CANCER 2017
FINDING OUR WAY TO BETTER CARE

- Oncology’s patient-centered medical home on shaky ground
- To screen or not to screen? The public’s keen on tests that have no proven value
- Real-world evidence for cancer faces some real-world obstacles
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www.managedcaremag.com
Recommended starting dose is 0.75 mg. Dose can be increased to 1.5 mg for additional A1C reduction.

*In clinical studies, the range of A1C reduction from baseline was 0.7% to 1.6% for the 0.75 mg dose and 0.8% to 1.6% for the 1.5 mg dose; the percentage of patients achieving A1C <7% ranged from 37% to 69% for 0.75 mg and 53% to 78% for 1.5 mg.1,4-7

Trulicity [(dulaglutide)] is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use: Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans. Prescribe only if potential benefits outweigh potential risks. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease.

Select Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS
In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Trulicity and inform them of symptoms of thyroid tumors (eg, mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.

Please see Important Safety Information for Trulicity, including Boxed Warning about possible thyroid tumors including thyroid cancer, on the following page and accompanying Brief Summary of Prescribing Information. Please see Instructions for Use included with the pen.
WARNING: RISK OF THYROID C-CELL TUMORS

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The most common adverse reactions (excluding hypoglycemia) reported in ≥5% of Trulicity-treated patients in placebo-controlled trials (placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg) were nausea (5.3%, 12.4%, 21.1%), diarrhea (6.7%, 8.9%, 12.6%), vomiting (2.3%, 6.0%, 12.7%), abdominal pain (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), and fatigue (2.6%, 4.2%, 5.6%).

Gastric emptying is slowed by Trulicity, which may impact absorption of concomitantly administered oral medications. Use caution when oral medications are used with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to a clinically relevant degree.

Pregnancy: Limited data with Trulicity in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. Based on animal reproduction studies, there may be risks to the fetus from exposure to dulaglutide. Use only if potential benefit justifies the potential risk to the fetus.

Lactation: There are no data on the presence of dulaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Trulicity and any potential adverse effects on the breastfed infant from Trulicity or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of Trulicity have not been established and use is not recommended in patients less than 18 years of age.

Please see Brief Summary of Prescribing Information, including Boxed Warning about possible thyroid tumors including thyroid cancer, and Medication Guide.

Please see Instructions for Use included with the pen.

Trulicity® is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates. Trulicity is available by prescription only.

References
1. Lilly [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC, 2015.
2. Lilly [Instructions for Use]. Indianapolis, IN: Lilly USA, LLC, 2014.
Trulicity® (dulaglutide)

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS

- In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including MTC, in humans, as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined.

- Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with use of Trulicity and inform them of symptoms of thyroid tumors (eg, mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.

INDICATIONS AND USAGE

Trulicity® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: Not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans. Prescribe Trulicity only to patients for whom the potential benefits outweigh the potential risk. Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It is not a substitute for insulin. Has not been evaluated in patients with severe gastrointestinal disease, including severe gastroparesis. Not recommended in patients with pre-existing severe gastrointestinal disease.

CONTRAINDICATIONS

Do not use in patients with a personal or family history of MTC or in patients with MEN 2. Do not use in patients with a prior serious hypersensitivity reaction to dulaglutide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-Cell Tumors: In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon–like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including MTC, in humans, as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined. One case of MTC was reported in a patient treated with Trulicity. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). Cases of MTC in patients treated with iraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. Trulicity is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Trulicity and inform them of symptoms of thyroid tumors (eg, mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Pancreatitis: In Phase 2 and Phase 3 clinical studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to Trulicity versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). After initiation of Trulicity, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain. If pancreatitis is suspected, promptly discontinue Trulicity. If pancreatitis is confirmed, Trulicity should not be restarted. Trulicity has not been evaluated in patients with a prior history of pancreatitis. Counsel other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia Incidence: (%) of Documented Symptomatic (<70 mg/dL Glucose) Threshold and Severe Hypoglycemia in Placebo-Controlled Trials: Add-on to Metformin at 26 weeks, Placebo (N=177), Trulicity 0.75 mg (N=304), Trulicity 1.5 mg (N=304), Documented symptomatic: Placebo: 1.1%, 0.75 mg: 2.7%, 1.5 mg: 5.6%; Severe: all 0. Add-on to Metformin + Pioglitazone at 26 weeks, Placebo (N=141), Trulicity 0.75 mg: (N=280), Trulicity 1.5 mg (N=279), Documented symptomatic: Placebo: 1.4%, 0.75 mg: 4.6%, 1.5 mg: 5.0%; Severe: all 0. Add-on to Glimipiride at 24 weeks, Placebo (N=60), Trulicity 1.5 mg (N=239), Documented symptomatic: Placebo: 1.7%, 1.5 mg: 11.3%, Severe: all 0. Add-on to Insulin Glargine with or without Metformin at 26 weeks, Placebo (N=153), Trulicity 0.75 mg (N=250), Trulicity 1.5 mg (N=250), Documented: Placebo: 30.0% 1.5 mg: 35.3%; Severe: Placebo: 0%, 1.5 mg: 0.7%; Hypoglycemia was more frequent when Trulicity was used in combination with a sulfonylurea or insulin. In a 78-week clinical trial documented symptomatic hypoglycemia occurred in 39% and 40% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea.

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symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg, and 1.5 mg, respectively, was co-administered with prandial insulin. Heart Rate Increase and Tachycardia Related to Adverse Reactions: Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4%, and 1.6% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3%, and 2.2% of patients treated with placebo, Trulicity 0.75 mg, and Trulicity 1.5 mg, respectively.

Lactation: Dulaglutide is not a lactogenic drug, and no data are available on its excretion in breast milk. A decision to use a drug in a breast-feeding woman or to discontinue breastfeeding, taking into account the benefit of the drug to the mother and the risk of possible adverse effects on the breastfed infant, should be based on an assessment of the clinical benefit of breastfeeding to the mother's clinical need for Trulicity and any potential adverse effects on the breastfed infant from Trulicity or from the underlying maternal condition. Pediatric Use: Safety and effectiveness of Dulaglutide have not been established in pediatric patients. Dulaglutide is not recommended for use in pediatric patients younger than 18 years. Geriatric Use: In the two randomized placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) were 75 years of age and over. No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored. Gastrointestinal: Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (e.g., nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

• Inform patients that Trulicity causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their physician. • Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Trulicity promptly, and to contact their physician, if persistent severe abdominal pain occurs. • The risk of hypoglycemia may be increased when Trulicity is used in combination with a medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. Review and reinforce instructions for hypoglycemia management when initiating Trulicity therapy, particularly when concomitantly administered with a sulfonylurea or insulin. • Patients treated with Trulicity should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with Trulicity of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs. • Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of Trulicity and other GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, patients must stop taking Trulicity and seek medical advice promptly. • Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant. • Prior to initiation of Trulicity, train patients on proper injection technique to ensure a full dose is delivered. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations. • Inform patients of the potential risks and benefits of Trulicity and of alternative modes of therapy that are available. • Instruct patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and advise patients to seek medical advice promptly. • Each weekly dose of Trulicity can be administered at any time of day, with or without food. The day of once-weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before. If a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, it should be administered as soon as possible. Thereafter, patients can resume their usual once-weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume Trulicity with the next regularly scheduled dose. • Advise patients treated with Trulicity of the potential risk of gastrointestinal side effects. • Instruct patients to read the Medication Guide and the Instructions for Use before starting Trulicity therapy and review them each time the prescription is refilled. • Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens. • Instruct patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

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Additional information can be found at www.trulicity.com

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Cancer: A Canny Foe Forces Us To Be Canny Opponents

By Frank Diamond

Unless someone can pry from drug companies’ hands the top-secret pill that cures cancer (remember the pill that cures AIDS that was kept from us, as well?), the disease is going to continue to break hearts and bank accounts. The technology keeps improving. That’s good from a humane perspective, but jaw-droppingly daunting for those trying to keep a lid on costs. In other words, for you, dear readers.

That lid keeps popping off despite the best efforts to create systems that would seal it, such as the oncology patient-centered medical home (PCMH). As author Lola Butcher points out (page 18), the PCMH assumes that commercial insurers are all too happy to pay for extra services that oncologists deliver in the hope that the investment will save them money down the road. Well, no because—for one thing—the oncology spend is already so high. Employers who sponsor self-funded plans have been especially wary of efforts to domesticate cancer care.

The technology does, indeed, keep on improving. Take the genomic tests that Contributing Editor Joseph Burns writes about (page 25). A fascinating, potentially powerful development in cancer diagnosis. But again cost and its restless bedfellow, coverage, are an issue.

A story about the cancer screening controversy? Senior Contributing Editor Timothy Kelley was game (page 26). He is the brave war correspondent of this issue of Managed Care. Cancer screening is one of American health care’s combat zones, and Kelley emerged from it with a balanced, well-told story.

The dominions of the emperor of all maladies includes so much territory: From the challenges facing therapies based on chimeric antigen receptor T cells (page 37) to just how real-world evidence is going to fit into the complex ecosphere of cancer drug testing, approval, and regulation (page 35).

Read this special issue on cancer, please. You may also want to keep it as a reference.
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Oncology Medical Home on Shaky Foundation

Here’s the deal: Insurers pay for extra services that oncologists deliver in the hope that the investment will save them money down the road. Not surprisingly, commercial plans aren’t buying in.  By Lola Butcher

Keytruda Crosses Finish Line First

Approval of Merck’s checkpoint inhibitor is further evidence that cancer treatment decisions are increasingly dependent on the PD-L1 biomarker and other molecular-level differences in tumor cells.  By Thomas Reinke

Plans Cool on Genomic Prostate Cancer Tests

Insurers say there’s just not enough good evidence yet that the tests are needed. The labs say insurers have made a calculation that if they wait a few years, then it’s Medicare’s problem.  By Joseph Burns

To Screen or Not To Screen?

For years, the question was rhetorical. Doctors screened and health insurers anted up. The public still likes cancer screening, but many critics say that many tests have yet to show lifesaving benefit.  By Timothy Kelley

Real-World Evidence Faces Real-World Challenges

RWE is a relatively new kid on the block. How exactly it will fit into the complicated world of cancer drug testing, approval, regulation, and marketing is uncertain.  By Thomas Reinke

Challenges Abound for CAR T-cell Therapy

Chimeric antigen receptor T cells are being touted as a cure for some cancers. On the problem-with-that list: cytokine release syndrome and finding ways to produce them efficiently.  By Jack McCain

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Oncology Care Model aims high.
Breast Cancer Provides Unique Test For Acceptance of Value-Based Care

When cancer strikes, people want the best treatment. Too often, however, patients equate cost with quality, thinking that pricier treatments offer the best chance of killing the demon, or at least holding it at bay for a few years until reinforcements (breakthrough technologies and treatments) arrive.

Value-based care isn’t on the minds of many people in such situations. That’s the challenge of incorporating such care into oncology, according to a study in the Journal of the National Cancer Institute.

Researchers at the University of Texas MD Anderson Cancer Center noted that in recent years there has been a marked increase in bilateral mastectomy and reconstruction for early breast cancer. “While some of these procedures are clearly medically indicated, the choice for mastectomy is often driven by nonmedical factors such as patient preferences for more ‘complete’ cancer treatment by extirpating the entirety of the affected organ....”

Researchers measured complications within two years of diagnosis. Complications included infection, hematoma/seroma, breast pain, fat necrosis, radiation pneumonitis, rib fracture, graft/implant complication, implant removal, and other postoperative complications.

Cumulative net payer cost within two years of diagnosis was calculated using all inpatient and outpatient claims from within two years of diagnosis. All costs were adjusted to 2014 dollars.

Researchers gathered information about women under age 65 via the MarketScan Commercial Claims and Encounters database. MarketScan provided claims data from 45 large employers and more than 100 health insurance plans.

Data for Medicare beneficiaries came from the National Cancer Institute’s SEER database. The beneficiaries lived in 16 geographic areas.

The study identified 105,211 women (44,344 MarketScan; 60,867 SEER-Medicare) with early breast cancer that was diagnosed between 2000 and 2011.

Lumpectomy plus whole breast irradiation treatment was the most common treatment. But the researchers found that mastectomy plus reconstruction was nearly twice as likely to cause complications than lumpectomy and irradiation treatment (54.3% vs. 29.6% complication risk among younger women with private insurance and 66.1% vs. 37.6% complication risk among older women with Medicare).

In addition, mastectomy plus reconstruction cost more (an average of $22,481 more for younger women; an average of $1,748 more for older women with Medicare) in total costs. There was also a higher cost related to complications (an average of $9,017 greater for the younger cohort; $2,092 greater for the Medicare cohort).

The findings underscore “an important conflict that will be increasingly confronted in an era focused on ‘value’ in health care,” according to the lead author, Benjamin Smith of the University of Texas MD Anderson Cancer Center, and his colleagues. Patients might prefer the more expensive treatment for nonmedical reasons.

“If such a patient is receiving care from a health care entity with a financial stake in promoting ‘high-value’ care, the entity may profit financially if the patient receives the lower-cost intervention and, conversely, may experience a financial loss if the patient receives the higher-cost intervention,” the authors stated.

Iowa Blue, Aetna Exit ACA Exchange

Thousands of Iowans will have to scramble for health coverage after last month’s announcement by two major insurers that they will no longer be participating in the state’s ACA exchange. Wellmark Blue Cross and Blue Shield and Aetna both say that they were not making enough money on the exchange because those enrolling tend to be a sicker population that’s costly to care for. The lack of...
participation by young invincibles is a structural problem long noted by both opponents and proponents of Obamacare.

Officials with both health plans also noted Washington’s inability to clearly define for insurers what awaits them. Republican plans to repeal and replace Obamacare were shelved in March for lack of enough GOP support in the House.

Aetna and Wellmark’s moves amount to a one-two punch for Obamacare in Iowa. Reuters: “According to data provided by Iowa, Aetna accounted for most of the plans sold on the federally run Healthcare.gov website in 2016. Wellmark accounted for most of the plans sold in the state that comply with Obamacare but are not sold on Healthcare.gov.” Aetna has about 30,000 covered lives under Obamacare; Wellmark about 21,000.

Aetna hasn’t made any decisions about remaining on the exchanges in Delaware, Nebraska, and Virginia. And Aetna isn’t the only health insurance plan showing hesitation.

Reuters reported that many health plans “worry that Republicans have not said they will extend billions of dollars of subsidies into 2018 and that lawmakers might make other major changes, such as scrapping the requirement that all Americans must have health coverage or pay a fine.”

Wellmark’s CEO John Forsyth told the New York Times that “while there are many potential solutions, the timing and relative impact of those solutions is currently unclear. This makes it difficult to establish plans for 2018.”

Wellmark covers about 1.7 million people in the state, most of them through employer-sponsored health plans.

Doug Ommen, Iowa’s insurance commissioner, pointed out that his is not the only state faced with this reality. “It’s concerning given that Iowa has now had two carriers leave the ACAs individual health insurance market,” he said. “We will continue looking for ways to protect Iowa consumers.”

**New Cancer Drugs Costing a Bundle**

Competition has sometimes worked to reduce the cost of some drugs for some diseases. Health insurers and PBMs can bargain with several drug makers for the best price for drugs for the same indication with similar efficacy.

That’s not happening with cancer immunotherapies, though, where some of the oncologic drugs can cost $250,000 a year.

The supply is growing, which should, theoretically, lower prices. The number of cancer drugs in the approval pipeline expanded by 63% between 2005 and 2015, according to QuintilesIMS Institute.

Steve Miller, chief medical officer at Express Scripts, told Reuters that “for cancer drugs in general … it is hard for us to drive down cost.” Miller said that the makers of immunotherapies benefit from coverage requirements, benefit plan structures, and a dearth of studies that gauge how the new drugs fare in head-to-head competition.

It’s like this, says Aaron Kesselheim, MD, an associate professor at Harvard Medical School and author of several studies of drug pricing: “Cancer drugs don’t compete on price,” he told Reuters. “Drug companies have market exclusivity and we require payers to cover cancer drugs—Medicare has six protected classes, including cancer.”

The five other protected classes are HIV/AIDS, antidepressants, antipsychotics, seizure disorders, and organ transplantation.

The combination of scientific progress and pricing power makes the area an irresistible lure for pharma companies.

Peter Bach, MD, director of Memorial Sloan Kettering’s Center for Health Policy Outcomes in New York, told Reuters: “Most of the strategy on the part of pharmaceutical companies assumes unrestrained pricing power. We don’t see evidence that companies are pursuing cost-effective strategies.”

**Uneducated Whites’ ‘Deaths of Despair’**

There’s an unhealthy dynamic at work for poorer, less educated whites in the United States. The fewer their job prospects, the worse their health, and that worsening health limits job prospects even further. In a follow-up to their ground-breaking 2015 study Mortality and Morbidity in the 21st Century, Princeton professors Anne Case and Angus Deaton argue that the labor-participation rates for this cohort in the U.S. is one of the lowest among the developed countries.

Case and Deaton have traced an increase in midlife mortality for whites with a high school diploma or less to increases in the number of “deaths of despair”—death from drug and alcohol abuse and suicides. The whites with limited education have also not benefited as much from the gains against heart disease and cancer.

In 1999, the mortality rates for whites with no more than a high school degree was about 30% lower than the mortality rates of blacks, in the 50–54 age group. About 15 years later, the relationship reversed: The mortality rate for whites with that level of education was about 30% higher than blacks, according to Case and Deaton’s research.

Whites with a college degree not only tend to live longer than whites without one, but the gap between
the two groups is actually widening, states the updated version of the study, which was published by the Brookings Institution in March.

But why?

“We propose a preliminary but plausible story in which cumulative disadvantage over life, in the labor market, in marriage and child outcomes, and in health, is triggered by progressively worsening labor market opportunities at the time of entry for whites with low levels of education,” according to Case and Deaton.

Time is already a critical factor, the study argues. Even public policies that can successfully improve job prospects or redistribute income will “take many years to reverse the mortality and morbidity increase, and that those in midlife now are likely to do much worse in old age than those currently older than 65.”

Briefly Noted

Better detection and prevention of the risk factors associated with heart disease have led to a 20% decline in cases of the disease, according to a research letter in JAMA. Despite the
progress, more can be done in terms of tackling risk factors such as high LDL cholesterol levels, high blood pressure, and smoking. The expansion of Medicaid under the ACA did not overburden primary care physician (PCP) offices as feared, according to a research letter in *JAMA Internal Medicine*. For the most part, PCPs were able to reorganize their offices to better handle the increased volume. The proliferation of wearable fitness devices comes with some knotty questions about employee privacy, *ReadWrite* reports. And more employers are dangling the devices in front of their employee. In 2013, about 2,000 companies around the world offered workers fitness trackers; that number jumped to 10,000 in 2014. "Employees are too cavalier about the privacy implications of using corporate-provided wearables," warns Gary Eastwood, a tech writer. "Employees need to understand why this is a problem before readily accepting a company distributed wearable and whether it is a good idea." The worst performing VA medical centers are in Texas and Tennessee, according to the agency’s internal data. *USA Today* obtained the VA star rating reports, which the VA has refused to release, claiming they are for internal use only. "VA hospitals in Dallas, El Paso, Nashville, Memphis, and Murfreesboro [Tenn.] all received one star out of five for performance as of June 30, the most recent ratings period available," the newspaper reports. A much smaller percentage of teens in treatment for heroin and opioid abuse are getting medication-assisted treatment (MAT) than their adult counterparts, according to a study in the *Journal of Adolescent Health*. Only 2.4% of adolescents in treatment for heroin received MAT compared with 26.3% of adults, and just 0.4% of teens in treatment for opioid abuse received MAT vs. 12% of adults, the researchers found. The data was from 2013, so it’s possible the teen–adult gap in MAT may now be narrower. Informed consent? It’s not really and is more about lawyerly deflection of lawsuits than helping patients understand medical decisions, said Mikkael Sekeres, MD, and Timothy Gilligan, MD, both of the Cleveland Clinic, in a biting opinion piece in the *New York Times*. The “farce of informed consent” is even worse when it comes to medical research and clinical trials, they said. Patients in clinical trials are given a “25-page document that describes the trial’s purpose, its design, the medications you’ll receive, other standard treatments, and the complications you may suffer. Oh, and we’ll tell you that you are responsible for any medical costs not covered by insurance or the trial sponsor. That’s for the lawyers, again. We will then ask you to sign the final page, acknowledging your understanding and your agreement to participate in the trial.” Their suggestions included encouraging patients to ask doctors to drop the abstruse medical jargon and use common words. Patients should also repeat back to the doctor what has been said: “That way, if you’ve misunderstood what we did a poor job of explaining, there will be a chance to straighten it out.” The VA’s efforts to prevent MRSA infections seem to be working, although MRSA transmissions in acute care spinal cord injury units have not decreased, according to a study published in the *American Journal of Infection Control*. The VA’s MRSA Prevention Initiative was launched in October 2007. Over the next eight years, various indicators show MRSA infections decline in ICUs and other parts of the hospitals and in long-term care facilities. The exception is MRSA transmission in the spinal cord injury units. Some paramedics are being enlisted to help mentally ill patients and not just automatically take them to hospital emergency departments, Kaiser Health News reports. The paramedics are being trained to de-escalate situations that might get out of control. After questioning the patient about his or her mental health history, they then decide where to take the patient to the hospital. Telestroke units that will have clot-busting tPAa, portable CT scans, and a telemedicine link to a hospital will soon be taking to the streets in Chicago, reports mHealth Intelligence. Both Northwestern Medicine Central DuPage Hospital and Rush University Medical Center are launching the units. "The question is whether the telestroke units are sustainable," reports mHealth Intelligence. The van costs "roughly $1 million to outfit and will cost that much to keep on the road each year. Both units are currently funded by grant money." People who commit suicide often act on impulse. Kaiser Health News features a story about a vet who came close to killing himself but now counsels others. He aims his advice specifically at gun owners. His tips include knowing the signs of depression and keeping the weapon and ammo well away from each other. Also, call some friends. The more patients with diabetes served by a primary care practice means the greater chance that those patients will receive higher quality care for the disease, according to a study in the *Annals of Internal Medicine*. Researchers with the University of Toronto conducted a cohort study of over a million adults with diabetes to examine the link between PCP patient volume and quality. A push by some employers for telemedicine is running into a wall. Many workers know it’s available but don’t really trust remote health care consultations, reports the *Chicago Tribune*. The newspaper cites a report by the National Business Group on Health that says that while 70% of large employers offered the service, only 3% of employees at those companies used it during the first half of 2016. — Frank Diamond

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GOP Jumps Back Into High-Risk Pools. But Will the Money Run Dry Again?

About $2 billion a year is earmarked for the pools in the AHCA legislation. Evidence suggests that more like $100 billion may be needed.

By Richard Mark Kirkner, Contributing Editor

One thing is certain about the future of the health care marketplace as the calendar counts down to the June 18 deadline for plans to file their 2018 rates: uncertainty prevails. But if you’re looking to place bets on one component of the nongroup market that has the best chance of enduring, you might want to put your money on state-run high-risk pools. Like the cockroach that will survive a nuclear attack, this is one animal that has a good chance of living another day.

High-risk pools are not new. Before the ACA, 35 states had them. Today, only a handful still function. But in March, HHS Secretary Tom Price encouraged a comeback, sending letters to governors inviting them to apply for ACA innovation waivers to implement state-by-state high-risk pools and reinsurance programs. Alaska was the first to take the bait, and, as we went to press, Minnesota’s legislature was clearing the way to be next in line. High-risk pools were also an important part of House Speaker Paul Ryan’s replacement plan for the ACA before he yanked the legislation back because it didn’t have enough votes to pass.

Cecil Bykerk, a former chief actuary at Mutual of Omaha from back in the day when the company sold traditional health plans, is now treasurer of the National Association of State Comprehensive Health Insurance Plans (NASCHIP), the association for state high-risk pools. He’s also executive director of high-risk pools for three different states, including Alaska.

High-risk pools are supposed to make individual coverage available to people with high-cost, pre-existing conditions who couldn’t otherwise afford the premiums, explains Bykerk, although they would still pay more than people who buy coverage in the regular nongroup market. The markup is typically about 50% over regular market rates, according to Bykerk. It can be as much as two times higher.

“Chump change”

An amendment to Ryan’s American Health Care Act (AHCA) which is still languishing in the legislative pipeline, would create a $15 billion risk-sharing fund for 2018 through 2026. Beginning in 2020, states could take over the program. That’s a paltry $1.7 billion a year nationally. Larry Leavitt of the Kaiser Family Foundation calls it “chump change.” Indeed, back in 2008, health care advisers to Sen. John McCain’s campaign figured more than 50 times as much money would be needed.

A 2010 HHS analysis estimates that almost 18 million people with pre-existing conditions were uninsured at the time, and the cost for all of them to go into high-risk pools would’ve been $195 billion in 2010 dollars, with premiums covering only $103.3 billion, leaving a $92 billion shortfall that’s in the ballpark of what McCain’s advisers came up with.

The numbers for covering people with pre-existing conditions are daunting. Up to 133 million nonelderly Americans—or about half the adult population—have a pre-existing condition. Simply getting older is a risk factor: More than 80% of Americans, ages 55 to 64, have at least one pre-existing condition, according to the HHS analysis. Whom among them would enter the high-risk pools has not been spelled out in either Price’s letter to governors or the House Rules Committee’s AHCA amendment.

The pre-ACA experience

The high-risk pools prior to the ACA had lots of problems. Jean Hall, a health policy professor at the University of Kansas Medical Center, notes that they were very expensive for the people who enrolled in them and the states that administered them. “They tend to have limited coverage, high out-of-pocket costs, and people who enroll in them, even though they have insurance, are often underinsured,” she
says. Moreover, siphoning off people with high medical expenses didn’t do much to bring prices down in the rest of the nongroup market, says Hall, who has researched high-risk pools for the Commonwealth Fund.

An analysis by the National Conference of State Legislatures found that these high-risk pools enrolled 226,615 people by the end of 2011. On average, state high-risk pools covered about 2% of the people participating in the nongroup market—ranging from a low of 0.02% in Florida to a high of 10.2% in Minnesota, according to a Kaiser Family Foundation analysis of NASCHIP data.

Thomas Huelskoetter, a health policy analyst for the liberal Center for American Progress, noted in a recent blog post that high-risk pools are a clunky way for high-cost individuals to get coverage and leave people far short of the uncapped coverage that is available to them under the ACA. In California, enrollees with pre-existing conditions had to wait three months to get into the pool—a shorter wait time than average for pre-ACA state high-risk pools—and saw their benefits capped at $75,000 annually and $750,000 lifetime. Then the state capped enrollments and extended wait lists. The premiums got so high that many Californians simply dropped out.

Even a high-risk pool advocate like James Capretta, an American Enterprise Institute fellow and an associate director of the Office of Management and Budget under President George W. Bush, sees a seemingly intractable problem with high-risk pools. In a 2010 National Affairs piece about high-risk pools, Capretta mentioned “the large mismatch between the number of people who need them and the amount of money made available to subsidize them.”

Copy Plan D
The ACA set up a transitional high-risk pool program called the Pre-Existing Condition Insurance Plan (PCIP) to cover people with pre-existing conditions until 2014, when the law’s rules barring discrimination based on health status kicked in. Karen Pollitz, a senior fellow at the Kaiser Family Foundation, wrote in a detailed report earlier this year that by the end of 2012, only 100,000 people had enrolled, and the plan had burned through nearly half of its $5 billion appropriation. Other problems with PCIP: Premiums were typically 150%–200% above market rates, which would have made them outliers under pre-ACA state-run high-risk pools, and the claims-to-premiums ratio climbed steadily from under 200% in 2011 to 600% in 2013.

Hall says HHS has had a model for covering high-cost lives under its nose since 2006: the GOP-backed Medicare Part D drug benefit, which pays plans risk-adjusted benefits and reinsurance for high-cost beneficiaries. “It’s a great model,” she says. “No one has ever debated that they shouldn’t do it that way.” The ACA had similar mechanisms—risk adjustments, reinsurance, and risk corridors—for nongroup marketplace plans, but the reinsurance and risk corridors were only temporary, and the Republican-controlled Congress defunded the risk corridors before their three-year lifetime expired.

Invisibility cloak
Successful high-risk pools need more than just money thrown at them, although enough money would certainly help. In Bykerk’s opinion, they need a network of providers who are willing to accept lower fees for serving a population that otherwise wouldn’t pay anything—almost like found money, if you will. If there’s anything to take away from those pre-ACA high-risk pool days, it’s that states could have fewer limitations in dealing with providers. “A lot of states weren’t able to cut those deals,” Bykerk says.

Another challenge from the pre-ACA days was just getting people to sign up, he says. “The most difficult part about high-risk pools is that it seems to be hard to communicate with the constituent that they’re available,” he says. “There’s also a certain degree of stigma to it.”

Alaska’s newly enacted reinsurance pool will subsidize carriers for certain high-risk beneficiaries. It’s an example of one of the GOP’s proposals for solving the stigma problem: Make the high-risk pools “invisible” by having marketplace plans administer the benefits while the pool quietly pays the claims in the background. The enrollee might not even realize he or she is in a high-risk pool, says Bykerk.

Even if invisibility helps with the stigma, the difficult math of high-risk pools remains, and, so far, Republicans don’t seem prepared to spend the money to make them work. XG
It was the first pay-for-performance program launched by the ACA and the first step in transforming Medicare from a buyer of health care to an agent of change. The Hospital Value-based Purchasing Program (VBP) signaled that CMS would no longer foot nearly a quarter of the nation’s health care tab without demanding some accountability from hospitals in return.

The approach of VBP’s implementation kept a lot of hospital executives up at night. Today, it barely merits a shrug.

What happened between then and now? You’ll get a lot of opinions, but most everyone seems to agree that the money at stake isn’t worth the effort. The program withholds 2% of hospitals’ Medicare pay and redistributes most of it to high-performing hospitals.

But 2% is the theoretical maximum penalty. The average bonus or penalty for high- and low-performing hospitals is much smaller (see next page). In absolute dollars, that worked out to a $213,000 average bonus or an average $1.2 million penalty in 2015, according to an analysis by the Advisory Board.

“You’ve got a relatively small percentage of providers in the winning circle, a relatively low or equal number of providers in a loser’s circle, and anyone else is more or less in the middle with indistinguishable performance,” says François de Brantes, vice president and director of the Center for Payment Innovation at Altarum Institute in Ann Arbor, Mich. The center was formerly known as the Healthcare Incentives Improvement Institute, or HCI3.

In fact, most bonuses and penalties fall below one half of one percent. When you factor in payer mix, the net effect on a hospital’s bottom line is even less, according to a report by Leavitt Partners. It’s barely enough to justify the amount of expense and effort involved in redesigning care processes and information systems to meet the demands of the program.

VBP bases bonuses or penalties on a hospital’s total performance score across four domains: clinical care, which includes a mix of process and mortality measures; efficiency, which tracks Medicare spending per beneficiary; safety, which includes hospital-acquired infections; and patient experience of care, incorporating eight Hospital Consumer Assessment of Healthcare Providers and Systems measures. In all, there are 21 measures. Improvement in any one domain requires significant investments of time and money, according to the Leavitt report, and improvement on a single measure is unlikely to produce meaningful change in a hospital’s overall score.

Moreover, says de Brantes, the structure of the program—designed to keep it budget-neutral—makes the return on investment uncertain.

“You don’t get to know what your performance is until the end of the performance period because it’s a tournament-style program,” he says. Rather than allowing hospitals to establish benchmarks on which to base improvement goals, VBP pits hospitals against one another, diluting the reward pool. “When you’ve got a low probability of knowing what the outcome of your work is and the prize is relatively weak, you’re not going to get a whole bunch of people super excited about focusing a lot of energy on it.”

Any program designed to drive quality improvement should include a handful of measures that providers can control, says François de Brantes of the Center for Payment Innovation.

Mishmash of measures
A financial lever based on a hospital’s overall quality score neither helps hospitals prioritize areas for improvement nor does it make a program easy to understand. In an article published last year in the Journal of Ambulatory Care Management, Richard Averill and colleagues at 3M
Health Information Systems argued that mixing process and outcomes creates a bland cocktail that “is not an effective way of measuring value or controlling expenditures.”

The use of process measures for payment purposes, they wrote, creates an administrative burden that takes the focus off the objectives of the effort. “With process measures that range from clinically significant to micro administrative, the inevitable result is a composite score derived from arbitrary and complex rules that are difficult for health care delivery organizations to understand and use for real quality-improvement efforts,” they wrote.

Perhaps more importantly, there’s no evidence that this formula has improved mortality outcomes, according to a study published in BMJ last year. In an analysis of CMS data, Jose Figueroa and colleagues at Harvard’s T. H. Chan School of Public Health found that three years into VBP, 30-day, risk-adjusted mortality rates for AMI, heart failure, and pneumonia—the only three outcomes measures in the VBP program—had not changed significantly. What’s more, declines in mortality rates slowed after VBP’s initiation.

The evidence is discouraging to those who have been advocates of pay for performance. One of those, Ashish Jha, MD, a co-author of the BMJ study, wrote on JAMA Forum earlier this year that VBP was destined to fail because it lacks all of the key elements of a successful pay-for-performance program: a simple design, a focus on a small number of high-value measures, and “incentives that are large enough to motivate hospitals to make sizable investments in improving care.”

If that’s not enough, VBP was based on what Jha believes was a flawed pilot. VBP was modeled on the Premier Hospital Quality Incentive Demonstration, which ran from 2003 to 2009 and included more than 200 hospitals. CMS handed out more than $60 million in incentive payments for hitting quality marks, but there was no effect on patient outcomes. What became clear, Jha wrote, was that the Premier demonstration essentially rewarded hospitals for doing what they already did well, but otherwise it had

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**VBP: 5 years of middling results**

After five years, rewards and penalties to hospitals under the Value-based Purchasing Program suggest no discernible trends in overall performance.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of hospitals rewarded</th>
<th>Number of hospitals penalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>1,557</td>
<td>1,235</td>
</tr>
<tr>
<td>2014</td>
<td>1,713</td>
<td>1,806</td>
</tr>
<tr>
<td>2015</td>
<td>1,806</td>
<td>1,612</td>
</tr>
<tr>
<td>2016</td>
<td>1,235</td>
<td>1,343</td>
</tr>
<tr>
<td>2017</td>
<td>1,473</td>
<td>1,371</td>
</tr>
</tbody>
</table>

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**Take a little here, give a little there**

Average rewards and penalties in the VBP program remain below 1%. For a handful of top-performing hospitals, bonuses have grown beyond the amount CMS withholds, but nobody has yet to feel the sting of losing it all.

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS withhold</td>
<td>1%</td>
<td>1.25%</td>
<td>1.5%</td>
<td>1.75%</td>
<td>2%</td>
</tr>
<tr>
<td>Average hospital bonus*</td>
<td>0.23%</td>
<td>0.24%</td>
<td>0.44%</td>
<td>0.66%</td>
<td>0.71%</td>
</tr>
<tr>
<td>Average hospital penalty*</td>
<td>0.21%</td>
<td>0.26%</td>
<td>0.30%</td>
<td>0.48%</td>
<td>0.48%</td>
</tr>
<tr>
<td>Top hospital bonus*</td>
<td>0.83%</td>
<td>0.88%</td>
<td>2.09%</td>
<td>3.02%</td>
<td>4.03%</td>
</tr>
<tr>
<td>Top hospital penalty*</td>
<td>0.90%</td>
<td>1.14%</td>
<td>1.24%</td>
<td>1.75%</td>
<td>1.83%</td>
</tr>
</tbody>
</table>

*Above or below standard DRG reimbursement.
Source: MANAGED CARE analysis of CMS data
Who cares about 2%, anyway?

Reacting last November to the latest round of lackluster VBP results, many hospital administrators said the financial swing isn’t material enough to get excited about the program. VBP withholds 2% of hospitals’ DRG-based reimbursement and divvies up the pot to hospitals on the basis of quality scores.

Interestingly, 2% was also the threshold for the Premier Hospital Quality Incentive Demonstration, the model for VBP. Most commercial pay-for-performance programs also use 2%, says François de Brantes, vice president and director of the Center for Payment Innovation at Altarum Institute. “Why is it that they are all 2%?” he asks.

Finding no justification for 2% in the literature, de Brantes talked with a few knowledgeable people and learned that anything over 2% was difficult to get CFO or actuary approval to implement. One percent wasn’t enough to get anyone interested. So, 2% fell into common use.

But de Brantes and others argue that a 2% ceiling on penalties doesn’t garner much interest, either—especially in VBP, where payment adjustments average based on one half of one percent. In a February article in *JAMA Forum*, Ashish Jha, MD, at Harvard’s T.H. Chan School of Public Health, wrote, “Why pay high-mortality hospitals 99.6% as much as low-mortality hospitals? Incentives that put 5% or even 10% of a hospital’s Medicare payments at risk would ensure hospitals pay attention.”

And just what is happening?

Maybe too many things at once, argues de Brantes, who ticks off a list of competing interests for hospitals: the Medicare Shared Savings Program, mandatory bundled payments, and commercial payer programs focused on total cost of care. It creates a mix of incentives that compete for staff and financial resources.

“It’s time to bring the policy people, physicians, hospitals, and seniors into a single meeting place and make some decisions about what the next round of payments for traditional Medicare will look like,” Gail Wilensky, former HCFA director and the first chair of MedPAC, told a forum at Harvard’s Kennedy School of Government in February. There are so many alternative payment model demonstrations going on at once, she said, “it has to make it confusing for everybody.”

De Brantes, whose Center for Payment Innovation is a leading adviser on bundled payment arrangements, says that any program designed to drive quality improvement should include just a handful of measures that are tightly related to what the provider can control. In VBP, that took the form of process measurements, which are easy to measure and may have been an easy default in the wake of provider outcry about burden of measurement and risk adjustment. But, he says, “that put the kibosh on outcomes measures, which are what really matter.”

At the episode-of-care level, however, patient-reported outcomes become relevant, says de Brantes. “Patient-reported outcomes for a hospitalization is an oxymoron. But a patient-reported outcome for the management of a chronic condition or a specific treatment or a procedure—that means something. That’s a unit of measurement.”

De Brantes adds, “What matters to patients—which is, ‘How I was treated for a specific health care need’—also matters to the frontline clinician. That is what we should be getting to.”

Where we wind up, of course, depends largely on the fate of the ACA. Wholesale repeal of VBP’s enabling legislation would have effectively ended the program, along with the Bundled Payment for Care Improvement Initiative, the Readmissions Reduction Program, and health systems’ financial responsibility for hospital-acquired infections. With the failure of the House Republicans’ American Health Care Act, it’s unclear whether the Trump administration will prop up the ACA or undo it. If the ACA dies a death by a thousand cuts, then any of those programs could be shelved, modified, or combined à la the physician programs that were rolled into MACRA.
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The rapidly rising cost of cancer care was on every payer’s mind when the buzz started building about a nine-physician oncology practice on the outskirts of Philadelphia.

Since 2004, Consultants in Medical Oncology and Hematology had been implementing tenets of the patient-centered medical home—patient education, quick access to physicians, triage nurses to help patients manage symptoms—to improve care for its cancer patients. In 2010, practice leader John Sprandio, MD, began touting the results of all these changes: dramatic reductions in emergency department and hospital utilization—and an estimated overall cost savings of $1 million per physician per year.

Ebullient about what his practice had accomplished and rattling off statistics that backed up the enthusiasm, Sprandio quickly became the hottest ticket in oncology. Conferences wanted him to present his findings; oncologists wanted to know his secrets; and payers wanted to know how they could get those savings from the oncologists in their own networks.

Sprandio calls his new way of delivering care the “oncology patient-centered medical home,” the oncology version of the primary care patient-centered medical home, a model that uses standards set by the National Committee for Quality Assurance (NCQA). Others use the term “oncology medical home,” eschewing the NCQA terminology and standards, but embracing the medical home concept.

“I credit him with pioneering the model,” says Lindsay Conway, the top oncology expert at the Advisory Board. More than that, she admired the way Sprandio tirelessly proselytized about the oncology medical home’s potential for lowering costs and improving outcomes.

But there’s a catch. At every opportunity, Sprandio pointed out that running an oncology medical home practice is much more expensive in the short term than traditional cancer care and, at least initially, providers would be footing the bill. Patients needed to be educated to recognize symptoms early and to call a triage nurse for advice. The nurses need to be trained to provide evidence-based guidance that adheres to specific protocols. Practices need to provide many services—support in making and keeping appointments for tests and treatments, same-day access to a physician for evaluation of symptoms, extensive patient education, and telephone support. And there’s a need, of course, for more sophisticated information technology to support data collection.

But Sprandio was able to show that there was a real return on the investment. After his practice standardized its approach to educating patients about how to stay hydrated, fewer patients sought emergency department and inpatient care for dehydration. The practice’s standardized management of outpatient diarrhea cut the number of admissions for treatment of Clostridium difficile enteritis by more than half in five years.

The benefit of fewer emergency department and hospital inpatient visits to payers is obvious. So obvious, thought Sprandio, he assumed insurers would...
Fall of the Oncology Medical Home

be happy to pay for the extra services in exchange for the big savings down the road.  
“I thought within a couple years, we would have a different payment model,” he says. “Honestly, I thought by the end of 2011, we would have achieved that.”

So did a lot of other people. Many oncology practices scrambled to adopt the innovative model of care, and the federal government launched an oncology medical home demonstration project with seven practices across the country.

It was not to be. Sprandio eventually did get an oncology medical home contract with Aetna, but he terminated it after a year, declaring it a dud.

By that point, it was becoming clear that an oncology medical home payment model was not the solution to America’s cancer cost crisis. A working oncology medical home contract requires some delayed gratification: Insurers pay for extra services that oncologists deliver in the hope that the investment will save them money in the long run. But that, says Conway, has been a nonstarter with commercial payers.

Today, Sprandio—and a lot of other people—are back at the drawing board, in search of a good way to pay for cancer care.

An important test

While Sprandio was developing the oncology medical home concept in the Philadelphia area, Barbara McAneny, MD, the CEO of New Mexico Cancer Center, a large multidisciplinary oncology practice, was on a similar mission in Albuquerque. The biggest private payer in her market did not bite, but a much more important payer—CMS—was intrigued.

Like everyone else, CMS leaders believe payment reform that incentivizes oncologists to improve the value of their care is essential to reigniting unsustainable cancer care costs. The National Cancer Institute projects that cancer-related costs will grow to at least $158 billion in 2020, a 27% increase from 2010 based on population changes alone. If treatment costs increase at the rate of the recent past, the tally may reach $173 billion.

In 2012, CMS’s Center for Medicare and Medicaid Innovation (CMMI), the federal government’s incubator of health care delivery experiments, awarded a $19.8 million grant to Innovative Oncology Business Solutions, a company McAneny created to manage the grant and implement the practice model in seven practices across the country.

The Community Oncology Medical Home (COME HOME) grant funded a three-year demonstration. The goal was to prove that, by using patient-centered medical home concepts, oncology practices could improve outcomes, enhance patient care experiences, and significantly reduce costs of care.

The seven COME HOME practices implemented extensive patient education and medication management counseling, team-based care, around-the-clock access via telephone triage and extended clinic hours, and on-site or near-site imaging and laboratory testing. They used clinical pathways to guide decisions for imaging, pathology, molecular diagnostics, and all aspects of treatment, and they were supported with access to real-time data that allowed them to monitor quality, pathway adherence, and utilization at the provider level.

At the end of three years, the seven practices had reduced the rate of hospital admissions by 12.5%, emergency department visits by 6.6%, and the overall cost of care by 7.2%.

Then the demonstration ended. The COME HOME practices continued to have the expense of the medical

COME HOME program sees success

% of patients with ED visits

Source: Page RD et al., ASCO 2015 Educational Book
home infrastructure. But there was no payer support in sight, even though commercial insurers benefited from the lower costs.

“We were losing $50,000 a month on salaries so we scaled back some of our evening hours and some of the weekend hours,” McAneny says. “I kept talking to our local health plans, saying ‘You know I’m dying out here. I can’t keep this up for you unless you help me out.’”

Payers balk
It will never be known what results the COME HOME practices might have generated if the CMMI demonstration had continued on. Adopting the patient-centered medical home model and continuously fine-tuning a practice for better performance is a long, incremental process.

Sprandio’s practice was just getting started at the end of three years; by the end of the sixth year, it reported a 78% reduction in the use of emergency departments and a 50% reduction in hospitalizations.

That performance turned heads, but payers needed proof that the oncology medical home concept could be replicated and sustained. That made results from the COME HOME demonstration all the more important because they would come from seven markets across the country. And while a 7.2% reduction in the overall cost of care would seem to add up to real money, payers were unimpressed. “The results they were able to achieve in terms of quantified improvement in care quality and patient experience and overall value were kind of underwhelming—at least not sufficient to get commercial payers excited about spending more money to fund this different model of care,” says Conway at the Advisory Board.

Remodeling: Can the Oncology Care Model work when medical homes haven’t?

Nearly 200 oncology practices and 17 private payers jumped aboard the Oncology Care Model (OCM), a five-year multipayer program launched by CMS’s Center for Medicare & Medicaid Innovation (CMMI) last July. One of the federal government's first physician-led specialty care models, the OCM attracted many more practices than the Innovation Center originally envisioned, suggesting that oncologists liked the government’s offer.

So will the OCM become the standard way to pay for cancer care in the future?

No.

That’s the consensus of five individuals who have spent the past decade searching for a better way to pay for oncology services.

In addition to episode payments that cover Medicare Part A and B costs, the OCM is paying participating oncology practices $160 per beneficiary per month for care coordination and extra services, such as round-the-clock access to a clinician. The oncology practices can bill for multiple episodes for a single patient. And the shared savings provisions include one- and two-sided risk.

“I think that the OCM represents a transitional model,” says Michael Kolodziej, MD, national medical director for managed care strategy at Flatiron Health.

John Sprandio, MD, chief physician at Consultants in Medical Oncology and Hematology in Broomall, Pa., just outside Philadelphia, calls the OCM “a step in the right direction” because it gives practices and payers an opportunity to learn about value-based contracts. “It’s not perfect—there will be adjustments and modifications in terms of understanding what the real levers are in controlling the total cost of care,” he says.

At the Advisory Board, managing director Lindsay Conway also anticipates changes. “By no means have we seen the ultimate ideal payment arrangement that will sustain cancer care indefinitely in the future,” she says.

Horizon Blue Cross and Blue Shield in New Jersey elected not to participate in the OCM. Lili Brillstein, director of the insurer’s New Models and Episodes of Care program, says Horizon already has its own bundled payment program, which pays practices retrospectively, unlike the OCM. But she has encouraged the oncology practices in her network to participate: “I think it’s a really good program for the providers,” says Lili Brillstein of Horizon Blue Cross and Blue Shield in New Jersey.

“I think [the Oncology Care Model] is a really good program for the providers,” says Lili Brillstein of Horizon Blue Cross and Blue Shield in New Jersey.
In the end, it will be episode payment


There is a lot of heavy lifting between now and then, but many of those who think about cancer care payment reform for a living see episode payments as the finish line.

“I do see a place in the future where we’re predominantly paying cancer on episodes of care,” says Michael Kolodziej, MD, a medical oncologist who has worked on both the provider and payer sides of oncology.

What episode-of-care—or bundled—payments for cancer care will look like is not at all clear. Lindsay Conway, managing director at the Advisory Board, thinks that the University of Texas MD Anderson Cancer Center’s pilot with UnitedHealthcare sets a good example.

In an experiment limited to patients with head and neck cancers, UnitedHealthcare made a single annual payment to MD Anderson for all inpatient and outpatient care provided to a patient.

“Best of all, the patient receives just one bill for all of the care—surgery, radiation, chemo, or anything else—that they receive across the course of a year,” Conway says. “I love this because it’s high quality, it’s efficient, and it is patient-centered in a way that we haven’t seen from other models.”

Thomas W. Feeley, MD, head of the Institute for Cancer Care Innovation at MD Anderson and a senior fellow at the Harvard Business School, likes it too. The three-year pilot, which is wrapping up this year, enrolled 88 patients.

“We consider this a success, and we’d like to see more of it,” Feeley says. “We believe bundled pricing is the way all of health care should be paid for.”

The pilot received a lot of attention when it was announced in 2014, but no other insurers approached MD Anderson in search of their own bundled payment deal.

“We have reached out to United to see what they might want to do next, and frankly, we just haven’t heard,” he says. “It’s not for a lack of willingness on our part.”

Kolodziej, national medical director for managed care strategy at Flatiron Health, thinks MD Anderson’s pilot with UnitedHealthcare is too limited for there to be any strong takeaways. For one thing, MD Anderson is a powerhouse, an exception that can’t be used to prove the rule; for another, the pilot focused on such a small subset of patients that its applicability to a broader patient population is unclear.

UnitedHealthcare has another episode-payment initiative—this one is limited to medical oncologists—that also appears to hold promise. In a pilot that ran from 2009 to 2012, five community oncology practices were paid a single fee, in lieu of any drug margin, to treat their patients with breast and colon cancer. The pilot practices reduced the total cost of care for those patients by more than a third. Since then, five other oncology practices have joined UnitedHealthcare’s episode program, which now includes more than 650 oncologists, according to the insurer.

Meanwhile, Horizon Blue Cross Blue Shield of New Jersey’s episode-of-care program for breast cancer is going well enough that the insurer will expand to other cancer types in the near future, says Lili Brillstein, director of the insurer’s new models and episodes of care program.

In late 2014, Horizon contracted with Regional Cancer Care Associates, a multistate practice based in New Jersey, for the novel payment system. Horizon’s program works like many current bundled payment programs. Providers are paid using standard fee-for-service reimbursement during the patient’s treatment. Once the episode is over, a retrospective review determines whether quality metrics were met and if expenditures were less than projected, which would result in shared savings to the provider.

Horizon’s episode payment program is supported by a data platform that categorizes a patient’s cancer by molecular subtype. The information decreases the likelihood that time and money will be wasted on treatments that are not likely to work. The missing link for successful reform of cancer care payment is putting that kind of information into the hands of clinicians, Kolodziej says. His enthusiasm for CMS’s Oncology Payment Model has more to do with the data that can be assembled from the 200 participating practices submitting quality measures and patient clinical data than the payment reform model itself.

“In the U.S., those data don’t exist,” he says. “That could be paradigm shifting, really.”

Theoretically, that type of information, along with claims data, can be used to build decision-support tools that help oncologists and their patients understand upfront the best course of action—and what it is likely to cost. An episode of care would be more predictable, which is essential for oncologists and payers to sustain a way to pay for cancer care.
Getting payers excited would have been difficult regardless. A patient-centered medical home contract typically includes a per-member, per-month (PMPM) management fee to help a medical practice pay for the additional staff, data analysis, and care coordination. In addition, practices are typically eligible for shared savings at the end of a performance period. When it comes to cancer care, the idea of a PMPM fee makes health care purchasers blanch. Cancer only affects about 1% of covered lives, but commercial insurers shell out about 11% of their total annual expenditures on cancer care. While insurance executives might recognize the payoff of supporting a practice’s adoption of medical home amenities, the employers who sponsor self-funded plans do not want to hear it.

“My experience has been that when you go into those plan-sponsor meetings, and they look at their oncology spend, the idea that they’re going to spend more on a promise of return is a tough sell,” says Michael Kolodziej, MD, of Flatiron. He was national medical director for oncology strategy at Aetna when it launched an oncology medical home contracting program in 2013. Nearly 70% of Aetna’s commercial business is self-insured. Because sponsors of self-insured plans would not go along, the only patients eligible for the oncology medical home model—and the only patients that Aetna could pay a management fee for—were those who were in a fully insured product. “Eventually, we decided to abandon the management fee because it just wasn’t working,” he says.

Postmortems

Although there are a few oncology medical home contracts still in play, payers and providers in general see the concept as another example of how vexing payment reform for cancer care is turning out to be.

A decade ago, it seemed clear that the huge costs of emerging chemotherapy agents were the primary culprit in the rapid rise of cancer treatment costs. But a three-year episode-of-care pilot sponsored by UnitedHealthcare punched a hole in that theory. The five practices in the pilot reduced total medical costs for patients with breast, colon, and lung cancer by 34%—even though the cost of chemotherapy for the episode group was more than double that of a control group. That study was not designed to parse out exactly where the savings were generated, but the authors’ analysis did show a statistically significant decrease in hospital use by patients treated in the pilot practices. That finding piqued the thinking of the cancer care community.

Since then, attention has turned to emergency department visits and hospitalization as a driver of high cancer care costs that can be controlled. The Agency for Healthcare Research and Quality (AHRQ) estimates 27% of total medical costs for cancer care in 2014 were for inpatient hospital stays. The oncology care delivery model has been proven to reduce hospital use—but who’s going to pay for it to be implemented?

Still, McAneny and others hope that oncology practices will adopt the oncology medical home delivery model, even though payer support is iffy at best. The American Society for Clinical Oncology (ASCO) last year licensed the COME HOME name, its assessment protocol and implementation tools from McAneny’s effort and is marketing them to its members.

Unlike patient-centered medical home contracts for primary care, which may pay practices as little as $10 PMPM, the oncology medical home model is much more expensive. Based on her experience with the COME HOME demonstration, McAneny says the PMPM needed to sustain an oncology medical home practice varies by geography; in Albuquerque, where she practices, it is at least $220.

When the demonstration ended, CMS announced its Oncology Care Model, a five-year payment initiative that grew out of the COME HOME demonstration (see “Remodeling: Can the Oncology Care Model Work When Medical Homes Haven’t?” page 20).

The new program borrows heavily from the oncology medical home payment system, but adds performance targets that McAneny thinks are unrealistic: “The amount of payment that they are giving is not going to be enough to both pay for the data requirements they are putting on the practices and leave any money left over for practice transformation,” she says.

Her New Mexico Cancer Center practice is participating in the OCM, but, unless changes are made, McAneny worries that the program may mean the end of the oncology medical home concept. And that may mean more cancer patients spending time in the hospital, suffering from poorly controlled symptoms, and treated in the most expensive way possible.

Lola Butcher is a health care business and policy writer based in Missouri.
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The treatment of lung cancer took a dramatic step forward late last year when pembrolizumab (Keytruda) was approved as first-line therapy for lung cancer. Previously, pembrolizumab and the two other FDA-approved immune checkpoint inhibitors, nivolumab (Opdivo) and atezolizumab (Tecentriq), had indications only as second-line therapies.

But there's an important proviso to pembrolizumab's promotion to first-line status: It's only for a select group of metastatic non–small-cell lung cancer (NSCLC) patients who have a tumor progression score of 50% or more for the PD-L1 biomarker and whose tumor cells do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. The tumor progression score is the proportion of tumor cells exhibiting the PD-L1 protein.

In the KEYNOTE-024 clinical trial that was the basis of the FDA approval, the median progression-free survival was 10.3 months in the pembrolizumab group compared with six months in the group that received conventional chemotherapy. The objective response rate was 45% in the pembrolizumab group and 28% in the chemotherapy group, and overall survival was significantly longer for pembrolizumab patients. About 222,500 Americans will be diagnosed with lung cancer this year. But the obvious question is how many people with advanced NSCLC will meet the required PD-L1 threshold and qualify for treatment with pembrolizumab. Patient screening for the drug's clinical trials have shown that between 24.9% and 30.2% of patients have tumors with PD-L1 expression on ≥50% of tumor cells.

The tumor progression score of ≥50% for pembrolizumab was established in the early phase 1 trials and lower levels were not extensively tested in phase 3 trials. Merck’s phase 3 trial of pembrolizumab, KEYNOTE-042, is comparing the checkpoint inhibitor with chemotherapy in a broader group of advanced NSCLC patients with tumor progression scores of 1% or greater, meaning just 1% or greater of their tumor cells express PD-L1. Investigators may report the results early in 2018.

Pembrolizumab's approval as a first-line drug means new responsibilities for clinicians, notes Benjamin Levy, MD, a lung cancer specialist at Johns Hopkins. Now oncologists will have to test for PD-L1, in addition to EGFR and ALK aberrations, and the National Comprehensive Cancer Network has added routine PD-L1 testing to its guidelines. But testing for PD-L1 is more complicated than just adding another test to a panel. The immunohistochemistry (IHC) test for PD-L1 requires its own tumor sample separate from the one sent for molecular profiling of EGFR and ALK mutations. There can be real challenges in obtaining enough biopsy tissue and in coordinating the sample sent for each test, Levy explains.

There are also some questions about the validity of IHC testing. There are four commercially available tests with different platforms that may produce different results, says Alex Spira, MD, of Virginia Cancer Specialists, which is part of the US Oncology Network. The FDA’s approval of pembrolizumab specified one type of test, but oncologists may use other vendors. The problem stems partly from the inherent limitations of IHC testing, and the fact that the IHC tests for PD-L1 are largely unregulated, lab-developed tests that can vary from vendor to vendor. Moreover, variations in the concentration of PD-L1 cells in different regions of the sample can produce different test results.

Spira says these limitations argue for some flexibility in payers’ application of the ≥50% tumor progression score, but he says payers appear to be sticking with the FDA-specified threshold. Pembrolizumab and the other checkpoint drugs are priced well above $100,000 a year.

To Merck’s delight, pembrolizumab has sped past Bristol-Myers Squibb’s Opdivo and Genentech’s Tecentriq in getting a first-line indication for lung cancer. But Levy says the bigger story is that cancer treatment decisions are increasingly dependent on that PD-L1 and other molecular-level differences in tumor cells. A different era of cancer treatment may soon be upon us, if it isn’t already.
Many Health Plans Avoid Paying For Prostate Cancer Genetic Tests

One reason is that they figure that CMS will foot the bill because many of their beneficiaries age into Medicare. Also, for every insurer: churn, churn, churn.

By Joseph Burns
Contributing Editor

Churn. That’s the term health insurers use to describe how members move from one plan to another and from one insurer to another. Health plan administrators know that churn could make a big investment in health one year meaningless if that member has lower costs at another plan in the coming years.

Administrators also know that—like most everything in health care—there’s a way to turn a negative into a positive and use churn to your advantage. You simply don’t pay for expensive testing for a health plan member you know will shift to a different health insurer in the near future. And, in particular, if your plan has a number of members in their early 60s, you know they will age into Medicare soon so you might have an incentive to curtail coverage for services that will soon be on the government’s dime.

The buck doesn’t stop here

This is a game some insurers are playing with prostate cancer tests, says Elai Davicioni, PhD, president and chief science officer of GenomeDX. Urologists use the company’s Decipher Biopsy and Decipher Post Surgery tests to assess the chances that a low-risk prostate cancer will metastasize. According to Davicioni, health plan executives have told GenomeDX’s sales staff that they prefer not to cover these tests because soon enough these patients will become eligible for Medicare.

A February 2017 report from Piper Jaffray, a Minneapolis investment company, lends some credence to their claims. The company said that it tracked how 49 health insurers cover Oncotype Dx Prostate from Genomic Health. The report says the insurers either had no coverage policy or considered Genomic Health’s Oncotype DX Prostate test to be investigational or experimental.

Here’s where churn comes in: CMS has a program that has reviewed the prostate cancer tests of GenomeDX, Genomic Health, and Myriad Genetics and decided that Medicare, at least in the region Palmetto GBA serves, should cover those tests. Many, though not all, of the other Medicare administrative contractors, follow Palmetto’s guidance on this issue, Davicioni says.

As a result of the standards set by Palmetto, genetic test developers need to show that their tests have a direct bearing on treatment decisions if they’re hoping for Medicare coverage. So why don’t the private payers follow suit? asks Davicioni.

Phillip Krebs, the director of medical policy for Geisinger Health Plan, has a simple answer: “If we had good evidence that one of those tests was a game changer, we’d be covering it. The reason most carriers see these tests as unproven is because there is a paucity of good quality evidence to prove otherwise.”

All three tests are likely more useful than assessing risk via a man’s prostate-specific antigen (PSA) test, Krebs acknowledges. But that’s not saying much. “At the end of the day,” says Krebs, “most of these tests are probably helpful in counseling patients, but none of them can determine an outcome with certainty.”

And while Palmetto’s MolDx program is a welcome addition to the growing field of companies reviewing the clinical utility of molecular tests, its assessments often do not align with that of other companies evaluating genetic tests, such as Hayes and ECRI, Krebs says. What’s more, Palmetto doesn’t publish the data on its assessments, making it difficult to assess the reasoning behind its decisions, he says. Krebs says there’s a general problem of lack of regulatory oversight of molecular tests and poorly designed studies.

While private payers wait for more data, Davicioni says men with prostate cancer must pay about $3,000 out of pocket for genetic tests—or wait till they are old enough for Medicare coverage. Meanwhile, these men risk developing a deadly metastasized form of cancer, driving up the costs of Medicare coverage, according to Davicioni.

“Prostate cancer is unique in that the risk of getting more aggressive prostate cancer increases with age,” Davicioni says. "Which is why we think this is such a big problem."
Otis Brawley, MD, doesn’t often put his foot in his mouth. But when he responded to former Senator Bob Dole’s claim that prostate cancer screening had saved his life by questioning whether Dole’s life needed to be saved, the 1996 GOP presidential nominee had a quick retort.

“You’re obviously a Democrat,” he said.

Brawley didn’t mean that America could do without the droll Dole, only that the senator might have survived without being screened. Indeed, if a genie of perfect health care ever offered three wishes, one of them might be about cancer screening: If only it were as good as many of us—inadvertently, perhaps—have hoped it is!

Brawley, the American Cancer Society’s chief medical and scientific officer and executive vice president, gets frequent calls from women who complain that they followed ACS mammography guidelines religiously and still developed metastatic breast cancer. “How did this happen?” they demand to know.

“They assume a bad doctor read their mammogram or something,” says Brawley. “But all the studies we have on mammography indicate that at best it decreases risk of death by 30%. That means 70% of the people who were going to develop metastatic disease and die are still going to develop metastatic disease and die.” The problem, he says, isn’t just a public that is ill informed (some would say misled). “There are doctors who misunderstand this issue too.”

Meeting the devil

For a guy in a lofty post, Brawley, born 58 years ago on the Fourth of July and reared in a tough Detroit neighborhood, can be blunt when he needs to be. His provocative 2011 book, How We Do Harm: A Doctor...
Breaks Ranks About Being Sick in America, argued that the medical system wasn’t failing: “It’s functioning exactly as designed. It’s designed to run up health care costs.” One chapter recalled a chat with a cancer center marketer who—conceding that PSA screening hadn’t been proven to save lives—nevertheless boasted that he could project just how much business his center’s free prostate screenings would generate in radical prostatectomies, radiation therapy—even Viagra and incontinence procedures. Brawley realized, he wrote, that he’d been “granted an audience with Lucifer.”

But Brawley is Dr. Moderate on screening when compared with two more ardent skeptics—one east, one west. One is H. Gilbert Welch, MD, professor of medicine at Dartmouth Institute and Dartmouth’s Geisel School of Medicine and author of 2011’s Overdiagnosed: Making People Sick in the Pursuit of Health and 2015’s Less Medicine, More Health: 7 Assumptions That Drive Too Much Medical Care. The other is Vinay Prasad, MD, assistant professor of medicine at Oregon Health and Sciences University, coauthor of 2015’s Ending Medical Reversal: Improving Outcomes, Saving Lives, and a much-followed tweeter (@vinayprasad82).

“Most people think of course you want to be screened—it’s the best thing since sliced bread,” says Welch. “But the truth is much more nuanced.” Welch decries screening’s tendency “to turn people into patients unnecessarily.” The tests detect abnormalities, he says, but “we all harbor abnormalities.” And though we pretend otherwise, medical care has harms. For acutely ill or injured patients, those harms pale in comparison with the benefits. “But with a well population, everything changes,” says Welch. “It’s hard to make well people better, but it’s not hard to make them worse. Our society has promulgated the view that you can test yourself to health, and that’s not true.”

While false positives in mammography have received a lot of press, Welch says they’re just one of screening’s problems. More worrisome, in his opinion, is overdiagnosis: the way screening tests find genuine but nonaggressive cancers that would never have posed a problem but set in motion biopsies and treatment that can cause harm. And there’s the expense. Welch notes that medical costs are a leading cause of bankruptcy.

“There are real tradeoffs people need to understand,” says Welch. “And they’re particularly acute in breast- and prostate cancer screening.” But he sees difficulties even with screening for colorectal cancer, which he calls a “disappearing” disease. “Its death rate has been cut in half since my father died of it in 1978,” he says. This cancer’s sharp decline began before screening was routine, he says, contending that it can’t be credited fully to screening but may partly result from “changes in gut flora,” increased use of NSAIDs, and declining consumption of smoked and cured meats. He argues that America spends prodigiously on colonoscopy—

“There’s really only one screening test that we have pretty good evidence helps people live longer,” says H. Gilbert Welch, MD, of Dartmouth. “That’s lung cancer screening in heavy smokers,” a big money maker for hospitals—when no one has proved it superior to flexible sigmoidoscopy or fecal occult blood tests. “There’s really only one screening test that we have pretty good evidence helps people live longer,” says Welch. “That’s lung cancer screening in heavy smokers.”

A proven lifesaver?
Prasad, in Oregon, doesn’t disagree—except to partly topple the one bowling pin Welch leaves standing. Yes, the National Lung Cancer Screening Trial (NLCSST),

Taking credit for a good trend
Colon cancer’s sharp decline actually started before colonoscopies became common in the late ‘90s.

Age-adjusted U.S. colorectal cancer death rates by year

Source: National Cancer Institute, SEER Cancer Statistics Review 1975–2013
which randomized 53,454 heavy smokers, did show reductions in all-cause mortality rather than just mortality from lung cancer, he says. But to Prasad, the study’s control arm wasn’t a proper control because its members underwent chest X-rays, and that’s not the standard of care. “Limited evidence shows that screening with chest radiography may even increase lung cancer mortality,” he writes. He says a control group with no screening would have been more appropriate. More important, the difference between the screening group and the control group in the NLCST was greater for overall deaths than it was for deaths from lung cancer.

“So if you believe that the test improves overall mortality, you have to believe that CT screening for lung cancer saves lives from conditions other than lung cancer too,” says Prasad. “To me, that’s not plausible.”

It exasperates Prasad that people ignore “the elephant in the room”: Screening is widely promoted as a lifesaver, even though (except possibly in the case of lung cancer) it hasn’t been proven in randomized controlled trials (RCTs) to reduce overall deaths. “That’s the definition of ‘saves lives,’” he says.

To prove that screenings save lives overall, says Prasad, would require high-powered trials 10 times the size of even the large extant studies of breast and lung cancer. To him, such an expenditure would be worthwhile in view of the billions now spent on screening. Whether that’s ever going to happen is, of course, another question, and the answer is probably no.

Prasad insists he’s no anti-screening crusader. “If an informed patient chooses to be screened, I support that,” says Prasad. “What I don’t support is any deceit or omission of truth in telling people about the process.”

And he believes such deceits and omissions currently rule the day. He cites a public-opinion research study in which 62% of women thought mammography at least halves the risk of getting breast cancer, and 75% believed a decade of screening can prevent 10 breast cancer deaths per 1,000 women. “Even the most optimistic estimates of screening do not approach these numbers,” he writes.

**Cars that don’t go**

If Prasad is exasperated, he’s got nothing on Daniel B. Kopans, MD, founder of Massachusetts General Hospital’s Breast Imaging Division and a professor of radiology at Harvard Medical School (who stresses that he no longer gets paid to read mammograms and thus has no personal financial stake in the debate). He’s fed up to the eyebrows with skeptics offering argument after argument against screening—all of which, he says, he’s refuted. “It’s like playing whack-a-mole,” he complains. “As soon as one argument against screening is refuted by science the skeptics dream up another.”

Kopans decries the distinction made by the U.S. Preventive Services Task Force (USPSTF) when it recommends biennial mammography for women 50 to 74 but says 40-somethings should discuss the screening with their doctor. “Everybody should talk it over with their doctor!” he says. “There’s no magic in age 50—and no data that support using that age as a starting point for screening.”

**Putting screening to the test of what we know—or believe**

It was in 1975 in the 11th grade English classroom of Father Richard Powalski, at the University of Detroit Jesuit High School, that Otis Brawley, MD, learned the critical-thinking maxim he applies to medicine today: “Say what you know, what you don’t know, and what you believe—and label it accordingly.”

Brawley, chief medical and scientific officer of the American Cancer Society, has made this mantra so well known that it pops up at the end of a 2016 *BMJ* analysis of cancer screenings co-written by Vinay Prasad, MD, of Oregon Health and Sciences University. But Prasad renders the key phrase as “what we simply believe.” His point is that, even though backers say screening “saves lives”—and even though some studies have shown that screening does reduce deaths from a particular cancer—almost no studies have demonstrated that screening reduces mortality from all causes.

Brawley himself, however, has a slightly different take. Carefully labeling what we know doesn’t mean we can’t act in the absence of certain knowledge, he believes. “I’m willing to settle for a cancer-specific mortality reduction,” says Brawley, noting that most of the studies now cited weren’t designed to show all-cause mortality. “It’s unfair, in my mind, to say we shouldn’t do a screening test because we have no study proving it increases overall survival when, indeed, we’ve never tried to run a study to show that.”

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Cancer screening may have its skeptics, but respondents to a MANAGED CARE reader poll are not among them. Colorectal, cervical, breast, prostate, and lung care cancer screening were rated as highly beneficial by the 168 respondents to the online survey, although prostate and lung cancer screening were viewed somewhat less favorably than the other three.

About half the respondents indicated that new treatments for early-stage cancer were a result of screening for those five cancers. A much smaller percentage identified the problems often mentioned by screening skeptics—false positives, overdiagnosis, and overtreatment—as consequences of screening.

Medimedia Research conducted the poll from March 31 to April 10. Medimedia Research is part of Medimedia Managed Markets, an Icon plc company. MANAGED CARE is owned by Medimedia Managed Markets.

About one in three of the respondents identified their organizations as being provider organizations (either a medical group or an integrated delivery system). About one in five identified their organization as being a health plan or insurer. Insurers aren’t necessarily anti-screening, but they may be more attuned to its possible harms. The favorable view of screening among the survey respondents may reflect—at least in part—the skew toward provider organizations among the respondents.

The respondents didn’t completely exonerate screening. For example, 28% indicated that breast cancer screening resulted in too many false positives, and 22% indicated that it resulted in overdiagnosis.

Similarly, 33% indicated prostate cancer resulted in too many false positives, and 37% said it resulted in overtreatment.

### Ratings of various cancer screenings in terms of their effect on American health

<table>
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<tr>
<th>Cancer Type</th>
<th>Percent Rating 8, 9, or 10</th>
<th>Average Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
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<td>9.8</td>
</tr>
<tr>
<td>Cervical</td>
<td>78%</td>
<td>9.5</td>
</tr>
<tr>
<td>Breast</td>
<td>78%</td>
<td>9.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>56%</td>
<td>8.5</td>
</tr>
<tr>
<td>Lung</td>
<td>54%</td>
<td>8.4</td>
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</table>

### Level of agreement with USPSTF screening recommendations

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Percent Rating 6 or 7</th>
<th>Average Rating</th>
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<tbody>
<tr>
<td>Colorectal</td>
<td>59%</td>
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<tr>
<td>Lung</td>
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<tr>
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</tr>
<tr>
<td>Prostate</td>
<td>27%</td>
<td>3.7</td>
</tr>
</tbody>
</table>

### Organization type of respondents

- Medical group: 22%
- Consultant: 14%
- Integrated delivery system: 18%
- Health plan/insurance provider: 14%
- PBM: 6%
- Mental/behavioral health organization: 13%
- Other: 26%

Source for all charts: MediMedia Research
A favorable view of the consequences of screening

About half of the respondents identified the development of new treatments for early stage-stage cancers as a consequence of cancer screening. But a sizable minority also identified too many false positives for breast and prostate cancer screening as a consequence.

<table>
<thead>
<tr>
<th>The development of new treatments for early-stage cancers</th>
<th>Colorectal cancer</th>
<th>Cervical cancer</th>
<th>Breast cancer</th>
<th>Prostate cancer</th>
<th>Lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too many false positives</td>
<td>5%</td>
<td>10%</td>
<td>28%</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Overtreatment</td>
<td>5%</td>
<td>6%</td>
<td>21%</td>
<td>37%</td>
<td>5%</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>4%</td>
<td>5%</td>
<td>22%</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>Poor use of health care resources</td>
<td>4%</td>
<td>4%</td>
<td>8%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Too many false positives</td>
<td>4%</td>
<td>5%</td>
<td>9%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>None of the above</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Less than 10% indicated that too many false negatives were a result of cancer screening. However, false negatives were rated as the most harmful of the drawbacks (5.4 on a 1–7 scale), followed by overtreatment (4.7), false positives (4.7), and overdiagnosis (4.5).

Agreement with U.S. Preventive Services Task Force (USPSTF) recommendations was strongest for colorectal screening—59% of the respondents indicated that they strongly agree with the recommendation that screening start at age 50 and continue through age 74. It was weakest for the USPSTF prostate cancer screening recommendations—just 27% indicated strong agreement—although the survey was conducted before the USPSTF issued a new draft recommendation in early April that said prostate cancer screening should be an individual decision.

Cancer screening’s pros and cons are complicated and fiercely debated by experts. Very few (7%) of the survey respondents believe that the American public understands the pros and cons of screening well, and a large group (27%) believes the public has little, if any, understanding of them.
In messaging, an unfair fight: ‘Save your life!’ vs. eyes-glazed-over explanation

Cancer screening isn’t a public health imperative; it’s a personal choice,” says H. Gilbert Welch, MD, of the Dartmouth Institute. Skeptics like him insist they’re not out to stop screening, only to give consumers an honest account of its benefits and risks. But screening advocates fear that skeptics are muddying the water, helping people rationalize skipping mammograms and other recommended tests and thus putting lives at risk. Still, screening boosters can take comfort in one thing that’s firmly on their side in the public debate: emotion. A call to action to save your life is a lot more compelling than dull scientific prose full of qualifiers.

As Lisa Rosenbaum, MD, wrote in a 2014 New England Journal of Medicine editorial on mammography decision making, “the visceral appeal of ‘catching something early’ easily eclipses the difficult mental calculations one must undertake to figure out why early detection does not necessarily mean living longer.”

Screening tests play with our emotions, Rosenbaum argued. A negative finding is reassuring while a positive one brings “gratitude that disease was caught early.” If a positive turns out to be false, we’re mostly just happy we don’t have cancer. And if a positive finding leads to successful treatment, we’re ready to share our compelling story. But some of those dramatic testimonials proclaiming “Screening saved my life!” are from people whose cancers actually might never have bothered them.

In recent years, the U.S. Preventive Services Task Force (USPSTF) has cut back on some screening recommendations. In 2012, it came out against routine PSA screening for prostate cancer in men, although a draft recommendation last month revised that advice to a suggestion that screening should be an individual decision. The USPSTF advises that women get mammograms biennially between ages 50 and 74, adding that the tests may also be chosen by women in their 40s “who place a higher value on the potential benefit than the potential harms.” Set against slick marketing appeals—sometimes from hospitals looking to reel in new patients with free screening—such committee-wrought prose is pale stuff.

What can a health plan or provider organization do to rectify this imbalance and encourage judicious consideration of screening’s downside along with its up? “Work on making your message more appealing if you really want to persuade people that, for example, getting a mammogram every year might not be in their best interests,” advises Sara E. Gorman, author—with her father, psychiatrist Jack E. Gorman, MD—of the 2016 book Denying to the Grave: Why We Ignore the Facts That Will Save Us.

Gorman finds the USPSTF website “really boring—just numbers and statistics. It reflects the way scientists are taught to communicate, but it doesn’t take into account what we now know about how people interpret information.” She says health care organizations need to invest in research to develop “scientifically rigorous knowledge about what kind of messaging works, and what doesn’t,” says Sara E. Gorman, author and public health expert.

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While agreeing that mammography is imperfect, Kopans contends that women should receive annual mammograms starting at 40. “The only harm is that more women will be recalled for a few extra pictures or an ultrasound,” he says.

Kopans charges Welch with deliberately confusing the issue by “throwing together ductal carcinoma in situ with small invasive cancers as if they’re the same.” While DCIS lesions cannot kill, they can turn into invasive ones, he says, and no one should leave an invasive cancer untreated. “We just don’t know which DCIS cases will go on and invade and potentially kill someone,” says Kopans. “But that’s a treatment issue, not a detection issue.”

Indeed, he exonerates mammography screenings themselves from the overdiagnosis and overtreatment that sometimes follow. “Folks like Welch” who suggest that women may wish to avoid these problems by not...
getting screened, he says, are like people who say, “If we just take the engines out of our cars, we can stop automobile accidents.”

Mammography “has been shown in RCTs to be able to reduce deaths from breast cancer,” says Kopans, who cites research going back to the first RCT of breast cancer screening, the Health Insurance Plan of New York study in 1971, which revealed a 23% decrease in breast cancer deaths for 32,000 women aged 40 to 64 who were invited to be screened. (Because it looked only at invitations—“no one can be coerced to participate in screening,” he writes—he says that study actually understated screening’s benefit.)

While critics of screening see conflicts of interest in the role of professionals—radiologists’ groups, for example—who advocate screening from within the screening business, Kopans turns the charge around. The National Cancer Institute, he says, is dominated by screening foes, and that affects what research it decides to support.

“That’s a huge conflict of interest that never gets mentioned,” he says.

Kopans blames the Canadian National Breast Screening Study for the NCI’s decision back in 1993 to drop support for screening women in their 40s. But he says that study was underpowered and afflicted with poor-quality mammography. (Brawley counters that it was upheld in a quality audit by the Canadian Justice Department, and Welch says the mammograms did “exactly what they were supposed to do.”)

This window on the decades-old mammogram controversy reminds us that the clamor over cancer screenings is more than just noisy and vituperative. It’s a seemingly endless thicket of methodological detail. Thus urologist William Catalona, MD, of Northwestern University, lauds the seven-nation, 162,387-man European Randomized Study of Screening for Prostate Cancer, which indicated that PSA testing lowered prostate cancer-specific mortality, and trashes the 76,693-man U.S. Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial, which suggested it did not.

Otis Brawley does the opposite. Even in the European trial, says Brawley, data from five nations out of seven showed no benefit, and one disproportionate contributor to the affirmative result—Sweden—has been shy about letting others review its data. Catalona points out that in the U.S. study, some 90% of the men in the theoretically unscreened control group underwent PSA testing outside the study, making the advantages of screening less apparent. “What he doesn’t tell you,” Brawley pipes up, “is that he worked really hard to get those biases in that study—to sabotage it.”

Catalona denies it was sabotage; he says many men who had been enrolled in a PSA study of his in St. Louis “subsequently enrolled in the PLCO trial because it offered free chest X-rays and colonoscopies,” and half of them were randomized to the control arm. He’s also critical of the “innuendo” in Brawley’s book about screening advocates’ motives and finds it “remarkable” that Brawley, who is black, would be “biased against prostate cancer screening” because blacks are especially vulnerable to the disease. And so it goes.

“I think people like Gilbert Welch are throwing away the baby with the bath water,” Catalona says. He concedes that two decades ago U.S. medicine was overdoing prostate cancer treatment. (As Prasad puts it, “the country was punch-drunk on PSA.”) But he regrets the USPSTF’s 2012 decision to cease recommending routine PSA screening. “It’s creating a generation of family practitioners and internists who’ve been taught that screening for prostate cancer is a bad thing,” he says, with the result that “we’re now seeing many more men come in with advanced, incurable disease—we’re undoing the good that was done over the past 25 years.”

Catalona believes all reasonably healthy men should have a baseline PSA blood test for risk stratification, so that if their level later rises dramatically they can be checked out to make sure prostate cancer isn’t the cause. He also thinks screening critics are aiming their guns partly at the overtreatment of the past rather than the reality of screening today. “I’m actually going to agree with Bill Catalona on that one,” says Brawley, noting that as overtreatment goes down, screening’s benefit/harm ratio changes.

Does he also agree that a new wave of advanced prostate cancers is upon us?

“I don’t know,” Brawley says. “I have an open mind about that. But I do know that prostate cancer mortality is going down in 21 countries, only four of which have a lot of screening. So it seems to be declining at least partly for some reason other than screening and aggressive treatment of localized disease.”
By Zachary Hafner
Advisory Board

Last fall in Managed Care, I talked about opportunities to help “Joe” better meet the challenges of cancer care through an integrated care model, a concept strongly supported by rapidly evolving trends in the health care environment.

What a difference six months can make. The 2016 election has brought sea change to Washington, calling into question the future of the ACA, value-based payment models, and key tenets of value-based care itself. Even without the election, 2016 was an eventful year: MACRA was finalized, site-neutral payment solidified, and CMS-driven, oncology-specific payment reform was launched. While these factors do not fundamentally change key market pressures—such as increasing consumerism—they do potentially affect how payers and providers respond to those pressures.

So what does all of this mean for Joe and other cancer patients and the integrated care I was so optimistic about last year?

Historically, three generalizations held true for cancer patients: They were deferential to physician recommendations for care, unlikely to switch providers, and generally satisfied with the care they received. However, the rise of the consumer-oriented marketplace and growing customer financial exposure have led to better-informed patients who are more likely to shop for cancer care. This has led to a “borderless” competitive environment where access, transparency, brand, experience, outcomes, cost, and quality are differentiators that set one program apart from another.

Competition for more patients is intense. Significant investment is pouring into the development of cancer centers where research, diagnostics, treatment, and support services are co-located and coordinated, packaged with an exceptional customer service wrapper. This push to enhance the customer experience plays well in either fee-for-service or fee-for-value constructs, and—interestingly—has been a boon for top-rated cancer programs, which are expanding rapidly through arrangements where they lease their brands to regional providers.

On the funding front, two key trends have particular relevance to the development of integrated cancer programs: continued growth in the self-funded employer market and booming expansion of Medicare Advantage. Both shift financial risk from traditional stakeholders to new ones, and these new stakeholders have demonstrated critical differences in thinking from their predecessors. They appreciate the “total cost of care” concept. Anyone taking on financial risk in health care quickly discovers that a small number of individuals typically drive a significant portion of total spend in any given year, so they are motivated to prevent costly acute episodes, even if it means making upfront investments in new capabilities to do so. While today’s integrated cancer centers are not typically known for low unit costs, reducing total cost of care is one of their key objectives. They are also willing to narrow the provider network. For those providers that are able to demonstrate a real value proposition that includes lower total cost of care, this trend is of paramount importance and will play a key role in driving future growth.

Room to innovate

In recent years, payers and providers have also made huge investments in tools and technologies to better coordinate and manage care. For all the dollars spent, few have enjoyed commensurate gains in market position. This may not seem surprising—when everyone is making similar investments it amounts to basically keeping up with the pack. Perhaps, more importantly, the level of true innovation (and integration) has been low. This presents an opportunity for payers to redesign how their investments are put to use in ways that monetize benefits through clear wins for the customer.

So, back to the outlook for our friend Joe. It is clear quite a bit has changed over the past six months. The incentives motivating key market players look a lot different than they did not long ago. Despite this, the argument for building integrated, effective cancer programs remains strong. And that should give Joe—and all of us—great hope for the future.

Zachary Hafner leads the Advisory Board’s strategy consulting practice.
The use of real-world evidence (RWE) by clinicians and drug manufacturers is rapidly unfolding in oncology. RWE has the potential to provide oncologists with fresh insights into treatment decisions, given the wide variation in patients’ responses to medications. Drug manufacturers are also expanding their use of RWE in oncology through risk contracting with payers, in drug discovery, and to identify unmet therapy needs. RWE is also coming into play in pharma’s health economics and outcomes research (HEOR) programs, as companies seek to demonstrate the value and comparative effectiveness of their products.

But RWE is a relatively new kid on the block, and it has its own real-world challenges. How exactly it will fit into the complicated world of cancer drug testing is just many of the questions that come to the fore.

**By Thomas Reinke**
*Contributing Editor*

The cancerLinQ program, launched in November 2014, is set up as a wholly owned, not-for-profit subsidiary of ASCO to allow data-sharing partnerships with health care providers and business relationships with drug companies. So far, about 80 health systems and 2,000 oncologists are using the network, and it now includes a database of about 2 million patient records. More than 100 additional practices have expressed interest in joining, says CEO Kevin Fitzpatrick, a former executive vice president of the American College of Cardiology.

The LinQ in CancerLinQ stands for “learning intelligence network for quality.” Fitzpatrick describes it as a rapid learning system for medical oncologists. Each practice’s EHR is connected to the network so it can capture both clinical and business data. The network’s platform allows oncology practices to analyze detailed information about their own patients while giving them access to de-identified data for every other patient in the network. The hope is that the analytics will produce insights into practice patterns, the efficacy and cost effectiveness of therapy regimens, and safety issues. With CancerLinQ, ASCO has created a tightly integrated data collection, filtering, curation, and reporting platform. It captures text from unstructured notes in EHRs and uses natural language tools to process that information. But to improve the quality of the data, it goes a step further and has trained clinical staff who review and curate questionable text.

CancerLinQ is expanding beyond medical oncology. “We are looking to establish a database and analytic engine that provides a 360-degree view of the patient journey,” says Fitzpatrick. CancerLinQ is collaborating with other specialty societies, including the ones for radiation oncology, pathology, surgery, and pharmacy. “We see ourselves as a utility for the entire cancer community.”

Real-world data will be made available to other specialties and organizations, including drug companies, the FDA to develop a program for incorporating RWE into its activities.

**Lots of sharing**

In many ways, ASCO is setting the standard for data collection, curation, analysis, and reporting of RWE with its CancerLinQ program. Launched in November 2014, CancerLinQ is set up as a wholly owned, not-for-profit subsidiary of ASCO to allow data-sharing partnerships with health care providers and business relationships with drug companies. So far, about 80 health systems and 2,000 oncologists are using the network, and it now includes a database of about 2 million patient records. More than 100 additional practices have expressed interest in joining, says CEO Kevin Fitzpatrick, a former executive vice president of the American College of Cardiology.

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Real-world data will be made available to other specialties and organizations, including drug companies,
through CancerLinQ Discovery, a data repository for researchers, clinicians, and life science companies, Fitzpatrick says. When CancerLinQ announced Discovery, it also announced a nonexclusive strategic relationship with AstraZeneca, which is supporting the effort and will have access to the database for its own business purposes.

Hungry for RWE

Drug companies have a growing appetite for RWE because it gives them an understanding of their products beyond the womb of the randomized clinical trial and across their entire life cycles. Cardinal Health Specialty Solutions, the specialty drug consulting division of Cardinal Health, partners with drug companies to conduct HEOR studies using real-world data. Bruce Feinberg, DO, the chief medical officer of Cardinal’s specialty drug division, says oncology RWE helps drug companies and other stakeholders gain insights into the cost of care and resource utilization of a typical patient. RWE may also reveal aspects of care and a drug’s use that were rare or didn’t occur in the more limited circumstance of a clinical trial, he says.

In one study for a drug manufacturer, Cardinal looked at the comparative effectiveness of several kidney cancer therapies using claims data to identify patterns of care and resource utilization, including emergency room visits and hospitalizations. It found a statistically significant difference between leading kidney cancer therapies in the number of patients that had an emergency department visit during their first-line treatment. That type of real-world data is important as a potential safety signal for further research and also in demonstrating value to payers, Feinberg notes.

RWE is definitely trendy. Kevin Carr, MD, with PricewaterhouseCoopers, warns that it’s easy to get in over your head. “The hard part of RWE is understanding the data set that is truly required to answer a question,” says Carr. Information technology makes it relatively easy these days to mine huge amounts of data from EHRs, claims data, and other sources. The problem comes with building a database that is reliable and complete. Carr has seen projects shut down because the underlying information was inaccurate, incomplete, or otherwise unreliable. There’s simply no escaping the ironclad rule of garbage in, garbage out. Moreover, real-world studies are complex. They require complete records with multiple data fields that can be cross-tabulated, such as patient age, diagnosis, and medication dose. When complete records are not available, databases on which RWE is built get shaky.

FDA staffers, including then-commissioner Robert Califf, sounded a warning about shoddy RWE in an opinion piece in the Dec. 8, 2016, issue of the New England of Journal Medicine. “The confluence of large data sets of uncertain quality and provenance, the facile analytic tools that can be used by nonexperts, and a shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions,” they wrote.

Looking before they leap

Partly because of the 21st Century Cures ACT, RWE seems poised to become an increasingly important part of the regulatory oversight of drugs. But so far, neither ASCO nor NCCN is using RWE in the development of clinical guidelines. NCCN Senior Vice President Joan McClure says two categories of real-world data may become relevant to guideline development, while the use of a third remains more questionable. One of the two likely categories is patient-reported outcomes related to quality of life and the tolerability of regimens. Another is pharmacovigilance and the tracking of rare adverse events or toxicities that aren’t fully understood. For example, McClure says diarrhea from immunotherapy may be different from diarrhea from traditional chemotherapy, and RWE might help physicians make decisions about how to manage the two problems differently.

The RWE trouble spot might be in the crucial area of efficacy. McClure explains that efficacy data from real-world studies is problematic because of the likelihood of some built-in biases and limitations. Many factors go into a physician’s selection of a therapy, and they will be hard to capture in EHRs. As a result, efficacy data culled from EHRs may not include important information that affected treatment choices, and that blind spot may affect the efficacy data. 

Efficacy data generated through real-world studies may seem to be useful in guideline development, but NCCN VP Joan McClure says built-in biases and limitations make it problematic.
As components of the adaptive immune system, ordinary T cells are formidable defenders. They recognize non-self antigens (e.g., peptide remnants of viruses or intracellular bacteria that have infected a cell) presented to them on the cell surface by major histocompatibility complex (MHC) glycoproteins, and then wield a variety of defensive countermeasures. T cells can destroy cancer cells, too, but cancer has ways of suppressing the MHC mechanism.

In the context of cancer, what could a souped-up, bioengineered T cell made from the patient’s own T cells accomplish? A mighty cell (or, if you prefer, for an autologous product, my T cell), that would recognize cancer cells by antigens on their surface and then destroy them, independent of MHC.

Such agents exist and are known as chimeric antigen receptor (CAR) T cells, which is one of several types of adoptive cell therapy (see the Glossary on page 45). Researchers have been working on them for decades, and one, being developed by Kite Pharma in Santa Monica, Calif., is expected to receive FDA approval by the end of 2017. Additional CAR T cells under development at Novartis and Juno Therapeutics may be approved soon, too. (See Table 1 on page 38 for a list of selected clinical trials of CAR T-cell therapy that are underway.)

Judging by remarks made by representatives and observers of the pharmaceutical industry during the past few years (see box at right), CAR T cells are the next big thing in oncology—so much so that some proponents have not been shy about saying “cure” when they discuss CAR T cells. In a presentation in March 2017, “Focused on the Cure,” Kite Pharma told investors that its in-house clinical manufacturing facility is fully operational and can produce more than 4,000 patient therapies per year, using a process that takes about 16 to 18 days per therapy. Kite has even trademarked a term, eACT, which stands for engineered autologous cell therapy, to encompass CAR T cells and related products.

Several of the pharmaceutical companies in the forefront of this field have forged partnerships with academic institutions (see Table 3 on page 41), and their academic partners have been more circumspect in their remarks.

CAR T cells have been described as “living drugs” with supraphysiologic properties (Sadelain 2013). They also have been explained as simultaneously incorporating cellular therapy, immunotherapy, and gene therapy. The therapy is delivered by infusion of T cells (cellular therapy) that spurs an immune response to cancer cells (immunotherapy), and genetic modification via viral vectors (gene therapy) triggers a stronger, more targeted immune response. From another perspective, CAR T cell therapy weaves together three therapeutic strategies: transplantation, vaccination, and engineered antibodies (Lim 2017).

Early versions
The first CAR T cell was described in 1993. They’ve now gone through three generations of refinement, with more generations envisioned.

CAR T cells are modular, and the molecular engineers who assemble them have countless combinations to choose from. They can be programmed to recognize antigens specific to a tumor, as opposed to those shared by normal cells. They can also be equipped with different signaling domains to control their activity.”

Hope, hype, and high expectations
“CAR T cells merge into the fast lane of cancer care.”
— Headline in the American Journal of Hematology, January 2016

“[This] technology… is expected to grow at a double-digit growth rate, creating a multibillion absolute dollar opportunity for industry players in the near future.”
— Coherent Market Insights, March 2017

“I think that a cure for cancers such as leukemia and lymphoma through a CAR technology is plausible.”
— Usman Azam, MD, then head of Novartis’s Cell and Gene Therapies Unit, quoted by Wall Street Journal, October 2014

“While poised to revolutionize cancer therapy, the optimism and T cell cancer therapies remains tempered by concerns about safety and off-target toxicity, as well as the development of resistance. Meanwhile, the field also awaits a clear demonstration of clinical efficacy in solid tumors.”
— Wendell Lim (University of California–San Francisco) and Carl June (University of Pennsylvania), writing in Cell (Feb. 9, 2017)
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<tr>
<td>ZUMA-3</td>
<td></td>
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</tr>
<tr>
<td>NCT02625480</td>
<td>axicabtagene</td>
<td>CD19</td>
<td>ALL (pediatric, young adult)</td>
<td>1/2</td>
<td>75</td>
<td>Kite Pharma</td>
<td>Dec. 2015 June 2017</td>
</tr>
<tr>
<td>ZUMA-4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02926833</td>
<td>axicabtagene, atezolizumab</td>
<td>CD19</td>
<td>DLBCL</td>
<td>1/2</td>
<td>31</td>
<td>Kite Pharma, Genentech</td>
<td>Sept. 2016 June 2018</td>
</tr>
<tr>
<td>ZUMA-6</td>
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<td></td>
</tr>
<tr>
<td>NCT02445248</td>
<td>CTL019 (tisagenlecleucel-T)</td>
<td>CD19</td>
<td>DLBCL</td>
<td>2</td>
<td>130</td>
<td>Novartis</td>
<td>July 2015 Jan. 2024</td>
</tr>
<tr>
<td>JULIET</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT02435849</td>
<td>CTL019 (tisagenlecleucel-T)</td>
<td>CD19</td>
<td>ALL</td>
<td>2</td>
<td>72</td>
<td>Novartis</td>
<td>April 2015 Jan. 2023</td>
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<tr>
<td>ELIANA</td>
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<td>NCT02535364</td>
<td>JCAR015</td>
<td>CD19</td>
<td>ALL</td>
<td>2</td>
<td>110</td>
<td>Juno</td>
<td>Aug. 2015 March 2018 (suspended)</td>
</tr>
<tr>
<td>ROCKET</td>
<td></td>
<td></td>
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<tr>
<td>NCT02706405</td>
<td>JCAR014, durvalumab</td>
<td>CD19</td>
<td>B-cell NHL (DLBCL, MBCL)</td>
<td>1b</td>
<td>42</td>
<td>FHCRC; AstraZeneca, Juno, MedImmune, NCI</td>
<td>Nov. 2016 Dec. 2019</td>
</tr>
<tr>
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<tr>
<td>NCT02631044</td>
<td>JCAR017</td>
<td>CD19</td>
<td>NHL, DLBCL, FL, MCL, PMBCL</td>
<td>1</td>
<td>144</td>
<td>Juno</td>
<td>Dec. 2015 Jan. 2018</td>
</tr>
<tr>
<td>TRANSCEND</td>
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<tr>
<td>NCT02028455</td>
<td>JCAR017</td>
<td>CD19</td>
<td>Acute leukemia (age 1–26 years)</td>
<td>1/2</td>
<td>80</td>
<td>Seattle Children’s Hospital</td>
<td>Jan. 2014 Jan. 2020</td>
</tr>
<tr>
<td></td>
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<tr>
<td>NCT02315612</td>
<td>JCAR018</td>
<td>CD22</td>
<td>FL, ALL, NHL, LCL (age 1–30 years)</td>
<td>1</td>
<td>57</td>
<td>NCI</td>
<td>Nov. 2014 June 2017</td>
</tr>
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<td></td>
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<tr>
<td>NCT02311621</td>
<td>JCAR023</td>
<td>CD171</td>
<td>Neuroblastoma, ganglioneuroblastoma</td>
<td>1</td>
<td>40</td>
<td>Seattle Children’s Hospital</td>
<td>Nov. 2014 Nov. 2017</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>NCT02706392</td>
<td>JCAR024</td>
<td>ROR-1</td>
<td>Cohort 1: CLL, MCL, ALL; Cohort 2: stage 4 NSCLC, metastatic TNBC</td>
<td>1</td>
<td>60</td>
<td>FHCRC, NCI</td>
<td>March 2016 Dec. 2021</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>NCT02498912</td>
<td>JCAR020</td>
<td>MUC16</td>
<td>MUC16+ solid tumors</td>
<td>1</td>
<td>30</td>
<td>MSKCC, Stanford, Juno</td>
<td>Aug. 2015 Aug. 2018</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>NCT02746952</td>
<td>UCART19 (allogeneic)</td>
<td>CD19</td>
<td>ALL, CLL (age ≥16 years)</td>
<td>1</td>
<td>12</td>
<td>Servier</td>
<td>Aug. 2016 June 2018</td>
</tr>
<tr>
<td>CALM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02808442</td>
<td>UCART19 (allogeneic)</td>
<td>CD19</td>
<td>ALL (age 6 mos. –17 years)</td>
<td>1</td>
<td>10</td>
<td>Servier</td>
<td>June 2016 July 2019</td>
</tr>
<tr>
<td>PALL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02658929</td>
<td>bb2121</td>
<td>BCMA</td>
<td>MM</td>
<td>1</td>
<td>50</td>
<td>bluebird bio</td>
<td>Jan. 2016 Dec. 2018</td>
</tr>
</tbody>
</table>

This table shows selected clinical trials of CAR T-cell products that are in progress and sponsored by pharmaceutical companies and their collaborators that are in the forefront of this field. In 2015, Kite launched four pivotal trials, ZUMA-1 through ZUMA-4, aimed at winning FDA approval for its lead product, axicabtagene (axi-cel, also known as KTE-C19). Through these trials, Kite hopes to secure indications for several types of NHL. ZUMA-5, ZUMA-7, and ZUMA-8 (not listed) are expected to begin in 2017, enrolling patients with NHL, DLBCL, and CLL, respectively.

a. Unless noted, all conditions are relapsed or refractory.


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Chimeric Antigen Receptor T-Cell Therapy

consider. The critical modules are the extracellular antigen-binding components, which, in theory, can target any molecule that can be bound by a monoclonal antibody, and the intracellular components that transmit signals inside the cell upon binding of the antigen. One of the early versions of a CAR T cell incorporated only those two components and consisted of a single polypeptide chain of an extracellular binding module (known as the single-chain variable fragment, or scFv) fused directly to an intracellular signaling module. Another first-generation design inserted a hinge module between the antigen-binding module and the intracellular signaling domain. These and other first-generation CAR T cells were biologically active, but they didn’t eradicate tumors efficiently in preclinical studies. Researchers learned that CAR T cells relying upon a single signaling domain, CD3-zeta (CD3ζ) couldn’t produce complete T-cell activation and expansion (Daniyan 2016).

To address this problem, CAR T-cell designers adopted the approach employed by native T cells and developed CAR T cells with a co-stimulatory signal for T-cell activation. Second-generation CAR T cells contain a co-stimulatory domain derived from either CD28 or CD137 (4-1BB), which is fused into the polypeptide chain just before the CD3ζ signaling domain. Third-generation CAR T cells contain two or more additional co-stimulatory domains, but it remains to be seen whether third-generation T cells are superior to second-generation T cells (Daniyan 2016).

As the field advances, researchers may add, subtract, and otherwise tinker with CAR T cells as they look for ways to improve response rates while also improving the safety profile of CAR T cells. Safety concerns often arise from “on target, off tumor” adverse effects that occur when the target is found on normal, healthy cells as well as cancerous ones.

**Hitting the target**

The ideal target for CAR T cells would be an antigen found on the surface of cancer cells—and on all of them, not just a subpopulation of the cancer in question—and nowhere else. But such a target does not seem to exist. Often antigens found on cancer cells occur on normal cells as well. And the antigens that are special to a cancer often aren’t found on all the cancerous cells, so they aren’t recognized and elude

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve response to CAR T-cell therapy</td>
<td>Strengthen intracellular signaling by complementing the single singling domain (e.g., CD3ζ) of a first-generation CAR with a second intracellular signaling module such as CD28 or CD137 (second-generation) Add two or more intracellular signaling modules (third-generation)?</td>
</tr>
<tr>
<td>Improve expansion of CAR T cells</td>
<td>Add hinge domain between extracellular and intracellular modules</td>
</tr>
<tr>
<td>Address cytokine release syndrome (CRS)</td>
<td>Treat severe CRS (life-threatening) with tocilizumab (IL-6 receptor antagonist) Administer tocilizumab before IL-6 reaches peak level? Treat patient with CAR T-cell therapy before disease burden becomes high? Employ tool to predict which patients are likely and unlikely to develop severe CRS?</td>
</tr>
<tr>
<td>Address on-target, off-tumor adverse effects</td>
<td>Replenish antibodies via IVIG when CD19 (found on cancerous and healthy B cells) is the target Use AND- or NOT-gate circuits to spare healthy cells while killing cancer cells that bear the same target antigen? Add “suicide switch” to CAR T cells that can be activated by physician to eliminate T cells in event of emergency?</td>
</tr>
<tr>
<td>Prevent resistance to CAR T-cell therapy</td>
<td>Employ engineered receptors that can recognize two different antigens found on the cancer cells? Administer combination therapy or sequential therapy targeting antigen that persists on cancer cells despite loss of original target?</td>
</tr>
<tr>
<td>Increase rate of durable complete responses</td>
<td>Administer CAR T-cell therapy while disease burden is low</td>
</tr>
<tr>
<td>Treat solid tumors</td>
<td>Create “armored” CAR T cells endowed with genes that express anti-cancer cytokines (e.g., IL-12, IL-18) to facilitate tumor penetration? Employ synNotch T cells customized to express molecules that enhance killing by the CAR component or alter the tumor microenvironment? Use dual-specific T cells activated by a vaccine?</td>
</tr>
<tr>
<td>Expense of autologous product</td>
<td>Use allogeneic product?</td>
</tr>
<tr>
<td>Time to prepare autologous product</td>
<td>Use allogeneic product?</td>
</tr>
</tbody>
</table>
Patients with such advanced B-cell malignancies as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The target antigen, CD19, is found only on B cells, both cancerous and normal B cells. When the normal B cells are destroyed by CAR T cells targeting CD19, intravenous immune globulin can replenish the supply. Moreover, clinicians regard the continued presence of B-cell aplasia (the absence of CD19+ cells) as a welcome sign because it shows that the CAR T-cell therapy still works (Barrett 2015).

**Boolean logic**

Further improvements in efficacy, and especially in safety, may arise from the addition of more modules to T cells, specifically a second chimeric antigen receptor that creates a gated circuit. The Boolean operators AND, NOT, and OR have been used to classify such circuits (Lim 2017).

**AND-gate circuits.** In AND-gated design, CAR T cells are given receptors that target two different antigens on a cancer cell in order to make them more likely to destroy only cancer cells. The problem has been that binding of a single antigen still has been enough to activate the CAR T cells, jeopardizing normal cells that bear that antigen. In one design, one receptor contains the usual CD3ζ signaling domain while the other contains a different co-stimulatory signaling domain. The idea is that full activation of the CAR T cell will occur only when both receptors have bound with their different targets on the cancer cell.

A different AND-gate circuit features a dual-receptor design. Upon binding to its target, one receptor acts as a primer. Instead of activating the T cell as ordinary CAR T cells do, it triggers the release of an intracellular transcription factor that migrates to the nucleus and causes the T cell to express a second chimeric receptor. Upon binding to a different target antigen, this receptor stirs the T cell into action so that it destroys the cancer cell (Roybal 2016). This new class of receptors is known as synthetic Notch (synNotch) receptors, named for a chimeric Notch receptor. It has been shown in preclinical studies that synNotch AND-gate T cells can discriminate between tissues bearing two target antigens and those bearing only one (Morsut 2016). That means if a pair of antigens can be identified that is particular to a given...
type of cancer cells, AND-gated CAR T-cell therapy could be designed to home in on cancer cells while leaving other normal cells with just one of the antigens alone.

**NOT-gate circuits.** Another strategy to spare normal cells bearing an antigen that also is found on cancer cells is to create CAR T cells featuring a NOT-gate circuit. In this design, one chimeric antigen receptor that targets an antigen on cancer cells (and, problematically, on some normal cells) and contains the expected intracellular signaling domain that activates the T cell while another chimeric antigen receptor targets a different antigen found only on the normal cells. In contrast to its mate with T-cell activating potential, the second chimeric receptor antigen contains a signaling domain derived from inhibitory receptors such as PD-1 or CTLA-4 (Fedorov 2013). When a CAR T cell designed this way encounters a normal cell bearing both target antigens, the inhibitory signaling prevents or diminishes T-cell activation. But, at least in theory, if it encounters a cancer cell that lacks the antigen that triggers inhibitory signaling, the T cell is fully activated and the cancer cell is destroyed.

These AND- and NOT-gated approaches, which are aimed at preventing on-target, off-tumor adverse effects, should be safer than administration of high-dose corticosteroids or resorting to “suicide switches”—modules inserted into CAR T cells that can trigger T-cell apoptosis in the event of an emergency such as a severe case of cytokine release syndrome (CRS). CAR T cells have been designed that incorporate CD20 or EGFRt as such switches; administration of rituximab (Rituxan) and cetuximab (Erbitux) targets each, respectively, and destroys the cell. Another method of controlled CAR T-cell destruction employs an enzyme, caspase-9, that is activated by administration of a small-molecule drug, rimiducid.

**OR-gate circuits.** One mechanism by which resistance to CAR T-cell therapy can emerge is loss of the target antigen by cancer cells. A strategy to prevent this from occurring may be to design CAR T cells with chimeric receptors capable of binding with either of two distinct antigens found on the cancer cell. Malignant B cells can become resistant to CAR T-cell therapy targeting CD19 by ceasing to express CD19, so a CAR T cell that targeted an additional antigen specific to the B cells, such as CD22, might be a way of dealing with this resistance.

### table 3: Collaborations between academia and industry to advance CAR T-cell therapy

<table>
<thead>
<tr>
<th>Institution</th>
<th>Pharmaceutical company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor College of Medicine</td>
<td>bluebird bio</td>
</tr>
<tr>
<td></td>
<td>Celgene (also collaborates with bluebird)</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center</td>
<td>Juno Therapeutics</td>
</tr>
<tr>
<td>Leukemia &amp; Lymphoma Society</td>
<td>Kite Pharma</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Juno Therapeutics</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>Kite Pharma</td>
</tr>
<tr>
<td>Seattle Children’s Hospital</td>
<td>Juno Therapeutics</td>
</tr>
<tr>
<td>Tel Aviv Sourasky Medical Center</td>
<td>Kite Pharma</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Novartis</td>
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<tr>
<td></td>
<td>Tmunity Therapeutics</td>
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</tbody>
</table>

**Taking on solid tumors**

If CAR T-cell therapy is to become a major advance in cancer treatment, it will need to demonstrate that it is safe and efficacious in the treatment of patients with solid tumors. In addition to providing a nearly ideal target (CD19), the B-cell malignancies against which CAR T-cell treatments have been most effective exist in an environment where CAR T cells enjoy relatively easy access to the cancerous cells. The microenvironment created by solid tumors is far more hostile to T cells (Wu 2015). Solid tumors make it more difficult for T cells to infiltrate the tumor in the first place. If T cells manage to breach that defense, cells in solid tumors are equipped to impede the survival, proliferation, and function of T cells and induce T-cell apoptosis by upregulating proteins such as PD–L1. Since checkpoint inhibitors against PD–L1 and its receptor found on activated T cells, PD-1, are in clinical use to treat malignant melanoma and lung cancer, a logical approach would be to combine these drugs with CAR T cells (Lim 2017).

Recent preclinical studies using a murine model have suggested that dual-specific T cells may warrant further study for treating patients with solid tumors. A viral vaccine was administered to activate T cells bearing a TCR for an antigen delivered by the vaccine. The T cells also were given a CAR for HER2. This approach resulted in durable complete remission of various HER2+ tumors and their metastases, even though the mice also had normal tissues (breast, brain) expressing HER2 (Slaney 2017).

**Efficiency gains**

Currently, most CAR T-cell therapy depends on using the patient’s own T cells. The autologous approach means the therapy has to be prepared on an individual, patient-by-patient basis. It is a time-consuming and labor-intensive process that takes from five
Chimeric Antigen Receptor T-Cell Therapy

were or were not most likely to develop severe CRS (Teachey 2016). As in the ALL trials mentioned above, the rate of complete response was high: 90% among the first 30 patients (25 adults, five children) (Maude 2014). All 30 patients had CRS, and 94% (48/51) of the larger group had CRS (Figure). The 14 patients with severe CRS were treated with tocilizumab, as were seven of the 15 patients with moderate CRS. Patients responded rapidly to tocilizumab. Twelve patients also received corticosteroids and two received etanercept (Enbrel).

Although ALL disease burden at the time of infusion had been thought to correlate with the degree of CRS severity, that hypothesis didn’t hold up: low disease burden was found to have strong negative predictive value, but high disease burden lacked strong positive predictive value. Instead, after comparing the cytokine profiles (cytokine encompassing 43 cytokines, chemokines, and soluble receptors) of

A more efficient approach might be the use of allogeneic CAR T cells prepared with T cells from a single donor and used as an off-the-shelf treatment for multiple patients. Pfizer and Servier are testing such a product, UCART19, in clinical trials (see Table 1 on page 38). Another allogeneic CAR T-cell product (Cellectis) targeting CD123 was expected to begin phase 1 trials in 2017.

Avoiding adverse events

In addition to all the steps needed to prepare CAR T-cell therapy, patients are often treated with lymphocyte-depleting chemotherapy to eliminate cells that would compete with the infused CAR T cells for growth factors. And after the CAR T-cell infusion, patients must be monitored for the development of adverse effects, notably CRS. When large numbers of CAR T cells are infused, they secrete a flood of cytokines that not only kill targeted cancer cells but also trigger CRS, a systemic inflammatory response that presents as a flu-like malady, usually emerging within one to five days of the infusion. CRS is mild in some but life-threatening in others. Patients with CRS may develop hypotension, decompensated shock, renal insufficiency, and respiratory distress. In severe cases, mechanical ventilation and aggressive vasopressor treatment is required. Some patients also develop self-limited neurotoxicity that may be a manifestation of CRS.

In three phase 1 trials enrolling patients with relapsed ALL who were treated with CAR T cells targeting CD19, complete responses were observed in 67% (N=21), 88% (N=16), and 90% (N=30) of patients. CRS was reported in 100% of patients in two of these trials (N= 16, N=30) and in 76% in the third trial (N=21) (Oluwole 2016). Most cases of CRS were mild (56% to 73%). All were reversible with no therapy-related mortality reported. Tocilizumab (Actemra), corticosteroids, or both were used to treat most of these patients.

Using data from two clinical trials that enrolled 51 patients with refractory or relapsed ALL (an adult cohort of 12 patients and a pediatric and adolescent cohort of 39 patients, ages 5–23) who were treated with CTL019, researchers recently developed a tool to predict which patients were or were not most likely to develop severe CRS (Teachey 2016). As in the ALL trials mentioned above, the rate of complete response was high: 90% among the first 30 patients (25 adults, five children) (Maude 2014). All 30 patients had CRS, and 94% (48/51) of the larger group had CRS (Figure). The 14 patients with severe CRS were treated with tocilizumab, as were seven of the 15 patients with moderate CRS. Patients responded rapidly to tocilizumab. Twelve patients also received corticosteroids and two received etanercept (Enbrel).

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all the patients, they found that peak levels of 24 cytokines were statistically significantly associated with severe CRS (grades 4–5) compared with less severe CRS (grades 0–3).

For predicting which patients were likely to be at low risk of CRS, two cytokines, IFNγ and sgp130, stood out because they peaked during the first three days after infusion and before patients became critically ill (usually triggering treatment with tocilizumab). For the combined adult and pediatric cohorts, the top logistic-regression predictive model had 86% sensitivity and 89% specificity, using Day-3 peak levels of sgp130, IFNγ, and IL-1RA. For the pediatric cohort, the top logistic-regression model had 100% sensitivity and 96% specificity using Day-3 peak levels of IFNγ, IL-13, and MIP-1α. Although IL-6 (the target of tocilizumab) is strongly associated with CRS over the first month after infusion, its levels change little during the first three days after infusion.

The next step would be to use these and other predictive models in clinical trials to determine whether early intervention in patients at high risk of CRS adversely affects the efficacy of CAR T-cell therapy. If early intervention does not impair the efficacy of CAR T-cell treatment, high-risk patients could be monitored and treated in time to preclude the development of life-threatening complications.

Autologous CAR T-cell therapy is likely to be priced very high, so anything that reduces the risk of severe adverse events and the costs associated with treating them will be appealing to those attempting to manage costs. In addition, better understanding of the biology of CRS and its treatment could help move CAR T-cell therapy beyond specialized centers. The development of allogeneic products could also help widen the use of CAR T-cell therapy and possibly lower its price.

The future for CAR T
At this point, it remains to be seen how widely CAR T-cell therapy will be used. One fork in the road will have it restricted to a relatively small group of patients with advanced leukemia and lymphoma, such as those with advanced B-cell malignancies who have exhausted all other treatment options. Another will find it to be safe and efficacious in the treatment of a wide range of other malignancies, especially solid tumors. There are other forks—and branches off those forks—that CAR T-cell therapy might take.

Of course, healthy skepticism about next-big-things in cancer treatment is wise. For instance, it is not unusual for innovative treatments to produce dramatic results in a narrow group and out because they peaked during the first three days after infusion and before patients became critically ill (usually triggering treatment with tocilizumab). For the combined adult and pediatric cohorts, the top logistic-regression predictive model had 86% sensitivity and 89% specificity, using Day-3 peak levels of sgp130, IFNγ, and IL-1RA. For the pediatric cohort, the top logistic-regression model had 100% sensitivity and 96% specificity using Day-3 peak levels of IFNγ, IL-13, and MIP-1α. Although IL-6 (the target of tocilizumab) is strongly associated with CRS over the first month after infusion, its levels change little during the first three days after infusion.

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The Penn–Novartis connection
Novartis and Penn have strong ties. They joined forces in 2012 to speed development and commercialization of CAR T-cell therapy. Penn's Perelman School of Medicine now houses the Novartis–Penn Center for Advanced Cellular Therapeutics, which opened in February 2016 to enhance Penn's substantial program in CAR research. Novartis gave Penn $20 million to support the new center, and Penn gave Novartis an exclusive worldwide license to CTL019 and future CAR-based therapies developed through the collaboration.

This collaboration developed because the first person to receive an investigational CAR T-cell therapy, developed by Carl June, MD, Penn's star immunologist, and colleagues, was treated at the Hospital of the University of Pennsylvania in 2010. At the time he enrolled in the small pilot study, the 65-year-old patient, Bill Ludwig, had run out of options for treating his advanced chronic lymphocytic leukemia. The trial itself was on financial life support, too, until the Alliance for Cancer Gene Therapy, founded by a Penn alumnus and his wife, came through to support the phase 1 study (Popp 2015).

Two weeks after receiving the new treatment—CTL019 (tisagenlecleucel-T)—Ludwig's condition began to decline, as he experienced chills, fever, and fatigue. He deteriorated to the point that ICU clinicians summoned Ludwig’s family to his bedside because he wasn’t expected to live through the night (Popp 2015). Instead of dying, however, Ludwig rallied, and soon he was discovered to be in complete remission. Two other patients were enrolled in the pilot study. One achieved a complete remission and the other a partial remission. Then the money ran out. So June and his colleagues published their findings in a brief report in the New England Journal of Medicine (Porter 2011) and in an article in Science Translational Medicine (Kalos 2011). The pair of articles led to additional funding to support further clinical research, and the collaboration with Novartis soon followed.

Ludwig was still in complete remission when the Novartis–Penn center opened in February 2016, an event that he attended. The disbanding of the Novartis unit does not affect its collaboration with Penn, which continues, and Novartis says the company remains committed to CAR T-cell therapy and related emerging therapies, including its lead CAR T-cell product, CTL019 (Carroll 2016a). Indeed, in late March 2017 the FDA accepted Novartis’s filing for a Biologics License Application and granted CTL019 priority review for treatment of pediatric and young adult patients with relapsed and refractory B-cell ALL. These actions were supported by the results of ELIANA, a phase 2 trial sponsored by Novartis as the first global study of a CAR T-cell therapy, enrolling 57 patients at 25 centers (Grupp 2016).


Coined to encompass CAR T cells and related cellular therapies such as tumor-infiltrating lymphocytes (TIL) and T-cell receptors (TCRs).

**Adaptive immune system.** Defense employing two types of antigen-specific lymphocytes, B cells and T cells. B cells produce antibodies that combat pathogens in blood plasma and extracellular fluids. T cells combat intracellular pathogens (all viruses, some bacteria and parasites), which can’t be detected by antibodies.

**Axicabtagene ciloleucel** (axi-cel; Kite Pharma). Also known as KTE-C19. CAR T-cell therapy targeting CD19. In late stages of development; FDA approval anticipated in late 2017, likely as first in class.

**ALL** (acute lymphoblastic leukemia), acute lymphocytic leukemia. Originates in immature lymphocytes in bone marrow, then quickly spreads into blood and beyond (lymph nodes, liver, spleen, CNS). For 2017, ACS estimates 5,970 new cases of ALL and 1,440 deaths in the United States.

**AML** (acute myeloid leukemia). Cancer of bone marrow and blood that progresses rapidly without treatment, primarily affecting cells that aren’t fully developed. Accounts for about a third of all cases of adult cases of leukemia in the United States. For 2017, ACS estimates 21,380 new cases, mostly in adults, and 10,590 deaths, nearly all in adults.

**bb21.** Investigational autologous CAR T-cell therapy being developed as treatment for multiple myeloma by bluebird bio. Targets B-cell maturation antigen.

**B cells.** Together with T cells, a lymphocyte that is a mainstay of the adaptive immune system, mediating the humoral response involving antibodies.

**BPDNCN (blastic plasmacytoid dendritic cell neoplasm).** Formerly natural killer cell leukemia/lymphoma. Form of AML, usually with features of lymphoma and leukemia. No established first-line treatment. No current treatments result in prolonged remission.

**CD3-zeta (CD3ζ).** A component of T-cell receptors (TCR) that is nearly always present. In CAR T cells, CD3 ITAMs are a very commonly employed module for signal transduction, in conjunction with one or more co-stimulatory signaling modules.

**CD19.** Expressed on healthy and cancerous B cells alike. Acts a co-receptor with CD21 and CD81. Targeted by numerous investigational CAR T cells.

**CD20.** Expressed on B cells. Facilitates B-cell development and differentiation. Targeted by rituximab (Rituxan).

**CD22.** Expressed on most B-cell malignancies, including ALL cancer cells that have lost CD19. Target of Juno’s JCAR018.

**CD28.** Co-stimulatory molecule used to enhance signaling power of CAR T cells.

**CD123.** Also known as IL-3Ra, as it is the IL-3 receptor α chain. Expressed on bone marrow stem cells, granulocytes, monocytes, megakaryocytes. Also expressed on malignant cells in AML and BPDNCN. Target of UCART123.

**CD137.** Also known as 4-1BB. Co-stimulatory molecule whose signaling domain has been used to enhance the signaling power and clinical effect of CAR T cells. Component of CART19 T cells developed by June and colleagues at University of Pennsylvania.

**CD171.** Also known as L1-CAM. Cell-surface adhesion molecule important for normal nervous system development but overexpressed in neuroblastoma.

**CLL (chronic lymphocytic leukemia).** Cancer cells in CLL are called small lymphocytes, found in blood and bone marrow. For 2017, ACS estimates 20,110 new cases and 4,660 deaths from CLL in the United States.

**IFNγ.** Cytokine produced by some T cells and natural killer cells. Activates macrophages. Produced at high levels in early days following CAR T-cell infusion. May help predict patients at high risk of CRS.

**IL-6 (interleukin 6).** Cytokine central to development and progression of inflammatory diseases, cardiovascular disease, and cancer.

**IL-13 (interleukin 13).** Produced by T cells, and at high levels in early days following CAR T-cell infusion. May help predict patients at high risk of CRS.

**ITAM (immunoreceptor tyrosine-based activation motif).** Intracellular portion of T-cell receptors essential for signaling, found in various CD3 chains. CD3ζ ITAMs are used in CAR T cells.

**JCAR015.** Investigational autologous CAR T-cell product targeting CD19 whose development was halted by Juno Therapeutics in March 2017 after 5 deaths from cerebral edema in phase 2 trial, enrolling patients with relapsed/refractory ALL.

**JCAR017.** Investigational autologous CAR T-cell product targeting CD19 being developed by Juno Therapeutics. Has different construct from JCAR015, such as 1:1 ratio of CD8+:CD4+ CAR T cells (vs CD3+ enriched peripheral blood mononuclear cells), CD28 co-stimulatory domain (vs CD137). Also incorporates ablative technology (“suicide switch”), truncated form of epidermal growth factor receptor (EGFRt) that can be targeted with cetuximab (Erbitux) if rapid killing of CAR T cells is required.

**JCAR018.** Juno’s investigational CAR T-cell product targeting CD22. CD22 is present on most B-cell malignancies but...
also persists on cancerous B cells that have lost CD19.

**JCAR020.** Juno’s investigational “armored” CAR T-cell product targeting MUC-16, a protein overexpressed in about 70% of ovarian cancers but not found on surface of normal ovary cells. Originally developed by Memorial Sloan Kettering Cancer Center.

**JCAR024.** Juno’s investigational CAR T-cell product targeting ROR-1, expressed on all CLL and MCL cells and in subsets of ALL and several solid tumors. Originally developed by Fred Hutchinson Cancer Research Center.

**KTE-C19.** Kite’s axicabtagene. leukocyte. Any white blood cell. lymphocyte. Class of white blood cells bearing variable receptors for antigens on their surface. The two main types are T cells and B cells.

**MCL** (mantle cell lymphoma). Represents about 5% of lymphomas. Most common in men (early 60s). Often advanced by time of diagnosis. Originates in lymphocyte in mantle zone of lymph node.

**MHC** (major histocompatibility complex). MHC class I molecules are cell-surface molecules that present intracellular antigenic peptides (fragments of pathogens that have entered the cell, such as viruses) to T cells bearing CD8. MHC class II molecules present T cells bearing CD4 with antigenic peptides that are fragments of extracellular pathogens that have been brought into the cell.

**MIP-1α** (macrophage inflammatory protein 1α). A proinflammatory chemokine. Expressed at high levels during first few days after CAR T-cell infusion; may help predict patients at high risk of cytokine release syndrome.

**MM** (multiple myeloma). Second-most prevalent hematopoietic malignancy. Results in excessive numbers of plasma cells in bone marrow, osteolytic bone lesions. Disease recurrence is common despite advances in treatment (5-year relative survival rate now 50%, vs 25% in 1977). ACS predicts 30,280 new cases (male, 58%) and 12,590 deaths (male, 52%) from MM in 2017.

**Neuroblastoma.** Cancer originating in neuroblasts of sympathetic nervous system. About a third begin in nerve-like cells in medulla of adrenal glands and about a fourth in the abdominal ganglia. Nearly always occurs in infants and children aged <10 years. Most common cancer in infants.

**NHL** (non-Hodgkin lymphoma). Seventh-leading cause of new cancer cases in US, representing about 4% of all cancers. Nearly always originates in B lymphocytes, found in lymph nodes and other lymphoid tissues (spleen, thymus, adenoids & tonsils, digestive tract, bone marrow). For 2017, ACS projects 72,480 new diagnoses and 20,140 deaths the United States.

**PD-1** (programmed death-1). Inhibitory receptor specifically expressed on activated T cells. Its signaling domain is being studied as a component in a novel approach to avoiding off-target immunotherapy responses. See also CTLA-4.

**PD-L1** (programmed death ligand-1). Receptor that binds to inhibitory receptor PD-1. Uplregulated by inflammatory cytokines. Inhibition of PD-L1 may enhance effectiveness of T cells attacking cancer cells.

**PMBCL** (primary mediastinal B-cell lymphoma). Subtype of DLBCL, representing 2% of all lymphomas. Named for site of origin (mediastinum, behind sternum). Most common in young women (30s).

**ROR-1.** Protein overexpressed on many cancer cells, including all B-cell CLL and MCL cells and a subset of NSCLC, TNBC, pancreatic cancer, prostate cancer, and ALL. Target of JCAR24.

**scFv** (single-chain variable fragment). Extracellular module of chimeric antigen receptor that lets it bind a specific antigen expressed on the surface of a cell). Upon binding to the scFv, intracellular signaling domains within the CAR T cell are triggered.

**sgp130** (soluble glycoprotein 130). Inhibitor of trans IL-6 signaling. High levels of sgp130 have been found in patients within a few days of CAR T-cell infusion. May be helpful in predicting which patients are at high risk of CRS.

**T cells** (T lymphocytes). Together with B cells, a mainstay of the adaptive immune system. T cells originate in bone marrow and mature in thymus, from which they get their name.

**TCR** (T-cell receptor, T-cell antigen receptor). Cell-surface receptor for antigen. Some TCRs have two variable chains, α (TCRα) and β (TCRβ), and T cells with this TCR thus are known as αβ T cells. Other TCRs have different variable chains, γ and δ. In either TCR, the constant portion, which executes the signaling function of the receptor, consists of CD3 and ζ proteins. Engineered TCRs can recognize a specific MHC/peptide combination of interest (e.g., cancer-associated proteins) and act like the patient’s T cells upon re-infusion, resulting in lysis of tumor cells.

**TNBC** (triple-negative breast cancer). Breast cancer that is estrogen-receptor (ER) negative (≤10%), progesterone-receptor (PR) negative (≤10%), and human epidermal growth factor-receptor 2 (HER2) negative. Metastatic TNBC is target of JCAR20.

**tocilizumab** (Actemra). IL-6 receptor antagonist indicated for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. Used off-label as first-line treatment for cytokine release syndrome (CRS).

**UCART19.** Allogeneic CAR T-cell product targeting CD19. Being co-developed by Servier (Suresnes, France) and Pfizer. In 2015 Servier gained exclusive rights to UCART19 from Cellectis (France). Pfizer acquired a minority stake in Cellectis in 2014 and is working with Servier to advance UCART19.

**UCART123.** Allogeneic CAR T-cell product (Cellectis) targeting CD123. Expected to begin phase 1 trials in AML and BPDCN in 2017.
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Oncology Care Model Headed for Shades of Gray

By Neil Minkoff, MD
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Chief Medical Officer, EmpiraMed

The CMS’s Center for Medicare and Medicaid Innovation (CMMI), a creature of the ACA, launched its Oncology Care Model for CMS on July 1, 2016. It’s a five-year program, designed to do nothing less grand than transform how oncology is practiced in the United States.

Under the new administration, CMS is delaying the start of some important bundled payment programs. So far, though, the oncology program seems to be going forward as planned.

Regardless of your politics, the motivation behind a program designed to curtail cancer costs is clear. Cancer epidemiology (the old are disproportionately affected), coupled with 21st century demography (longer life expectancy, aging boomers), means cancer costs are going up. CMS has projected its annual cancer treatment costs will reach $150 billion by 2020, a 25% increase from 2010.

The Oncology Care Model creates a payment system tied to episodes of care rather than fee for service. Each six-month episode starts, basically, with the initiation of chemotherapy. A single patient may have multiple episodes under the program if they have multiple rounds of chemotherapy. The episode payment is supposed to cover all the costs that would have been incurred in Medicare Part A (payments to hospitals) and Part B (payments to physicians). Only a sliver of Part D (outpatient drugs) costs are included.

To participate, many oncology practices will have to revamp the way they’ve been working. For example, the model requires them to provide patients 24/7 access to a clinician who can treat the patient’s issue with real-time access to clinical records. Practices must also have treatment plans that include the 13 components recommended in the Institute of Medicine’s 2013 report on high-quality cancer care. This may be the most onerous of the requirements because the treatment plans must, among other things, address treatment and its expected duration, expected response and prognosis, treatment goals, and expected patient costs. The practices must also follow clinical pathways and submit clinical and quality data to CMMI. If CMMI finds flaws—which it will—then the practices must follow up with a quality-improvement process.

It’s a lot of work and expense. Payment changes are supposed to make it worth their while. The model includes a $160 monthly stipend for each patient. The episode payments are based on practices’ baseline costs (although cost reductions are built into those targets). Practices can share in cost savings if they spend less than the expected episode, as long as they meet certain quality targets.

So far, about 200 practices and more than a dozen private payers are participating in the program. The payers are required to pay the participating physicians in a way that resembles the CMS scheme.

If it’s successful, the Oncology Care Model could help make bundled-based payment the norm in American health care and give ACOs a significant boost. Success, though, will be in the eye of beholder.

I think we’re probably headed for a lot of gray area. This is likely one of those programs that CMS touts as a big success, due to savings to the system, but physicians and practices will find it hard to implement and frustrating to manage. Practice redesign is difficult.

My best guess is that a fair number of practitioners will drop out over the five years. I expect CMS to do some tweaking, reduce demands on practices, increase reimbursement, and extend the program beyond five years. In other words, it will unfold much like the CMS ACO programs.

Your turn: Post your response at medicaldirectorsforum.com/curbsideConsult
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