrates the various data sources and paves a path for precision medicine that would be immensely valuable to all stakeholders (patients, pharmaceutical companies, scientists, and physicians) alike. **EBO**

References

1. Levin-Carter J. New clinical trials designed to better leverage precision medicine. OBR green. 2014;8(3). http://obroncology.com/obrgreen/article/New-Clinical-Trials-Designed-to-Better-Leverage-Precision-Medicine. Accessed March 25, 2014.

2. The lists: top 10 clinical trial failures of 2013. Genetic Engineering and Biotechnology News website. http://www.genengnews.com/insight-and-intelligence/top-10-clinical-trial-failures-of-2013/77900029/. Published February 3, 2014. Accessed March 25, 2014.

3. Benson DA, Clark K, Karsch-Mizrachi I, Lipman DJ, Ostell J, Sayers EW. GenBank. *Nucleic Acids Res.* 2014;42:D32-D37.

4. McEntyre J, Lipman J. GenBank - a model community resource? *Nature*. http://www.nature.com/nature/debates/e-access/Articles/lipman.html. Published 2007. Accessed February 27, 2013.

5. Bioinformaticsweb website. http://bioinformaticsweb.net/data.html. Accessed March 5, 2014.

6. NIH working definition of bioinformatics and computational biology. National Institutes of Health website. http://www.bisti.nih.gov/docs/CompuBioDef.pdf. Accessed March 5, 2014.

7. Walter Goad papers. American Philosophical Society website. http://www.amphilsoc.org/mole/view?docId=ead/Mss.Ms.Coll.114-ead.xml. Accessed March 4, 2014.

8. The GenBank submissions handbook. NCBI website. http://www.ncbi.nlm.nih.gov/books/NBK51157/. Accessed March 4, 2014.

9. Tamimi NA, Ellis P. Drug development: from concept to marketing! *Nephron Clin Pract.* 2009;113(3):c125-c131.

10. Katara P. Role of bioinformatics and pharmacogenomics in drug discovery and development process. *Netw Model Anal Health Inform Bioinforma*. 2013;2:225-230.

11. 2013 profile: pharmaceutical research industry. PhRMA website. http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf. Accessed March 6, 2014.

12. Herper M. The cost of creating a new drug now $5 billion, pushing big pharma to change. *Forbes* website. http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/. Published August 11, 2013. Accessed March 6, 2014.

13. Reducing and preventing adverse drug events to decrease hospital costs. Agency for Healthcare Research and Quality website. http://www.ahrq.gov/research/findings/factsheets/errors-safety/aderia/index.html. Accessed March 10, 2014.

14. Industry partnerships. The European Bioinformatics Institute website. http://www.ebi.ac.uk/industry. Accessed March 5, 2014.

15. Readhead B, Dudley J. Translational bioinformatics approaches to drug development. *Adv Wound Care (New Rochelle)*. 2013;2(9):470-489.

16. National health expenditure projections 2012-2022. CMS website. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/proj2012.pdf. Accessed March 10, 2014.

17. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *NEJM*. 2012;366(6):489-491.

18. Kennedy GD. Enterprise informatics: key to precision medicine, scientific breakthroughs, and competitive advantage. Remedy Informatics; 2013.

19. N-of-One launches 'Variant Interpreter' app to provide easy access to molecular interpretation of next generation sequencing data for oncologists and researchers. N-of-One website. http://www.n-of-one.com/news/2014-0312-VariantInterpreter.php. Published March 12, 2014. Accessed March 12, 2014.

20. TIMe™ – the informatics marketplace. Remedy Informatics website. http://remedyinformatics.com/mosaic-platform/time-the-informatics-marketplace/. Accessed March 14, 2014.

21. MD Anderson taps IBM Watson to power "moon shots" mission [press release]. Houston, TX: MD Anderson Cancer Center; October 18, 2013. http://www.mdanderson.org/newsroom/news-releases/2013/ibm-watson-to-power-moon-shots-.html. Accessed March 27, 2013.

22. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369(11):1023-1034.

23. New method can diagnose a feared form of cancer. MedicalXpress website. http://medicalxpress.com/news/2014-03-method-cancer.html#nwlt. Published March 21, 2014. Accessed March 26, 2014.

24. Cortez MA1, Ivan C, Zhou P, Wu X, Ivan M, Calin GA. microRNAs in cancer: from bench to bedside. *Adv Cancer Res*. 2010;108:113-157.

25 .miRBase: the microRNA database. miRBase. http://www.mirbase.org/. Accessed March 14, 2014.

26. The role of microRNA-29b in the oral squamous cell carcinoma. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT02009852?term=microRNA&rank=1. Accessed March 14. 2014.

27. A pilot study to assess microRNA biomarkers in early and later stage multiple sclerosis. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01737372?term=miRNA+multiple+sclerosis&rank=1. Accessed March 14, 2014.

28. miRNAs and mRNAs in Psoriasis. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01604902?term=miRNA+psoriasis&rank=1. Accessed March 14. 2014.

29. Bader AG, Lammers P. The therapeutic potential of microRNAs. *Innov Pharm Technol*. http://www.mirnarx.com/pdfs/The%20Therapeutic%20Potential%20of%20microRNAs.pdf. Published March 2011. Accessed March 14, 2014.

30. Guidance for industry: adaptive design clinical trials for drugs and biologics. FDA website. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf. Published February 2010. Accessed March 27, 2013.

31. Dangi-Garimella S. USPSTF recommends *BRCA* testing in women based on familial history. *Evidence-Based Oncology*. In press.

32. Matloff ET. Integrating genetic counseling into an oncology practice can benefit high-risk families. OncLive. http://www.onclive.com/publications/oncology-business-news/2014/February-2014/Integrating-Genetic-Counseling-Into-an-Oncology-Practice-Can-Benefit-High-Risk-Families. Published February 26, 2014. Accessed March 13, 2014.

33. Pollack A. A genetic entrepreneur sets his sights on aging and death. *The New York Times*. March 5, 2014:B1.

34. Aetna and the center for biomedical informatics at Harvard Medical School announce research collaboration [press release]. Hartford, CT: Aetna; November 17, 2011. http://newshub.aetna.com/press-release/health-care-professionals-and-networks/aetna-and-center-biomedical-informatics-harvard. Accessed March 14, 2014.

Genetic Testing
(continued from cover)

This battle has resulted in some genetic counseling centers reporting that referring clinicians have begun to request, or demand, that their patients' BRCA testing be sent to a particular laboratory. In several instances it was discovered that these clinicians were either paid consultants for such laboratories, or received speaking fees or research funding from those entities. This is clearly a conflict of interest in violation of a physician's ethical obligations "to regard responsibility to the patient as paramount" and to discharge their "responsibility to participate in activities contributing to the improvement of the community and the betterment of public health."[3] Concerns about such manipulative tactics led us to develop a position statement stipulating that decisions about which genetic testing laboratories to use should focus on test quality, turnaround time, cost, and whether or not the laboratory shares its data in public databases (**Table 1**).


Rachel E. Barnett, MS

Our patients deserve for decisions regarding where their genetic testing is performed to be unbiased and free of conflict.

Without its patent-protected monopoly, Myriad now appears to be relying on trade secrets to maintain its share of the BRCA market.[4,5] The "trade secrets" are actually a database of BRCA variants of uncertain significance (VUS) derived from the thousands of patient tests they have performed over the past decade.[5] The company once contributed its data to a public database maintained by the National Institutes of Health, but ceased doing so in 2004.[4] Several Myriad scientists and executives have stated that the public variant databases are not properly curated and that contributing to such resources would cause more harm than good; however, by at least 1 account, Myriad disclosed that it made its decision to stop sharing data for the purpose of retaining data as a trade secret.[4,6] In Myriad's Q3 Earnings Call Transcript of May 6, 2014, the company publicly acknowledged that in the context of PARP inhibitors, "*Our competitors' reliance on public databases with high VUS and error rates will further restrict patient access to this life-saving medicine.*"[7] The decision to hoard patient VUS data, even while recognizing that this decision will restrict patient access to lifesaving treatment, is incongruent with the American Medical Association's (AMA's) policy on Genome Analysis and Variant Identification (**Table 2**) and is considered unethical behavior according to the AMA's Resolution E-9.095 on "the use of patents, trade secrets…or other means to limit the availability of medical procedures."[8,9]

Although variant classification is important, few BRCA tests result in a variant of uncertain significance (ie, 4.4% at Ambry Genetics[10]). Myriad itself reports a 3% overall variant rate, slightly lower than other labs' and presumably attributable to the superior testing experience enabled by its patents.[11] Therefore, the vast majority of patients (~95%) are not impacted by a variant of uncertain significance, although the company describes its information as "vastly superior" and leverages variant classification ability as a major differentiator.[5]

Take-Away Points: The battle for the multi-million-dollar BRCA testing market has resulted in some laboratories skewing data and using aggressive and manipulative tactics to capture market share.

- Patients, clinicians, and scientists have the opportunity to choose laboratories based on patient-centric criteria, such as quality, turnaround time, cost, and open access to past, present, and future data.
- These patient-centric criteria can and should be used by payers in choosing genetic testing laboratories with which to partner.

Other laboratories offering BRCA testing have teamed with clinicians, scientists, and patients to expand the pool of publicly available genetic information for the betterment of clinical care and research as part of the Free the Data movement (http://www.free-the-data.org). This movement recognizes that patients, clinicians, scientists, and insurers could all benefit from pooling such information. It has gained traction in patient communities, and some patients now request that their genetic testing be sent to laboratories that share data. Many of these competing laboratories are advertising their data-sharing policies as a way to gain market share. As this movement progresses, creating public genetic databases that feature proper curation of data, transparency on how variant classification decisions are made, and open forums for discussion will be critical.


Robert Nussbaum, MD

With the growing number of laboratories offering testing, insurers are beginning to contract with particular laboratories for BRCA testing, designating certain laboratories as their in-network providers.[12] Before negotiating such partnerships, payers and regulators have the opportunity to choose to partner only with high-quality laboratories that pledge to share all past, present, and future data in public databases. As Cook-Deegan et al write, "National health systems and insurers, regulators, researchers, providers, and patients all have a strong interest in ensuring broad access to information about the clinical significance of variants discovered through genetic testing."[3] This is particularly relevant for publicly funded insurers that could create incentives or make data sharing a stipulation for coverage.[4,13]

Our patients deserve for decisions re-

Table 1. Genetic Testing Position Statement, Cancer Genetic Counseling Program, Yale School of Medicine/Yale Cancer Center, New Haven, CT, February 2014

With the emergence of new testing technologies and the 2013 Supreme Court decision banning gene patenting, the available cancer genetic testing options and the laboratories offering testing have expanded exponentially and are likely to continue to do so. As providers we have a responsibility to our patients to make the best decisions regarding which laboratory to use and which tests are most appropriate based on what is best for the patients. Our decisions will not be swayed by political, personal, and/or financial gain.
Whenever possible,[a] we will choose a laboratory based on these 4 criteria:
1. Quality—is the test being offered accurate and comprehensive compared with what else is on the market?
2. Time—how long will the patient have to wait for his or her test results?
3 Cost—will our patient's insurance carrier cover this test at this laboratory?
4. Open access—has this facility pledged to Free the Data? Whenever possible we will choose laboratories that have pledged to make all their past, present, and future gene data publicly available in order to allow this important information to be freely accessible to all clinicians and researchers, to further the advancement of medical knowledge, and to best serve patient care. We will not support laboratories that hoard data.
To avoid any real or perceived conflicts of interest, we will not accept gifts (including trips, speaking stipends, stock options), funding, or personal or financial support from testing laboratories. We pledge to update our laboratory choices over time as these choices evolve, choosing the best option for our patients and clinical research.
As clinicians, insurance plans, patient groups, and professional organizations nationwide begin to decide which laboratories to use in this quickly evolving marketplace, we ask that they join us in this pledge.

[a]Laboratory choices must sometimes be based on insurance plan regulations, test availability, or the lab's previous experience with a rare familial mutation.

Table 2. D-460.971 Genome Analysis and Variant Identification

Our AMA (1) encourages payers, regulators, and providers to make clinical variant data and their interpretation publicly available through a system that assures patient and provider privacy protection; and (2) encourages laboratories to place all clinical variants and the clinical data that was used to assess the clinical significance of these results, into the public domain which would allow appropriate interpretation and surveillance for these variations that can impact the public's health. (Res. 519, A-13)

AMA indicates American Medical Association. American Medical Association, www.ama.assn.org

garding where their genetic testing is performed to be unbiased, free of conflict, and based upon considerations unrelated to the clinician's self-interest. Moreover, sharing of genetic data will benefit patient care and clinical research, which may lead to lower healthcare costs for all moving forward. The choice to use only laboratories that are committed to quality, efficiency, and facilitating progress for all through sharing of data represents an important opportunity as our healthcare system evolves. **EBO**

References

1. Jolie A. My medical choice. *The New York Times*. http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html/?_r=0. Published May 14, 2013.

2. Supreme Court of the United States. Association for Molecular Pathology v Myriad Genetics, 2013 WL 2631062 (June 13, 2013).

3. American Medical Association. Principles of medical ethics. http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/principles-medical-ethics.page. Accessed May 7, 2014.

4. Cook-Deegan R, Conley JM, Evans JP, Vorhaus D. The next controversy in genetic testing: clinical data as trade secrets. *Eur J Hum Genet*. 2013;21:585-588.

5. Pollack A. Despite gene patent victory, Myriad Genetics faces challenges. *The New York Times*. http://www.nytimes.com/2011/08/25/business/despite-gene-patent-victory-myriad-genetics-faces-challenges.html?pagewanted=all&_r=0. Published August 24, 2011.

6. Ray T. In tackling the VUS challenge, are public databases the solution or a liability for labs? Pharmacogenomics Reporter. http://www.genomeweb.com/clinical-genomics/tackling-vus-challenge-are-public-databases-solution-or-liability-labs. Published February 12, 2014. Accessed February 27, 2014.

7. Seeking Alpha. Myriad Genetics' (MYGN) CEO Peter Meldrum on Q3 2014 Results - Earnings Call Transcript. http://seekingalpha.com/article/2196503-myriad-genetics-mygn-ceo-peter-meldrum-on-q3-2014-results-earnings-call-transcript?page=3. Published May 6, 2014. Accessed May 7, 2014.

8. American Medical Association. D-460.971 Genome analysis and variant identification policy statement. www.ama-assn.org. Published June 2013. Accessed May 2, 2014.

9. American Medical Association. Amendment to Opinion E-9.095 Trademarks, patents, copyrights, and other legal restrictions on medical procedures. www.ama.assn.org. Published November 2007. Accessed May 6, 2014.

10. Ambry Genetics. BRCA 1/2 Test Information Fact Sheet. http://www.ambrygen.com/tests/brca1-and-brca2. Accessed May 6, 2014.

11. Eggington JM, Burbidge L, Copeland K, et al. Current variant of uncertain significance rates in BRCA1, BRCA2, and Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM) testing. Poster presented at the European Society of Human Genetics (ESHG) Congress 2012.

12. National Society of Genetic Counselors. Cancer Special Interest Group listserv postings. www.nsgc.org. May 2 and May 5, 2014.

13. News Briefs. *Genetics in Medicine*. 2014; 16(5):357-358.

Reimbursement
(continued from cover)

Right now, the divide looks like this: payers have seen a new cost category explode across their balance sheets; they are determined to understand what they are funding and whether tests are necessary. Molecular diagnostic companies, meanwhile, say they can't understand what they call a penny-wise, pound-foolish approach. Why, they say, should insurers pay ever-rising sums for cancer drugs, with prices measured in tens and hundreds of thousands of dollars, but balk at a $3000 test[3] that would tell doctors whether the drug will work?

"We overtreat people continuously in this country," said Macey Johnson, vice president of managed care and reimbursement at bioTheranostics, based in San Diego, California. "It's overkill to give people all these drugs, with oncology being the poster child."

Rina Wolf

As both regulators and testing companies implement a new reimbursement law, many stakeholders see opportunities for change. "It brings the industry into the bright light," said Mike Barlow, vice president of operations at Palmetto GBA of South Carolina, the Medicare contractor that developed the MolDx program to create billing expertise around an emerging industry. "Too often, the lab industry has been operating as an afterthought."

What's harder to gauge is how much the recent reimbursement woes are driving the science—either by slowing new discoveries or directing research toward tests for which payment is perceived to be easier. Some say there's no doubt that venture capitalists who make decisions on whether to invest in molecular diagnostic companies find the current landscape unsettling.

There's a direct connection between science and the funding that pays for it, said Rina Wolf, vice president of commercialization strategies, consulting, and industry affairs at XIFIN, a California-based firm that provides research, technical, and health economics support for the molecular diagnostics industry. Today's uncertainty can make venture capitalists nervous, Wolf said, especially as the bar for reimbursement gets higher. "You can have a company that has a tremendous protocol from a scientific standpoint, but if they can't raise the money to validate it, especially the clinical utility piece, it's not going to go anywhere."

Most of the focus on reimbursement for molecular diagnostic testing has been on CMS, for obvious reasons: first, most commercial payers use CMS payment schedules as a benchmark[4]; second, many new, sophisticated tests involve cancer diagnoses, and cancer increasingly strikes Medicare-eligible seniors.[5]

The recent adoption of a federal law aims to put molecular diagnostics on a path to certainty.[6] However, unhappiness over current CMS reimbursement policy prompted a lawsuit filed April 16, 2014.[7] The California Clinical Laboratory Association, on behalf of some members and an unnamed Medicare beneficiary, sued HHS in federal court in the District of Columbia, asserting that today's interim billing practices place too much control in the hands of regional Medicare contractors. As a result, the suit alleges, contractors are using pricing policy gaps to make decisions about whether a test should be covered at all, which unfairly denies patients access.[7]

Myriad Genetics and UnitedHealthcare Sign a Deal

On May 6th, Myriad Genetics and UnitedHealthcare (UHC) signed an agreement that would make Myriad's BRCA gene test and the myRisk Hereditary Cancer test available to UHC for evaluation of eligible patients.[1] The myRisk Hereditary Cancer test has a 25-gene panel, with a focus on 8 major cancers: breast, colon, ovarian, endometrial, prostate, pancreatic, gastric, and melanoma. The test, which uses next-generation sequencing, has been evaluated in several clinical trials, and was deemed more sensitive than current syndrome tests. In addition to the test results, the myRisk test report provides guidelines to use the results for risk management.[2]

References

1. Myriad and UnitedHealthcare sign three-year agreement making myRisk(TM) Hereditary Cancer Test available to United Members [press release]. Salt Lake City, UT: Myriad Genetics; May 6, 2014. http://investor.myriad.com/releasedetail.cfm?releaseid=845492.

2. Myriad myRisk™ Hereditary Cancer. Myriad Genetics website. https://www.myriad.com/products/myrisk-hereditary-cancer-panel/. Accessed May 8, 2014.

A Scientific and Regulatory Stew

As with any maturing industry, one challenge has been defining it: there are different types of tests with different levels of oversight. The FDA has jurisdiction over some tests but not others. FDA may give "clearance" to a companion diagnostic developed alongside a specific drug. Laboratory-developed tests, or LDTs, are not FDA-regulated but must be standards of the Clinical Laboratory Improvement Amendments (CLIA) before their results can be considered valid.[8] The pace of science, however, may mean that a companion diagnostic with FDA's blessing may be superseded by an LDT test if the

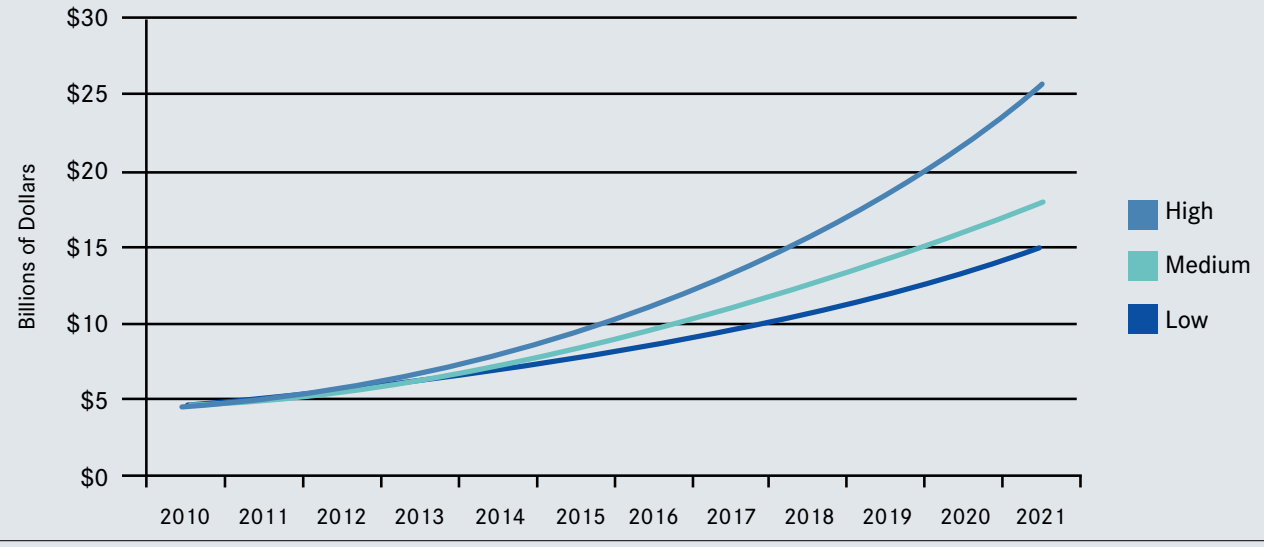
approved therapy is found to have wider applicability.

Wolf and others point to the example of a companion diagnostic for a *BRAF* mutation that Roche developed in tandem with vemurafenib for the treatment of late-stage skin cancer.[9] "When Roche went through FDA, there was only 1 known mutation," for which the drug was indicated, Wolf said. "Now there are 3."

Then there is the emerging area of multi-analyte algorithmic tests, which determine risk factors based on algorithms that are often proprietary. Billing for these tests has been controversial—some within CMS believe that Medicare should only cover elements that detect the presence of something in the body, not a calculation.[4]

Molecular diagnostic testing presents 2 distinct regulatory challenges for CMS. First, it is never easy when scientific advances this important happen this quickly, so quickly that they threaten to outpace the expertise within the agency that must fund them. Second, and perhaps more critically, long-term regulatory rhythms and lab fee schedules were never designed for such complicated tests, so CMS must now build a brand new framework for this industry, propelled by the provision tucked into the recent "patch" of the Sustainable Growth Rate (SGR).[6] Even when change is good, any time a regulatory agency does something for the first time, there's uncertainty during the transition from the old way of doing things to the new one. The fact that all this is occurring alongside the high-profile rollout of the Affordable Care Act (ACA) only complicates matters.

Figure. Illustrative Growth Scenarios for Molecular Diagnositc and Genetic Testing Spending, 2010-2021



Source: UnitedHealth Center for Health Reform & Modernization, 2012.

Big Splashes and Growing Pains

Molecular diagnostic testing is still a comparatively young discipline. The Association for Molecular Pathology (AMP) formed in 1995[10]; AMP cofounded the *Journal of Molecular Diagnostics* in 1999.[11] Commercialization took hold over the next decade, with companies like Myriad Genetics and Genomic Health becoming well known, particularly in the field of breast cancer. By the time AMP secured its June 13, 2013, US Supreme Court victory over Myriad on the question of whether the company could patent a gene, Myriad's footprint in *BRCA1* and *BRCA2* testing was firmly established.[12]

Genomic Health, meanwhile, made successive splashes at the 2003 and 2004 June meetings of the American Society of Clinical Oncology (ASCO) with its Oncotype Dx test, which predicts both chemotherapy response and potential for recurrence in breast cancer. (Genomic Health's 2004 results were featured at ASCO's "Best of Oncology" session.)[13]

For tests to gain widespread use, companies had to bill insurers and CMS. During the next decade, the industry grafted its fees around a billing system designed for less sophisticated clinical laboratory tests. What emerged was a process called "stacking," in which each step in the chain had its own code.[4] In a May 2013 presentation in New Orleans, Michael Longacre, reimbursement director for corporate/shared services, Becton Dickenson, offered an example in which a single test had 6 different codes.[14] What was worse, according to a UnitedHealthcare report, was that the same 5 or 6 steps could describe vastly different tests. A bill for a genetic test for Canavan disease might look just like a test for Tay-Sachs, leaving payers unable to tell what they were funding, much less whether it was medically necessary.[4]

As molecular diagnostic testing became more common, payers winced at rising costs in a category that did not even exist a few years prior, coupled with their inability to fully track spending. Many advocates for molecular diagnostics also concede that code stacking was not sustainable.

Payers began to push back. As reported in *Evidence-Based Oncology*, on the scientific front, around 2011 payers shifted from seeking proof of clinical validity to asking for evidence of clinical utility, or studies that show a given test directly guides or alters physician behavior. As Beth Davis, senior director of health policy and reimbursement for MDx Health, told *Evidence-Based Oncology* at the time, "showing how doctors use a test in real-world settings can be difficult if payers will not cover it, because that has the practical effect of making it unavailable to most patients."[15]

By 2012, multiple efforts were afoot to address payment in molecular diagnostic testing. The rise of the clinical utility standard led the Baltimore-based Center for Medical Technology Policy (CMTP) to develop an Effectiveness Guidance Document, or EGD. This multi-stakeholder effort, supported by leaders in the pharmaceutical and diagnostic testing industries as well as by payers, represented an effort to develop criteria for evaluating tests in personalized medicine.[15]

The bigger battle, however, involved getting rid of "stacking." Commercial payers and CMS were both determined to get their arms around a market that CMS' chief medical officer called a "tsunami," which by 2010 had grown to $6.2 billion and was increasing by 15% to 20% a year.[14]

Starting in 2009, the American Medical Association (AMA) Current Procedural Technology (CPT) editorial panel worked to collapse all the stacked codes into 127 new CPT codes. After a year of talks, CMS elected to adopt the new codes effective January 1, 2013.[4,14,16] There was just one problem, however. The AMA cannot set prices; only CMS does that. And CMS punted.

The Year of Living Dangerously

There was hope that CMS would adopt the streamlined codes with existing prices, but that didn't happen. Instead, in late 2012, CMS set off a year of uncertainty by letting its regional billing contractors set their own prices, a process known as "gap-fill."[17] The expressed mission was to collect pricing data that would lead to new maximums, or National Limitation Amounts, by January 1, 2014.[4] Trouble was, the old "stacking" system meant most contractors were in the dark about what they had been paying for a complete test, and chaos ensued. Many molecular diagnostic companies spent the early months of 2013 not being paid at all. For some, payment did not start until after *Forbes*' Scott Gottlieb, MD, wrote a March 27, 2013, column on the topic, stating, "This sort of bungling may be without precedent, even for the Medicare agency."[18]

Having developed MolDx, Palmetto GBA of South Carolina emerged as a potential solution for the nation. The MolDx program has unique identifiers to differentiate between various types of tests, such as the difference between FDA-approved tests and LDTs. Some hoped that Palmetto GBA would fill the void for all, while others vehemently opposed this idea. As with all things in molecular diagnostics, opinions differ widely based on individual interests and experience, and that's been one of the challenges in resolving the payment quagmire.

Of the vast clinical laboratory industry, sophisticated molecular diagnostic tests make up a small part, and they are a smaller part still of what gets paid by Medicare. Getting Congress' involvement is difficult when the industry itself is split on what solutions should look like. Wolf said the message from Congress has been, "'When you come to some consensus amongst yourselves, come talk to us.' Different stakeholders have different agendas."

Lobbying ensued throughout 2013 to address molecular diagnostic payment issues while CMS worked on the Medicare fee schedule, and, of course, the disastrous launch of the ACA website, www.HealthCare.gov. In December 2013 came another surprise: plans to revamp the entire Clinical Laboratory Fee Schedule (CLFS), with an eye toward annual summer updates based on technological advances. The tumultuous year ended with as much uncertainty as it began.

Toward a Long-Term Solution

What's happening in molecular diagnostic reimbursement is happening alongside the broader movement in healthcare reform. The quest is on to get payers, and CMS in particular, away from a fee-for-service model that rewards lots of procedures and instead pay for things that help patients. Molecular diagnostic testing companies insist they will have a good story to tell—they will prove their value in reducing waste and improving safety and cancer survival rates. Getting from here to there will be the hard part.

Of course, molecular diagnostic testing companies are just 1 part of cancer care and a sliver of the healthcare system. This spring, their cause was tucked into a louder drama over the effort to scrap the SGR in favor of value-based reimbursement. On April 1, 2014, Congress enacted a final fix, or "patch", to forestall drastic cuts to Medicare payments, which would have covered shortfalls in forecasting.

The patch came with a provision, "Improving Medicare Policies for Clinical Diagnostic Laboratory Tests," which stabilizes prices and gives everyone a timeout to develop a long-term payment structure. The law calls for a transition to "market-based" pricing, which some have called "value-based." Come January 1, 2015, the law will strip CMS of its authority to apply annual CLFS changes based on "technological changes," as announced in December. But, the law comes with price tags, in the form of significant reporting requirements—and fines of up to $10,000 a day for failure to comply.[6]

From afar, the law appears to provide more time, along with outside expertise and oversight, to the process CMS attempted in 2013. Key deadlines include:

- An expert advisory panel must be in place by July 1, 2015
- Labs must start reporting payer rates by January 1, 2016
- CMS must start filling in codes for certain existing tests now paid under miscellaneous codes by January 1, 2016
- A market-based system for advanced diagnostics will be effective January 1, 2017.[6]

Overall, molecular diagnostic companies are cautious, but optimistic. A typical response came from Genomic Health:

"We are encouraged to see value-based pricing included in the SGR Patch legislation that passed in March, with a new reimbursement methodology designed to align private managed care and public Medicare rates. We believe this will provide transparency and predictability to the reimbursement process under the Medicare program for diagnostic tests like ours," said Emily Faucette, vice president of corporate communications and investor relations at Genomic Health.

Myriad's Capone said attracting investment requires certainty in what he called "the three Rs" of the field—reimbursement, regulation, and "rights to intellectual property," which covers whether a company's discoveries can be patented and refers to interpretations from multiple Supreme Court rulings. While Capone believes these interpretations are a step in "the wrong direction," on the intellectual property front, he is more optimistic about progress on the first two Rs in light of the new law.

"As always the devil is in the details, but we're very confident this legislation is good for the industry," Capone said. A movement toward market-based pricing will take ambiguity out of reimbursement.

But that doesn't mean the process will be easy. Some industry sources said they will be watching who makes up the advisory panel. Others said recent turnover at CMS, coupled with the agency's duties to implement healthcare reform, may make it hard to retain focus. And that's on top of a fundamental question: just what is "market-based" pricing?

Mark Capone

Said Palmetto GBA's Barlow, "This is not a service that is truly market driven. To say that you are developing market-based pricing is going to require significant effort to determine, 'What is the market?' "

Apart from implementing payment, the process may yield discussion on what gets covered in the first place, and what levels of evidence should be required. This is where the industry may see great divergence, with more established companies taking advantage of their ability to raise capital for studies. Barlow indicated that scientific bars will remain high, not go lower. "The days of 'do more, get more' have to come to an end," Barlow said. "The utilization of services has to be based on need for the services. It has to be good for the patient."

How Much Regulation? Different Views

All the uncertainty has raised the question: would FDA regulation of more of the market, cumbersome as that might be, bring more certainty of scientific acceptance and prompt payment?

The FDA has had its eye on the industry for some time, and issued a report in October 2013, "Paving the Way for Personalized Medicine,"[19] outlining its potential role in nurturing molecular diagnostics. In fact, industry experts like Bruce Quinn, MD, PhD, of Foley Hoag LLP, have highlighted the contrast between the FDA's view of the role of molecular diagnostics compared with CMS. In a February presentation in San Diego, California,[20] Quinn highlighted the FDA's 60-page report, which was being prepared while CMS was issuing 5 new proposals to cut prices for molecular diagnostics.

But overall, as far apart as they are on other issues, both industry sources who spoke with *Evidence-Based Oncology* and Palmetto GBA's Barlow said those who look to the FDA should be careful what they wish for. "Be careful of the devil you dance with," said Barlow, who said the molecular diagnostics industry would be wise to create its own standards for areas with regulatory gaps. "You cannot operate without oversight. The healthcare industry needs some sort of structure for how these tests come to market," he said.

Myriad's Capone said his company is prepared for more FDA oversight if it comes. "We generate the same level of evidence, regardless of whether the FDA would regulate the test or not," he said. Companies that are not currently funding research at that level would see higher costs if FDA had to approve every test, he said.

Overall, however, Capone is optimistic about where molecular diagnostic testing is headed. "We are truly at the very beginning of the journey," he said. "I do think we will be able to bring innovations to the market much faster, but ultimately the potential is extraordinary." **EBO**

References

1. Towse A, Ossa D, Veenstra D, Carlson J, Garrison L. Understanding the economic value of molecular diagnostic tests: case studies and lessons learned. *J Pers Med.* 2013;3(4):288-305.

2. Prior A. Myriad Genetics to acquire Crescendo Bioscience. MarketWatch. http://www.marketwatch.com/story/myriad-genetics-to-buy-crescendo-bioscience-2014-02-04-174851724. Published February 4, 2014. Accessed April 30, 2014.

3. Rizk E. Molecular diagnostic testing presents $5 billion conundrum. *Managed Care.* http://www.managedcaremag.com/archives/0904/0904.moleculartesting.html. Published April 2009. Accessed May 5, 2014.

4. Malone B. Molecular diagnostic reimbursement in flux: what will new codes mean for labs? Clinical Laboratory News. 2013; 39:1. http://www.aacc.org/publications/cln/2013/january/Pages/Molecular.aspx#.

5. FastStats, cancer. CDC website. http://www.cdc.gov/nchs/fastats/cancer.htm. Updated February 28, 2014. Accessed April 30, 2014.

6. Quinn B, Carey BP. Healthcare alert: summary of clinical laboratory fee schedule reform provisions in the Protecting Access to Medicare Act of 2014. Boston, MA: Foley Hoag LLC; April 3, 2014.

7. Overly J. Medicare sued over erratic payment policies. Law360.com. http://www.law360.com/articles/530713/medicare-sued-over-erratic-payment-policies. Published April 22, 2014. Accessed April 25, 2014.

8. Keichle FL. What is molecular diagnostics? GoMolecular.com http://www.gomolecular.com/discover/what_is_molecular_diagnostics.html. Accessed April 20, 2014.

9. Ong, FS, Das K, Wang J, et al. Personalized medicine and pharmacogenetic biomarkers. *Expert Rev Mol Diagn*. 2012;12(6):593-602.

10. Association for Molecular Pathology website. http://www.amp.org/. Accessed May 5, 2014.

11. *The Journal of Molecular Diagnostics* website. http://www.amp.org/JMD/index.cfm. Accessed May 5, 2014.

12. Liptak A. Justices, 9-0, bar patenting human genes. *The New York Times*; June 14, 2013, A1. http://www.nytimes.com/2013/06/14/us/supreme-court-rules-human-genes-may-not-be-patented.html?_r=0. Accessed April 20, 2014.

13 .Corporate history. Genomic Health website. http://www.genomichealth.com/en-US/Company/History.aspx#.U2gwAld1kgU. Accessed April 13, 2014.

14. Longacre M. The unintended consequences of addressing molecular pathology stacking codes. Presentation at: International Society for Pharmacoeconomics and Outcomes Research. 18th Annual International Meeting; May 18-22, 2013; New Orleans, LA. http://www.ispor.org/meetings/neworleans0513/releasedpresentations/FORUM-2-HTA_SIG_Longacre.pdf. Accessed April 30, 2014.

15. Caffrey MK. A test to prevent repeat biopsies? perhaps, if the bar for clinical utility can be met. *Am J Manag Care.* 2014;20(SP2):SP30-SP31.

16. CPT codes for molecular pathology. Mayo Medical Laboratories website. http://www.mayomedicallaboratories.com/test-notifications/molecular-path-2013.html. Accessed May 2, 2014.

17. Coalition to Strengthen the Future of Molecular Diagnostics website. http://protectmdx.org/about/. Accessed May 2, 2014.

18. Gottlieb S. Medicare has stopped paying bills for medical diagnostic tests: patients will feel the effects. *Forbes.* http://www.forbes.com/sites/scottgottlieb/2013/03/27/medicare-has-stopped-paying-bills-for-medical-diagnostic-tests-patients-will-feel-the-effects/. Published March 27, 2013. Accessed May 2, 2014.

19. Simoncelli T. Paving the way for personalized medicine: FDA's role in a new era of medical product development. Silver Spring, MD: FDA. http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf. Published October 2013. Accessed March 7, 2014.

20. Quinn B. Update from Washington: Payment for Molecular Diagnostics. Presentation at: Q1 Productions' 5th Annual Diagnostic Coverage and Reimbursement meeting; February 25, 2014; San Diego, CA.

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 ($AUC_{0\text{-}24}$) 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
GRX-40188 January 2014

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.

TEVA Oncology