RETOOLING CANCER MANAGEMENT

CMS’s Oncology Care Model brings bundled payments to cancer treatment
Risk stratification of screening
Insurers eye value-based tools warily
Active surveillance gains traction

Red Tape Ties Up Cancer Clinical Trials ....................... 7
Q&A: Controversial Oncologist Wants To See Better Evidence ...... 30
Smart Plans Will Capitalize On Medicare Stars Changes .......... 38

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Xiidra is the first and only prescription eye drop FDA-approved to treat both the signs and symptoms of dry eye disease (DED), a multifactorial disease of the tears and ocular surface. DED, which is often chronic and can be progressive, is associated with inflammation of the ocular surface that can be triggered by abnormal tear composition.1-4

Diagnosing DED is complex.5
Symptoms of DED are among the most common patient complaints to eye care professionals. DED diagnosis is based on the assessment of both signs and symptoms, which do not always correlate.2,6,7

Only Xiidra is indicated to treat both the signs and symptoms of DED.

Clinical studies demonstrated Xiidra’s effectiveness.1
The safety and efficacy of Xiidra compared with vehicle were studied in 4 well-controlled, 12-week trials (N=2133). Safety was studied in 1 additional year-long trial (N=331).1,8

Xiidra demonstrated a larger reduction in inferior corneal staining score (ICSS) in 3 of the 4 studies at Week 12.1
Xiidra improved ICSS, a well-recognized sign of DED, compared with vehicle.14

ICSS was recorded at each study visit (0=no staining, 1=few/rare punctate lesions, 2=discrete and countable lesions, 3=lesions too numerous to count but not coalescent, 4=coalescent). The average baseline ICSS was ~1.8 in Studies 1 and 2 and 2.4 in Studies 3 and 1.

Xiidra demonstrated a larger reduction in eye dryness score (EDS) at Weeks 6 and 12 in all 4 studies.1

In 2 of the 4 studies an improvement in EDS favoring Xiidra was seen at Week 2.1

EDS was rated by patients using a visual analogue scale at each study visit (0=no discomfort, 100=maximum discomfort). The average baseline EDS was between 40 and 70.1

References:

Indication
Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

Important Safety Information
In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Prescribing Information on next page.

NOW APPROVED
XIIDRA™ (lifitegrast ophthalmic solution) 5%
BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC ). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
EDITOR’S MEMO

The Hope–Hype Navigation

By Peter Wehrwein

These are go-go times in oncology, particularly for immunotherapy. By Centerwatch’s count, the FDA has granted approvals for eight new oncology indications this year—three of them for immunotherapeutic agents—after giving the green light to 21 indications in 2015.

One of the first waves of cancer immunotherapy brought anti-PD-1 drugs like pembrolizumab (Keytruda) and nivolumab (Opdivo) onto the market. On page 17, you can get acquainted with Jonathan Friedlaender, a melanoma patient for whom pembrolizumab has made a remarkable, life-extending difference.

Meanwhile, the Obama administration’s Cancer Moonshot is supposed to accelerate research into the genetic underpinnings of cancer and prevention as well as new, effective treatments.

Hope. Optimism. All good.

Then along comes Vinay Prasad, MD, who in a Q&A in this issue on page 30 says the Cancer Moonshot is more like a puddle jump and cancer immunotherapy is, so far, only effective in a small fraction of patients.

Some might dismiss the young Oregon oncologist as contrarian, a gadfly. But in our pages and elsewhere (Ending Medical Reversal, the book he wrote with Adam Cifu, is well worth your time), Prasad is raising important questions about standards of evidence used to justify new treatments in oncology—and in health care in general.

Commercial interests are partly to blame, in his view. But Prasad says part of the problem is the strong, intuitive appeal of the explanations for how interventions work—and the metaphors used to convey them—in contrast to the often tedious labor of collecting the evidence that they actually do. Cancer immunotherapy that “harnesses the immune system” so it swarms after cancer—that’s an appealing story.

Hope keeps us going and shouldn’t be discarded. Hype can send us off in the wrong direction. Good evidence is what we should steer by.

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CMS Wants To Remodel Cancer Payment, Care
The Oncology Care Model is bringing bundled payments to the front. The 195 participating practices will need to figure out ways to control costs if they want to beat the government's financial benchmarks.

Plans Not Using Tools To Measure Value, So Far
Perhaps with some justification. The organizations that develop these techniques do so with patients and doctors in mind, not insurers. One patient's experience illustrates drug pricing's important role.

Selective Screening May Be More Cost-Effectiven
Genetic tests could be the answer. They may add upfront expense, but might eventually lead to savings by winnowing out unnecessary screening. Concern about false positives helps push this movement along.

Sometimes It's Best To Hold Off
Patients and doctors fight the urge to rush in and treat as more types of cancer lend themselves to active surveillance. The advent of precision medicine makes this a more inviting option.

Q&A: Controversial Oncologist Wants Evidence
Vinay Prasad, MD, thinks that providers should offer medical therapies that do more good than harm. Well, who doesn't? He believes the problem lies in the dearth of good evidence for many interventions.

Changes Aplenty in Medicare Star System
Health plans can't just weather the storm; they need to keep an eye on the future when it comes to a rating system that's constantly evolving. The bar has been set higher as the program becomes permanent.
Get Cancer Clinical Trials Out of the Bureaucratic Ditch

Cancer clinical trials occupy a precious space in the healthcare system, especially with patients. For many, the trials represent the last chance for a cure or, at least, a staving off, of the relentless and deadly disease.

The trials, though, are often bogged down by redundancies and bureaucratic muck from beginning to end, according to a report issued jointly by the American Society of Clinical Oncology (ASCO) and the Association of American Cancer Institutes (AACI).

They’ve become more challenging to conduct, as they must comply with often costly and inefficient federal and state regulatory requirements, according to researchers from several universities and institutions.

When federal and state governments take notice, it can become like the old E.F. Hutton commercial where everybody freezes. That’s because “institutions and sponsors often interpret these requirements conservatively and thereby add to the complexity and perceived (but often highly theoretical) risk of conducting clinical trials,” the report states.

To find a way to break these logjams, ASCO and AACI launched the Best Practices in Cancer Clinical Trials Initiative. The initiative was overseen by a group of hematologists, oncologists, research nurses, administrators, and managers. The FDA and the National Cancer Institute provided input. A survey of 1,200 stakeholders in the fall of 2015 yielded about 310 usable responses.

The responses pointed to two issues: Getting the trials up and running, and then conducting those trials in a smooth fashion. The top three barriers to getting the trials started were contract negotiations with sponsors, contract negotiations with contract research organizations (CROs), and complying with industry requirements.

The three biggest problems in conducting the trials were site-monitoring visits, managing regulatory documents, and reporting of adverse or serious adverse events.

Among the suggestions for improving the launch of trials were developing master agreements between sites and sponsors to cover agreements that do not vary across trials, a centralized repository of templates and tips for negotiating contracts, and working with stakeholders to create worksheets that identify services that aren’t related to oncology for each trial.

Suggestions for making trials run more smoothly included harmonizing training requirements, deployment of cancer-specific electronic data capture systems, and convening stakeholders to examine why FDA guidelines haven’t been adopted.

Clinical trial sites will often do an insurance coverage analysis to identify routine costs that can be billed to insurers. But the coverage analysis can be a mess that includes many redundancies, according to the ASCO–AACI report: “Coverage analyses are completed by a myriad of research team members with various levels of knowledge, skill, and expertise in the arena of clinical trials coding and billing.” The report suggests developing a Turbo Tax-type app that would let sites conduct coverage analyses quickly. It also suggests writing guidelines that would delineate the boundary between routine care and research.

ASCO and AACI plan to expand the effort, focusing on adverse event reporting, site qualification, and insurance coverage analysis.

High-Need Adults Fall Through Cracks

The insurance industry has some catching up to do when it comes to providing care for “high-need” adults, according to an issue brief by the Commonwealth Fund. High-need adults have three or more chronic conditions and cannot easily care for themselves or perform routine daily tasks, such as shopping or preparing food.

The findings show that having a functional limitation in combination with multiple chronic diseases imposes a greater burden on patients than multiple chronic diseases alone, the researchers stated.

The average annual spending for high-need adults is about $21,000 per person. That’s nearly three times the average for adults with multiple chronic diseases only (about $7,500) and more than four times that for all adults (about $4,800). In addition, 20% of high-need adults went without or delayed receiving needed medical care or prescription medication in the past year, compared with 8% of all Americans.

One of the takeaways from the Commonwealth Fund brief is that the unmet need varied quite a bit with the type of insurance. Unmet needs were greatest among high-need adults with private insurance (32%), followed by those with Medicaid alone (28%). Unmet need was about half as great among high-need adults with Medicare (14%).

The Commonwealth Fund researchers used nationally representative data from the 2009–2011 Medicare Expenditure Panel Survey. They found that 1 in 20 Americans, ages 18 and older, fit the definition of a high-need patient. That works out to about 12 million people. It’s important to note, though, that the survey does
not include institutionalized patients. Far more Americans—about 79 million—have three or more chronic illnesses but no functional limitations.

Among the other findings was that high-need patients with a good rapport with their physicians were more likely to follow treatment regimens, have better outcomes, and reported more care satisfaction. That’s not a big surprise. Rapport was defined as providers spending enough time, showing respect, listening carefully, and explaining things in an easily understood way.

“Private insurers will need to consider how they might improve benefit and network design to reduce unmet needs among high-need patients covered by commercial insurance,” the researchers stated. The answer might be found in the patient-centered medical home approach to care. In general, said the researchers, whether looking at comprehensive care, accessible care, or responsive care, high-need patients were more likely than patients in other groups to report their usual provider offered such care.

Cholesterol Screening
For Kids on Hold
The U.S. Preventive Services Task Force says there’s not enough evidence to recommend for or against pediatric high-cholesterol screening among asymptomatic children or teenagers.

In reaching this conclusion, the USPSTF reaffirmed its recommendation statement from 2007. The task force noted that whether to routinely screen children and teens is an often revisited topic because atherosclerosis starts when people are young, and lipid levels in younger people correlate with atherosclerosis in adulthood.

If children and teens are to be screened routinely, we need better evidence that screenings and corresponding interventions would lead to better cardiovascular health in those children when they become adults, the task force noted.

“Screening in children and adolescents may identify those with undiagnosed familial hypercholesterolemia or multifactorial dyslipidemia,” the task force stated. “However, the clinical health benefits and risks among children and adolescents identified with and treated for dyslipidemia have not been sufficiently studied, making the role of screening in children and adolescents uncertain.”

The task force did recommend screening children aged 6 and older for obesity.

The recommendation statement also bows to physician discernment when it comes to making the call to screen: “Clinicians should understand the evidence but individualize decision making to the specific patient or situation.”

The task force’s recommendation statement includes an almost throw-away line about cascade screening that may merit further investigation. Cascade screening involves finding cases among relatives of patients with confirmed familial hypercholesterolemia and testing for genetic variants identified in the proband. Cascade screening is done in the United Kingdom and the Netherlands, according to the task force, but not in the United States.

Poorer Countries
Fight Hypertension
It’s a good thing that fewer people on this planet are starving, but better life doesn’t mean better health in all respects. For the first time in history, the
number of people in low- and middle-income countries with hypertension outnumber those in high-income countries with the condition, according to a study in *Circulation*.

The study states that 31.1% (1.39 billion) of the adult population worldwide had high blood pressure in 2010. Of those, 28.5% (349 million) of the adults lived in high-income countries and 31.5% (1.04 billion) lived in low- and middle-income countries.

“Aging and urbanization with accompanying unhealthy lifestyle may play a role in the epidemic of hypertension in low- and middle-income countries,” the study states.

The rate of hypertension in low- and middle-income countries increased by nearly eight percentage points from 2000 to 2010. The rate in higher income countries decreased by nearly eight percentage points in the same time period.

The study’s main author, Jiang He, of Tulane University School of Public Health, told the *Washington Post* that “people who live in the countryside engage in the farmer lifestyle and have manual labor. When they move to the city, they get office jobs and stress.”

This department is called News & Commentary, and Managed Care would like to make this comment: Most people faced with a choice between a life of backbreaking farm labor that barely maintains subsistence, and one in which there’s a chance to earn some leisure time, would move off the farm pronto—stress, bad eating habits, and all.

Still, the study makes the point that the awareness of hypertension and the means of fighting it haven’t made as much of an inroad into poorer countries as an increase in the standard of living.

The poorer countries often lack a health care infrastructure that hinders access to care. Even cheap hypertensive medications may be too expensive for people to buy. Overburdened health care providers and low patient health literacy are also barriers to efforts that might target hypertension.

Jiang He told *Science Daily* that because hypertension doesn’t present symptoms and because many people in low- and middle-income countries do not have access to regular preventive health care, the condition is often underdiagnosed.

**Briefly Noted**

Antimicrobial resistance could eventually cause more deaths than cancer, according to an international review board headed by a U.K. economist and working closely with the World Health Organization. The board said that if immediate action isn’t taken to curb the spread of so-called superbugs, antibiotic resistance could lead to 10 million deaths a year around the world by 2050. On the board’s suggested to-do list: a massive global awareness campaign and curbing unnecessary antibiotic use in agriculture.

*The women and men treating patients’ stress are often themselves under a lot of stress. That’s why a program at Mayo Clinic, among other medical centers across the United States, that helps physicians with burnout is garnering a lot of attention, reports the Minneapolis Star-Tribune. There are costs to low morale and feeling overwhelmed, the newspaper reported. “Professional burnout includes emotional exhaustion, an inability to connect with other people, and a low sense of meaning in work. Research has shown it can contribute to medical errors and increase job turnover”… The estimated annual cost of treating patients with sepsis is approximately $20 billion in the United States, making sepsis the costliest medical condition in this country. Each year, an estimated 750,000 people die from sepsis in the U.S. FierceHealthIT, summarizing a study published in the *Journal of the American Medical Informatics Association*, reported that a hospital in Huntsville, Ala., has been able to reduce sepsis-related deaths by half through a program focused on staff education and an electronic surveillance system… Too many elderly patients receive unnecessary end-of-life care, according to a meta-analysis published in the *International Journal for Quality in Health Care*. The researchers found that a third of elderly patients were given nonbeneficial interventions such as admission to the ICU or chemotherapy in the last two weeks of life while others with do-not-resuscitate orders were still given CPR. The analysis combined the results from 38 studies conducted over two decades…. In what’s being hailed as the first-of-its-kind effort, California is revamping the way it collects data from cancer diagnoses so that the collection almost happens immediately, according to Kaiser Health News. “That represents a significant change for the registry, which traditionally relies on data up to two years old.”… One of the body’s natural healing mechanisms is a good night’s sleep, and some children’s hospitals are going to great lengths to ensure just that for their young patients, Kaiser Health News reports. Those hospitals “are enforcing quiet hours after dark, clustering things like overnight blood draws and medication doses to minimize interruptions, and bringing in tools like white noise machines to promote a soothing environment”… A retrospective study of skin infections in a dozen nursing homes in the Denver area found a lack of clinical evaluation after patients started taking antibiotics. In 41 of the 100 cases studied, no evaluation was done in the first 48 hours after the patient started taking an antibiotic. The researchers note that careful “antibiotic stewardship” is crucial in nursing homes because of the high rates of inappropriate use of antibiotics (25% to 75%, according to some research), the risk of drug-resistant organisms, and a growing problem with *C. difficile* infections…. The overall depression rate among adolescents rose from 9.9% between 2012 and 2013 to 11% between 2013 and 2014, according to a report by the Substance Abuse and Mental Health Services Administration. “The findings in this report suggest a continuing need for programs to address depression among adolescents,” the report states.

— Frank Diamond
ACA: Phoenix of—or Cooked in—This Dumpster Fire of an Election

The fate of the health care reform law will be determined by the outcome of a joyless election.

By Richard Mark Kirkner

With open enrollment for the Health Insurance Marketplace starting on November 1—exactly one week before Election Day—and with UnitedHealthcare and Aetna pulling out of the exchanges in many markets, a core element of the Affordable Care Act may be headed for the dustbin of history.

The blame game is going full tilt. One of the boldest plays came when five senators sent Aetna CEO Marc Bertolini a letter accusing the company of pulling out of the exchanges to pressure the Justice Department to approve its merger with Humana. There also has been talk in capitol corridors about what might be done to repair the teetering ACA exchanges in the next Congress.

Of course, what will happen depends on what many are describing as a dumpster fire of an election with little enthusiasm for either candidate. A Pew Research Center survey in September found that far more respondents felt frustrated (57%) or disgusted (55%) by the election than interested (31%), optimistic (15%), or excited (10%).

A President Hillary Clinton and a Republican Congress could prolong Washington’s inertia while Clinton’s HHS works out administrative tweaks to the ACA. Perhaps President Clinton and a Republican Congress might rouse themselves from Beltway stasis and cobble together some legislative remedies. A third possibility and a long shot at best, Clinton and a Democratic Congress could collaborate on ACA remedies.

President Donald Trump and a Republican Congress would undoubtedly set about to dismantle the ACA and replace it with other means for covering Americans that would likely rely on the private market. But all the talk about dismantling the ACA on Day 1 notwithstanding, undoing the law would be a long process. Furthermore, the de-ACA-ing of American health care would depend on Trump working with Congressional Republican leaders, who have embraced their nominee with all the enthusiasm of a kid given a pet rattlesnake.

Keeping the bipartisanship afloat

Congress could put together an ACA fix, as it did in passing MACRA legislation last year to fix physician reimbursements, says Leighton Ku, a professor at the Milken Institute School of Public Health at George Washington University. “From a budget perspective, that was a much bigger deal than we’re talking about with the exchange problems,” he says, “but it was something where after many years of frustration people decided they could just agree. So that’s what might happen in this coming term.”

Says Mark Hall of Wake Forest University School of Law: “If there’s political willingness, then there’s a lot of things that could be done, starting with the public option.” A contentious election like this can do a lot of things to either strengthen or weaken political will, says Hall.

Still, a public option might be too heavy a lift for Clinton and the Democrats. If they prevail in the election, it probably won’t be by much. Smaller efforts that could generate bipartisan support—like fixing reinsurance for exchange plans or tweaking individual mandate requirements—might be more realistic, especially if the purveyors of Congressional intransigence are left feeling somewhat burned after this election.

Ku says the departures from the ACA exchanges need to be kept in perspective, some of the big players who’ve left may be just small potatoes on the exchanges they’re pulling out of.
"Of course, the market would work better if we had stronger risk protection mechanisms, but I think it’s still possible that the market will work OK without a couple of them,” says Mark Hall of Wake Forest University School of Law.

Columbia exchange and has seen how plans make business decisions with regard to their participation. “My impression is that if you’re an insurer that has a large volume, you don’t want to discontinue that line,” he says.

The exits can cause a problem when only two or three plans—or, worse, one or none—participate in an exchange. But before the ACA, in most markets, consumers had a few individual plans to choose from, Ku says.

In other words, we may return to baseline, which isn’t great, but it isn’t a total disaster, either.

Re-upping reinsurance
The ACA had some mechanisms that were supposed to keep the exchanges healthy and keep a decent number of health plans participating.

To say that the co-op plans have struggled is an understatement. Only six of the original 23 co-ops are still in business. The co-ops were devised as a substitute for a full-fledged public option and were one of the many compromises made in passing the ACA. The co-ops had troubles before, but some say they went from serious to dire last year when Congress made risk corridors budget-neutral. Those corridors were supposed to give co-ops a financial cushion.

The ACA also created a temporary reinsurance program for plans on the exchanges that are not co-ops. Billions have paid out. The program is scheduled to end this year.

Extending reinsurance could get a fresh look once the election smoke clears, Wake Forest’s Hall says. “It’s worth asking do we perhaps need it for a couple more years. It might be taking longer than we first thought for this market to mature due to some of these disruptions,” he says. Reinsurance is a fixture in Medicare Part D.

The exchanges are an essential element in achieving universal or near-universal coverage, says Commonwealth Fund Vice President Sara Collins. “To the extent that policymakers share that view, there will need to be stabilizing options, and extending the reinsurance program could have bipartisan support because it is budget neutral,” she says.

When CMS issued a report in August that claimed the risk pool in the individual market was improving, AHIP CEO Marilyn Tavenner shot back with a rebuttal. “The reality is that the risk pool has not significantly improved,” she said. Among her ideas for fixing the risk pool: revising accounting regulations to include partial-year enrollments and prescription drug data; tightening requirements for special enrollment periods; and expanding outreach to draw more of the uninsured into the market.

It seems CMS listened to its former administrator in proposing rules for 2018. Those rules incorporated her ideas, along with a transfer mechanism to spread the risk of high-cost enrollees.

Hall suggests other ACA fixes that could improve risk on the exchanges: “Toughening up the individual mandate—maybe increasing the penalty from $700 to something with a little more bite—or changing the rule that lets you come back into the market any time you want; that is, if you don’t buy insurance when you’re eligible, you have to sit out for a period of time.”

Autocorrections
The exchanges might also benefit from experience. The ACA provision that grandfathered noncompliant plans will sunset in 2019, which will send in a new group of buyers. “They are likely a healthier group of people since they were underwritten in their plans, so that could also have a potentially significant effect on both the risk pools and enrollment,” says Collins of the Commonwealth Fund.

And actuaries have more historical data to draw on for their risk projections. “Perhaps there’s less need for those risk mechanisms than there was at the beginning of the exchanges,” Hall says. “Of course, the market would work better if we had stronger risk-protection mechanisms, but I think it’s still possible that the market will work OK without a couple of them.”

An ACA-less world
What if the political will to fix the ACA doesn’t coalesce? The individual market could end up looking a lot like it did before 2010. But even that might not be so straightforward, as Ku of George Washington University points out. “There aren’t preexisting condition exclusions anymore,” Ku says. Trump has said while he would scrap the ACA and the individual mandate, people with preexisting conditions would still be able to get health insurance. So it seems that no matter who emerges from this dumpster fire of election, the ban on denying coverage because of preexisting conditions may survive.
Time For An Overhaul: CMS Wants to Remodel Cancer Payment, Care

CMS’ Oncology Care Model program is bringing bundled payments to cancer care. With drug costs so high and hard to control, the 195 participating practices will have to figure out other ways to control costs if they want to beat financial benchmarks and earn bonuses.

**By Thomas Reinke**  
Contributing Editor

This summer, CMS launched what might be its most ambitious alternative payment model to date. The federal health care agency’s aspirations for its Oncology Care Model (OCM) are sky high: Transformation of cancer treatment through more comprehensive patient and care management while simultaneously controlling the cost of all services through bundled payments for chemotherapy episodes lasting six months.

The new oncology model encompasses virtually all cancers treated with chemotherapy and all stages of those cancers. This is not a knock on other specialties, but the complexities of selecting the best chemotherapy agents for cancer patients—balancing efficacy, toxicity and an individual patient’s response—exceed those of CMS’ other bundled payment programs for cardiac care and hip and knee replacement. On top of the clinical issues and guidelines, physicians are supposed to generate savings in a circumstance where the price and expenditures for cancer drugs are unpredictable and difficult if not impossible to manage.

And yet the number of practices that agreed to participate in OCM has exceeded expectations. About 100 practices were expected to sign up. Roughly 450 expressed interest by submitting letters of intent to participate. Ultimately, 195 practices ended up in the program. The participants run the gamut from small private practices to large national physician networks to academic medical centers and even physicians tied closely to hospitals. Cancer treatment has been an important service line and major source of revenue for hospitals, and they have been reluctant to make changes that venture from fee for service.

The OMC program also includes 16 private health insurers that are patterning their payment models after CMS. These payers will add support to practices—and some much-needed horsepower to the OMC model. “I have to give CMS credit for the foresight to include private health plans,” says John Fox, MD, associate vice president for medical affairs at Priority Health, a Michigan insurer.

Community-based oncology practices are disproportionately represented in the OCM and outnumber hospital-employed oncologists or practices that are part of integrated health systems, according to Lindsay Conway, managing director of research at the Advisory Board.

“I have to give CMS credit for the foresight to include private health plans” in the OCM program, says John Fox, MD, of Priority Health, one of the participants.

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**Participating private insurers**

1. Aetna
2. Blue Cross Blue Shield of Michigan/Blue Care Network
3. Blue Cross and Blue Shield of New Mexico
4. Blue Cross and Blue Shield of Oklahoma
5. Blue Cross and Blue Shield of Texas
6. BlueCross BlueShield of South Carolina
8. Cigna Life & Health Insurance Company
9. EmblemHealth, New York City
10. Health Alliance Plan, Urbana, Ill.
11. Highmark, Inc., Pittsburgh
13. SummaCare, Akron, Ohio
14. The University of Arizona Health Plans
15. UPMC Health Plan, Pittsburgh
16. VIVA Health, Birmingham, Ala.
Board, the Washington, D.C., research, technology, and consulting company. That skew makes sense to Conway. “Community-based oncology practices have really been in the forefront in terms of designing and implementing new care models and considering new payment arrangements,” she says. Their revenues have dropped over the past 10 years because of changes in drug reimbursement, so they have made a virtue out of necessity by being inventive. “They have been pushed to innovate and think more creatively about the financial model because they need to stabilize it if they’re going to continue to exist,” says Conway.

The drug reimbursement changes she refers to include steps by CMS to limit the profit margin on drugs that are designed to take away the financial incentive to prescribe more expensive medications. In March, CMS proposed reducing the allowed markup on Part B drugs from 6% to 2.5%. The reduction would be offset partly by a flat fee of $16.80 per drug, per day.

Many oncologists have also been attracted to OCM as an alternative to forthcoming reimbursement changes under MACRA. “OCM is better than Medicare’s alternative,” says Lalan Wilfong, MD, director of quality programs at Texas Oncology, one of

### How OCM works

CMS’s Oncology Care Model is a five-year program that requires participating practices to implement six care management requirements, including 24/7 patient access to clinicians, expanded services provided by nurse navigators, and implementation of NCCN or ASCO guidelines. In exchange, practices will receive an enhanced payment of $160 per patient per month during an episode. The episodes are triggered by a Part B or D claim and last six months. If a Medicare beneficiary receives chemotherapy after those six months, it restarts the clock on another six-month-long episode. The program will also measure performance using a variety of quality metrics. The intention is to prevent practices from inappropriately reducing services to curb expenditures so they come in under their financial benchmarks and, naturally, to improve patient outcomes.

On the financial side, practices are on the hook for managing the total cost of care for all services, including inpatient and outpatient hospital services and those from other specialists. Practices can choose to participate in either a one-sided or two-sided financial risk arrangement. Most are opting for the one-sided risk, whereby they receive a bonus if they are able to hold down the cost of an episode so it is below a financial benchmark but won’t be penalized if spending goes over the benchmark. The benchmark is calculated separately for each practice and is based on an analysis of what the practice has spent in the past over a three-year period. CMS will use a formula that gives more weight to the most recent year because it’s a better indicator of future expenditures. There are also provisions that make adjustments that take into account newly approved drugs.

OCM is a bundled payment program. That may suggest that practices are getting paid in lump sums. But the program doesn’t work that way. Instead, practices will file claims just as they always have. Their actual expenditures are then reconciled with their benchmarked expenditures to see if they are eligible for a performance payment.

### Performance-based payment: OCM

1. CMS will calculate benchmark episode expenditures for participating practices
   - Based on historical data
   - Risk-adjusted, adjusted for geographic variation
   - Trended to the applicable performance period

2. A discount will be applied to the benchmark to determine a target price for OCM episodes
   - Example: Benchmark = $100 → Discount = 4% → Target price = $96

3. If actual OCM episode Medicare expenditures are below target price, the practice could receive a performance-based payment
   - Example: Actual = $90 → Performance-based payment up to $6

4. The amount of the performance-based payment may be reduced based on the participant’s achievement and improvement on a range of quality measures
twelve practices in the U.S. Oncology Network that is participating in the OCM. He is referring to the Merit-based Incentive Payment System (MIPS), the track of MACRA that most practices are expected to be in. Relative to MIPS, OCM has a clearly defined care model and payment terms that are set for five years. Many of the details of MIPS have not been finalized, and its physician payment model has clearly defined downside risks.

**Squeezing nondrug costs**

CMS has emphasized that the objective of OCM is to transform cancer care, with several requirements to boost individualized patient management, but cost savings are also a central requirement. To remain in the program, however, practices must achieve a cost savings by the third year of operations.

One of the big questions hovering over the program is just where will these savings come from. The spotlight has been trained on the high price of drugs, including cancer drugs, but OCM may shift some of the attention to other aspects of cancer treatment. The Medicare Payment Advisory Commission (MedPAC) calculated that the average Medicare expenditure for a 180-day chemotherapy episode for lung, breast, and colon cancer was nearly $41,000—and that was in 2010–2012, before the wave of expensive targeted therapies hit the market. About half—46% ($18,900)—of the money was spent on Part B oncology drugs and their administration, according to MedPAC. The rest went for inpatient hospital services (20%, $8,200), payments to physicians and other suppliers (18%, $7,400), outpatient services (12%, $4,900), and home health and hospice services (4%, $1,600).

Earlier this year, the Community Oncology Alliance, the lobbying organization for community oncologists and an opponent of the proposed Part B payment reforms, released its own analysis of annual cancer care costs for Medicare and commercial plans.

### Commercial plans spend roughly 75% more per episode of cancer care than Medicare

<table>
<thead>
<tr>
<th>Service</th>
<th>Medicare $51,566</th>
<th>% of episode cost</th>
<th>Amount</th>
<th>Commercial $90,656</th>
<th>% of episode cost</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>18%</td>
<td>$9,280</td>
<td>20%</td>
<td>$18,130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient hospital</td>
<td>24%</td>
<td>$12,380</td>
<td>18%</td>
<td>$16,320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outpatient</td>
<td>21%</td>
<td>$10,825</td>
<td>28%</td>
<td>$25,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer surgeries</td>
<td>11%</td>
<td>$5,670</td>
<td>13%</td>
<td>$11,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiology</td>
<td>8%</td>
<td>$4,125</td>
<td>10%</td>
<td>$9,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute</td>
<td>8%</td>
<td>$4,125</td>
<td>1%</td>
<td>$900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional services</td>
<td>5%</td>
<td>$2,580</td>
<td>4%</td>
<td>$3,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation oncology</td>
<td>3%</td>
<td>$1,550</td>
<td>4%</td>
<td>$3,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency room</td>
<td>2%</td>
<td>$1,030</td>
<td>1%</td>
<td>$900</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Community Oncology Alliance
care costs for Medicare and commercial patients. The alliance’s analysis, conducted by Milliman, showed that the per-person, per-year cost of a chemotherapy episode paid for by Medicare averaged $51,566 in 2014. For commercial payers, it was $90,656, or roughly 75% more than what Medicare spends. Milliman’s tally includes all the services during the course of the year, not just those for a six-month chemotherapy episode that MedPAC added up.

A breakdown on where the money goes can be found on page 14. It shows some large differences in Medicare and commercial insurer payment for drugs ($9,280 vs. $18,130), outpatient services ($10,825 vs. $25,400), and cancer surgery ($5,670 vs. $11,800).

In Texas, all in

Health plans, PBMs, employers, even CMS—they have all had difficulty reining in drug prices, and experts question whether OCM will do better. OCM does not include a requirement for practices to specifically target drug costs. In fact, under OCM, Medicare’s current Part B drug payment arrangement remains in place for physician practices that buy and administer cancer medicines. Similarly, for physicians affiliated with hospitals, the current hospital outpatient prospective payment system (OPPS) arrangement remains in place. Squeezing savings out of other services will be difficult because under traditional Medicare, patients are free to go to any provider that accepts Medicare.

Yet Texas Oncology has gone all in on OCM. Its entire set of more than 420 physicians and 175 sites of care are participating. Wilfong, the director of quality programs, says that although he would like to see some modification, CMS is essentially on the right track with OCM and is developing a workable care and financial model in oncology.

OCM has many requirements that fit with the innovations his group is already pursuing, he says. For example, the group has 24/7 access to on-call clinicians at all of its locations. Wilfong says the group plans to enhance this access with a beefed-up effort at next-day follow-up, which will involve contacting patients who have called in to see how well their problem was handled. Texas Oncology is also developing its own urgent care capability for patients who need to be seen as soon as possible.

As far as controlling costs, Wilfong said the organization will continue to improve pathway programs with targeted analyses of published studies of treatments that may have new outcomes or safety data. It will also be keeping an eye on costs and cost-effectiveness research. Wilfong pointed to a head-to-head comparison between bevacizumab (Avastin) and cetuximab (Erbitux) as first-line therapy for colorectal cancer as an example of the kind of research that the group will use to put together a pathway. The cost for one eight-week cycle of treatment for cetuximab was almost three times higher than bevacizumab ($20,856 vs. $9,324), but at 24 months, the overall survival rate of the patients on the two drugs was nearly identical. Wilfong says Texas Oncology will also be expanding its analysis and monitoring of avoidable drug use.

The group is optimistic that having more cost data at its disposal will enable it to manage cancer more efficiently, says Lalan Wilfong, MD, who oversees quality.

Texas Oncology is optimistic that having more cost data at its disposal will enable it to manage cancer more efficiently, say Wilfong. “Currently it is very difficult for physicians to manage total cost of care because we only have information on the services that we provide,” he says. “We do not get information about the other services patients receive. We will have up to 15,000 patients in the program, and the cost and claim data we will be getting from Medicare on that volume of patients will help us to develop new cost- and care-management processes.”

Medical homes a head start

Priority Health believes its medical home program gave practices a good running start that will pay off in OCM. Four years ago, the Michigan insurer, working with Spectrum Health, a not-for-profit health care system in the western part of the state, created an oncology medical home program that now has six practices. The program included some cost-control strategies that are ahead of what CMS is shooting for. For example, the payment arrangement for physician-administered drugs is set at acquisition cost.

The six medical home practices plus an additional practice are now in OCM. OCM fits well with the existing medical home program, in Fox’s view. For example, the medical homes have been working on unnecessary emergency room visits and hospital admissions. “We continue working with them to share the data we receive about ER visits and admissions on a timelier basis to facilitate their intervention or follow-up as a way to control costs,” Fox says.

Priority and the practices are also refining pathways and developing end-of-life programs that should help them meet OCM requirements and financial benchmarks, he says. Markdown conversion was successful.
Value Tools Not in The Insurer Toolkit—Yet

Current versions by ASCO, NCCN, and others may not be right for insurers, but they are eyeing new ways to crunch the numbers for cost and outcomes.

By Ed Silverman

How much value can be found in a new crop of value tools?

Over the past two years, the American Society of Clinical Oncology (ASCO) and several prominent organizations have responded to the growing concern over prescription drug costs by developing different ways to assess the worth of new medicines. Yet even as understanding value becomes increasingly important for determining coverage, health plans are shying away from using these new tools.

We know this because Avalere Health consultants recently found that none of 11 plans surveyed use these new instruments, which look at cost and how much benefit drugs are actually providing after their effectiveness, quality of life, side effects, and other factors are included. Most of the plans do not expect to rely on the tools next year, either. In fact, only 9% of the respondents indicated that they were very likely to use the value tools.

Partly because pharmaceutical companies are pricing new cancer drugs so high, cancer organizations are on the vanguard of these efforts to compute value in an objective way. In addition to ASCO, the National Comprehensive Cancer Network (NCCN) and Peter Bach, MD, at Memorial Sloan-Kettering Cancer Center, have developed value calculators. The Institute for Clinical and Economic Review (ICER) in Boston has also got into evaluating pharmaceuticals.

ICER not included

The value-based tools are sometimes held up as a way out of the drug price vortex gripping American health care, but truth be told, Avalere’s findings are not at all surprising.

“Health plans have been in the business of evaluating evidence for medicines for a very long time,” says Caroline Pearson, an Avalere senior vice president. “And there is some question about the unique role of these frameworks. What is their audience and to what extent have they contributed to decision making? It seems unclear.”

Indeed, the ASCO and NCCN tools are actually focused on helping physicians and patients jointly make treatment decisions. Both organizations freely admit they did not develop their tools with coverage decisions in mind. And they have limitations, too. The ASCO framework, for instance, only makes comparisons between drugs that have been tested against one another in clinical trials.

“Our tool is not well-suited for health plans,” said Richard Schilsky, MD, ASCO’s chief medical officer. “It’s not a comprehensive assessment or ranking of one drug compared to another.”

Moreover, health plans largely rely on the various compendia when it comes to covering oncology treatments.

Still, the finding that 9% of the plans indicate that they will use a value-based tool next year shows some small measure of acceptance. Ironically, only ICER was shunned completely. ICER has worked hard to attract payers and, in fact, has created waves with its assessments, although its methodology has generated so much criticism that the not-for-profit group has solicited input for making changes.

ICER brushed aside the Avalere results, though, pointing to another survey that was conducted last fall by Dymaxium, a market research firm.

That poll found 46% of payers planned on integrating ICER data into their formulary evaluation process, and three quarters of those queried use ICER as a source of evidence for making pharmacy and...
therapeutic recommendations. So ICER may have gained some traction, but its long-term role remains undefined. Say a major public payer like CMS were to start applying its assessments to Medicare Part B coverage. If that were to happen, ICER would more likely become a force to be reckoned with, according to Avalere’s Pearson (no relation to ICER President Steve Pearson).

Coming soon
Regardless, it is certainly premature to say that the value-based tools are irrelevant to insurers or that insurers are turning their back on them. One reason is obvious—more information is better than less. Another is that the nature of health care payment is changing, which is forcing payers to look at new ways to assess most everything.

“The world is evolving toward a value-based system, and this will go in different directions,” says Roger Longman, chief executive of Real Endpoints, a consulting firm that helped Memorial Sloan-Kettering develop its Abacus value tool.

One possibility may involve placing more financial responsibility on providers to evaluate both clinical and economic considerations. Both providers and insurers are hiring so-called pathway companies to develop rulebooks for therapeutic choices. And eventually, indication-specific pricing and outcomes-based contracting will become more commonly adopted, which means yardsticks will be needed to be able to measure value.

“Some of this will also require a much more user-friendly framework that allows for specific decision making, and I don’t think the current frameworks do that yet,” Longman says. “But regardless of the scenario, these tools create a kind of transparency, which is another redeeming factor.”

Ed Silverman founded the Pharmalot blog and has covered the pharmaceutical industry for 20 years.

Value-based Health Care: One Patient’s Experience and What Really Matters

Everyone in health care seems to be talking about value these days—getting the biggest health care bang for our health care bucks.

Jonathan Friedlaender’s story may provide some insights into what cancer patients really value when the chips are down.

The 76-year-old retired professor of biological anthropology at Temple University in Philadelphia was diagnosed with stage 1 melanoma in 1996. That’s odd, he thought, there’s a bluish grey bump above my knee. Surgery confirmed the worst-case scenario, the M-word: malignant.

Since then, Friedlaender has endured the two decades of ups and downs of cancer treatment. Today, against the odds (and a reminder that they are odds, not foregone conclusions), he is alive and has emerged from active treatment.

When Friedlaender was diagnosed, there were no proven melanoma drugs. After the initial surgery and a follow-up biopsy of a sentinel lymph node in his upper thigh, he was told there was just a 20% chance of recurrence.

Friedlaender dutifully subjected himself to periodic chest X-rays. “They told me nothing was there, and I was more likely to die in a car accident than from melanoma.”

In 2003, he found a lump in the same lymph node bed that had been previously biopsied. His five-year survival chances tanked from 80% down to 20%. His priorities changed. He remarried, retired, and moved to a pretty spot in Litchfield County, Conn.

Disease had spread
After moving, he switched his care to an oncologist at Yale, Mario Sznol, MD, who thoroughly reviewed his records. More bad news: His disease had spread to his lungs. Sznol said he considered Friedlaender to be in stage IV of the disease, median expected survival, eight months.

Rather than being turned off by Sznol, Friedlaender continued on page 22
Provide your members with the option that’s

**FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS**

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

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

**COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24**

![Chart showing COMFORT-I Primary End Point](chart)

- Patients (%) ≥35% Spleen Volume Reduction From Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi® (n = 155)</td>
<td>42% (n = 65)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Placebo (n = 154)</td>
<td>0.7% (n = 1)</td>
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</tr>
</tbody>
</table>

**COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48**

![Chart showing COMFORT-II Primary End Point](chart)

- Patients (%) ≥35% Spleen Volume Reduction From Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi® (n = 146)</td>
<td>29% (n = 41)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BAT (n = 72)</td>
<td>0% (n = 0)</td>
<td></td>
</tr>
</tbody>
</table>

**Important Safety Information**

- Treatment with Jakafi® can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi®. Platelet transfusions may be necessary.

- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi®.

- Severe neutropenia (ANC < 0.5 x 10^9/L) was generally reversible by withholding Jakafi® until recovery.

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi® until active serious infections have resolved. Observe patients receiving Jakafi® for signs and symptoms of infection and manage promptly.

- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi® for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi®, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi® in patients with evidence of active or latent TB. Continuation of Jakafi® during treatment of active TB should be based on the overall risk-benefit determination.

- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi® and evaluate.

- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.

- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.

*COMFORT-I (COntrolled Myelofibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2-risk or high-risk myelofibrosis.† Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-γ, melphalan, acetylsalicylic acid, cytarabine, and colchicine.‡ COMFORT-II (COntrolled Myelofibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2-risk or high-risk myelofibrosis.
Indications and Usage

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

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

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo

- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy

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

When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations

Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia

The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness, and headache

A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy

Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

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

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

WARNINGS AND PRECAUTIONS

Thrombocytopenia, Anemia and Neutropenia

Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Dosage and Administration (2.1) in Full Prescribing Information] Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information].

Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Tuberous sclerosis Tuberous sclerosis has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with high prevalence of active tuberculosis, a history of active or latent tuberculosis where an appropriate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. FML Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. Hematologist patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. [see Adverse Reactions (6.1) in Full Prescribing Information].

Thrombocytopenia: A Thrombocytopenia, Anemia and Neutropenia are dose related. In a randomized, open-label, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache. [see Clinical Studies (14.2) in Full Prescribing Information].

Additional Data from the Placebo-controlled Study

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

Additional Data from the Placebo-controlled Study

25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi and 1% Grade 3 and no Grade 4 ALT elevations: 17% of patients treated with Jakafi and 8% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Clinical Trial Experience in Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxycarbons received Jakafi and 111 patients received best available therapy [see Clinical Studies (14.2) in Full Prescribing Information]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.
Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
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<td>0</td>
</tr>
<tr>
<td>Cough</td>
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<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

* Presented values are worst Grade values regardless of baseline

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
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</tr>
<tr>
<td>Anemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>5</td>
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<tr>
<td>Neutropenia</td>
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<td>Chemistry</td>
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<td></td>
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<tr>
<td>Hypercholesterolemia</td>
<td>35</td>
<td>0</td>
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<tr>
<td>Elevated ALT</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

* Presented values are worst Grade values regardless of baseline

**DRUG INTERACTIONS**

**Drugs That Inhibit or Induce Cytochrome P450 Enzymes**

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C39. CYP3A4 inhibitors: The Cmax and AUC of ruxolitinib increased 33% and 51%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [see Pharmacokinetics (12.3) in Full Prescribing Information]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [see Doseage and Administration (2.3) in Full Prescribing Information].

**CYP3A4 Inducers:** The Cmax and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see Pharmacokinetics (12.3) in Full Prescribing Information].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category C:** Risk Summary

There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal Data Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). Nursing Mothers It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 12-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use The safety and effectiveness of Jakafi in pediatric patients have not been established.

**OVERDOSAGE**

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

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says he appreciated the doctor’s direct but upbeat style. “He was very aggressive and optimistic. He told me, ‘Treating cancer is like soccer, I believe in taking shots on goal even if they are low percentages because some will pay off.’”

But things began to go downhill in 2011. The disease metastasized, and he was suffering blood loss. Friedlaender was treated with one of the new immunotherapy agents, ipilimumab (Yervoy), and it held his disease in check for about a year and half, but then the relentlessness resumed.

Three times he was rejected for trials of the anti-PD-1 immunotherapy drugs but finally was able to get Merck’s anti-PD-1 drug, pembrolizumab (Keytruda), in its expanded access phase.

Still, the cancer had metastasized so many places and it seemed time to face the hard truth.

“I reconciled myself to the possibility of death and I started end-of-life discussions with my family,” says Friedlaender. But he trusted Sznol. Tumors were blocking Friedlaender’s small intestine, but there was a real chance, Sznol advised, that this new therapy could eliminate the remaining disease after the surgery to relieve the blockages. So he went ahead with the surgery.

Now Friedlaender is in reasonably good health, a dramatic reversal from those dark days of 2014. Reflecting the optimism that helped carry him for 20 years, Friedlaender has elected to go off all immunotherapy medications, even though evidence supporting this choice is uncertain.

All those calculations, the tradeoffs, value math—it changes in life-threatening situations, says Friedlaender. “My risk–reward calculations changed dramatically as my survival chances declined,” he says. “I was ready to risk much more.”

Experts say increased “patient centeredness” is one of the most important elements to include in the transition to a value-based health care system. Friedlaender’s experience points to the primacy of the doctor–patient relationship. “The thing I valued the most was finding an oncologist who was extremely knowledgeable and communicative,” says Friedlaender. The interaction he had with Sznol fit perfectly with his desire and commitment to be so actively involved in his treatment. It doesn’t get talked about much, but putting American health care on a value-based footing, which often involves shifting financial risk to providers, could tarnish the doctor–patient relationship by insinuating cost considerations into treatment decisions.

If it were plugged into one of the value algorithms that ASCO and other organizations have put together, who knows how Friedlaender’s experience would come out. The cost of all of the treatments he has received easily exceeds $1 million. Friedlaender knows he’s been fortunate in this respect: His out-of-pocket costs have been a tiny fraction of that amount. “I have great coverage through Temple, plus Medicare,” he says. “I pay essentially nothing, not even monthly payments, because I prepaid for a plan with extra coverage before I retired.” He adds, “They don’t offer that package any more—and I may be responsible!”

Friedlaender wrote an essay for Health Affairs about his treatment experience that was published earlier this year and then excerpted in the Washington Post. He mentioned that his drug costs amounted to about $150,000 per year while the charges for a friend receiving the same treatment were four times higher. Drug companies charge whatever they think the market will bear, he wrote in the Post. “I strongly believe in introducing more competition to drug pricing and changing the way things are currently done,” says Friedlaender.

—Thomas Reinke, Contributing Editor

“My risk–reward calculations changed dramatically as my survival chances declined,” says Jonathan Friedlaender, a 20-year survivor of melanoma.

continued from page 17

CALL FOR PAPERS

MANAGED CARE is seeking article submissions. We welcome a wide variety of manuscripts, including drug class reviews, disease state management reviews, pharmacoeconomic analyses, strategies for coping with medication errors, and outcomes research. Interested? Write to our managing editor, Frank Diamond, at fdiamond@medimedia.com.
Cancer screening recommendations, long issued in one-size-fits-all, may be moving toward a bespoke approach, calibrated to more individualized risk factors and, perhaps eventually, a person's genes.

Currently, many screening recommendations hinge on just a few scraps of information about a person, including age and a family history of the disease. Meanwhile, the U.S. Preventive Services Task Force (USPSTF) and other groups have struggled with striking the right balance between the benefits of earlier detection and the risks of overdiagnosis and overtreatment. In 2012, USPSTF chose to steer clear of the perils of overdiagnosis and overtreatment when it recommended against routine PSA screening for prostate cancer, citing the harms of unnecessary biopsies and surgery and the difficulties of distinguishing slow-growing from aggressive malignancies.

But now the task force is revisiting that advice, and some researchers hope the result will be something of a comeback for PSA screening, but a new-and-improved version that takes into account more risk factors and stratifies screening more carefully by a man's chances of getting the disease. “My feeling and the feeling of a lot of people is that [the 2012 recommendation] was like throwing the baby out with the bath water,” says Mark Preston, MD, a urologic cancer surgeon at Brigham and Women's Hospital.

Preston coauthored a study that found that men, ages 45 to 69, with an elevated PSA were more likely to develop lethal prostate cancer later in life than men whose PSA is not elevated. (It should be noted, though, that the analysis was based on the Physicians' Health Study, with a study population and thus PSA readings primarily from white men.) In their results, published in August in the *Journal of Clinical Oncology*, Preston and his colleagues made the suggestion that screening could vary accordingly, so men with low PSA levels compared with the median PSA of their age group wouldn't need to be screened moving forward as often as those with high levels.

Another study, which began this year at NorthShore University HealthSystem in Evanston, Ill., is looking ahead to when genetic tests might become more routine. Jianfeng Xu, director of personalized medicine at NorthShore, has developed a risk score based on genetic tests for breast, colorectal, and prostate cancer. Now Xu and his colleagues have designed a study to find out whether people's screening behavior will change depending on their genetic risk score. Genetic tests like this will add some expense upfront but might save money if they winnow out unnecessary screening and the follow-up tests, they say. "We think that it's not going to necessarily increase health care costs, but rather make our utilization of precious health care resources much more efficient and beneficial," says Charles Brendler, MD, executive research director of the Program for Personalized Cancer Care at NorthShore.

**Homing in on high risk**

In its final research plan for the revision of the prostate cancer screening recommendation, the USPSTF has signaled its willingness to consider a risk-stratified approach to screening. One of the questions the task force decided to address is whether the PSA test's effectiveness varies with a man's age, race, ethnicity, family history, and other factors.

The prostate cancer screening is not the only cancer screening test getting a second look. Screening for lung cancer is a relatively recent development. In 2013, the USPSTF gave lung cancer screening with CT scans a “B” recommendation for adults ages 55 to 80 who have at least a 30-pack year history, including current smokers and those who have quit within the last 15 years. The task force's findings are highly influential, as any recommended test given an "A" or "B" rating must be covered by insurers under the Affordable Care Act.

**Low PSA readings**

through age 60 might mean that some men needn’t be screened again, says Mark Preston, MD, at Brigham and Women's Hospital.
Although it is more targeted than other kinds of cancer screening, lung cancer screening looked to be more expensive because it involves a CT scan, although some research suggested otherwise. For example, an analysis published in 2012 in *Health Affairs* found that the cost per projected life saved for lung cancer screening was $19,000, which was less than the per-life-saved cost for breast, cervical, or colon cancer screening. The low-dose CT screening test is expensive, and in this analysis the cost was pegged at about $250. But the economics of lung cancer screening are favorable because the screening is targeted, says Bruce Pyenson, the lead author and a principal consulting actuary at Milliman. “You have a concentrated risk population. You also have a cancer where the difference in survival between early and late stage [cancer] is very dramatic.”

But concern about false positives and the risks associated with lung biopsies and other procedures has led to some research of a strategy that might more precisely identify smokers at the highest risk of developing lung cancer, using factors like family history, an emphysema diagnosis, and body-mass index.

Earlier this year, a research team led by NCI researchers reported the results of some sophisticated computer modeling of this approach in *JAMA*. Their results showed that if lung cancer screening were to zero in on smokers with the highest five-year risk of developing lung cancer, it would be more effective. The number needed to be screened to prevent one lung cancer death would be 194 compared with 162 using the USPSTF recommendations. This research also found that it would be more efficient, with 116 false positives per prevented lung cancers compared with 133 using the USPSTF recommendations.

**More late-stage cancers**

But any tightening up of the criteria for screening carries with it concern that cancers will go undetected and be diagnosed at a later, less treatable stage. Some experts predicted that would happen after the 2012 USPSTF decision against routine PSA screening. And a study published earlier this year showed a small uptick in late-stage cases—those that have spread to the bone or other organs—in men ages 50 to 69 beginning in 2004 as various groups moved away from advising routine screening PSA tests. It’s a small increase, and it’s not yet known whether it will translate into more men dying from prostate cancer, notes Richard Hoffman, MD, one of the study’s authors and a general internist at the University of Iowa Carver College of Medicine. Even so, Hoffman says. “Going from overscreening to not screening at all, I think is a mistake.”

One middle-ground approach is to add some interpretation to PSA results that would help determine when and if further screening is necessary. In addition to identifying a correlation between above-median PSA results and lethal cancers, Preston’s study in the *Journal of Clinical Oncology* also found that if a man’s PSA levels stayed below the median level until he was about 60, the chance of him developing life-threatening prostate cancer was low. Further research is needed, but it might turn out that a man with a still-low reading at age 60 won’t need another PSA test, Preston says. “So what we can do is pretty effectively target our screening efforts,” he says.

At NorthShore, the primary care physicians involved in the study of the effect of genetic tests on screening will discuss the cancer risk score results with 500 patients. Hoffman, at the University of Iowa, says that genetic tests could eventually solve one of the biggest challenges in cancer: distinguishing between the slow- or non-growing malignancy that has little effect on a person’s health from the aggressive ones that should be treated. Meanwhile, it’s hard to know whether other risk-stratifying efforts—such as relying on a mid-life PSA—are meaningful, Hoffman says. Screening may catch the less harmful, slow-growing tumors while more lethal malignancies evade early detection regardless of the schedule. “We can’t say that if we looked for it earlier and more aggressively we’re going to make any difference,” says Hoffman, who hopes that the USPSTF will support a more personalized decision-making approach.

If genetic tests were developed to reliably predict risk (a big if, at this point) it might spare patients a lot of trouble—and the American health care system a lot of expense. Brendler at NorthShore points out that he’s gotten an annual PSA test for some 25 years. The total cost of those tests, he figures, adds up to more than $3,000—and his PSA level has remained unchanged. A genetic snapshot at age 40 might have suggested more occasional screening, he says.

*Charlotte Huff is a freelance health and business journalist in Fort Worth, Texas. She has written for* *Health Affairs*, *Medical Economics* and *Slate*, among many other publications.*
Imagine you have this growth in your body, cancer, the Big C. Society has indoctrinated you into believing that you must wage all-out war to defeat it—beat it before it beats you, kill it, excise it from your body—before it kills you. The martial metaphors abound.

But when she found out she had non-Hodgkin's lymphoma, Nancy Hughes, a 47-year-old patient at Memorial Sloan-Kettering Cancer Center in New York City, opted for a different approach. Instead of moving aggressively to kill or remove the tumor from her body, she decided to enter into a program of carefully watching the tumor for any changes.

“I remember thinking, this is insane,” Hughes recalls. “I have cancer, you have to get rid of it. And I think that's everybody's initial response.”

Doing nothing is a hard sell to people living with cancer.

Well, not exactly nothing. But yes, holding off on chemotherapy, radiation or an operation right away and deciding to weigh the burdens of treatment—both physical and financial—against the risk of the cancer growing and spreading out of control. Watch the cancer (with imaging tests and biopsies, if necessary) to see if it gets bigger—or if it just doesn’t do anything.

Active surveillance, a well-documented and increasingly common approach for monitoring prostate cancer in men, is gaining traction in many other types of cancer, from kidney to thyroid to breast and lymphoma. As with prostate cancer, active surveillance of cancers in other organs involves a selective approach; it’s only for low-grade, early-stage, and slow-growing tumors, and only for people expected to outlive the course of their disease and who aren’t anxious about the idea of living with the disease.

The appeal of active surveillance in prostate cancer, besides sparing men the side effects of radiation or surgery to treat a disease that may not reduce their life expectancy, is cost effectiveness. One study found that active surveillance in prostate cancer could save the health care system $1.32 billion a year nationally. Another study found active surveillance in prostate cancer can result in a net per-patient savings of $12,194 at five years and $4,329 at 10 years compared with immediate treatment.

But it’s not so easy to get people with cancer to broker a conditional peace with disease. Like real war, the war on cancer for the unwilling participants who are patients, to paraphrase Civil War General William Tecumseh Sherman, can be hell. The side effects of the treatments, not to mention the cost, can be debilitating. A 2013 article in the journal Clinical Thyroidology reported that people with cancer are twice as likely to declare bankruptcy than people who don't have it. And yet, people seem willing to wage that war. Results of a 2005 (granted, that is getting to be some time ago) survey published in the journal Medical Decision Making found Americans would overwhelmingly opt for cancer treatment even if it reduced their overall survival. The bluntly worded title of the article: “Cure Me Even If It Kills Me: Preferences for Invasive Cancer Treatment.”

Why now?

Active surveillance is gaining acceptance because of greater public awareness about cancer—think of the surge in colonoscopies after Katie Couric had one—and improvements in screening and access
today detect many cancers at an earlier stage. Medical imaging and diagnostic techniques have translated into better tools for monitoring small tumors and slow-growing cancers. More effective treatment means patients and doctors are more willing to hold off on immediately treating a cancer. Doctor-patient relationships are less dominated by doctors, so there’s a check on doctors who push treatment at all costs; shared decision making has made some inroads. Don Liss, MD, vice president of clinical programs and policy at Independence Blue Cross in Philadelphia, notes that despite all the professional guidelines about how and when to treat cancer, “in many circumstances there are lots of gray areas.” With no set path forward, active surveillance might be a choice.

The escalating cost of treating cancer may be another factor. In addition to putting individuals into bankruptcy, cancer treatment is eating up larger and larger chunks of Medicare and other budgets. The National Cancer Institute estimates that cancer care costs the United States $147 billion annually, and the cost curve bends north in every projection.

But active surveillance, with its many appointments, imaging tests, and biopsies, is hardly a free lunch. Definitive cost-effectiveness research is hard to come by, according to some doctors. “There needs to be more robust analysis of costs for each situation where surveillance is feasible,” says Bradley C. Leibovich, MD, chair of urology at the Mayo Clinic.

However, in a study published last year, Massachusetts General Hospital researchers compared the lifetime cost of active surveillance for breast cancer to prophylactic mastectomy and found that surveillance actually costs more—up to $2,000 more than a single prophylactic mastectomy and up to $21,000 more than mastectomy of both breasts. The cost variations depend on the type of reconstruction these patients undergo after mastectomy.

Emad Kandil, MD, an endocrine surgeon and thyroid specialist at Tulane University in New Orleans, was the lead author of an opinion piece discussing the treatment–active surveillance tradeoff published in JAMA Otolaryngology—Head & Neck Surgery earlier this year. Thyroidectomy for papillary thyroid microcarcinomas removes the primary tumor and decreases the need for further intervention. But the favorable outcomes may be because the microcarcinomas are slow growing, and Japanese researchers have reported similar outcomes when patients were in active surveillance programs, Kandil and his coauthors noted. That might argue for more active surveillance of patients with papillary thyroid microcarcinomas. But the plot thickens once you factor in costs. Active surveillance programs aren’t free, and patients may eventually need surgery. Yet Kandil says thyroid cancer is one of the most common cancers that affect out-of-pocket liabilities for patients with cancer, so overdiagnosis and overtreatment is a concern.

With all the beribboned survivors, it is hard to imagine, but it wasn’t that long ago that a cancer diag-

### Primary factors to consider when evaluating cost and value of treatment options for papillary thyroid microcarcinomas (PTMCs)

<table>
<thead>
<tr>
<th>Factors to consider</th>
<th>Surgery</th>
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</table>

* Data obtained from Japanese studies on active surveillance for PTMC. Applies to 7% to 16% of patients.

b Values estimated from the Nationwide Inpatient Sample–Healthcare Cost and Utilization Project. The cost is adjusted for the inflation rate to reflect the 2014 dollar value.

c Currently, there are no data to show the cost of follow-up surveillance only.

d Complications also contribute to cost estimates and range from $101 to $22,050 (depending on the type of complication).

Source: Kandil E et al., JAMA Otolaryngology—Head & Neck Surgery, January 2016
nosis was a death sentence. That’s not necessarily the case anymore, says medical ethicist Robert Arnold, MD, director of the Institute for Doctor–Patient Communication at the University of Pittsburgh. “The issue is that once you say, ‘You have cancer,’ people stop hearing the rest,” he says. “They’re nervous about not doing the right thing, or not doing as well, and they’re worried about the cancer spreading.” In other words, he doesn’t think a diagnosis of cancer is as fatalistic as it used to be.

But having cancer certainly means something. Nancy Hughes’s doctor at Memorial Sloan-Kettering sees that in his clinical practice daily. “This is an invasion in the body that does not belong there and they want to get rid of it,” says John Gerecitano, MD.

Gerecitano estimates that about half of his patients with indolent, or slow-growing, non-Hodgkin’s lymphoma are on active surveillance, but each case requires an individualized approach. “The two biggest tenets are a good education and constant conversation, and showing them we are actively following them and we are not leaving them by the wayside,” he says.

Mayo’s Leibovich says even just starting the conversation about active surveillance of kidney cancer with a patient takes commitment and extra time. “Most of these patients come in having had a primary care physician discover these tumors accidentally when they’ve had a scan for some other reason,” he says. “Most of them have been told, ‘You’ve got a kidney cancer and you have to get something done right away’.” He estimates his average conversation that just introduces the idea of active surveillance to a patient is at least a half hour and in some cases may last as long as an hour.

With small kidney tumors, as well as prostate cancer, the fear triggered by the very word cancer can get in the way of a meaningful conversation, says Leibovich. A growing number of oncologists think cancer is the wrong word and are advocating for calling very early stage, indolent cancers “indolent lesions of epithelial origin,” or IDLEs.

“They’re called cancers, but we know that not all cancers are destined to do a patient harm, no matter how long the patient is going to live,” Leibovich says. “Once we get that idea across to the patient, that this may or may not be harmful, and that in some circumstances you have the option of intervention now or intervention down the road if we think you need it, and that the outcome is just as good no matter which one you choose, no matter how long you live, then we can make progress.”

For patients with small renal masses diagnosed incidentally, providers typically recommend repeat imaging at three to six months initially, repeat imaging in six more months, and then annually, provided no changes are seen. “For patients with very small renal masses, I tell them right up front that the likelihood that the renal mass will affect how long they live or affect their quality of life is exceptionally low—but if they’re going to blow it off and not follow surveillance recommendations, then they could get themselves in trouble,” Leibovich says.

Physicians also have to change the way they think about cancer, says Arnold. His education outreach involves “trying to help physicians be more cognizant of the fact that just because you have cancer doesn’t mean you’re going to die of cancer. Some of it is just helping physicians be smarter about that.” For doctors, talking with people about their cancer involves attending to their emotions—something physicians are not necessarily trained to do, he notes.

Watch for information overload

Health plans have to walk a fine line in the conversation about active surveillance. If they push too hard, they’ll be seen as forcing patients to forgo life-saving treatments to benefit the bottom line, although the evidence on the cost effectiveness of active surveillance for cancers beyond the prostate is inconclusive at best. On the other hand, if plans are too lackadaisical they risk being accused of not informing cancer patients of all their options.

“In areas where there is controversy among experts, Independence Blue Cross believes the best approach for patients is to talk with well-trained, caring physicians who will engage them in shared decision-making,” says Liss. The health plan’s job is to provide information to members and access to a broad network of cancer specialists “whom we rely on to exercise their best professional judgment in recommending appropriate services in each individual case.”

Cigna relies on the National Comprehensive Cancer Network guidelines for determining what interventions are appropriate, says Bhuvana Sagar, MD, a clinical oncologist and Cigna medical director. “Our coverage policies are based on nationally recognized guidelines and evidence-based medicine guidelines, which are critical to avoid overtreatment

It’s important to constantly interact with cancer patients to show that “we are not leaving them by the wayside,” points out John Gerecitano, MD.
or undertreatment in these specific scenarios," she says. “When coverage is in question, we try to get as much clinical information as possible from the physician and look to clinical evidence to support the decision-making process.”

Arnold says that health plans should help people deal with not just what to do about their cancer, but to think through how it’s going to affect their own lives. “We need to be a little less caught up in the issue, ‘Do I have a disease?’ and think a little bit more about, ‘What does it mean for the quality of my life?’ It may mean things for the quality of life, but it may not,” he says.

Health plans, along with physicians and other providers, can help to “slow people down” in the decision-making process, he says. They need to be careful about how they present information: “It’s not just a matter of flooding patients with information,” says Arnold, noting that psychologists have studied information and how people make decisions. Insurers, he continues, need to think about the quantity of information they share, its presentation, and people’s emotional reactions to it.

So far, health plans haven’t done a very good job of this, in Arnold’s view. “Often, insurance companies have done what they do when people are choosing their insurance plans: They give you so much information that it doesn’t help—it just overwhelms most normal people,” he says. “We need to get them to slow down, to see if we can get people to realize that they have time and we want to help them make the best decisions possible.”

Teach risk tolerance
The former chief of hematology/oncology at the University of Chicago, Richard Schilsky, MD, has seen cancer care come full circle. Thirty-five years ago, oncologists couldn’t do much beyond watching and waiting for people with advanced, metastatic colon cancer that wasn’t causing any discomfort or other symptoms.

“It was not uncommon in those years to just observe the patient for a period of time before deciding on any intervention,” Schilsky says. “I had many patients we would observe for three, six months, even as long as a year without any worsening of the metastatic colon cancer.”

Now the senior vice president and chief medical officer of the American Society of Clinical Oncology, Schilsky sees the following as the challenges that must be met before active surveillance is widely accepted as an approach to more types of cancers:

- Physicians need more and better tools to diagnose and monitor tumors. “The more sensitive those tools are, the more useful they’re going to be in determining if the cancer is progressing,” Schilsky says.
- Physicians need better ways to evaluate the overall health of individual patients, specifically if patients have other medical problems that they may die from before the cancer runs its course.
- Consumers need to better understand—and tolerate—the risks associated with active surveillance. “There are some patients who are so frightened about the implications of the cancer diagnosis that, psychologically, they can’t tolerate the idea of active surveillance without some sort of intervention,” Schilsky says.

Genetic panels
In the not-too-distant future, advances in identifying genetic panels that reliably predict the future course of a cancer could be the tipping point for active surveillance that brings it fully into the mainstream. Say doctors could talk with certainty to their patients about the genetic evidence that shows that their cancers are highly unlikely to progress and cause health problems. Who wouldn’t consider active surveillance in such a circumstance?

With very small thyroid cancers, the difficulty is separating out the tumors that will progress to more consequential disease, he says. “We all agree that there could be a gene panel that will predict metastasis and recurrence,” says Kandil at Tulane. The problem is identifying all genes that need to be included—and excluding the ones that don’t.

Precision medicine—tailoring treatment to a person’s genetic makeup, environment, and other factors—is ripe territory for active surveillance, says Schilsky. “In a sense, it’s begging for that kind of approach because each tumor is different,” he says. “You have to be able to understand the characteristics of each individual person’s tumor and to assess the risk that the tumor poses in the context of the patient’s general health and risk tolerances.”

Kirkner reported on his own experience as a prostate cancer patient in active surveillance in the October 2015 issue of Managed Care.
The future of cancer treatment looks bright to Managed Care readers. But it’s optimism with a catch because they are also concerned about the cost of treatment—and most are dubious that efforts to rein in costs will do much good.

In an online survey conducted from September 9 to September 20, almost half (48%) of the respondents said they were optimistic about significant progress expected for cancer treatments over the next five years.

A larger proportion (86%) indicated that they were very concerned about the increasing cost of treatment, and about half (47%) had little confidence that the cost of cancer treatment could be controlled. “There’s plenty of optimism out there about where cancer treatment is headed,” says Mark Spickler, an analyst for MediMedia Research, which conducted the survey. “But it’s optimism with strings attached because of concerns about costs.”

MediMedia Research is part of MediMedia Managed Markets, which owns Managed Care. MediMedia Managed Markets is an ICON plc company.

There were 104 respondents to the survey, about a third of whom were pharmacists.

Precision medicine that guides treatment was top pick of the respondents among the various strategies for controlling costs: 36% of the respondents gave it a high rating. Bundled payments had few fans, despite the fact that CMS is rolling out a program that applies bundled payments to oncology. Only 14% were confident that bundled payments could significantly slow down the cost of cancer treatment.

In September, an outside group of experts made 10 recommendations for research priorities for the Obama administration’s Cancer Moonshot. Respondents to the MediMedia survey rated implementation of evidence-based approaches to prevention and early detection as the most important of the 10.

Source for all charts: MediMedia Research

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**MEDIMEDIA SURVEY ON CANCER TREATMENT**

**COSTS CAST SHADOW ON OPTIMISM ABOUT TREATMENT**

**Optimistic about significant progress in treatments over next 5 years**

Scale = 1–7; 1 = Not at all optimistic, 7 = Extremely optimistic

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**Confidence that the cost of cancer treatments can be controlled**

Scale = 1–7; 1 = Not at all confident, 7 = Extremely confident

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**Confidence in particular approaches to controlling treatment costs**

Scale = 1–7; 1 = Not at all confident, 7 = Extremely confident

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<td>Pathways</td>
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<td>Step therapy</td>
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<td>Reducing buy-and-bill incentives</td>
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Red: Mean

Green: Median

Blue: Mode
To ‘First, Do No Harm,’ You Must Start With Good Evidence

The intrepid young oncologist’s criticism of cancer screening and surrogate endpoints has stirred up controversy. He says he just wants drugmakers, others to meet high standards of evidence.

Interview by Peter Wehrwein

I gather you’re not too popular in the oncology community. You have a lot of thoughts that are skeptical and throw cold water on some current enthusiasms. You could say, certainly in the oncology community; probably the medical community. I did write something recently that kind of pushed the issue of precision medicine in Nature. I made a joke today that I got many, many emails in reply, and they were either one of two variety: Thank you for writing a great article, or curse you for writing the worst article.

How do you respond to being a person who stirs up controversy? Does it excite you?

No, I neither seek it out, nor do I avoid it. I just think that if people who read my book and the papers we publish, they’ll see it’s a fairly consistent viewpoint being applied to many different situations, and at the end of the day, that’s what happens when you apply any sort of a consistent viewpoint to some different examples.

What’s that consistent viewpoint that you just referred to? I think the consistent viewpoint is that we should recommend medical therapies to patients that, on average, do more good than harm. By “good” I mean things that matter to people, which is living longer, living better. That’s the consistent viewpoint. And then the controversies that arise are about what’s the level of evidence you need before you recommend a practice. I think when you take the long view of medicine, you tend to conclude that you really want better evidence than what is offered a lot of times, because we’ve been burned before when we didn’t ask for better evidence. And, we’ve harmed people before when we didn’t ask for better evidence.

We want medicine that makes people better off, and the question is, is specific practice X doing that? I think often the sobering answer is no, or we don’t know.

Evidence-based medicine got started 15, 20 years ago. We’ve had an idea and an agenda that’s supposed to address your concern about things entering clinical practice that aren’t proven. Why has it been such a failure? It’s been a success in one way, which is that, for many people, it’s been a very influential idea that is contrary to ideas in every other period of time in all of medicine, where the justification for an intervention was some mechanistic rationale of why it might work or some endorsement by a prominent figure. We finally entered an era where we realized the

The transcript of this interview has been edited for length and clarity.
best endorsement of a medical practice is some proof that it actually does what you think it does.

But then, the question is, “Why has it been unsuccessful in many ways?” I think it’s been unsuccessful in that there’s been resistance from people who like the old method, which is that it doesn’t matter if it’s been proven to work; it just matters that it’s plausible that it does work. That’s good enough. I think those people still exist.

A lot of people benefit from the lower bar. If you’re making something that’s a marginal product, or maybe doesn’t even work at all, you can still get it to market. So you can still make a lot of money if people don’t really ask you for proof that it works. That’s one.

Two, it’s tedious. It’s not glamorous to develop evidence. Three, evidence sometimes doesn’t apply to situations where you have patients with a unique set of problems in front of you, and it’s nice to be able to sort of, you know, make things up on the spot. Sort of improvise. And I think to some degree, we all do that. But I think the less attention we pay to the evidence, the psychologically easier it is to do that, perhaps, and the more confident you are that your extrapolations are correct.

I’d like to discuss two areas that you write about in Ending Medical Reversal. One is screening, and the other is surrogate endpoints. It seems to me that in describing medical reversals, it can often be chalked up to research in which the control group isn’t really a control group, that we needed to do sham surgery. Or the endpoint was subjective. But screening seems to have its own dynamic. I think you put it well. It has its own dynamic. The problem with screening is the endpoints that have been met in trials are not the endpoints we wish we had met, and we confuse the two of them.

With screening, we’re taking a lot of healthy people—they’re not patients, they’re healthy people—they come to you, and as a doctor, as a health care provider, and they say, “I feel great and I’m doing fine; is there anything that you have that could make me better off?” And screening tests are an answer to that question. But the truth is, we don’t really have good evidence that they actually do make you better off. We make a lot of assumptions, and we kind of fool ourselves into thinking that they do.

There are two types of cancer screenings. There are the ones that have some evidence, and there are the ones that have absolutely no evidence. And both are actually used a lot in practice. You know, CA-125 is used to screen for ovarian cancer, and that’s something that’s failed in multiple randomized trials, even to decrease dying from ovarian cancer. Forget about patients living longer, living better.

Even for the screening tests that do decrease the rate of dying from that cancer, we point out that that’s technically not really what you care about. When you get your sigmoidoscopy, you are doing it to decrease your rate of dying from colon cancer, yes. But that’s because you think that’s going to increase your life expectancy overall, or decrease your morbidity. And the truth is we don’t actually have proof that it does these last two things.

So screening is such a hot mess of a health care issue. Do you think there are ways out of it? Do you think doing some risk stratification would help? I think that mammography, prostate cancer screening—they really are hot messes. I mean, they’re public health disasters. And your question is good, which is that, why, when we embarked on the screening thing, did we ever have this idea that the screening test has to be one-size-fits-all for everybody? I think that was kind of a foolish idea. We should be looking at this first in very high-risk people. You know, the things we know are high risk—family history and certain risk factors. This is a general principle of medicine, which is that if you have a new drug, like a statin medication, the first randomized trial of statins was not statins in the tap water. The first trial was to people who had a heart attack with very, very high cholesterol. They picked very high-risk people and they proved mortality benefits.

In screening, that’s how we should have done it. We should have said, pick people at very high risk of breast cancer and screen them and show mortality benefit. And then, expand. But we didn’t do it that way. We always tried to get everyone with one fell swoop, and that’s completely the wrong strategy. And it’s unprecedented in medicine to want to do that.

Do you think that using genetic testing to assess vulnerability could be the ultimate risk factor stratifier, maybe the thing that solves the cancer screening problem? You’re on the right line of thinking, which is that maybe there are some prognostic factors that may be so predictive that they really do rid us of this dilemma of overdiagnoses, overtreatment, all those things.
I would say that genetics may continue to identify small groups of people. Right now we have a few germline mutations in, for example, the BRCA genes, where we know that they result in such a high risk that women benefit from things like prophylactic removal of the ovaries. So, we have a couple of examples. I'm open to more. I would be willing to consider evidence if somebody did come up with a gene signature that could risk stratify. But if I had to bet money on that, I would bet that it probably will be not the perfect risk tool because a lot of these common cancers tend to have multigenetic causes: Many, many genetic factors may slightly increase or decrease risk. So my gut instinct is that it won't be a perfect solution. But I do think avenues of investigation along those lines should be pursued, and it's the right way to think about screening and solving this problem.

If you were an insurer, what would you do about all this screening? Would you stop paying for it? There are many things in medicine that I would stop paying for. Screening is probably the one issue that I would be reluctant to use that kind of blunt-force tactic because of the extreme emotions it generates. If I were an insurer I would actually pay for a randomized trial of screening. Get the people who are on the fence—and there are many—and ask them to enroll in the randomized study. And the study has potential to really answer this question in a very definitive way and probably change future practice.

I would also mandate that healthy people are told the hard facts about screening: No, it has not been shown to improve overall mortality, and details of overdiagnosis and false positives—an honest discussion alone will likely result in many people choosing not to have it.

I want to change the subject to surrogate endpoints. There is a general discussion about how surrogate endpoints can put us on the path to ineffective interventions. You end up treating the lab value rather than the clinical condition. But with cancer, there's an argument that without surrogate endpoints, with people living longer with cancer, to get the definitive survival data that you would need for a statistically significant result, that takes years. In the meantime, people might be literally dying because they don't have access to this therapy. Or dying sooner, to be more precise. I hear that point a lot. Does waiting for survival take a very long time? That's built into this question. That's actually, to some degree—I hate to say it—it's kind of a fallacy. And I'll tell you why. The time it takes to generate a statistically positive result is, in some way, contingent on the rate of the event, which is death in this case. And, it is contingent on the rate of death; the longer that takes to happen, the longer it takes to generate the result. But it is also contingent on the sample size, and many modern trials have huge sample sizes.

We've looked at many of the oncology trials, and

The problem with screening is the endpoints that have been met in trials are not the endpoints we wish we had met, and we confuse the two of them.

these trials that are being run in oncology are huge trials. We're running oncology trials that are so powerful, they can detect survival benefits in a very short period of time. They are often overpowered to detect trivial differences.

The other thing this is all contingent upon is which indications do you develop cancer drugs for first? I think it is a mistake to think the manufacturers' intent is to bring the drug to market as fast as possible. Manufacturers' incentive is to bring the drug to market with as large a market share as possible. And in doing so, they often make decisions to chase a surrogate, even if that takes a longer period of time for a large indication. We have some examples of drugs that could have been brought to market even faster if we went for second rather than first line in a particular cancer.

So where should we allow surrogate endpoints? I think we should allow them in cases that are dire, where without a drug approved on a surrogate, people will pass away in a short period of time. I'm okay with them when there are a few other treatment options, for people who have very few options, like melanoma maybe five, six years ago. That's where you want an accelerated approval. There's literally nothing else we have to give people with that condition.

I also think there has to be a yin to the yang. There should be post-marketing commitments in randomized trials so they actually do what we think they do. And those should be enforced. And we've done studies where we show that with about five years of follow-up of 36 drugs approved based on a surrogate, only five later improved survival. Currently, we are failing at enforcing these commitments.

Is that what you are saying in your recent paper in Mayo Clinic Proceedings? That was in JAMA Internal Medicine a year ago. In the Mayo paper, we go even further. We show that many of these drugs getting approved on surrogate endpoints are getting full ap-
proval, meaning there’s no post-marketing efficacy commitment. And when they’re giving full approval, the FDA’s own regulatory language says, “We will do that only when we have proof that a surrogate is ‘established.’ And we show that in a big chunk—37% of those cases—these established surrogates had no data that have ever even looked to see if they correlate at all with survival, let alone being established. There’s no study on the topic.

So you want those approvals to be contingent upon post-market studies that will test the proposition whether that surrogate marker is, in fact, related to survival or quality of life. Yes. And I would just add to that I want those post-marketing randomized trials to be done in a timely fashion.

I would also say that I want the accelerated approval to be given in the right settings, where things are dire, rare, and there are few other options. Not when there’s 83 other regimens approved for the treatment. And in fact, we have some unpublished data where we show that is, in fact, the case. People call something an unmet medical need, and you look and there’s 80 different treatments. On what planet is that an unmet medical need?

What do you think of the Right to Try laws? I think they’re terrible. They’re disingenuous. They’re written by people who want to weaken the FDA. That’s their ultimate purpose. They’re written under the guise of helping patients, but they do no such thing. In fact, FDA data shows that 99% of all requests for compassionate use are granted by the FDA, but very few requests are actually granted by companies. The companies are the barriers. Companies don’t want to give you their experimental drug so that this person can take it and have some side effect and then kill the whole drug development pipeline. That’s the real barrier.

There’s a lot of enthusiasm about cancer treatment. Do you think we’re in a bubble that’s going to burst? We’re absolutely in a bubble. We have this huge amount of years of life lost because of cancer. It’s a horrible problem. It’s probably, by some measurements, worse than cardiovascular disease. People always say like, death from cardiovascular disease is greater, but that’s not the right metric. The metric is, you know, cancer is killing people at untimely ages. 40-year-old people. That’s a huge loss of years of life.

I mean, the moonshot is right. We need to actually, as a society, do something about this problem. And I believe with the proper moonshot, we might be able to do something about it. But this is a joke of a moonshot. I call it a puddle jump. I mean, this is, you know, $700 million when you’ve been spending $5 billion a year, year after year. That’s not even on the right scale.

And all of these things that get touted in the moonshot, we already know they’re not going to bend these cancer statistics markedly. Immunotherapy. Immunotherapy has 20% to 30% response rates in a handful of cancers. If you made a pie of all the cancers that are killing people, and you highlighted all of the cancer indications that are amenable to immunotherapy, you’ll have a piece of pie that is too small to serve in a restaurant. I mean, it’s a sliver of the pie.

You’re critical of screening; you think many drug approvals are based on misleading surrogate markers; the excitement about immunotherapy you think is misplaced. So where would you put our efforts? I think the one thing that has to be done is an unconflicted clinical trials agenda. We have cooperative groups doing a few important randomized trials, but we have almost nobody setting a vigorous clinical trials agenda, where we compare, you know, the things we have in different dosing, different schedules, different strategies.

Right now, 9% of patients are on clinical trials. People always say that it should be higher, but I would actually say something different. I would say that it should be much higher, but specifically, randomized trials conducted by nonconflicted sponsors. I would say the federal government should create an agency of nonconflicted randomized control trials, where people who design the trials are experts who are without conflicts. And they should have Medicare pay for the drugs in the study. Now we depend on the company donating the drug, and the company will only donate the drug if we ask the question the way the company wants to ask it. That’s a big problem.

I also think you have to fund cancer biological science research very broadly, and in a non-fad way. Giving people high doses of chemotherapy and giving bone marrow transplants—that was in vogue for 10 years. Before that, it was multidrug combination therapy. There was targeted therapy, and now we have the immunotherapy and precision medicine. Maybe it is a little harsh to call these fads, because they had many real successes, but they are fads in the sense that in the years they were in vogue, there was little funding or attention for anything else. I don’t think funding should be subject to such fads. It should be more consistent and broad.

Feedback Please!
Send your letters and comments to editors@managedcaremag.com
A few years ago, as a young relative was enjoying a motorcycle ride in the countryside of western Pennsylvania, a truck pulled out in front of him from a side road, resulting in a horrible accident. As his mother watched, the first responders stabilized his multiple fractures to prepare him for a flight to a trauma center. He had many injuries but the most severe were fractures of his arms and pelvis.

The goals of the orthopedic surgeons were to preserve his blood supply, provide anatomic reduction of the bones in his arms, and create stable fixation. Overall, they were doing everything they could to allow him to become active as soon as possible so he would heal faster, staving off all the complications of immobility. Repairs of fractures have to be strong enough to keep a person’s weight and motion from moving the bones until they had a chance to heal. To do that, surgeons can use traditional casting, place nails inside the bone’s medullary cavity, or screw plates of metal to the outside of the bones to align and stabilize the fracture.

The surgeons allowed the bones to heal in a normal alignment, and after months of physical therapy, he has normal function and range of motion. Today he’s back to work at a physically demanding job.

However, while I was visiting him last winter, he mentioned that the plates ache when it gets cold. Don’t get me wrong: He was not complaining. But his cold weather aches are real.

Metal plates, nails, and screws have been used for decades in orthopedic treatments. They are used to stabilize many of the roughly 600,000 fractures of the long bones of the legs and arms that occur in the United States each year. They are manufactured by a number of major orthopedic supply companies. Like nails and screws you buy at a hardware store, they come in common standard sizes and shapes, and the plates are not just flat pieces of material but have a concave shape to the back to conform to the cylinder shape of the bones they are designed to treat. The plates come in a variety of forms— including straight, angled, and T-shaped—to allow them to be used for dozens of different types of fractures.

But metal implants have some serious drawbacks. For one thing, imaging is problematic. Normal dose X-rays don’t penetrate metal well, and metal implants interfere with MRI images of the soft tissue near the metal.

Metal is rigid, and that is important to keep a fractured bone properly aligned. On the other hand, some motion at a fracture site is beneficial and stimulates bone tissue to heal. In fact, scientists discovered decades ago that small amounts of motion around a fracture site actually creates a small electrical current and hastens healing. Electrical stimulation devices have been used for years to try to reproduce this electrical current and, in fact, the FDA has approved numerous bone-growth stimulator devices, and CMS and commercial insurers cover the treatments.

Cold-weather problems
Another problem with metal as material for implants is that it transfers heat at a different rate than human tissue. That difference is the reason my relative and many others with metal implants have aches and pains during cold weather. Often it is tolerable, but sometimes the pain is severe enough that people ask to have plates and screws removed long after healing is complete.

Material Gain: CarboFix’s Carbon Fiber Hardware Better Than Metal Implants

Carbon fiber is more flexible than metal, so it may help fractured bones heal faster. Carbon fiber hardware may also have an application in oncology.

Thomas Morrow, MD

Thomas Morrow, MD, is the chief medical officer of Next IT. He has been the founding medical director of five HMOs and a disease management company, a medical director at Genentech, and president of the National Association of Managed Care Physicians. You can contact him at TMorrow@ManagedCareMag.com.
For these and other reasons, researchers have been searching for years for an alternative material for orthopedic screws, pins, and plates. Carbon fiber, which is not a new discovery—early forms were first used in 19th century as a filament in light bulbs—was an early candidate. But there have been a lot of advances in how carbon fiber is made, and today’s composites are used to construct race cars, drones, sports equipment, bikes—even much of the body of the Boeing 787. Drawing on its strength and low weight, early medical applications included limb prosthetic fabrication and wound dressings.

Carbon fiber has many physical, chemical, and biological characteristics that would seem to make it an ideal material for orthopedic hardware. Besides its resistance to corrosion, it has high heat tolerance and an astounding strength-to-weight ratio. It also flexes, so it’s just as elastic as real bone and should help fractures mend.

But there were some problems early on with using carbon fiber instead of metal. Results of some studies in the 1980s of plates made of many thin sheets of carbon fiber stuck together with epoxy resin showed some promise but also high infection rates. The plates were also expensive and difficult to mold into the correct shape. Research sputtered and, for the most part, stalled.

Now a small company called CarboFix Orthopedics is helping revise hope and interest in carbon fiber orthopedic implants. Headquartered in Israel, CarboFix has come up with a new adhesive, polyether ether ketone (PEEK), and a special lamination process. In numerous clinical trials, CarboFix’s plates and nails have been shown to be better than traditional metal in several ways. They are stronger and less stiff than metal implants, including those made out of titanium, and show less wear and tear. Importantly, given the track record of earlier carbon fiber implants, the CarboFix Orthopedics products haven’t triggered inflammatory reactions.

**Benefit for cancer patients**

CarboFix’s carbon fiber products may have advantages beyond traumatic orthopedic injuries, particularly for some cancer patients. For patients with malignant bone and soft tissue tumors, wide surgical resection can add to the risk of pathologic fracture (a fracture related to the tumor). Radiation, cryosurgery, and argon beam coagulation can also add to this risk and to poor healing of such fractures (termed persistent nonunion). So to prevent complications, bones are commonly treated prophylactically with intramedullary nails or plates. However, traditional stainless steel or titanium implants can obstruct imaging, making it challenging to detect recurrent disease. CarboFix’s products create significantly less MRI signal loss as well as minimized artifact on CT imaging. They also do not interfere with radiation treatment in the way that metal implants can. Physicians have dubbed the carbon fiber nails the “invisible nail” because of its benefits.

But CarboFix implants are marked with faint radio-opaque markers so they are not totally invisible to X-rays, and some of the products have predrilled holes so they can be attached with standard metal screws.

Like the metal implants, CarboFix’s plates are designed for specific regions of specific bones including the proximal humerus, distal radius (standard and narrow sizes), distal fibula, diaphyseal distal femur, and others. Similarly, nails are specifically designed for the various locations of fractures of the humerus, tibia, femur, and ankle. These devices come in numerous lengths, diameters, and with a variety of number of predrilled holes for the screws.

CarboFix is currently involved in a side-by-side study to prove that the semi-flexible nature of its devices promote better healing than traditional metal implants, something that numerous orthopedists have reported anecdotally.

In Europe, CarboFix has also brought to the market what some are calling “the ultimate in orthopedic implants”—carbon fiber pedicle screws and rods for spinal surgery. They offer a real improvement in spinal surgery because radiolucency is very important in this application. These spinal surgery products aren’t on the market yet. In the United States, they have been approved for investigational study.

CarboFix’s pricing policy is noteworthy. Virtually all device and pharmaceutical companies price a superior product higher. CarboFix has chosen to price their devices competitively to the traditional metal devices.

After several decades of development, carbon fiber has finally come to the forefront of orthopedics and could mean a huge advance in treatment of fractures from trauma and the various orthopedic challenges in oncology.
The NIH estimates that somewhere between $150 billion and $200 billion will be spent annually on cancer care in the United States by 2020. No doubt, the rising costs of cancer treatment drugs make managing oncology expenditures a steep hill to climb. But despite all the attention that their six-figure price tags have gotten, cancer drugs aren’t the only culprit and are just part of the story.

According to an analysis of Medicare data, 40% of cancer patients have one or more comorbidities and 15% have two or more, the most common of which are diabetes, chronic obstructive pulmonary disease, and congestive heart failure. Many people with these chronic diseases are able to manage them well with routine care so that drug therapy, nutrition, and other important factors are well monitored and nothing “falls through the cracks.” But for cancer patients with comorbidities, the cracks tend to get bigger and also harder to see. Diseases like heart disease or diabetes can complicate cancer care on multiple levels—and vice versa. And, ultimately, that can lead to huge expenditures, expensive interventions, and poor outcomes for patients. Here’s an example, a composite of what can happen: Joe has congestive heart failure and is seen regularly by his cardiologist, who helps him manage the condition with medications. Joe does his part by changing his diet, exercising regularly, and taking his pills as directed. On the whole, he is living well with congestive heart failure and can work full time and spend quality time with loved ones. But then Joe finds out he has late-stage lung cancer. Oncologists, pulmonologists, thoracic surgeons—he has appointments with them all. He has little mind share left for CHF.

Joe slacks on his diet and exercise and doesn’t take his meds on days when he’s feeling too tired or sick from chemo. He gains weight quickly and frequently experiences shortness of breath, telling signs of worsening congestive heart failure but also common side effects of cancer treatment. Joe has to stop working when the swelling in his legs gets too painful and makes it hard to walk. He eventually has a set of acute episodes that leave him hospitalized. In the hospital, Joe learns that his heart failure has advanced quickly and he is no longer a candidate for chemotherapy.

Lung cancer is a serious diagnosis. It requires top-notch care and aggressive treatment. But so is congestive heart failure. Even though Joe could live well with the disease while it was managed correctly, it has seriously affected his quality of life with cancer. As it has progressed, his heart failure has also become much more expensive. Each stay in the hospital, for instance, costs upward of $10,000—and one day in the ICU can cost $10,000 per day.

So what can we do for...
patients like Joe? We need to integrate care, which in this context means bringing together the care for cancer with the care for all the other health problems that patients might have. Cancer programs famously form interdisciplinary teams of medical oncologists, surgical oncologists, and radiation oncologists to treat cancer—but just cancer. Other conditions and the specialists with the expertise to treat them are not included. That needs to change.

Here are four suggestions for how cancer care for people with comorbid conditions could be better managed:

- Assign a care “quarterback” and integrate the care plan across all providers (inside and outside of oncology) so that one person is directing the care experience starting at diagnosis. Primary care physicians make great quarterbacks.
- Embed the quarterback in the cancer care team (and if your program is large enough, also include cardiologists or an endocrinologist) and routinely address noncancer care needs in the same office visit at which a patient is seeing a medical oncologist. (Pro tip: If your contracts are fee-for-service, then you’ll need to bill for them separately, including different diagnoses for the two visits.)
- Bake in palliative care seamlessly, so that all providers on the team—and patients and families themselves—are aware of the goals, resources, and benefits of palliative care and are explicitly aware of the patient’s goals for treatment, pain management, and quality of life.
- Round out the care team with care managers and behavioral health services, including psychosocial screenings, to be sure that factors that are often overlooked like depression and family dynamics aren’t getting in the way of care.

If you think this sounds unrealistic, then you might have a point. This level of coordination will take work and a ton of cooperation among providers. And in many markets, the financial incentives still perversely reward uncoordinated care.

But you have to consider where health care is headed and shift toward population health management. CMMI’s new Oncology Care Model, for example, is nudging providers toward performance-based payment based on total cost of care (including care for nonrelated accidents and comorbidities). We’re already moving toward a more holistic approach, with accountability for cost explicitly shared across a broader team of providers. That is an important development. There are millions of Joes out there. And with an aging, sicker, population on the horizon, Joe may just be the new face of cancer.

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Maureen Dwyer Liberti
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Fault Lies Not in the Stars But in Plans’ Implementation

Success in the Medicare Stars ratings system requires a culture that looks beyond short-term success to ensure long-term survival.

By Vanessa Pawlak
Principal, Ernst & Young, LLP

The Medicare Five-Star Quality Rating System constantly challenges health plans to keep an eye on the future because they’re in a unique, unprecedented turning point in the industry. This turning point has been marked by resource constraints in the aftermath of an economic recession, the greatest amount of regulatory change in American health industry history, baby boomers entering Medicare age, and more government scrutiny than ever before.

Health plans that are disproportionately focused on weathering the storm rather than thinking about the future will find it difficult to foresee and predict changes with an evolving program like Stars.

The Stars system is no longer a demonstration project, and CMS has given plans ample time to familiarize their operations with Stars requirements and improve their performance. The bar has been set higher as Stars has become permanent and CMS’s expectations have risen.

Moreover, health plans have an added incentive to improve their marks now that a rating of four stars or better is required for quality bonus payments (QBP). But it’s also much harder for new plans to enter and earn a QBP without highly effective implementation of quality improvement and systems to measure it. As CMS changes the measures year to year, organizations will have to adjust to the new measures and CMS’s system for weighting certain measures more than others. These implementation efforts should not be taken lightly, particularly if a plan expects to stay competitive.

CMS also learned from the demonstration project to modify the methodology for calculating Part D measures, in addition to including measures for complex care, such as within Special Needs Plans (SNPs). Beneficiaries in SNPs are often elderly with multiple chronic conditions. Now that more is expected of health plans, more complex measures are being added, and seamless coordination is required to obtain a rating of four stars or better.

Ways to improve

To drive better Medicare star ratings, it is important to think about ways to enable increased integration of the medical and pharmacy benefit. Some of the highest-rated plans over the demonstration period were contracts that had more integrated health care benefit designs.

Influencing the medication therapy management program not only helps with managing chronic conditions, where plans have traditionally struggled, but also helps with the member experience, patient safety, and drug pricing. The idea is to enable programs and improvement initiatives that simultaneously impact the clinical, administrative, and operational aspects of the care continuum and the stakeholders within it.

Plans must also focus on improved data governance and management. Improvements here mean data integrity, the ability to drive timely insights through analytics, and the ability to make more accurate and informed decisions.

Communication is another area to focus on. Finding effective communication channels for frequent and relevant education for members and providers is essential to managing important issues and dynamics that may be outside the direct control of the health plan.

Health plans are starting to assign “practice managers” to their provider groups to establish a more direct connection to physicians and what happens inside the patient room.

Health plans must focus on two questions when it comes to members: First, what should be communicated and, second, the best means for communicating it. The “what” should be information that benefits the members, and the “how” must be easy to understand and follow.
member’s health, such as reminders to schedule a routine mammogram. The “how” might be something as familiar and old-school as a birthday card with that reminder, or it could be new channels of connectivity, such as wearable technology or a text message. Especially with the volume of baby boomers aging into Medicare—who are more familiar with digital technology than their parents were, even if they can’t keep up with the millennials—digital and online communication is increasingly important.

**Like someone trying to lose weight**

Earning five stars means making the Stars program a priority and demonstrating real commitment. Health plans often start out with good intentions but fall short when it comes to follow-through and implementation. A continuous culture of quality is needed within the organization. All individuals in the health plan are quarterbacks of quality in their span of control and influence. An enterprise-run Stars model is how successful Medicare Advantage plans minimize the challenge of achieving five stars. This model is supported by data governance and management in which the architecture and access to data is infused and integrated across all functional areas touched by the Stars program ratings. Most health plans lack anything that is even close to that. Instead, they have a fractured data environment devoid of formal Stars purpose.

CMS is moving away from the imposed thresholds for stars measures. It’s a constructive change. Currently, the immediate motivations for plans are each measure’s target threshold. Plans push to reach a threshold number. At times, those efforts can mean using unsustainable methods, overworking their member services teams or sending a flurry of last-minute, untracked mass mailings. It is analogous to someone who wants to lose weight. If he targets a number, sometimes he’ll use drastic methods just to reach the target and soon gain the weight back rather than changing behaviors relating to diet and exercise gradually and in a way that can be sustained. Health plans and the Stars program are similar. They tend to look at each of the Stars measures in an isolated, siloed way and thus try to hit that target rather than working to improve the whole through end-to-end, systemic clinical, operational, and administrative behavioral changes.

**What works**

As the Stars program has progressed and evolved, we have seen some common threads to success. One is that not-for-profits tend to outperform for-profit health plans. Further, plans that have been in the Medicare business longer have also tended to fare better in the Stars arena. Why are the not-for-profit plans more successful? For one thing, they are more accustomed to the reinvestment of dollars into their organizations. Effectiveness with reinvestment is an essential component of improving stars ratings over time within the Stars program. Plans with Medicare experience are, as you might expect, more familiar with the kind of scrutiny that occurs in the Stars program and are more likely to have leaders who understand how to deal with CMS’s expectations, intent, and rules.

We’ve also found that health plans that perform better in the Stars program have, in fact, found ways to drive more effective care coordination and delivery. They’re also better at the integration of the medical and pharmacy benefit. Medicare Advantage plus Part D plans (MA-PD) are some of the higher scoring plans and the ones that have trended upward with scores over time.

Plans that do well are truly “member-centric” clinically, operationally, and administratively. These plans more effectively manage members holistically across their continuum of care, from the patients’ room to the member’s phone call to the health plan’s call center. Health plans that manage their members well are adept at working directly with members but also indirectly through providers and families.

**A star-studded future**

When we look at the Stars program in the context of the multitrillion dollar American health care industry, it may seem like just another program, a small fish in the sea, even if billions of dollars are at stake. However, the Stars program is cutting edge in the move toward a consumer-driven health care landscape. The incentives are strong enough so the Medicare market has responded to the Stars program, bringing the accountability and transparency that consumers—the American public—are coming to expect. It’s only a matter of time until the Stars program—or something very much like it—spreads to the country’s Medicaid programs, the ACA exchanges, and eventually to the employer-based market. We’re facing a star-studded future. Now is the time for health care organizations to familiarize themselves with the changes to the Medicare Stars ratings program, learn what it takes to drive higher scores, and make achieving Stars success a priority.

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Vanessa Pawlak is a principal at Ernst & Young LLP and on the firm’s Global Advisory Health Sector team. The views expressed here are hers and do not necessarily reflect the views of Ernst & Young LLP.
Worldwide costs of oncology drugs will rise above $150 billion by 2020, according to a report by the IMS Institute for Healthcare Informatics. Many factors are in play, according to IMS, including the new wave of expensive immunotherapies. Pembrolizumab (Keytruda), priced at $150,000 per year per patient, and nivolumab (Opdivo), priced at $165,000, may be harbingers of the market for cancer immunotherapies. They came on the market in 2014, and their “rapid uptake reflect their remarkable clinical profile and successive expansion of indications,” the report states. More than 135 clinical trials involving 30 tumor types are going on for the two drugs, according to IMS.

Some factors may put some downward pressure on spending for cancer drugs in the coming years. Patent expiration, for one thing, and possibly biosimilar competition as well. But tugging in the other direction are increases in prevalence and treatment rates. And if therapies become more effective, cancer patients will live longer—wonderful news but also a factor that must be taken into account for those trying to keep the cost of cancer treatment in line.

Moreover, many patients who aren’t candidates for existing cancer therapies might be eligible for the new products, the report states.

Immuno-oncology PD-1 inhibitor uptake in the U.S.

Global oncology costs and growth, 2010-2020

EUS = France, Germany, Italy, Spain, United Kingdom.
Pharmerging = Tier 1: China; Tier 2: Brazil, India, Russia; Tier 3 Group 1: Poland, Argentina, Turkey, Mexico, Venezuela, Romania, Saudi Arabia and Colombia; Tier 3 Group 2: Vietnam, South Africa, Algeria, Thailand, Indonesia, Egypt, Pakistan, Nigeria and Ukraine.