Help Wanted: Endless Hours, No Pay Only Caregivers Need Apply .......... 27
Will Plans Follow VA’s Lead And Cover Exoskeletons? ............. 32
Q&A: Thomas H. Lee, MD, Puts Suffering In Perspective ...... 35
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Patients With Metastatic Bladder Cancer Have an Unmet Need

Bladder cancer research has seen few advancements over the past 30 years. No new agents have been approved for metastatic bladder cancer since 1998.1-3

Metastatic Bladder Cancer4:

- Approximately 4% of new diagnoses represent metastatic disease (stage IV)
- 5-year relative survival rate of patients with metastatic disease is 5.4%
- Mortality rates for metastatic disease have remained relatively constant since 1975

“Against the background of no new drug approvals for advanced bladder cancer in decades, immunotherapy research is giving new hope to patients and physicians.”

–Michael R. Harrison, MD, Duke Cancer Institute

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REFERENCES
Health—With a Little Bit of Luck

By Peter Wehrwein

Kevin Volpp, MD, should know better.

Volpp is the founding director of the Center for Health Incentives and Behavioral Economics at the University of Pennsylvania. He has studied lotteries and knows the tricks they play on the human brain. Invariably, people tend to overestimate small probabilities that are near zero, Volpp explained in a talk last month at Penn.

But despite the vanishingly small, 1 in 292 million odds, Volpp chipped into the office pool that bought tickets for the $1.6 billion Powerball lottery drawing on January 13.

Volpp said he was motivated partly by a desire to avoid regret. What if his officemates did win and he hadn’t joined in?

Lotteries can also be viewed as entertainment, Volpp told me after his talk. I can relate to that. I am writing this piece because my Powerball ship did not come in. But for a couple of hours there, I had a great fantasy life going. How much for the kids, my mother, my siblings, some friends and cousins? How much for some kind of civic project for my neighborhood in Philadelphia or a journalism endeavor? It went on and on.

Because of research by Volpp and others, health plans are tapping into the human weakness for games of chance. We’re seeing it firsthand here at Managed Care. Our Aetna plan is offering us a chance to win a Fitbit if we fill out a health assessment and participate in a “health journey” aimed at addressing one of a variety of health issues, including sleep, stress, and losing weight.

Getting certain preventive health services, such as a screening colonoscopy or an annual physical, will also get you entered. Do both and an unnamed grand prize could be yours, we’ve been told.

I am curious about the health assessment and am overdue for a physical. The Fitbit lottery will give me a little extra motivation to get with Aetna’s program. But I am also thinking about playing Powerball a little more often.

Aetna’s program may improve my health, but Powerball—that did wonders for my fantasy life.
The Doctor Is In, Hip, Cool, and With It (Dig?) 19
Even if some young docs happen to be nerds that one would never describe as groovy (is that still a word?), it doesn’t matter. They bring a mindset. They’re willing to work in teams and focus on the sort of evidence-based medicine that can guide health care’s transformation into a system based on value.

Caregivers Need More Than Respect 27
Nearly 15% of the population cares for a loved one. They spend an average of 24 hours a week on caregiving, and nearly 60% have to tackle complex medical tasks, such as giving injections. They need training, and many argue that they also deserve financial help. Some health plans agree.

Q&A: Tom Lee Brings Back ‘Suffering’, ‘Empathy’ 35
Simple words sometimes hold the most complex ideas, and this nationally known health care expert drives this idea home in his latest book, *An Epidemic of Empathy in Healthcare*: “Empathy is a necessary step toward actually taking action to help reduce a patient’s suffering.”

Original Research
Constipation Treatments Compared 41
Researchers conclude that linaclotide is less expensive and just as effective as lubiprostone for treating chronic idiopathic constipation. Total direct costs were $946 per linaclotide-treated patient and $1,015 per patient-treated with lubiprostone.

DEPARTMENTS
Editor’s Memo ........................................... 1
Health care lotteries might be the ticket.

News & Commentary ................................. 10
Concern about PPIs and kidneys.

Legislation & Regulation ........................... 13
What regulators weigh in mega-mergers.

Biologics in Development ......................... 16
Biosimilars nearing end of phase 3.

Viewpoint ............................................. 26
Doctoring runs in Stefanacci family.

Tomorrow’s Medicine ................................. 32
Exoskeleton takes major step forward.

Cancer Watch ........................................... 39
Moonshot has uncertain trajectory.

Outlook .................................................. 49
Cancer still deadly but less so in 2016.
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Proton Pump Inhibitors Associated With Higher Risk of Chronic Kidney Disease

Even relatively rare adverse effects from medication can strain the health care system if millions of people use that drug, a study in *JAMA Internal Medicine* points out.

Researchers looking at data from two observational studies found a link between the use of proton pump inhibitors (PPIs) and chronic kidney disease (CKD), which affects about 13.6% of American adults.

“More than 15 million Americans used prescription PPIs in 2013, costing more than $10 billion,” states the study “Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease,” which was published online on January 11. It adds that “up to 70% of these prescriptions are without indication and that 25% of long-term PPI users could discontinue therapy without developing symptoms. Indeed, there are already calls for the reduction of unnecessary use of PPIs.”

Those making such calls already have used this study to bolster their argument. In an accompanying editorial, Adam Schoenfeld, MD, and Deborah Grady, MD, of the University of California–San Francisco, argued that a “large number of patients are taking PPIs for no clear reason—often remote symptoms of dyspepsia or heartburn that have since resolved. In these patients, PPIs should be stopped to determine if symptomatic treatment is needed.”

Exactly how PPIs affect the kidneys is not known, though the study’s researchers, headed by Morgan Grams, MD, of Johns Hopkins University, noted that other research links PPIs to interstitial nephritis.

The study reviewed data on 10,482 people who were part of the Atherosclerosis Risk in Communities (ARIC) study. The data were analyzed from May to October 2015. Of 322 PPI users, 56 developed CKD, meaning that if they were tracked for one year, 14.2 out of 1,000 would get CKD. Of 10,160 nonusers of PPIs, 1,382 got CKD, meaning that if they were tracked for one year, 10.7 out of 1,000 would get CKD.

Researchers found that PPI use led to a “20% to 50% higher risk of CKD, after adjusting for several potential confounding variables, including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications.” Meanwhile, use of H2 receptor antagonists, which are also prescribed for PPI, “was not independently associated with CKD.”

The other study involved tracking 248,751 patients in the Geisinger Health System between Feb. 13, 1997 and Oct. 9, 2014. In this case, 1,921 patients among 16,900 PPI users developed CKD, while 28,226 of 231,851 nonusers developed CKD. The study states that “the 10-year absolute risk of CKD among the 16,900 baseline PPI users was 15.6% and the expected risk had they not used PPIs was 13.9% (absolute risk difference, 1.7%).”

The usual caveats about observational studies apply. The data can only show an association, and the higher risk of CKD may be for reasons other than PPIs. In both the ARIC and Geisinger studies, participants were more likely to be obese, have hypertension, and take more medications.

Births Outside Hospital Are Riskier

Babies born to women who opt to give birth outside of hospitals are 2.4 times more likely to die during the birth process or in the first month after birth than babies born in the hospital, according to a study in the *New England Journal of Medicine*.

“It’s not as bad as it sounds, however. Because only a tiny fraction of births in the United States occur outside of hospitals, the probability of something going wrong is still slight. Researchers looked at about 80,000 pregnancies in Oregon from Jan. 1, 2012 through Dec. 31, 2013.”

“Perinatal mortality was higher with planned out-of-hospital birth than with planned in-hospital birth, but the absolute risk of death was low in both settings,” concluded researchers at Oregon Health and Science University. The study states that 3.9 out of 1,000 planned out-of-hospital births resulted in a baby’s death, compared with 1.8 deaths out of 1,000 in planned hospital births.

During the study period, 75,923 births occurred in the hospital as planned while 3,203 occurred outside the hospital as planned (1,968 at home and 1,235 at a birth center). The “as planned” distinction is crucial, one reason being that 601 women planned to give birth outside of hospitals are 2.4 times more likely to die during the birth process or in the first month after birth than babies born in the hospital, according to a study in the *New England Journal of Medicine*.

“Perinatal mortality was higher with planned out-of-hospital birth than with planned in-hospital birth, but the absolute risk of death was low in both settings,” concluded researchers at Oregon Health and Science University. The study states that 3.9 out of 1,000 planned out-of-hospital births resulted in a baby’s death, compared with 1.8 deaths out of 1,000 in planned hospital births.

The researchers said they used data from Oregon because at the national level “there is still no way to disaggregate hospital births that were intended to occur at a hospital and those that had not been intended to occur at a birth center.”
hospital,” the study states. In other words, when something goes wrong with an out-of-hospital birth the mothers are often rushed to a nearby emergency department.

Oregon introduced new questions on birth certificates in 2012 that pin-point when that happens.

The study’s numbers don’t entirely explain its headline-grabbing impact when it was published December 30. The birth-in-hospital vs. birth-outside-of-hospital debate can be contentious, but both sides reportedly found the NEJM study to be fair.

“Very well done,” is how Mary Lawlor described the study to the New York Times. She’s the executive director of the National Association of Certified Professional Midwives.

There are “clearly pros and cons to the different birth settings, both with benefits and risks to moms and babies,” Joseph Wax, MD, of the American College of Obstetricians and Gynecologists, told the newspaper.

The study found that 24.7% of women who delivered in the hospital had cesarean deliveries compared with just 5.3% of women who had planned out-of-hospital births and who wound up having cesarean deliveries.

Women who planned out-of-hospital births were less likely to have induced labor but more likely to have maternal blood transfusions.

Cultural issues were also at play, and most of the women who planned out-of-hospital deliveries were white, had private health insurance or paid out of pocket, and were older than 35.

“Women who choose out-of-hospital birth have different values and goals for their delivery (e.g., control over surroundings and a nonmedicalized experience without unnecessary interventions) than do women who choose hospital birth (e.g., the availability of pain relief and access to emergency services).”

Researchers cite studies showing that out-of-hospital births in Europe can be as safe an option for women than hospital births thanks to uniform standards for training midwives. In the U.S., such training and credentialing is piecemeal.

Births at home and at birth centers accounted for 1.28% of all births in 2012, according to government data. That’s a small percentage, but it’s an increase from 0.79% in 2004.

More women might want to avoid hospitals because of the approach generally used for women who’ve had a cesarean section. As the study states, the fact that “U.S. hospitals generally decline to allow vaginal birth after a woman has undergone cesarean may be associated with the increase in home births.”

**Discharge Notes Confuse Patients**

Only 1 in 4 patients sent home from hospitals have reading skills that would allow them to follow discharge instructions, according to a study in the American Journal of Surgery. The problem is probably worse, because patients who use English as a second language were not included in the study. Poor health literacy adds more than $73 billion to the national health care tab each year, Mayo Clinic researchers noted.

HHS, NIH, and the American Medical Association say that for the average adult to understand discharge instructions, they should be written at the sixth grade level.

Mayo Clinic researchers looked at 497 patients admitted for trauma from Aug. 1, 2014 to Dec. 31, 2014, and examined their discharge notes using the two standard scales of reading level.

One of the reasons for confusion is that discharge notes are aimed at two different audiences—patients and their doctors. Patients should be told what information is meant for them and what’s meant for their doctors, say the authors. In addition, there should be a clear demarcation indicating who is meant to read what.

The study states that the “average dismissal note requires reading skills of a college graduate.... Adults, on average, read five grade levels lower than the highest educational level obtained.” In this study, 65% of patients had functional reading skills lower than the grade level at which the note was written.

Specialists might need to be more cognizant of the problem. The study states that discharge notes written in the trauma center were more likely to fit the patient’s comprehension ability than those written by non-trauma center personnel “likely due to the use of more complex terminol-
ogy in the more specialized fields. As a result, we recommend that health care providers explain terminology in their respective fields to aid in patient comprehension.”

There’s also the matter that patients discharged from a hospital are usually far from 100%. Martin Zielinski, a trauma surgeon at Mayo and one of the study’s authors, told Reuters that “even if patients believe they understand what occurred during their hospitalization and the instructions they are to follow upon dismissal, they can become confused after they leave the hospital environment as their memory can be clouded by medications they were administered, the stress of hospitalization, and, particularly within our patient population, traumatic brain injuries such as concussions.”

But note this: The researchers did not actually measure the reading skills of the patients. Instead, they were inferred from education levels, and some people might read at a higher level than their educational level might suggest. Moreover, education level information was available for only 314 of the nearly 500 study participants.

Defibrillators Do Indeed Help Women

Implantable cardioverter defibrillators (ICDs) help women with heart failure as much as they help men, a study in Circulation: Heart Failure stated last month, again making the argument that gender-neutral guidelines for use of the devices should be followed.

They aren’t now, because in the randomized clinical trials that established the effectiveness of the devices years ago, only about 10% to 30% of the people who were enrolled were women.

Because ICDs have been proven to be effective, “ethical challenges make it unlikely that there will ever be a trial of primary prevention ICDs in women,” says the study, which was published online January 12. That sets up a Catch-22, because one reason women don’t get an ICD as often as men might arise from physician concern about the “paucity of evidence” that women would benefit.

Researchers with the Duke Clinical Research Institute mined Medicare data supplied by 264 hospitals enrolled in the Get With the Guidelines Heart Failure Registry. Looking at data from 2005 through 2012, they compared survival rates for patients with ICDs or who had been scheduled to receive one (430 women; 859 men) with patients with similar characteristics but no ICDs. The risk of death was more than 20% lower in both men and women with an ICD after three years. In addition, 40.2% of women with ICDs died, compared with 48.7% of women without the devices. For men, 42.9% with ICDs died, while 52.9% without them died.

Researchers touted how much effort went into matching patients in ICD and non-ICD groups in terms of age and severity of illness but concede that the study does not carry the same weight as a study that would randomly assign some of the patients to receive ICDs.

There’s a hard lesson in that, said lead author Emily Zeitler, MD, a research fellow at Duke: “When we don’t equitably enroll women or other important groups in trials, we can be left with less-clear answers on how to treat heart disease.”

— Frank Diamond

Fewer die from heart failure in hospitals and nursing homes

The percentage of heart failure–related deaths that occur in a hospital has been decreasing steadily — from 42.6% in 2000 to 30% in 2014, according to CDC researchers. The percentage of deaths attributed to heart failure in nursing homes or long-term care (LTC) facilities decreased from 30.1% in 2000 to 26.7% in 2014. Rates of heart failure–related death are now nearly the same across hospitals, nursing homes or LTC facilities, and at home.

Though deaths from heart failure have been falling, there has been a recent uptick, according to the CDC. The age-adjusted rate in 2014 was 84 deaths per 100,000 Americans, up from 81.4 deaths per 100,000 in 2012.

The CDC researchers noted that the underlying cause of heart failure–related deaths for adults, ages 45 and older, has been shifting. In 2000, roughly a third of heart failure deaths were attributed to coronary heart disease. In 2014, it was closer to 1 in 5. Put another way, the proportion of heart failure deaths that have a cardiovascular cause other than coronary heart disease or a noncardiovascular cause (cancer or diabetes, for example) has been increasing.

Prisms are one of the oldest tools ophthalmologists use to examine misaligned eyes. The prism bends light rays but does not focus them and lets the doctor measure, in millimeters, the deviation between two eyes.

In trying to get a read on how regulators will examine the alignment of the Anthem–Cigna and Aetna–Humana mega-mergers, antitrust attorney Matthew Cantor found his prism in, of all things, the food service industry. In July 2015, the Federal Trade Commission (FTC), blocked the $8.2 billion merger of Sysco and US Foods—the two biggest food service companies in the country. The commission successfully argued in court that the merger would reduce competition both nationally and in many local markets. Instead of appealing the ruling, both parties walked away from the deal.

“That to me could be the prism through which these insurance mergers are being viewed,” Cantor says.

But while observers and watchers like Cantor use prisms, the federal and state regulators assessing the effect these deals will have on insurance markets will be using microscopes, particularly one called the Herfindahl–Hirschman Index (HHI).

Calculating market concentration

The Herfindahl–Hirschman Index, which the Department of Justice and Federal Trade Commission use to evaluate market concentration, is calculated by squaring the market share of each firm competing in the market and then adding up those numbers. An example the DOJ uses looks at a market with four companies, two with 30% market share and two with 20% market share. The HHI of that market would be 2,600 (30^2 + 30^2 + 20^2 + 20^2 = 900 + 900 + 400 + 400 = 2,600). A score above 2,500 is considered a highly concentrated market. A score of 10,000 (100 squared) represents a monopoly.

That large deals like this will get close scrutiny that takes the better part of the year is a given; trying to predict the results is good sport for legions of antitrust and health care observers.

Hints from DOJ antitrust chief

Assistant Attorney General William Baer, who heads the Department of Justice (DOJ) Antitrust Division, was appropriately circumspect at a Yale Law School conference on health care law in November. Some might see his remarks as an indication that the department is taking a tough stance on the health insurer mergers. “Our job is to block mergers that threaten to reduce competition; our job is to challenge competitors who want to conspire rather than compete; and our task is to ensure that companies do not raise barriers that deny competitors the opportunity to enter new markets or expand their existing market presence,” Baer told the Yale audience.

He also attacked what he called the “second 800-pound gorilla defense” that hospitals and insurance companies use to justify mergers. “Hospitals want to merge to get leverage over a dominant insurer; insurers want to merge to get leverage over a dominant hospital,” Baer said. “Courts have long rejected the notion that ‘countervailing market power’ justifies anticompetitive mergers or agreements.” Baer hinted that the DOJ would examine these deals for their consumer benefit. “Consumers do not benefit when sellers—or buyers—merge simply to gain bargaining leverage,” he said. “Consumers benefit when there is entry, expansion, innovation, and competition.”

Regulators’ microscope

The Herfindahl–Hirschman Index is one of the measures that the DOJ uses to determine if a merger is going to benefit consumers. The HHI, as it is commonly known, measures market con-
centration. Guidelines the DOJ and FTC have issued classify a market with an HHI of 1,500 to 2,500 as moderately concentrated, and one with a score above 2,500 as highly concentrated.

The same guidelines also take into account how much a merger increases the HHI. In moderately concentrated markets, an increase of more than 100 points can warrant scrutiny. In highly concentrated markets, an increase of 100 to 200 points often merits some time under the microscope, and an increase of 200 or more is even more likely to trigger close scrutiny.

But the DOJ can be swayed, at least in theory: “The presumption may be rebutted by persuasive evidence showing that the merger is unlikely to enhance market power,” the guidelines state.

Here’s why that may not bode well for the Anthem–Cigna merger: Both the American Hospital Association and American Medical Association sent letters to the DOJ making the case that most health insurance markets are already considered “highly concentrated” based on the HHI.

Market share analyses
The medical association has urged DOJ to block the mergers outright, while the hospitals have taken a more moderate stance with a call for the “closest scrutiny” and possible divestitures.

Both associations have done market share analyses of the mergers. The medical association gathered market share data on the two largest insurers in 388 different markets in the United States. Indiana is the only state where Anthem and Cigna are the two largest plans and, according to the medical association’s analysis, they would have a 69% market share in the combined HMO–PPO–POS markets there, and a whopping 83% in Terre Haute, one of Indiana’s larger cities. Still, Anthem and Cigna have “limited overlap,” Anthem spokeswoman Jill Becher says.

The hospital association’s analysis showed that the Anthem–Cigna deal threatens to reduce competition in at least 817 markets nationwide. It would drive the HHI to over 2,500 and cause increases of 200 points or more in 600 markets. In another 217 markets, the tie-up would result in a post-merger HHI above 2,500.

Both Anthem and Aetna have taken exception to these analyses. The focus of the Aetna–Humana merger is their Medicare Advantage business, where combined they would have a 26% market share, which would be larger than UnitedHealthcare’s 20% share, according to a Kaiser Family Foundation analysis last year. Aetna says that market share comprises just 8% of total Medicare beneficiaries when traditional Medicare is included. An Aetna spokesperson also notes that over the past four years, there have been 28 new companies offering 104 new plan options in 24 states that represent 13.6 million Medicare beneficiaries.

Divest or run?
One precedent health care legal specialist Rob Fuller found is in the big oil mergers of the 1990s. The FTC approved the $81 billion merger of Exxon and Mobil, then the two largest oil companies, after they agreed to sell off 2,400 gas stations. Around the same time, BP–Amoco gobbled up Atlantic Richfield and Chevron acquired Texaco. Large regional players provided a counterbalance to big oil in individual markets, says Fuller, a former hospital executive who has advised clients on antitrust issues.

“You get the same thing in these large health insurance plans,” he says. “Even though you may let Anthem buy up Cigna, you’re still going to locally have the Molinas and the Kaisers and Intermountain and all these other insurers that are viable insurance plans that can offer products to employers and individuals. As long as you have large regional players supported on the state level, the antitrust authorities, despite the very large numeric size of the deals, are going to approve them.”

Antitrust lawyer Cantor sees one scenario that could derail the Anthem–Cigna deal: An order that would force one of the companies to split off or divest its business in the growing self-insured market. Anthem and Cigna are among the three largest companies in that market, says Cantor. If they were to combine, it would reduce the choices of national employers like Walmart and Lowes. So one possible outcome is that the FTC approves the merger but orders a major divestiture.

“It could be something as large as divesting the entire Cigna self-insured business but that would be the crown jewel of the merger,” notes Cantor. Anthem and Cigna might say that’s too big a price to pay and back out of the deal.

All of this should come into much clearer focus after regulators zoom in with their microscopes and start making some decisions.
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September .............The 2016 election
October .................Cancer
November ...............Medical directors
December ..............The year in preview

Please email your submissions to:
Frank Diamond,
Managing Editor
fdiamond@medimedia.com
Biosimilars in Development Near End of Phase 3 Trials

Amgen's biosimilar candidate ABP501 proved comparable to AbbVie's adalimumab (Humira) for patients with moderate to severe plaque psoriasis, based on results from a head-to-head phase 3 study. The study met its primary endpoint of improvement from baseline to Week 24. Amgen is also developing biosimilars of cetuximab (Erbitux) and bevacizumab (Avastin).

Amgen's own etanercept (Enbrel) is the target of biosimilar development. A 52-week study of CHS0214, by Coherus, demonstrated PASI-75 equivalence at Week 12 for the treatment of moderate to severe plaque psoriasis. The trial, which is still ongoing, is measuring mean percent change from baseline and the proportion of subjects achieving 75% improvement in PASI in patients given CHS0214 versus those given etanercept.

Novartis is waiting for FDA approval of a long-acting treatment for boosting white blood cell count, a biosimilar of Amgen's pegfilgrastim (Neulasta). This is Novartis's third biosimilar submission, with 10 more planned filings over the next three years. Novartis's previous filings also targeted Amgen drugs; the FDA is reviewing its application to market a copy of etanercept for rheumatoid arthritis and other autoimmune diseases, and Novartis's Sandoz subsidiary launched Zarzio, a filgrastim (Neupogen) biosimilar, in September. The company's other biosimilar prospects include Johnson & Johnson's infliximab (Remicade) and Genentech's trastuzumab (Herceptin).

HCV successes at AASLD

Oral combination medicines and regimens made headlines at the American Association for the Study of Liver Diseases (AASLD) 2015 Liver Meeting in San Francisco. Merck's once-daily elbasvir/grazoprevir tablet showed sustained virologic response 12 weeks after the completion of treatment (SVR12) in 95% of patients with chronic hepatitis C (HCV) who inject illegal drugs. Conducted in patients with HCV genotypes 1, 4, and 6, the C-EDGE CO-STAR study was of interest because limited research has been conducted in patients undergoing treatment for injection drug use.

Other AASLD presentations: In the ongoing TOPAZ-II study, 95% of adults with HCV genotypes 1a or 1b treated with AbbVie's Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) achieved SVR12 after 12 or 24 weeks of treatment. Participants in TOPAZ-II are being followed for 5 years post-treatment to evaluate the long-term impact of SVR12 on the progression of liver disease. In a systematic review of clinical trial data, patients with HIV and hepatitis C virus (HCV) co-infection, a once-daily regimen of daclatasvir (Daklinza) and sofosbuvir (Harvoni) achieved superior SVR12 compared with a regimen of sofosbuvir/ribavirin. The analysis was conducted by the Boston-based Health Economics and Outcomes Research Analysis Group and Bristol-Myers Squibb, maker of daclatasvir. Sofosbuvir is manufactured by Gilead.

Pleasing, puzzling CV data

Patients with type 2 diabetes and cardiovascular (CV) disease receiving the glucose-lowering agent empagliflozin (Jardiance), a sodium glucose cotransporter-2 (SGLT-2) inhibitor, were less likely than those taking placebo to die from CV causes, according to results of the large EMPA-REG OUTCOME study. The findings, published in the Nov. 26 issue of the New England Journal of Medicine, were hailed as landmark, as this is the first glucose-lowering drug to show superiority in a CV-outcomes trial. Investigators, however, admitted that they have yet to understand the outcome.

Setbacks in cancer trials

Bevacizumab combined with the chemotherapy agent lomustine for treating first recurrences of glioblastoma did not improve overall survival (OS), according to findings from the EORTC-26101 trial. OS was not statistically different between the two study arms, with a median OS of 9.1 months in the combination group versus 8.6 months in a control arm of patients receiving lomustine alone. Progression-free survival (PFS) data seemed more promising, however—4.17 months among patients receiving the combination treatment versus 1.54 months for the lomustine-alone group. 8.8% of patients in the combination-therapy arm had no progression at 1 year, compared with 1.9% of patients in the lomustine arm. Data were presented at the 20th Annual Scientific Meeting of the Society for Neuro-Oncology.

The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the treatment of gastrointestinal stromal tumors (GIST), but secondary resistance remains an issue. New results from a group of patients who have been followed since 2004 show that those with high- or intermediate-risk GIST and who were given imatinib (Gleevec) after surgery had no gain in OS, but imatinib did appear to have long-term...
## BIOLOGICS IN DEVELOPMENT

### New marketing approvals

<table>
<thead>
<tr>
<th>Date (type)</th>
<th>Manufacturer</th>
<th>Drug (trade) name; administration</th>
<th>Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct. 16 (BLA)</td>
<td>Boehringer Ingelheim</td>
<td>idarucizumab (Praxbind); intravenous injection</td>
<td>Reversal of anticoagulation effects of dabigatran (Pradaxa) in patients needing emergency surgery or who have life-threatening or uncontrolled bleeding</td>
<td>First reversal agent for dabigatran received accelerated approval in a study of healthy volunteers. Continued approval may be contingent on results of an ongoing cohort case series study. WAC is $3,500.</td>
</tr>
<tr>
<td>Oct. 27 (BLA)</td>
<td>BioVex/Amgen</td>
<td>talimogene laherparepvec (Imlygic); intralesional injection</td>
<td>Local treatment of unresectable lesions in patients with recurrent melanoma</td>
<td>First FDA-approved oncolytic viral therapy is a genetically modified live herpes virus. Injected directly into melanoma lesions, it replicates and causes apoptosis. Average cost: $65,000.</td>
</tr>
<tr>
<td>Nov. 5 (NDA)</td>
<td>Gilead</td>
<td>elvitegravir/cobicistat/emtricitabine/tenofovir (Genvoya); subcutaneous injection; oral tablet</td>
<td>HIV-1 in ARV-naive patients or to replace current therapy in patients whose HIV is suppressed; for patients age ≥12 years</td>
<td>Approval of 4-in-1 tablet based on four clinical trials of 3,171 patients randomized to Genvoya or another approved HIV treatment, depending on the trial. Genvoya reduced viral loads and was comparable to other treatments. Label carries black box warning about liver toxicity. Annual list price of $31,362 is in parity with its predecessor, Stribild.</td>
</tr>
<tr>
<td>Nov. 10 (NDA)</td>
<td>Genentech</td>
<td>cobimetinib (Cotellic); oral tablet</td>
<td>Unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib (Zelboraf)</td>
<td>Coadministration of cobimetinib (a MEK inhibitor) with vemurafenib (a BRAF inhibitor) is designed to counter effects of resistance to a single targeted treatment. In the coBRIM trial, PFS was 12.3 months in combination patients vs. 7.2 months in patients given vemurafenib alone.</td>
</tr>
<tr>
<td>Nov. 13 (NDA)</td>
<td>AstraZeneca</td>
<td>osimertinib (Tagrisso); oral tablet</td>
<td>Metastatic, EGFR T790M mutation-positive non–small-cell lung cancer</td>
<td>For use in patients with disease progression after treatment with an EGFR tyrosine-kinase inhibitor. FDA also approved a companion diagnostic to detect the T790M mutation. Approval based on surrogate ORR in AURA phase 2 open-label trials.</td>
</tr>
<tr>
<td>Nov. 20 (NDA)</td>
<td>Millenium/Takeda</td>
<td>ixazomib (Ninlaro); oral capsule</td>
<td>In combination with lenalidomide (Revlimid) and dexamethasone in patients with MM who have received 1 prior therapy</td>
<td>Approval creates first all-oral regimen for MM with a proteasome inhibitor (PI). In the TOURMALINE-MM1 clinical trial of 722 patients, PFS in the study group was 5.9 months greater than in the lenalidomide/dexamethasone/placebo group. $8,670-per-cycle cost is comparable to bortezomib (Velcade), an injected PI from the same maker.</td>
</tr>
<tr>
<td>Nov. 24 (BLA)</td>
<td>Eli Lilly</td>
<td>necitumumab (Portrazza); intravenous injection</td>
<td>In combination with gemcitabine and cisplatin for first-line use in patients with metastatic squamous non–small-cell lung cancer</td>
<td>In the SQUIRE trial, OS gain vs. chemo-alone arm (1.6 months) was statistically significant, though &quot;marginal,&quot; according to one FDA advisor. An economic analysis at ASCO 2015 found that necitumumab must cost &lt;$1,300 per 3-week cycle to be cost-effective. Its cost: $11,430 per month.</td>
</tr>
<tr>
<td>Dec. 16 (BLA)</td>
<td>Eli Lilly</td>
<td>insulin glargine (Basaglar); subcutaneous injection</td>
<td>Improve glycemic control in adults with types 1 and 2 diabetes and children with type 1 diabetes</td>
<td>Not technically a biosimilar because it was approved under the 505(b)2 pathway, Basaglar is the first approved follow-on to Sanofi’s Lantus. The long-acting insulin analogue demonstrated similarity in two clinical trials enrolling 1,278 patients.</td>
</tr>
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</table>

ARV=antiretroviral, BLA=biologics license application, EGFR=epidermal growth factor receptor, MM=multiple myeloma, NDA=new drug application, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, 505(b)2=abbreviated new drug pathway.

benefit for relapse-free survival. In patients given postsurgical imatinib, relapse-free survival was 84% at 3 years, compared with 66% in an observation group. At 5 years, the rates were 69% and 63% respectively.

Genmab has stopped its study comparing ofatumumab (Arzerra) with Genentech’s rituximab (Rituxan) in the treatment of relapsed follicular non-Hodgkin’s lymphoma (NHL). The decision followed an interim analysis conducted by an independent data monitoring committee. The analysis concluded that rituximab was unlikely to show superiority if the trial were to conclude as planned. The trial randomly assigned 516 patients with follicular NHL to receive either ofatumumab or rituximab by intravenous infusion in four weekly doses, with PFS being the primary outcome. Data from the study will be presented at a future scientific conference.

**Cholesterol-fighting booster**

Adding alirocumab (Praluent) to standard-of-care therapy for low-density lipoprotein (LDL) cholesterol reduction is beneficial, according to a posthoc analysis of the six phase 3 ODYSSEY trials. An injection of alirocumab 75 mg lowered 74% of patients’ LDL to a prespecified target within 8 weeks. The remaining 26% of patients achieved their goal by Week 24 when dosing was increased to 150 mg. Results were based on a pooled analysis of 1,291 patients with high CV risk or heterozygous familial hypercholesterolemia.

**Have you heard?**

Bioethics International, a not-for-profit organization focused on the ethics and governance of how medicines are researched, developed, and made accessible, published a study ranking large pharma companies by the transparency of their clinical trial results. On average, for each drug, only two thirds of clinical trials that supported new drug approvals in 2012 were disclosed, falling below legal and ethical standards. In addition, almost half of all FDA-reviewed drugs had at least one undisclosed phase 2 or 3 trial.

According to Bioethics International, three of 10 companies—GlaxoSmithKline, Johnson & Johnson, and Pfizer—publicly disclosed all clinical trial results for at least one of their reviewed drugs. The lowest-scoring company, Gilead, disclosed only 21% of trial results for Stribild, its HIV medication.

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**The troublesome state of oncology clinical trials**

Although more than two thirds of the biologics pipeline is in oncology, conducting a clinical trial continues to be troublesome. Consider these:

- The National Cancer Institute estimates that up to 40% of oncology trials fail to achieve minimum enrollment. Covance estimates that more than 60% of phase 3 trials do not reach planned enrollment.
- Cancer patients who live on less than $50,000 a year take part in clinical trials at a rate one third lower than those who make more. The absence of low-income participants makes researchers’ findings less representative of the general population.
- Various surveys suggest that 50% to 80% of patients do not have any information on potential clinical trials for their condition.
- Patients and providers often believe the default “standard of care” is better—or at least less risky—than a clinical trial.
- Patients are often selected on the basis of comorbidities. A Duke University study found that up to 40% of patients would not have received the trial drug if they were already receiving it for a comorbidity.
- Novel agents for cancer, such as ibrutinib, work by mechanisms distinct from chemotherapy and have shown efficacy regardless of prior regimens. But as additional drugs are approved, enrollment becomes more difficult. Studies often require participants to have either received or not received another approved drug.
- Biomarkers are increasingly a target in oncology, and some approved drugs are accompanied by a protocol to use a biomarker or a companion diagnostic to inform use. Payers can be expected to restrict access to costly targeted treatments, but simultaneously, makers of therapies with biomarkers can expect that eligible patients who test positive for a biomarker or mutation will be approved for coverage.
- Clinical trials are becoming more and more complex. For an average phase 3 trial, the number of endpoints and/or eligibility criteria has increased by at least 50% in the last 10 to 15 years.
- A study in the Journal of the National Cancer Institute found that 62% or recent phase 3 oncology trials failed to achieve results with statistical significance. Failed clinical trials are a huge cost to the drug sponsors, patients, and society as a whole.

—Katherine T. Adams

Sources: CovanceClinicalTrials.com; Duke Cancer Institute; Fred Hutchinson Cancer Research Center; JAMA Oncology; Gan HK et al, J Natl Cancer Inst. 2012;104:590–598.

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**BIOLOGICS IN DEVELOPMENT**

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There was good news for health plans and health systems at the inaugural conference for a new health law center at Yale Law School last November: Getting today's newly minted physicians to accept value-based payment and ACOs—and the goals that go with them—may be easier than you think.

The happy tidings came from William Sage, MD, JD, a University of Texas law school professor and a professor of surgery and perioperative care at the university's new Dell Medical School. He suggested that for a number of reasons, today's young doctors are more receptive to managed care than were their predecessors in the difficult 1990s.

“We don’t really account for generational change when we talk about how professionals think,” Sage tells Managed Care. “Or we may react to just one aspect that makes us uncomfortable—saying, for example, ‘Millennials don’t work as hard as baby boomers did.’”

But it’s an important fact that today’s young doctors are different across the board, he argues. Their life experience has prepared them to be open to collaborating with other professionals and to delivering cost-effective, population-focused care—and if you are running a health plan, that’s really good news.

Sage says he was asked at Yale to talk about the.They’re primed to work in teams, not fazed by large organizations, open to all kinds of measurement—and, of course, are tech savvy. But how well will this new generation of data-driven MDs deal with patients?
effect of ACOs and other new delivery models on physicians, and that there seemed to be an implicit assumption that the effect was negative. “I thought that was erroneous,” he says.

Sage’s message fits into a developing picture of today’s young doctors that’s mostly—but not completely—reassuring. It recalls the largely enthusiastic verdict that E.M. Forster gave in Two Cheers for Democracy when he lauded popular government but withheld a third “cheer” because of its tolerance of mediocrity. Young doctors understand not just the Hippocratic Oath but also the need for prudent use of resources. Cheer! They play better with nonphysician colleagues. Cheer! And the missing third huzzah? Some observers fear that these savvy young docs—so adroit with anything involving a screen—may have lost something in personal skills at the bedside.

Why docs are different now
“I’m sure there are things we’re losing,” Sage concedes. “But it would be hard for me to suggest that anything we’re losing could outweigh the possibility of saving a trillion dollars of wasted health care expenditure every year in this country that could be used both privately and publicly for other really pressing and underfunded needs.” And by and large, he believes, today’s young MDs are ready to start chipping away at that trillion.

The roster of positives about medicine’s current generation? Here are some checks that Sage puts in the plus column:

- more willing to work in teams with other health professionals
- expect to be engaged in the community and to have contact with health care outside of the acute-care hospital setting
- more apt to move in fluid groups rather than rigid tribal categories
- more evenly distributed by gender
- much more comfortable than their predecessors working as part of a large organization
- less insistent on entrepreneurial independence, thanks to a desire for work–life balance
- much more comfortable with electronic information exchange

All of these characteristics, says Sage, make today’s doctors better suited to modes of health care financing and delivery that are moving away from fee-for-service and volume to shared-risk arrangements and incentives that reward value. They can be traced, in turn, to the ubiquity of computers and social media in the lives of today’s young adults and—to a limited extent—to important changes in medical education.

Computers, of course, lie at the heart of the rapid change in health care today. And we know from Eric Topol’s 2012 The Creative Destruction of Medicine that health care—just in time for these savvy new docs—is on the cusp of a “wondrous revolution” in which their data will help us all—eventually—live longer, healthier lives. But what does a skeptic say?

Cheers from a noncheerleader
It’s not fair to tag Robert Wachter, MD, professor and associate chair in the Department of Medicine at the University of California–San Francisco, purely as a health-tech Cassandra. He acknowledges computerization’s tremendous potential, just as Topol concedes its problems. But Wachter’s 2015 book The Digital Doctor did rain on Topol’s parade with a number of worrying examples showing that, as he writes, “health care’s path to computerization has been strewn with land mines, large and small.” So it’s interesting that this realist agrees with Sage’s good-news report on today’s young docs.

“It strikes me as completely accurate,” says Wachter. “Certainly it’s true that younger people today don’t enter the field with an expectation of unfettered autonomy. It must be 10 or 15 years since I last heard one of my residents or students say, ‘My goal is to go out there, hang up a shingle, and be a self-employed entrepreneur,’” says Wachter.

Today’s young doctors are indeed “perfectly comfortable with computers,” Wachter says, but he adds an IT-related wrinkle. Older physicians are usually...
pictured as grumpy about today’s health IT while their younger peers are content with it, he says, but that’s not quite right. “Of course the younger doctors expect medicine to be digital,” he says. “But they’re just as unhappy as older docs with the state of digital technology in medicine, because it’s 15 years behind what they see in the rest of their lives.”

**Glued to the screen**

Wachter worries more than Sage does about the downside of today’s medical generation. “They grew up looking at screens, and perhaps texting their mother when she was one floor away,” he says. “Sometimes they’re perfectly comfortable sitting in front of a screen all day while their patients are two floors away wondering where their doctor is. That doesn’t mean they don’t care. But they’ve gotten used to the notion that most of their life comes in and out via that screen. And I wish we would bring back a little bit of the old sense that what a doctor does is spend a lot of time at the bedside talking to people and touching them. For some of the younger physicians, that’s not as natural an act.” Wachter sees a feedback loop taking hold: young doctors feel awkward at the bedside, so they spend less time there, and so get even more awkward at dealing with patients in person.

John Bulger, DO, chief medical officer of Pennsylvania-based Geisinger Health Plan, agrees that this is a danger, but also offers a more optimistic possibility by flipping the issue on its head. “I’m 46, and I started in a paper world,” he says. “Doctors in my generation had to teach ourselves how to incorporate computers into care.” Precisely because they’ve grown up with screens ubiquitous in their lives through social media, phones, and tablets, he believes, today’s younger physicians “may be able to bridge that gap between the screen and the patient better.” Rather than seeming to divert their attention away from patients, they may be able to use computers and data as tools in collaboration with patients.

For all his concerns about bedside manner, Wachter praises the medical students he sees at UCSF as “incredibly bright and enthusiastic, with wonderful values.” He recalls ruefully one day when he addressed a group of them and, for some reason, was in a mood to shake them up. “You folks are entering a profession completely different from the one I entered 30 years ago,” he warned them in his gravest voice, “because you will be under relentless, unremitting pressure to figure out how to deliver the highest-quality, safest, most satisfying care at the lowest possible cost.”

Says Wachter: “One student raised his hand and asked: ‘What exactly were you trying to do?’ I remind myself of that when we’re going through these transitional pains. What’s odd is not that we’re being forced to think about value and get better at delivering it. What’s odd is that that’s new.”

Young doctors today are better primed for that “new” challenge partly because their conditioning and attitudes have changed, Wachter suggests. “Take the whole notion of systems thinking. The way I was socialized as a student and resident back in the ’80s was that the work of a doctor was to take care of the patient in front of you. It was somebody else’s job to create the system. In the last 10 or 15 years we’ve learned that the system is us.”

**‘Health care delivery science’**

It isn’t just socialization; young doctors are different today partly because their formal training is different. Many medical schools are adjusting their curricula to stress the principles and methods of team-based care, preventive and cost-effective medicine, and population health.

Since the 1980s, there’s been a lot of talk about medical education reform, but not much was actually happening, according to Sage. That’s changed. Now, curricula are being rewritten to include “flipped” classrooms (class time is spent on exercises while lectures are on take-home videos), online simulations, and competency-based education. The accrediting bodies have revised their standards, says Sage, and...
Forget about “publish or perish.” A program developed by Anthem lets young physicians publish to flourish. Anthem’s American Resident Project (ARP) provides an opportunity for a select few up-and-coming doctors (the program calls them fellows) to write one blog post a month on a subject of their choice. In turn, this can lead to a host of networking and educational opportunities, many in person.

Anthem officials say they recognize the crucial role that young physicians will play in the ongoing transformation of the health care system and want to forge relationships early with these professionals. Sounds simple, but such physician–payer collaboration would have been difficult to envision until just a few years ago. Terms like “hassle factor” and “gatekeeper” reflected a pervasive lack of trust about an industry that many physicians considered Big Brother holding the purse strings.

Her own perspective
But today’s young physicians really do seem different. Kerri Vincenti, MD, a 31-year-old radiology resident at Pennsylvania Hospital in Philadelphia, approached Anthem’s program with wariness, not hostility. “I wanted to make sure that what I was writing would reflect my perspective and that someone wasn’t going to be changing the heart of the message during the editing process. And I haven’t found that that’s happened,” says Vincenti. “I even raised that concern in my interview prior to becoming a part of the project. I wanted to make sure that my articles were really written by me, not someone from some big health care plan looking at it and saying, ‘I don’t like what she’s saying. Change it. That goes against what we want.’”

Anthem launched ARP in 2013, and 14 participants have passed through the program so far. (Currently, there are 10 fellows, and the application process has just opened for the Class of 2016.) In 2015, there were nearly 17,000 visits to the program’s website, 14,000 unique visitors, and over 25,000 page views by people wanting to know what’s on young doctors’ minds. The fellows receive $2,000 a year.

Some of the participants’ writings are picked up by other online publications such as KevinMD, MedTech Boston, and the Figure 1 Blog. This virtual interchange extends to the real world. The ARP organizes, sponsors, or participates in events across the country. At some, fellows can pitch ideas on how to, for instance, improve primary care. These are delivered in front of a Shark Tank–style panel, which includes Anthem officials, other residents, and young physicians. These are the events that keep Arshya Vahabzadeh, MD, engaged in the Anthem program. Vahabzadeh is a psychiatrist at Massachusetts General Hospital and a director at a neuroscience startup, Brain Power. “You can be a panelist. You can be a judge. It lets medical students, young doctors, and other clinicians interact.”

Ready and willing
Vincenti and Vahabzadeh seem headed for leadership roles. Vahabzadeh, who hails from Great Britain, is triple trained in family medicine, psychiatry, and pediatric psychiatry, and last year he was named one of MedTech Boston’s 40 Under 40 Healthcare Innovators. Vincenti, who graduated from George Washington University School of Medicine and Health Sciences two years ago, serves as the lead radiology department representative on her hospital’s quality improvement council.

Craig Samitt, MD, Anthem’s chief clinical officer, says that “the future is in the hands of a younger generation that hasn’t grown up with a defined paradigm that we then have to change.” He adds only somewhat jokingly about the blog posts that, “I’d give up my day job...
FOR YOUNG PHYSICIAN LEADERS

just to be able to read all of the tremendous, thoughtful pieces that these residents and young physicians write, because they are the future of the industry.”

Drafi  Samitt continues: “Our industry is going through a period of full-scale value-based change, and I would even describe it as reinvention.” Previous generations of physicians who trained and practiced in an era when reimbursement was volume-based, access to information was rudimentary at best, and care models were hierarchical might have a tough time with such reinvention, he says.

But probably not so this youthful cohort of physicians. Vincenti says her generation brings a different mindset to medicine. “I think younger doctors embrace evidence-based medicine a little bit more readily. I think the older physicians tend to cite consensus-based medicine as a reason for why they do things a certain way: ‘Well, this is how it’s always been done,’ or, ‘This is what I’ve seen.’ Meanwhile, younger doctors are a part of a generation that tends to question a little bit more: ‘Why should we do it that way if the large-scale studies show that it should be done this way, and it’s better for the patient?’

Younger doctors also want more work-life balance. “We love what we do, and we love how it helps people, but there has to be a balance,” says Vincenti. “We want to have a life outside of our jobs, whether that’s for family or a more flexible lifestyle that allows us to pursue our nonmedical interests.”

Team players

That’s one of the possible reasons that young doctors seem more willing to work in teams, says Samitt. He doesn’t know whether medical education focuses more on teamwork these days, but the impetus for work-life balance makes younger doctors more open to handing off some duties. “They are going to do well in a team-based setting.”

Vahabzadeh says that older doctors may spend decades in a particular job in a particular hospital. He says younger doctors have an array of choices and may split their time among several different employers or enterprises. “Quite a number of my colleagues are involved in some kind of business or startup,” he says.

Vincenti hardly ever deals with health plans directly because she’s hospital-based; health plan haggling is an administrator’s job. Vahabzadeh, on the other hand, is a child psychiatrist, so he faces the parity issue. “I’ve had to spend time on the phone trying to get a person admitted to the hospital,” he says. He’s had to plead his case “whereas I know if it was an asthma attack or a problem with the liver, it would be a no-brainer.”

Sounds like an idea for a blog post. Vincenti appreciates the platform. “It’s an outlet for me. I enjoy writing, and I enjoy putting down into words what I feel I get out of medicine in a more creative way.”

— Frank Diamond

‘My priorities have shifted’

The American Resident Project (ARP) allows young physician leaders to blog about what’s important to them. “Finding Balance During Residency” was posted Dec. 30, 2015, by ARP resident Kerri Vincenti, MD, a 31-year-old radiology resident at Pennsylvania Hospital in Philadelphia. Here is an excerpt.

It’s also important to understand that the search for balance doesn’t mean the same thing for every person. When I entered medical school, I was already married and knew that having a family would be important to me. I worked hard to prioritize time with my husband among time spent studying for exams and getting to know my future colleagues. I made certain sacrifices in doing so, but for me, it was worth it because that form of balance kept me grounded. When I had my first child at the end of my third year of medical school, I was presented with additional challenges to balance my desire to be a good mother and a good physician. I subsequently chose to specialize in the field of radiology, where I knew I would have greater flexibility with my schedule, while still fulfilling my desire to directly impact patient care. As I have now been a resident for a little over a year, I’ve shifted back some of my focus to my work, desiring to know as much as I can, sometimes at the expense of being able to spend quality time with those I care about. As my priorities have shifted, I have likewise shifted the degree of attention I give to each part of my life while never forgetting that each individual part still exists.

Kerri Vincenti, MD

FEBRUARY 2016 / MANAGED CARE 23
teaching methods have followed: “In the last five years or so, I’ve finally begun to see distinct changes not only in how medical students are taught, but also in what they’re taught,” says Sage, who applauds the AMA—which has always been considered the old guard of medical professional opinion—for supporting medical education innovators.

“I do think it’s a new day,” says Susan Skochelak, MD, the AMA’s group vice president for medical education. The AMA has been working with 11 leading medical schools—and just added 21 more—to change the medical curriculum so that students come to understand the health care system, team-based care, and the requirements of population health, Skochelak says. She estimates that in participating schools, some 30% of curricula now focus on what she calls “health care delivery science”—methods of organizing quality, team-based care that are as rigorously studied as the efficacy of physical interventions. To make room for the new material, less time is spent reteaching the basic science already learned in pre-med undergraduate programs and “binge-and-purge” absorption of voluminous clinical facts “that change all the time when you get out of medical school anyway.” Medical education is indeed adapting to changes in health care delivery, but it needs to change a lot more, says Catherine Lucey, MD. She’s a colleague of Wachter’s at UCSF, and says her article in the Sept. 23, 2013, JAMA Internal Medicine was a “call to arms” for change. For the most part, the article charged, medical education—however clinically and pedagogically excellent—remains stuck in an old model of care delivery in which “the personally expert sovereign physician … was autonomous, independent, and authoritative.” Fortunately, she says, a number of medical schools are stepping up to the challenge she issued.

“I think Dr. Sage and I are on the same page,” Lucey tells Managed Care. But she doesn’t mind being the “glass half empty” voice. While she agrees that new physicians are more open to accountability and team-based care, she says that in medical education “we need to up our game.”

Lucey lauds the innovative programs now under way at medical schools such as Vanderbilt, Penn State, and the University of Michigan. But she complains that “most physicians are still educated in a mono-professional environment” better suited to a 1900s model when the doctor “was the team leader and was giving orders he expected all the others to comply with.” Such conditioning harks back to a day when the physician was the only medical professional in the room with an advanced degree, she says, and that “flies in the face of logic” in a time when there is advanced training for nurses, pharmacists, and often physical therapists and social workers.

Lessons for health plans

“We’ve learned from the mistakes of the 1990s,” Lucey says. Indeed, whatever one’s view about the mindset of young doctors, most observers seem to agree at least that their mindset matters. “They’re not just cogs in an economic machine, and if some managed care systems in the ’90s appeared to treat doctors as if they were, that’s one of the mistakes the industry has learned from.

“Payment incentives tell only part of the story,” says Sage, and Wachter agrees. Indeed, both doctors describe a growing recognition that success in health care is a function partly of medicine’s culture, not just its economic structures.

“If all you do is goose the payment mechanism, you may get a trained-seal phenomenon where people jump a little higher because you’re paying them a little more to do so,” says Wachter. “But those changes won’t be real or durable; they won’t be embedded in the fabric of care. You’ll end up with a cadre of burned-out people who are not capable of innovation and enthusiasm and creating good doctor–patient relations because they’re not enthusiastic themselves.

“Today’s young doctors are perfectly comfortable working for large organizations and being members of teams,” he goes on. “They understand the importance of systems. But they do want appropriate professional autonomy—they don’t want to be treated like someone who can’t be trusted.” Organizations
that find that balance are going to be the winners, he says, and will have better outcomes, happier patients, and lower costs.

Bulger, of Geisinger Health Plan—whose perspective admittedly may not be typical because of his plan’s close relationship with the dedicated Geisinger Health System—believes Wachter’s and Sage’s upbeat assessment of the current generation of physicians “has a lot of truth to it” and foreshadows good things for health plans. “The generation that’s coming out now understands that there’s a need for team-based care,” he says. “And I think that suggests that these doctors can help make collaboration between the medical group and the health plan side a lot more robust.”

When it comes to lessons for health plans, Sage is at first an uncharacteristically reticent prophet. “My sound bite about health plans is that they’re still trying to figure out what role they play in the future system,” he says. “This is a major area for them to think about, and each plan has to work it out for itself.”

But then he adds: “Look beyond the financial incentives.”

“To the culture?” he is asked.

“Yes, to the changing culture,” Sage replies. “And to professions beyond physicians, with greater confidence that they will work with physicians.”

Beyond the ‘iron triangle’

Coming of age in today’s era of health care, young doctors enjoy the benefit of something that isn’t strictly generational, but applies to all of us, young and old.

There’s been a shift in the understanding of the core challenge of health care, says Sage. Thinking was organized around an “iron triangle” of cost, access, and quality. That was very offputting for many physicians, Sage says, whether the manifestation was government setting of limits or private companies “trying to figure out how to make money by saying ‘no’ to people, which to my mind is only a slight exaggeration of 1990s-style managed care.” (Sage hastens to add that he was a supporter of managed care then, and remains one.) He credits Don Berwick and his Institute for Healthcare Improvement with shifting the focus from grim discussions of rationing to waste and inefficiency, which have perfectly palatable, even inviting, solutions. Young doctors today believe they can help improve the efficiency of how care is delivered and the health of populations, not just individual patients, says Sage. “They feel these are challenges—regardless of the economic effects on them personally—that they can take on ethically and productively, challenges that seem consistent with the reasons they went into medicine rather than at odds with them,” he says.

Unlike their predecessors a half-century ago, today’s young doctors won’t have to be, or pretend to be, godlike figures. That should be a relief to them—and to the other health care professionals who work with them. But they will need to be as actively compassionate as they are computer-smart—meeting patients’ eyes with a reassuring smile—and to cooperate in treating America’s health care bloat as well as actively helping individual patients to stay well and lead full lives. They seem better equipped than earlier generations for the task, but we’ll know more when the next few years put them to the test.

Timothy Kelley is a senior contributing editor of Managed Care and was the editor of the publication from 1995 through 1997.
A Personal Perspective On the Physician Generation Gap

By Richard G. Stefanacci, DO

For many, one of the most difficult challenges in managed care is managing physicians, not making utilization decisions. As being a physician who will be sandwiched between two generations of health care providers, I have a unique perspective that may provide insights in the development of tools and resources to better harness the range of the physician workforce. My 85-year-old father, also Richard Stefanacci (his middle name is George and mine is Gabriel), is still an active health care provider. After retiring from a surgical practice at the age of 70, my father built a skilled nursing facility in Newark, N.J., where he maintains active involvement in the day-to-day administration. Often called traditionalist, his generation of physicians—they bristle at being called health care providers—are frequently described as dedicated, conventional, respectful of order, and altruistic. They grew up in a world characterized by faith, patriotism, and justice. Given that traditionalists range in age from their late 60s to late 80s, most are either retired or serving in a leadership role. Their benefit to an organization is that they remain loyal and extremely hardworking while typically not working well with either teams or technology, although my father has mastered the iPhone and sends texts with an occasional emoji.

Contrast my father with my 20-year-old daughter, Morgan Stefanacci. A student at the University of Colorado Boulder, Morgan is now contemplating a career in health care. That in itself is a difference from my generation. My decision to go into medicine—which was made for and by me—was arrived at when I was about 10, in part because I was allowed to watch my father perform surgery at Saddle Brook General Hospital (rules have changed!). Today’s health care professionals are often coming from nontraditional pre-med backgrounds. In fact many schools, like Thomas Jefferson University where I work, are actively promoting this mindset to develop physicians with different kinds of experiences, including those that take place outside of the classroom.

Morgan is firmly planted in the millennial generation, a group that has come of age in a time of immediate access to almost boundless information and ever-advancing technology. Her generation is confident, practical, creative, and values technology. They are a valued resource in most managed care organizations because they work well in teams and with technology. One challenge managers may have is the high value they put on their personal and family time. Some attribute this outlook among young physicians to the limits on residency hours, motivated by concerns about patient safety. For today’s managed care organizations, it means hiring more physicians and physician extenders—nurse practitioners and physician assistants—to fill this productivity gap.

And me? I just turned 54. I graduated from medical school in 1989 when George H.W. Bush was president. I’m in the tail end of the baby boom; we boomers are typically characterized as feeling entitled, being competitive, and having appetites for instant gratification. But similar to my father’s generation, we often value hierarchy and a strong chain of command that can stand in the way of teamwork. There are early adopters among us, but as a rule, we’re less adept at dealing with new technology than my daughter’s generation. We also connect differently. My father’s generation and mine prefer phone conversations and in-person meetings while Morgan more commonly connects through the Internet, email, and instant messaging.

I see this generational range in the workforce. The differing work and communication styles mean leaders of managed care organizations need to connect and motivate in a whole variety of ways so they can get the most out of providers of all ages.

Source material
Caregivers Fill Crucial Role But Don’t Get Much Help

Their care of loved ones defrays costs that would otherwise have to be borne by the health care system, but they too often go it alone.

By Susan Ladika

Anna Boyle is struggling to figure out how to care for her mother. After a string of health issues put Doris Boyle in and out of Boyle’s care for the past three years, the 88-year-old was diagnosed with Alzheimer’s disease. (Names have been changed at the request of the family.) She has been living with Boyle’s family full time since Thanksgiving.

“This year, her decline has just been unbelievable. Today she failed to recognize my daughter for the first time and she’s very confused,” the 53-year-old legal assistant from Tampa, Fla., said shortly before Christmas.

“She’s been a strong woman all her life,” Boyle says. “Now it’s almost like she’s a baby again at times.”

Soldiering on

Boyle is facing what millions of Americans must cope with each day—taking care of loved ones who cannot properly care for themselves. And often these families soldier on, with no or limited outside support. The numbers are staggering, with 43.5 million Americans—or nearly 15% of the population—providing care to a loved one, a 2015 study by AARP and the National Alliance for Caregiving found.

As the population ages, the caregiving situation is expected to become more acute. The prime age for caregivers is 45 to 64, according to AARP. Right now, there are seven people in that age group for every person age 80 or older. By 2030, there are projected to be only four potential caregivers for every person age 80 or older.

Caregivers spend an average of 24 hours a week on caregiving, and nearly 60% have to tackle complex medical tasks, such as giving injections or dealing with catheters. Most have received no training.

“You cannot ignore these people,” Susan C. Reinhard, AARP’s senior vice president, says of caregivers. The unpaid care they provide came to $470 billion in 2013.

And a third of caregivers do it all on their own, without any paid or unpaid assistance. In fact, many have to pay out of pocket to provide financial assistance for their loved ones. A report by the insurer Genworth found they pay an average of $10,000 out of pocket a year.

All that unpaid care had an economic value of $470 billion in 2013, according to an AARP report. “The problem is that family caregivers are invisible, but you cannot ignore these people,” says Susan C. Reinhard, senior vice president at AARP. If the caregiver gets

Physical, emotional, and financial stresses from caregiving

<table>
<thead>
<tr>
<th>Physical strain</th>
<th>Not a strain at all</th>
<th>Very much a strain</th>
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<td>28%</td>
<td>26%</td>
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<tr>
<th>Emotional stress</th>
<th>Not at all stressful</th>
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<td>20%</td>
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<tr>
<th>Financial strain</th>
<th>Not a strain at all</th>
<th>Very much a strain</th>
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<tr>
<td>39%</td>
<td>22%</td>
<td>20%</td>
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Source: AARP, "Caregiving in the U.S.," June 2015
sick or is hospitalized, "things can fall apart quickly," acknowledges Philip Painter, chief medical officer at Humana. Yet they often are ignored. That can be to the peril of the patient and the caregiver alike.

**Takes a toll**

Caregiving may take a toll on the health of caregivers. Research has shown that the health of family caregivers can be adversely affected by the burden, notes Painter, and the risk increases with time and as the condition of the person being cared for worsens. A Genworth study found that caregiving negatively affected the health of more than 40% of caregivers, and a third reported extremely high levels of stress. AARP found 17% of respondents were in fair or poor health.

**Tennessee’s CHOICES program**

makes health plans take into account the needs of caregivers, says Patti Killingsworth, chief of long-term services at TennCare, the state’s Medicaid program.

It would seem to be in the interest of payers to support caregivers and keep them healthy. An overburdened, stressed-out caregiver might end up needing medical care for any number of conditions. The payers, covering the bills of those being cared for may also be affected. If a caregiver can’t keep up with her caregiving responsibilities because she is sick, the person being cared for may be at risk for hospitalization or admission to a skilled nursing facility.

Sandy Wollenhaupt, of Russell, Ky., was fortunate in many ways when she was caring for her mother, Imogene Vallance, who died in 2013 at age 80. Wollenhaupt is a nurse, and thanks to an understanding employer, she was able to come home during the workday to help care for her mother. Her husband, kids, and sister-in-law—also a nurse—pitched in. Still, it was difficult to do all that needed to be done, particularly as her mother lost mobility. Wollenhaupt’s blood pressure shot up, and she had to start taking medication to control it.

“It was frustrating and hard to try to balance being a mom and a daughter and full-time employment. A family is asked to do a lot if they want to keep family members at home,” she says.

Caregiving can also undermine people’s financial well being. Caregivers often must dip into savings to cover the out-of-pocket expenses of their loved ones, cut back on their work hours to provide care—or drop out of the workforce altogether. Boyle, the Tampa legal assistant, faces a common dilemma. She is worried about her mother having the care she needs when she and her supportive family are either at work or at school. “If I have to drop out of work, it would bankrupt us,” she says. She has lined up a spot at a nearby adult daycare center to provide care as needed.

More than half of caregivers said they had to work fewer hours, and one quarter said they missed out on career opportunities because of their caregiving responsibilities, Genworth found.

An AARP survey found that 10% of caregivers aged 50 and older quit their jobs or took early retirement to provide care, while 17% took a leave of absence. Those who left the workforce lost about $300,000 in wages and benefits. “We need to help them stay on the job,” says AARP’s Reinhard.

**12 weeks of paid leave**

The Family and Medical Insurance Leave (FAMILY) Act, which has been introduced in Congress, would provide workers at all companies with up to 12 weeks of paid leave if they are dealing with their own serious health condition or that of a family member. Workers would be able to earn up to two thirds of their monthly wages. California, New Jersey, and Rhode Island are the only states that offer paid family medical leave.

Almost half of states have unemployment insurance available for workers who voluntarily leave their jobs to serve as caregivers, but it’s seldom publicized and can be hard to collect, a study by AARP, the Commonwealth Fund and the SCAN Foundation found. Kathleen Kelly, executive director of the Family Caregiver Alliance, a national not-for-profit group based in California, had no idea before the study was conducted that California had unemployment insurance for caregivers. “We were as sur-

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**Most preferred financial support policy**

*Show caregivers the money!*

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<th>Policy</th>
<th>26%</th>
<th>32%</th>
<th>30%</th>
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<tr>
<td>Program where caregivers are paid for some hours of care</td>
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<td>Income tax credit</td>
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<td>Partially paid leave from work</td>
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<td>Not sure</td>
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Source: AARP, “Caregiving in the U.S.,” June 2015
prised as anybody else. It’s there in theory. In practice, I’m not sure how much it’s utilized.” One possible source of financial assistance for caregivers comes from Medicaid. Most states have programs that use a waiver to allow someone who is on Medicaid to select a personal care attendant, such as a family member.

The caregiver is then paid by Medicaid, Reinhard says. Program specifics can vary from state to state. However, “for the vast majority of middle-income Americans, there’s not much financial assistance,” Kelly says.

**Insurers take steps**

A few health plans have started to take some steps to recognize and support caregivers. Tennessee is at the forefront of caring for the patient and the caregiver through CHOICES, which provides long-term care through TennCare, the state’s Medicaid program.

The program is available for adults aged 65 and older, and for younger adults who have a physical disability. They must qualify for Medicaid long-term services and supports, and be unable to do everyday activities, such as taking medications and toileting.

Participants must either need the level of care provided in a nursing home or be at risk of having to move to a nursing home if they don’t receive the extra care. CHOICES can provide in-home care and help people stay in their homes longer. Payers should appreciate that remaining at home is far less costly than nursing home care. According to Genworth’s 2015 Cost of Care Survey, the cost of hiring a home health aide or homemaker services worker averages $20 an hour nationally. In comparison, living in an assisted-living facility averages $43,200 per year, while a semi-private room nursing home costs an average of $80,300 per year, and a private room costs $91,200.

As part of CHOICES, health plans now must take the needs of the caregivers into account, not just those of the patients. “It recognizes the very important role that caregivers play,” says Patti Killingsworth, chief of long-term services with TennCare.

**In-home assessment**

Within 10 business days, the state’s three Medicaid managed care organizations—Amerigroup, BlueCare Tennessee, and UnitedHealthcare Community Plan—are required to do an in-home assessment of both the

**Long-term care expenditures for the elderly**

![Graph showing projected long-term care expenditures, 2015–2050](image)

**With an expansion of LTC insurance coverage**

![Graph showing current distribution and projected distribution of long-term care expenditures](image)

Long-term care insurance could help defuse the looming baby boom retirement ‘disaster’

Long-term care is expensive for all concerned—those getting it, their family, caregivers, and taxpayers. And the situation is only expected to get worse as the American population ages.

“Everybody is acutely aware that as 10,000 baby boomers hit the senior citizens ranks every day, it’s a potential disaster,” says Marjorie Keymer, vice president and medical director of claims for the insurer Genworth.

Already, long-term care for seniors costs an estimated $231 billion each year, according to the American Council of Life Insurers (ACLI). That equals 7.5% of all money spent on health care in a given year. Medicaid and Medicare each cover about a third of those costs, while patients and their family members shoulder 20% of the burden, or $46 billion in out-of-pocket expenditures.

Spending on long-term care is expected to soar to almost $400 billion by 2030, while the number of employees paying taxes will shrink. In 2010, there were nearly three workers paying taxes for every retiree; by 2030, there will be just two per retiree.

One possible way to spread the financial burden is through private long-term care insurance. The ACLI calculates that if one quarter of consumers purchased long-term care insurance, Medicaid would wind up shouldering 25% of the country’s long-term care costs and individuals about 11%, while private insurance coverage would jump from less than 7% today to 26% in 2050.

For consumers, this may not be a good deal. Premiums vary with an individual’s age when purchasing the policy, the maximum daily or monthly amount the policy covers, and how long the policyholder will wait until the policy kicks in. Often, people choose a 90-day wait. Typically, policies today provide coverage for three or four years, and criteria are often an inability to do the “activities of daily living,” such as bathing, dressing, going to the bathroom, and feeding oneself.

If someone wants to file a claim with Genworth, a registered nurse will visit the individual and his family caregiver to assess his physical and cognitive functions, says Keymer. The nurse then will draw up a plan of care, outlining the type of assistance needed. Needs are reassessed over time.

Currently, nearly 7 million Americans have long-term care insurance, according to ACLI. The number of people covered by the insurance climbed 17% between 2007 and 2013. Much of that growth is in hybrid policies, such as ones that combine life insurance and long-term care insurance. A consumer would typically purchase a whole life policy, with long-term care coverage as a secondary benefit. The hybrid policies were introduced about 10 years ago.

Genworth, Guardian, and Nationwide are among the companies that sell hybrid policies. Consumers are advised to be a little wary because some hybrid policies offer very skimpy long-term care coverage. A hybrid policy generally costs about 5% to 15% more than a standalone life insurance policy. If the hybrid policyholder becomes ill or injured, the death benefit can be accelerated and used to pay for long-term care. However, that will reduce the life insurance payout to heirs when the person dies.

“It ends up being a living benefit of a life insurance policy,” says Frank Chechel, second vice president of life product management at the Guardian Life Insurance Co. of America.

State Partnership Programs, which link certain long-term care policies offered by private insurers with Medicaid, are another choice for people entering their care-need ing years. With these policies, if you have, say, $100,000 worth of coverage you can apply for Medicaid and still retain $100,000 worth of assets. Those are above a state’s Medicaid asset limit. In most states, the limit is $2,000 for a single person.

So, you could retain $102,000 worth of assets. The ACLI says partnership policies are available or pending in 42 states.
who need long-term care services and supports to receive that care in their homes and other community based settings.

“At the same time, we do want to support caregivers, and absolutely recognize that supporting caregivers is an essential aspect of helping older adults and people with disabilities live in their own homes,” Killingsworth says.

**Humana at Home program**

The challenges and burdens also are recognized by Humana, which has a strong presence in the Medicare Advantage market. The insurer has extensive resources for caregivers through its plans and on its website. As part of its Humana at Home program, for example, the insurer helps older adults to remain in their homes through services such as a personal care manager who is a nurse or licensed clinical social worker. The care managers talk with both the Humana members and their caregivers regularly, and they provide telephone or in-home services for about 1 million Humana members, says Painter, the chief medical officer.

“Things can fall apart quickly” if the caregiver gets sick, says Philip Painter, Humana’s CMO. Yet caregivers are often ignored, and that can be perilous for caregiver and patient alike.

They also have access to local resources for members and caregivers, such as information on adult daycare facilities or transportation options. “Over time, we’ve built up this very robust community resources directory,” notes Painter.

All caregivers can access Humana’s Caregiver’s Toolkit (even if you are not a Human customer). The booklet has pages for recording medications and medical conditions and some basic tips for how caregivers can take care of themselves, including the useful admonition to set some time aside for yourself.

Meanwhile, state and federal lawmakers are pushing ahead with legislation designed to help caregivers.

The family caregiver must be notified if a loved one is going to be discharged to another facility or released to the home.

Hospitals and rehabilitation facilities are required to provide explanations and in-person instruction about medical tasks that a family caregiver will need to provide at home, such as transferring a person out of a wheelchair, giving medications, or caring for wounds.

This may all seem like common sense—and none of it costs very much. Yet, says Kelly, these simple efforts often aren’t made.

One goal of the CARE Act is to reduce hospital readmissions, and offering instruction to caregivers may help in that regard, Reinhard says. Oklahoma became the first state to enact the CARE Act, in 2014. It was supported by Republican Gov. Mary Fallin, who had personal experience caring for her bedridden mother while raising a family of her own.

There are several efforts at the federal level that would ease the caregiver’s burden. At the end of 2015, the Senate approved the RAISE (Recognize, Assist, Include, Support, and Engage) Family Caregivers Act, which would set in motion a national strategy for supporting caregivers. The bill is pending in the House.

Earlier in 2015, members of Congress formed the Assisting Caregivers Today caucus, designed to bring more attention to the challenges facing caregivers. Rep. Lujan Grisham, a New Mexico Democrat, introduced a bill to create a national Care Corps, modeled after the Peace Corps, in which volunteers would provide services designed to help older adults and those with disabilities continue to live independently. Meanwhile, Rep. Nita Lowey, a New York Democrat, introduced the Social Security Caregiver Credit Act.

“The plan would provide Social Security earnings credit for caregivers who leave their jobs or cut back their work hours to care for a loved one. Hillary Clinton has come out in support of Social Security credits for caregivers and has proposed a $6,000 tax credit to cover expenses of those who serve as caregivers,” SAC.

Susan Ladika is based in Tampa, Fla., and has been a freelance writer for almost 20 years.
Making a walk is one of life’s simpler pleasures. But walking is also an everyday activity that we largely take for granted. A spinal cord injury that would suddenly rob us of our ability to walk is hard to imagine. But it happens to thousands of Americans every year. According to the National Spinal Cord Injury Statistical Center in Birmingham, Ala., about 12,500 Americans suffer a spinal cord injury each year and about a quarter of a million people in the country are living with the aftermath. Those statistics are for spinal cord injuries of all sorts. If the injury is in the cervical region, the result is either incomplete or complete quadriplegia. If the injury is lower down in the thoracic, lumbar or sacral regions, various levels or paraplegia—paralysis of the legs and lower body—may occur. About 40% of spinal cord injuries involve paraplegia with about half being complete and half being incomplete. The center estimates that the health care costs and living expenses during the first year after the injury are, on average, more than $500,000 and more than $65,000 each year after.

Regardless of the severity, a spinal cord injury often is a devastating injury at many levels—physical, emotional, medical, social, financial. Beyond the numerous associated medical conditions, these patients have a life that is severely hampered because of physical limitations. And the change is sudden—a very stark before-and-after contrast.

Historically, persons with paralysis have had only a few limited options for activities of daily living. The basic design of the wheelchair developed by John Dawson in England in the late 18th century remained virtually unchanged until electric motors and various other electronic adaptations were added.

**VA is buying**

Early versions of exoskeletons—wearable robotic suits that help people move—date back to the ’70s. But it was only recently that the technology became truly usable because of breakthroughs in computational power and battery technology. New exoskeleton devices have been developed by a number of companies. These amazing machines can translate the user’s body movements to activate motors, which, in turn, move the lower limbs through pre-programmed, coordinated gait patterns.

Only one version, developed by Rewalk Robotics in suburban Boston, has obtained FDA approval for home use. Late last year, the Veterans Administration announced that it would pay for ReWalk’s devices. The company’s stock price jumped up with that news. By some counts, 42,000 veterans have lost the use of their legs and as many as half of them might benefit from a ReWalk device. Although the VA needs to work through a number of operational issues such as ramping up their evaluation and training programs at the 24 VA centers that specialize in spinal cord injuries, it is conceivable that within a relatively short time we will start to see many people wearing exoskeletons in our communities.

The ReWalk exoskeleton allows the user with paralysis to perform a variety of maneuvers such as standing, sitting, and, yes, walking. People use the device to get up and down stairs, although FDA approval does not currently include an indication for stair use. The components of the ReWalk include a wristband remote con-
trol communicator, bilateral articulating legs consisting of thigh and calf components, pelvic band, straps and padding, ankle/foot bed, and backpack containing the main and auxiliary batteries. Motors in the exoskeleton control movements at the hip and knee joints. The ankle joints are assisted with a non-motorized exoskeleton mechanical and spring-assisted device integral to the ReWalk.

ReWalks need to be custom fitted to the user according to pelvic width, thigh length and shank length. Additionally, crutches attached to the user’s arms—or, alternatively, a walker—are needed to maintain balance. Candidates for the device should have hands and shoulders capable of supporting the crutches or a walker, healthy bone density, ability to stand using a device such as a standing frame, general good health, height between 5’3” and 6’2” and weight of 220 pounds or less.

To initiate use on the remote control communicator the user first sets the desired maneuver or “mode,” then he or she must initiate the desired motion by shifting the center of mass in various directions. The available modes include rising from a seated position, moving from standing to a seated position, walking and returning to a seated position. So, for example, to stand, the person sets the remote control communicator to the “standing mode.” A five-second pause is programmed into the cycle to permit time for proper crutch placement. During this time the user must also shift his or her center of mass forward to a position above the feet. The imbedded sensors ensure proper position and the device can then raise the user into a standing position. Numerous sensors ensure that the exoskeleton is in the proper position and will not initiate any motion unless proper positioning is present.

Walking involves combining body position, trunk posture, weight shifting, and proper placement of the arms and crutches or walker. The device won’t go into walk mode until sensors determine proper positioning and offloading of weight from the initiating leg. The next step is initiated once the initial leg has completed its swing motion and the user shifts the body weight onto this leg. This in turn allows the motors to initiate the same sequence on the contralateral leg if the user shifts the body to the proper position. The cycle is then repeated.

Ceasing the weight shift causes the device to cease to move the user forward.

The device has built-in hardware and software safety and emergency features. It has automatic testing features that will disable the system if any of the components are not functioning or communicating properly. It also has redundant controls and limits to prevent excessive joint flexion or extension.

**Ready to use**

Numerous studies have been done to ensure safety and efficacy, including studies on the cardiovascular system, energy expenditure, heart rate, and oxygen use. The research showed that metabolic demands—how much physical work the user must use—are well within acceptable levels. Those results helped build a case that ReWalk was ready for people to use and not some sci-fi project. Studies also demonstrated a training effect that created a more efficient use of energy (and speed) after the user became more adept at using the device.

The ReWalk device could revolutionize the care and treatment of spinal cord injuries and paraplegia no matter what the cause. Priced at between $80,000 and $100,000, it will be an expensive item for the VA system and some health plans. The current models are designed specifically for people with spinal cord injuries. But ReWalk may be modified for use by people with walking and other movement problems, regardless of the cause: stroke, cerebral palsy, spina bifida, traumatic brain injury, Guillain Barre syndrome (subject to FDA approval, of course).

ReWalk again demonstrates the speed at which miracles are occurring in Tomorrow’s Medicine.
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MediMedia Managed Markets is a strategic managed care agency that guides pharmaceutical and biotech clients through the ever-changing payer environment. We’re looking for big thinkers to join us on the journey.
A CONVERSATION WITH THOMAS H. LEE, MD

Physicians and Provider Organizers Should Ease Suffering, Invite Feedback

Suffering, empathy, competition, the patient experience. Thomas H. Lee, MD, Press Ganey’s chief medical officer and a member of our editorial board, connects some big ideas in his new book, An Epidemic of Empathy in Healthcare.

Interview by Peter Wehrwein

I’m curious about the genesis of the book. What prompted you to write it? You’ve known me in a variety of different contexts*, and this book actually was my attempt to tie it all together—all the things that I think, worry, talk, and write about related to making the health care system work.

How does the marketplace work? How do we make sure the marketplace is competing on the right things? That takes me into the Michael Porter stuff, the strategy of creation of value. What does value mean? It means meeting patients’ needs and doing it as efficiently as possible. That is the right thing, it’s a smart thing, but how do we actually do it?

I wanted to show that this stuff all fits together. It’s not the world gone mad. It’s actually “the world makes sense.”

And in that very last chapter, which is, like, five pages long, I tried to list those 10 things that are key steps that go from the very, very high, right on down to what kind of incentives I should be feeling when I’m sitting across from a patient.

I think it is impressive the way you knit together so many ideas. One of them is suffering and how health care should focus on relieving suffering. I squirm a little with the use of the word “suffering.” And in the book you talk about how you had reservations about it initially. It’s a word that makes people uncomfortable. We haven’t used it in health care until relatively recently. Now it’s being used more and more. I’d like to think that Press Ganey and I have something to do with that.

There are two things I would say. First, there has been so much medical progress, and we sort of break down problems and patients into narrower and narrower buckets where people with real expertise can bring the advance of science to people’s care. It’s progress that’s leading to that narrower focus. But now it’s easier to focus on a narrow problem than on the big picture. Second, there are so many distractions in life today. It’s important for me to look right at you when you’re a patient across from me, and muster the focus and the energy to think, “What is going on with him? What’s really important to him?”

But I think patients can really tell when physicians’ minds are wandering to other things. They’re flipping through papers, scrolling down a computer screen, glancing at their smartphones. So you need an idea like “suffering” to jar us into remembering to focus. The word is sensational. It commands attention. But that’s what we need to counter the distractions of modern life.

When you were getting trained, what word did people use instead of suffering? Everyone would use the same quote from Francis Peabody, which is, “The secret of the care of the patient is in caring for the patient.”

I don’t think that’s in the book. To me, it’s almost hard to say because it’s so obvious. It’s like “Do unto others as you would have them do unto you.”

Don’t you think suffering suggests passivity? Is that

*Lee was editor in chief of the Harvard Health Letter for several years while Wehrwein was editor.
a problem with this concept? I’m very aware of what you mean. It’s like “cancer victim.” People don’t want to be thought of as victims. The other thing I heard people say is, “Isn’t suffering good? Doesn’t suffering make you more noble?”

There’s a sense that you’re showing restraint when you suffer. And I hear that, and I respect where they’re coming from. But as a rule, I’m against suffering. I would rather have less of it than more of it.

Let’s shift to empathy. In the book, I think you’re trying to bring suffering and empathy together. Empathy isn’t about me feeling bad. It is about me doing the work to imagine what the patient is going through and what his needs are. Really looking at someone and understanding his context and what he needs—it’s work. Empathy is a necessary step toward actually taking action to help reduce a patient’s suffering. And part of it is conveying that you understand his needs. Showing that, “Yeah, I get it, that it must be really tough, you know, and here are some things we can do, and if things aren’t turning the corner by Saturday, call me, even though it’s a Saturday.” That kind of thing.

There’s a term that I like: “emotional labor.” Empathy involves emotional labor. Most people in health care are hard workers. They’re ready to do work if you lay out the work for them. You can’t make them better people than they are. They’re pretty good, but they’re human, so it’s good news that you can work at being empathic.

In the book, you compare empathy to acting. When I first read about that I was turned off. Now, I recognize that when I’m walking into a room to see a patient—and I think I put this in the book—I will stand at the door for a second, take a deep breath, pull myself together, and I walk into the room and go, “Hi, I’m Dr. Lee. I’m a close colleague and friend of Dr. Leonard. What can I do to help?” It’s like what I imagine actors doing before they stride onto a stage. We have to play a role and try to meet our patients’ expectations.

You’ve known hundreds of doctors; some are good and some would never be very good at this, right? There are people for whom this comes easier than others. I will say this: No one is as good as they could be or should be. All of us need to work at being the kind of physician we want to think of ourselves as being. Trying to create the context in which good people are at their best consistently—that’s part of the game.

And then there are people who just don’t care. How do you make them care? You need extra nudges reinforcing intrinsic motivations. I think transparency helps, but there are some people who just aren’t going to change. And in those cases, organizations have to ask: Should we part company? Toby Cosgrove at the Cleveland Clinic has said that every time he lets someone go, the first thing everyone says is, “What took you so long?”

How does this fit with shared decision making? It seems to be almost a throwback to empathic doctor being in a position of authority and power over suffering patients. I’m not against shared decision making. But I would say I don’t think it’s going to save health care in terms of quality or cost. It’s obviously the right thing to do—share information with patients. But patients are heterogeneous. There are some who really want to go back and forth with you. And there are others who are just ready to say, “What would you do?” In my own practice, there are more people in the “what would you do” category than in the “I want this kind of test” category. But I’ve got both. Part of being a good clinician is understanding that one size does not fit all.

There’s nothing wrong with shared decision making, and there are some good things about it. It’s not going to save the world, though. Some folks seem to think it might.

My wife recently used a Minute Clinic. She had a good experience. Maybe there’s an appetite for care that is businesslike and that is available when I want it. Do you see a tension between the Minute Clinic and convenience medicine, and what you’re describing in the book? I think paying attention to what people want is part of the definition of real empathy. It’s not projecting what you want them to want. My wife, Soheyla Gharib, is chief medical officer at Harvard University Health Services. And I was shocked to find out that many students don’t care about going to a famous place like Brigham and Women’s. They want convenience and access. When they get leukemia, it’s a different story.

People want different things at different times. So part of empathy is saying, “This is what matters most to this person.” So it can be empathic to give people convenience.

There’s no mention of payers or insurers in your book. Do you see a role for them in this empathic health care
system that you think we should aspire to? I hadn’t thought of that. But to a payer I would say, “You guys should be providing incentives for transparency on the patient experience.” Make 1% of payment linked to transparency.

The impact of having patients’ comments out online is enormous. It’s transformative. It changes the focus from classifying doctors on how they’ve been in the past to how are you going to be with the next patient you see. So, if I were a payer, I would encourage providers to put comments online in the way that University of Utah has.

Let’s talk about measurement and Press Ganey. In the book, you draw a distinction between patient satisfaction and patient experience. Experience is trying to get more at the totality of things that happen, not just “Did you like the food?” or something like that.

Patients want good outcomes. Death is the most important outcome, of course. Losing a leg, blindness, or stroke—things like that, those are hard clinical outcomes. The assumption is you’ve got to be in the game on the hard clinical outcomes. But it’s very difficult to pull away from the crowd and differentiate yourself on those outcomes. So you better start to differentiate yourself on what Michael Porter calls Tier 2 outcomes, which include the experience of care. That’s where you start getting into the realm of suffering. Patient experience is an outcome that reflects the extent to which we’re meeting patients’ needs.

So patient experience is, in some sense, a matter of relieving patient suffering. Yes. And I use those interchangeably. The other phrase I use is, “Are we meeting patients’ needs?”

It seems that measurement of patient experience still depends largely on patients’ answering questions. What questions do you ask? There are really two different types of questions—process questions and outcomes measures. Process measures are focused on whether or not the doctor or other personnel performed some task, like explaining test results or the purpose of medications. The focus of process measures is on the reliability of providers.

On the other hand, outcome measures are aimed at the question of how is the patient doing. There are clinical outcomes that you don’t need to ask the patient about—like death or amputation. But those measures don’t necessarily differentiate among providers as much as patient-reported outcomes, such as whether or not a patient has sexual function or incontinence after prostate surgery.

Patient experience questions that are really outcome measures tend to get at that critical question of whether or not patients have peace of mind—confidence in the clinician, confidence that clinicians are working well together on the patient’s behalf. One of the major goals—maybe the major goal—of health care is to give patients peace of mind, and I think their likelihood of recommending clinicians or hospitals reflects peace of mind.

In truth, I think that both kinds of measures are important but outcomes-type measures are more important. Certainly, for public reporting it is clear that patients are more interested in outcomes than process. Process measures are important but should be moved internal to organizations trying to improve their own performance.

You mentioned some major problems with measurement. One really fun book that you may know is Thanks for the Feedback by Douglas Stone and Sheila Heen at the Harvard Negotiation Project. They talk about how we get feedback all the time, and we don’t really want feedback. And the first thing people do is they look for reasons to push away that information. And what you really want is to get people into a frame of mind of wanting to pull the information toward them, as opposed to look for every possible reason to push it away.

With all kinds of quality information in health care, there’s the same dynamic of people wanting to push information away. This is the reason we need competition in health care. We need people to want to get better, and therefore pull whatever information they have toward them.

Are you saying the data are not going to be perfect but that isn’t what we should be focusing on? I think you could say, “Look, let’s be realistic. The data will never be perfect, and if what you really want is to find a reason to ignore the feedback, then don’t bother collecting any data.”

I know physicians who worry that the only patients who respond to surveys are people who are angry. That doesn’t seem to be true, given that 80% of the patients give a 5 on a 5-point scale. So, then they said, well, the data all clustered at the top, with people giving positive ratings, and there’s no differentiation. But 20% of people are not giving 5s, so there are plenty of opportunities to improve. The data may not be perfect but are you willing to blow it off and ignore it? Or are you going to try to get better? That’s ultimately a decision for the clinician and the organization. That’s really a core premise of the book, and a requirement to compete successfully in health care.
Patients With Metastatic Bladder Cancer Have an Unmet Need

Bladder cancer research has seen few advancements over the past 30 years. No new agents have been approved for metastatic bladder cancer since 1998.¹-³

Metastatic Bladder Cancer⁴:
• Approximately 4% of new diagnoses represent metastatic disease (stage IV)
• 5-year relative survival rate of patients with metastatic disease is 5.4%
• Mortality rates for metastatic disease have remained relatively constant since 1975

“Against the background of no new drug approvals for advanced bladder cancer in decades, immunotherapy research is giving new hope to patients and physicians.”

–Michael R. Harrison, MD, Duke Cancer Institute

Learn More About Immunotherapy Research

Visit http://www.researchcancerimmunotherapy.com

REFERENCES
President Obama’s announcement of a “cancer moonshot” to cure cancer in his State of the Union address is a reminder that cancer is now our most discussed and debated disease. No way would heart disease or diabetes stir up so many ideas and opinions. HIV/AIDS is still a terrible disease but it has faded as a hot-button issue. About 45,000 Americans are newly infected with HIV each year, according to the CDC. Fortunately, though, treatments have improved. Far fewer Americans are dying from disease (6,955 in 2013), and the tenofovir–emtricitabine combination being sold as a preventive pill may help tamp down the incidence rate.

But, as Donald Trump might say, everything is huge about cancer. Really huge. The number of Americans who get it each year (1.7 million), and the number who die from the disease (almost 590,000). The organized interest groups (the American Cancer Society, the American Society for Clinical Oncology, the American Association for Cancer Research, to name just a few), the specialized cancer centers (MD Anderson, Dana-Farber, Roswell Park), the government agencies (chiefly the National Cancer Institute), and the pharmaceutical industry—all huge.

And there’s the size of the bill that has to be paid. Several years ago, the Agency for Healthcare Research and Quality (AHRQ) estimated the total direct medical costs of cancer at $88 billion, which is slightly less than the estimate of $95 billion for heart disease that the agency made at about the same time. The AHRQ estimate was made before the recent wave of expensive oncology drugs, so the direct costs today are probably even higher.

National Cancer Institute (NCI) researchers projected that cancer costs could reach $173 billion in 2020, although like the AHRQ estimate, those projections were done several years ago, so they don’t factor in the oncology drug boom. The country’s total expenditures on health care exceeded $3 trillion in 2014 (the latest year for which there is an estimate), so spending on cancer is a relatively small proportion (3% to 5%) of American health care spending overall. Still, no one is going to argue that it’s less than real money.

Individual Americans are starting to experience the rising cost of cancer. Results of a survey of 4,719 cancer survivors published in the January 2016 issue of Health Affairs showed that about a third went into debt because of expenses related to the disease and 3% filed for bankruptcy. Over half of those who had gone into debt had taken on obligations of $10,000 or more.

**Political grind**

All of this—and, of course, the current excitement about treatment advances—adds up to a lot of interest in the cancer moonshot and jostling about how it should be organized and what should it try to achieve. As Carl Zimmer, writing for Stat, has pointed out, this is the third of Obama’s big scientific splashes. It may be years before we know whether the cancer moonshot and the two others—the BRAIN Initiative and the Precision Medicine Initiative—lead to real advances. On January 28th, Obama signed a memo creating a White House task force on cancer that Vice President Joe Biden will lead. Several days later, the White House announced that it would be asking for $755 million for cancer research in the 2017 budget.

Naturally, people will bring their prior beliefs and experience to this project. Initiatives—they sound like a fresh start but they never come out of nowhere. Researchers working on cancer vaccines will want to see funding for cancer vaccines, and those working targeted drug therapies (mTOR inhibitors and the like) will want to see funding for targeted drug therapies. Biden is the public face of the cancer moonshot, and Biden’s staff has reportedly floated two ideas as priorities: CMS coverage of tumor sequencing and a

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**Bring the Cancer Moonshot in for a Landing**

MD Anderson has some experience with this sort of ambitious effort, and its president has some can-do suggestions to make it work.

By Peter Wehrwein

Vice President Joe Biden is the public face of the cancer moonshot but will need a strong manager to coordinate the effort.

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government-based, open database of genomic information. But there’s a lot of debate yet on the value of tumor sequencing and who should pay for it. Insurers we have spoken with are scrambling to rein the cost of genetic testing of all kinds and don’t think they should be paying for research.

Michigan Republican Rep. Fred Upton has bucked some in his party and praised the cancer moonshot, partly because a concerted cancer effort could swing support behind his controversial 21st Century Cures legislation. Upton says the legislation would modernize drug and device research and approval. Critics say it will weaken FDA oversight.

Vincent DeVita, MD, who was interviewed about his book, *The Death of Cancer*, for our January issue, was chief of the medicine branch at NCI during the federal government’s last big push on cancer, the Nixon administration’s War on Cancer. DeVita is ardently optimistic about the future of cancer treatment, but also a veteran of cancer political and public relations machinations. The moonshot moniker worries him: “The implication is that it has a date certain.” DeVita says Mary Lasker’s promise, picked up by Nixon, that the War on Cancer would conquer cancer by 1976 was a big mistake. “Everyone in the field knew it was absurd,” he writes in his book. Promises this time may be kept more open ended.

**MD Anderson precedent**

But vagueness could also be a problem. “You don’t want to just fund activity,” says Ronald DePinho, MD, president of MD Anderson. “You want to fund milestone-driven projects that are going to meet a particular endpoint.”

DePinho, not an astronaut, does have some experience with cancer moonshots. MD Anderson, a master at public relations, launched its cancer moonshot program four years ago and is probably responsible for the working name of the Obama initiative. Thirteen different cancers are listed on the cancer center’s moonshot website. The goals vary. For B-cell lymphoma, it is to double the cure rate in five years. For chronic lymphocytic leukemia, it is replacing chemotherapy with ibrutinib (Imbruvica), a Bruton’s tyrosine kinase inhibitor.

DePinho says the key ingredients to MD Anderson’s program include multidisciplinary teams, sufficient funding (including intellectual property revenue), and teaming up project managers and other professionals to work with researchers. He says the federal effort must avoid the organizational pitfalls of failing to bring different teams of researchers together. Biden has political gifts, but if DePinho is right, it seems like he will need a brilliant, focused administrator by his side to herd the cats.

Should the cancer moonshot tackle skyrocketing cancer costs? Here DePinho was cautious and politic, noting that costs were complicated and efforts to tame them have to “preserve the interest in the private sector” in drug development. MD Anderson is hardly an idle bystander when it comes to drug development; DePinho describes it as the “number 1 clinical trial engine in cancer in the world” and mentions the intellectual property revenue more than once. He believes that “science-driven drug discovery” and a clearer understanding of cancer and targets at which drugs should be aimed can reduce the failure rate in clinical trials, which would, in turn, reduce development costs. “If 19 out of 20 drugs in clinical trials fail, you are paying for those failures as well as the 1 in 20 success,” DePinho says.

Cost savings could also be a side effect of efforts to integrate clinical and research data in DePinho’s view. He says that his medical center has developed an IT system that brings together the “separate universes” of clinical data from electronic health records and research data. That kind of data integration helps create a “learning system” that should lead to more accurate predictions about which patients will benefit from drugs, so the expense of treatment of patients for whom they won’t work (or will be too toxic) will be avoided.

One serious catch: Data integration ain’t cheap, so if there is cost savings, it may be apparent only in the long game. DePinho says MD Anderson spent hundreds of millions of dollars on its IT infrastructure to pull this off. [MC]
Economic Evaluation of Linaclotide for the Treatment of Adult Patients With Chronic Idiopathic Constipation in the United States

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INTRODUCTION

Chronic idiopathic constipation (CIC) is a common gastrointestinal disorder that is estimated to affect approximately 15% of the general United States population, and the prevalence increases with age (Higgins 2004, Stewart 1999). Symptoms include infrequent bowel movements and hard stools, as well as bloating, straining during defeation, and abdominal discomfort (Pare 2001). In addition to its clinical manifestation, CIC can also have a negative impact on patients’ quality of life, work productivity, and health care resource use. A recent analysis of commercially insured patients found that incremental all-cause costs associated with CIC were $3,508 per patient per year ($4,446 among CIC patients with abdominal symptoms) (Cai 2014). An analysis of the U.S. National Health and Wellness Survey reported patients with CIC to have statistically significantly lower levels of health-related quality of life, as measured by the SF-12v2, compared with matched controls, and statistically significantly higher levels of presenteeism (26% vs 19%, respectively) and overall work impairment (34% vs 22%, respectively) (Sun 2011). Patients with CIC were also shown to have statistically significantly more provider and emergency room visits when compared with controls (Sun 2011).

To date, relatively few pharmacological treatments have been approved for the treatment of CIC. Tegaserod was approved for the treatment of CIC in 2004; however, it was withdrawn from the market in 2007 due to concerns regarding an increased risk of cardiovascular events among patients receiving treatment (FDA 2007). Lubiprostone was approved by the U.S. Food and Drug Administration (FDA) for treatment of CIC in men and women in 2006 and until recently was the only prescription drug with a CIC indication in the U.S. Lubiprostone is a chloride-channel activator that promotes bowel transit by increasing the chloride concentration of intestinal fluid, which in turn increases the isotonic fluid in the lumen.

In August 2012, linaclotide, a minimally absorbed guanylate cyclase-C (GC-C) agonist, was approved by the FDA for treatment of CIC in both men and women. Linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. This results in an increase in both intracellular and...
Economic Evaluation of Linaclotide for Treatment of CIC

extracellular cyclic guanosine monophosphate (cGMP). Consequently, chloride and bicarbonate secrete into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. In addition, linaclotide has been shown to increase extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves and reduce visceral pain (Castro 2013, Linzess 2014).

With the FDA approval of linaclotide for the treatment of CIC, it becomes important to evaluate the economic impact associated with its use vs alternative prescription drug treatments (i.e., lubiprostone). A previously published economic evaluation of linaclotide vs lubiprostone among adult patients with irritable bowel syndrome with constipation (IBS-C) found linaclotide to be a lower-cost option for the treatment of IBS-C, with equivalent or improved patient response (Huang 2015). The aim of this study is to use techniques of decision analysis and mathematical modeling to evaluate the economic impact of linaclotide vs lubiprostone in the treatment of adults with CIC.

METHODS
Model Overview and Structure
This model was developed in Microsoft Excel (version 2010) spreadsheet format using a decision-tree modeling technique and draws upon linaclotide clinical trial data (both published and posthoc analyses), published scientific literature, publicly available FDA reviews of lubiprostone, and a survey of practicing physicians on resource utilization associated with treatment failure. The model population is comprised of adults who have been diagnosed with CIC and are candidates for prescription treatment.

The overall model structure follows that of the IBS-C model previously published by Huang and colleagues (Huang 2015). Hypothetical CIC patients enter the model as candidates for either linaclotide 145 mcg once daily or lubiprostone 24 mcg twice daily (Figure 1). Treatment discontinuation may occur immediately after initiation. Patients who discontinue therapy are assumed to show no improvement from their baseline symptoms and are assigned clinical and economic consequences associated with treatment failure. Patients who continue drug therapy have a probability of achieving response to the assigned treatment. The model assumes that patients who respond to treatment are assumed to accrue the pharmacy costs for linaclotide 145 mcg or lubiprostone 24 mcg and to have higher health utilities (i.e., higher quality of life) compared with those who do not respond. Patients who do not respond to treatment are assumed to accrue treatment failure costs and to have lower health utilities than patients who respond.

The model time horizon is 4 weeks, which is consistent with the publicly available lubiprostone phase 3 clinical trial data (12 weeks of phase 3 clinical trial data are available for linaclotide) (CDER 2006, Lembo 2011). Base-case analyses were performed from the payer’s perspective, including number of patients responding to treatment, quality-adjusted life-years (QALYs), and direct medical costs as model outputs. Indirect costs were also included in scenario analyses to provide results from the societal perspective.

Model Inputs
Treatment Comparators
Only prescription therapies currently approved and indicated by the FDA for the treatment of CIC were included in the model; therefore, only linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily were included as treatment options. Over-the-counter (OTC) remedies, such as laxatives (e.g., MiraLAX), were not considered as treatment comparators because of limited published data and lack of FDA approval for the CIC indication. The model assumes that patients are seeking treatment with a prescription agent.

Treatment Response
The primary endpoints among linaclotide and lubiprostone phase 3 clinical trials were not directly comparable (CDER 2006, Lembo 2011, Vieira 2012). Therefore, available linaclotide and lubiprostone data from phase 3 clinical trials were reviewed prior to

KEY POINTS

- Chronic idiopathic constipation is a common condition that affects 15% of Americans.
- The only prescription medications approved by the FDA as treatments are linaclotide (Linzess) and lubiprostone (Amitiza).
- The two drugs have not been compared in a side-by-side trial, so researchers constructed a model to make the comparison. They used data from the phase 3 trials of the two drugs.
- The model shows that per-patient costs are lower for linaclotide than lubiprostone.
- When response was defined by treatment satisfaction, linaclotide edged out lubiprostone (39.3% vs 35.0%). When response was defined by spontaneous bowel movement, lubiprostone was slightly better than linaclotide (59.6% vs 58.6%). The quality-adjusted life-year scores were similar.
- The model only covers 4 weeks of treatment because of the lack of longer-term data for lubiprostone.
Economic Evaluation of Linaclotide for Treatment of CIC

Model development and measures of treatment efficacy were selected based on comparability between trial data and suitability for use as definitions of response within the model framework. Among trial endpoints that were included in clinical trials of both treatments (e.g., global assessment of treatment satisfaction, spontaneous bowel movement [SBM] frequency), reported measures were analyzed using different definitions of treatment response or did not report findings necessary for robust economic modeling. Therefore, posthoc analyses of linaclotide clinical trial data were conducted to help ensure comparability with the data reported from the lubiprostone clinical trials (further details of posthoc analyses are described in a previous publication [Huang 2015]).

Treatment response was defined by: (1) having one of the best two satisfaction answers of a 5-point global treatment satisfaction scale at Week 4 or (2) having weekly SBM frequency ≥4 at Week 4. The primary endpoint in the phase 3 lubiprostone clinical trial was number of SBMs per week, where a responder was defined as a patient with weekly SBM ≥4 at Week 4 (Barish 2010, CDER 2006). Phase 3 clinical trials for both treatments included similar assessments of global treatment satisfaction using 5-point response scales (“not at all satisfied/effective” to “extremely satisfied/effective”) (Barish 2010, Lembo 2011). Response for treatment satisfaction was defined as having either of the top two answers (i.e., quite or extremely satisfied/effective) at Week 4. While not a primary endpoint in the clinical trials of either treatment, this definition of response was selected due to the consistency of measure collection and definition between trials, as well as its ability to evaluate treatment effectiveness globally from a patient perspective.

Only means and standard deviations were reported for the global assessment of treatment satisfaction at Week 4 for lubiprostone; however, the model requires the percentage of patients with either of the top two answers (i.e., a score of 4 or 5 on the 5-point assessment at Week 4) to define response. To address this issue, a beta distribution was fitted to the reported lubiprostone mean and standard deviation, using the properties of the cumulative distribution function to estimate the percentage of patients with a score ≥4. The choice of using a beta distribution was validated with the patient-level linaclotide clinical trial data by testing the goodness-of-fit using the sum of squared differences. The fit of the beta distribution was found acceptable but had a tendency to slightly underestimate the required percentage. To be conservative, a fitted linaclotide response, rather than the actual response from the posthoc analyses, was used.

Response-rate data for linaclotide were derived from data on the pooled intent-to-treat (ITT) populations of the clinical trials.

Because SBM frequency was the primary endpoint in the lubiprostone clinical trial, SBM frequency response rates were calculated as the pooled average from the two publicly available lubiprostone trials (CDER 2006). While SBM frequency during each week was evaluated during the linaclotide phase 3 clinical trials, the proportion with frequency ≥4 was not. Therefore, posthoc analyses of linaclotide trial data using the same response definition as lubiprostone were conducted to ensure comparability between response rates.

For both definitions of response defined above, placebo-adjusted odds ratios (OR) of response for linaclotide vs lubiprostone were constructed.

Additional Inputs
Additional model inputs include the rate of treatment discontinuation, drug costs, direct/indirect cost of treatment failure, and responsespecific health utilities. Values for each input are documented in Table 1 (next page) and were derived using various data sources and estimation techniques. The methodology for constructing these model inputs are documented in a previous publication (Huang 2015). Note that daily drug costs have been updated to 2015 values (Red Book Online 2015).

Model Outcomes
Model outcomes are primarily from
### Economic Evaluation of Linaclotide for Treatment of CIC

#### TABLE 1
Cost-effectiveness analysis base-case and sensitivity analysis model inputs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Range</th>
<th>Low</th>
<th>High</th>
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</thead>
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<tr>
<td><strong>Treatment response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubiprostone response (24 mcg BID)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Based on global assessment of treatment satisfaction*</td>
<td>35.0%</td>
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<td>Based on SBM frequency*</td>
<td>59.6%</td>
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<td>N/A</td>
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<tr>
<td>OR linaclotide 145 mcg once daily vs lubiprostone 24 mcg BID (indirect comparison using placebo)</td>
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</tr>
<tr>
<td>Based on global assessment of treatment satisfaction*</td>
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<td>0.88</td>
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<td>0.70</td>
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<tr>
<td><strong>Discontinuation</strong></td>
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<td>9.6%</td>
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<td>14.3%</td>
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<td><strong>Costs</strong></td>
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<td></td>
</tr>
<tr>
<td>Drug (daily)</td>
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</tr>
<tr>
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<td>Indirect cost (per patient)</td>
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<td>Based on global assessment of treatment satisfaction</td>
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</tr>
<tr>
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<tr>
<td><strong>Utilities</strong></td>
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</tr>
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<td>Based on global assessment of treatment satisfaction</td>
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<tr>
<td>Response</td>
<td>0.92</td>
<td>0.91</td>
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<td>Nonresponse/discontinued</td>
<td>0.89</td>
<td>0.88</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Based on SBM frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0.91</td>
<td>0.91</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Nonresponse/discontinued</td>
<td>0.89</td>
<td>0.88</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

Data sources:
- [a] Response rate ("quite a bit" or "extremely" effective) derived through fitting to a beta distribution based on mean and standard deviation reported in Table 10 and 22 in the FDA 2006 Statistical Review, ITT population (CDER 2005).
- [b] Response rate (weekly SBM frequency ≥4) obtained from pooled data from Table 4 and 16 in FDA Statistical Review, ITT population (CDER 2005).
- [c] Placebo-adjusted odds ratios derived from response rate ("quite" or "very" satisfied) of linaclotide (posthoc analysis of phase 3 clinical trial data) vs lubiprostone. Lubiprostone response calculated as described above in source [a]. Low and high estimates were derived from bootstrapping results.
- [d] Placebo-adjusted odds ratios derived from response rate (weekly SBM frequency ≥4) of linaclotide (posthoc analysis of phase 3 clinical trial data) vs lubiprostone. Lubiprostone response calculated as described above in source [b]. Low and high estimates were derived from bootstrapping results.
- [e] Discontinuation assumed to be zero in the base case; discontinuation rate for “any reason” used for sensitivity analysis from the linaclotide (posthoc analysis of phase 3 clinical trial data) and lubiprostone clinical trials (CDER 2005, Lembo 2011).
- [f] Truven Health Analytics Red Book 2015 WAC price for linaclotide. Low and high estimates only used for probabilistic sensitivity analysis; assumed to be ±1.0% of the base-case value.
- [g] Truven Health Analytics Red Book 2015 WAC price for lubiprostone.
- [h] Derived from the findings from a one-time, web-based survey of physicians on treatment patterns and resource use for patients with CIC who had not responded to a recent treatment course. The low bounds of the interquartile range (IQR) of the estimated base-case costs were used as the low estimates. High estimates were taken from a retrospective database analysis of Medicaid administrative claims.
- [i] Derived from data collected from the Work Productivity and Activity Impairment Questionnaire (WPAI) Questionnaire in the phase 3 clinical trials for linaclotide. Low and high estimates were calculated as ±25% of the base-case value.
- [j] Derived from the EQ5D scores from phase 3 clinical trials for linaclotide.

BID=twice daily, N/A=not available, SBM=spontaneous bowel movement, WAC=wholesale acquisition cost.
the third-party commercial payer's perspective and include the percentage of patients responding to each treatment, as well as the direct medical costs and QALYs associated with response/nonresponse.

**Sensitivity Analyses**

Indirect work productivity costs were not included in the base-case analysis; however, they were incorporated in a separate analysis to test the robustness of model results and include results from a societal perspective.

Sensitivity analyses to assess uncertainty in the results based on potential variation in base-case model inputs were also performed. Low and high estimates for the following parameters were included in the one-way analysis: direct and indirect costs for treatment failure; OR for treatment response; health utility values; and discontinuation rates. High estimates for discontinuation rates (9.6% for linaclotide [posthoc analyses] and 14.3% for lubiprostone [CDER 2006]) include the discontinuation rate for “any reason” from each treatment’s phase 3 clinical trial.

Probabilistic sensitivity analyses were undertaken using a second-order Monte Carlo simulation. The OR for treatment response (using a log-normal distribution with standard errors obtained from bootstrapping techniques), drug cost for linaclotide (uniform distribution between low and high estimates; assumed to be ±10% of the actual drug cost), the cost of treatment failure (using gamma distribution), and health utilities (using a uniform distribution) were varied within the model.

**Model Assumptions**

The demographic and clinical characteristics of the modeled patient populations are assumed to be consistent with the patient populations in the linaclotide and lubiprostone phase 3 clinical trials. It is assumed that all efficacy reported in the clinical trials is attributable to the study treatment effect of linaclotide and lubiprostone (i.e., the improvement in response rate vs placebo observed in the trials is attributable to linaclotide or lubiprostone, not due to other reasons such as difference in demographics). Patients who respond to treatment are assumed to respond immediately upon treatment initiation, and all responders have the same health utility, regardless of treatment (same assumption for nonresponders).

Treatment costs are based on recommended dosing and frequency of administration in each product’s prescribing information. The results from the physician survey on patient management (diagnostic tests, procedures, and physician visits) for a hypothetical patient reporting no satisfactory symptom relief during treatment are assumed to be representative of all patients who experience treatment failure. In addition, the Medicare fee schedule used to estimate costs of diagnostic tests, procedures, and physician visits is assumed to be applicable to private payers.

**RESULTS**

**Base-case Results**

When response was based on global treatment satisfaction, linaclotide 145 mcg once daily was found to be less expensive and more effective when compared to lubiprostone 24 mcg twice daily. The percentage of responders was 39.3% and 35.0% for patients receiving linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily, respectively. Total direct costs were estimated to be $946 per linaclotide treated patient and $1,015 per patient treated with lubiprostone. QALYs were numerically similar between linaclotide and lubiprostone over the 4-week analysis period (Table 2).

When response was based on SBM frequency, the percentage of responders was 58.6% and 59.6% for linaclotide and lubiprostone, respectively. Total direct costs were estimated to be $946 per linaclotide treated patient and $1,015 per patient treated with lubiprostone. QALYs were numerically similar between linaclotide and lubiprostone over the 4-week analysis period (Table 2).

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**TABLE 2**

Cost-effectiveness model results for 1,000 patients with chronic idiopathic constipation (direct costs only)

<table>
<thead>
<tr>
<th>Comparator arms</th>
<th>Direct cost per patient</th>
<th>Responders (%)</th>
<th>QALYs per patient</th>
<th>Direct cost per patient</th>
<th>Responders (%)</th>
<th>QALYs per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubiprostone 24 mcg BID</td>
<td>$1,015</td>
<td>35.0</td>
<td>0.07</td>
<td>$737</td>
<td>59.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Linaclotide 145 mcg once daily</td>
<td>$946</td>
<td>39.3</td>
<td>0.07</td>
<td>$727</td>
<td>58.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Incremental (linaclotide-lubiprostone)</td>
<td>$-69</td>
<td>4.3</td>
<td>0</td>
<td>$-10</td>
<td>-1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

BID=twice daily, QALY=quality-adjusted life-year, SBM=spontaneous bowel movement.

[a] Global treatment satisfaction responder: Having either of the best two satisfaction answers (i.e., “quite” or “extremely/very”) of a 5-point global treatment satisfaction scale at Week 4.

[b] SBM frequency responder: Having weekly SBM frequency ≥4 at Week 4.

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**Economic Evaluation of Linaclotide for Treatment of CIC**

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patients receiving linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily, respectively. Total direct costs were estimated to be $727 per linaclotide-treated patient and $737 per patient treated with lubiprostone (Table 2).

**Sensitivity Analysis Results**

When indirect costs were included in the analysis (i.e., cost of lost work productivity), results were similar to that of the base-case results (data not shown).

Using the definition of response based on global assessment of treatment satisfaction, linaclotide 145 mcg once daily was less expensive and more effective versus lubiprostone 24 mcg twice daily in all one-way sensitivity analyses except one. When the placebo-adjusted OR for treatment response (linaclotide vs lubiprostone) was set at the low estimate (0.88), linaclotide had a lower per-patient cost ($1,022 vs $1,033) and a slightly lower response rate (32% vs 35%).

When the definition of response was based on SBM frequency, linaclotide 145 mcg once daily was less expensive but less effective compared to lubiprostone in all one-way sensitivity analyses except for the following four cases: (1) When the placebo-adjusted OR for treatment response (linaclotide versus lubiprostone) was set to the high estimate (1.22), linaclotide was less expensive and more effective compared to lubiprostone; (2) When the placebo-adjusted OR for treatment response was set to the low estimate (0.70), linaclotide was more expensive and less effective than lubiprostone; (3) When a 9.6% discontinuation rate was assumed for linaclotide and 14.3% for lubiprostone (both from trial data), linaclotide was less expensive and more effective compared to lubiprostone; and (4) When price of linaclotide was set to the high estimate ($10.16), linaclotide had higher per patient costs indicating linaclotide to be more effective and less expensive than lubiprostone for the treatment of CIC (Figure 2a). Analysis using the SBM frequency definition of response resulted in approximately 50% of the cost per additional responder scenarios in Quadrant 4 of the incremental cost vs response plane (linaclotide more effective and less expensive

**FIGURE 2A**

**Probabilistic sensitivity analysis results for cost per patient and probability of response (response based on global assessment of satisfaction)**

*Note: Each point on graph represents the result of 1 of 1,000 iterations of a second-order Monte Carlo simulation.

**FIGURE 2B**

**Probabilistic sensitivity analysis results for cost per patient and probability of response (response based on SBM frequency)**

*Note: Each point on graph represents the result of 1 of 1,000 iterations of a second-order Monte Carlo simulation.
Economic Evaluation of Linaclotide for Treatment of CIC

than lubiprostone). The other 50% were distributed among Quadrant 2 (linaclotide less effective and more expensive than lubiprostone) and Quadrant 3 (linaclotide less effective and less expensive than lubiprostone) (Figure 2b).

DISCUSSION
Results from this decision-analytic model show that linaclotide is associated with lower per-patient costs than lubiprostone when used for the treatment of CIC among adult patients ($946 vs $1,015 and $727 vs $737 for global assessment and SBM frequency definitions of response, respectively) from a third-party commercial payer’s perspective over a duration of 4 weeks. This observed difference in per-patient costs has the potential for significant effects on aggregate total costs for large health care organizations, particularly given the short time horizon in which a cost difference is established, as well as the high prevalence rate of CIC among the aging adult population. When treatment response was based on a global assessment of treatment satisfaction, linaclotide was also associated with somewhat higher response (39.3% vs 35.0%) and similar QALYs compared with lubiprostone. When treatment response was based on SBM frequency, linaclotide and lubiprostone had similar response rates and effects on QALYs. These results were robust in one-way sensitivity analyses, as well as with the addition of indirect work productivity costs as a model input. With only minor differences in response rates for either response definition, it is valid to conclude that both treatment options would provide similar effectiveness in a clinical setting. Therefore, under most scenarios and assumptions, linaclotide is a lower cost treatment option, with similar effectiveness, for patients with CIC when compared with lubiprostone.

Limitations
This study has various limitations, including a short time horizon and the need for additional analyses for several parameter estimates where available data were lacking. The time horizon for this model is relatively short (i.e., 4 weeks) due to the lack of longer term comparable data for lubiprostone, as well as the chronic nature of CIC. However, there is some suggestion that the benefits of treatment may extend over time. For example, in the 4-week randomized withdrawal period after completion of the 12-week phase 3 linaclotide clinical trial in CIC, it is observed that treatment efficacy outcomes (i.e., increase in weekly complete spontaneous bowel movements) are sustained for the patients who remain on treatment (Lembo 2011). For patients who discontinued treatment after the 12-week trial duration, weekly complete spontaneous bowel movements returned to a similar rate as baseline. The lack of comparable 12-week treatment trial evidence for lubiprostone limited the model to 4 weeks in duration. Further, longer-term clinical results would help extend the findings from this decision-tree economic model. The direct costs associated with treatment failure were derived from the findings from a one-time, web-based survey of 20 primary care physicians (PCPs) and 21 gastroenterologists that asked about treatment patterns and resource use among patients with CIC who were not responding to recent treatment. The classification of patient response and treatment duration in the survey differed from the response definition and time horizon used for the clinical inputs in the model. Additionally, several assumptions were required in calculating the cost estimate, including the assumption that all patients were seen by a primary care physician prior to being referred to a GI specialist. Therefore, there may be some bias in the estimates of direct medical costs. For instance, treatment failure costs may be slightly overestimated in the model given that all procedures specified in the survey may not occur during the 4-week model time horizon. This survey was undertaken because there are no published studies that present data on this issue. Resource use estimates from this survey of 41 physicians may be reasonably generalizable given that the surveyed physicians were heterogeneous in age, sex, patient volume, years of practice, and U.S. geographic region. In addition, costs are based on Medicare fee schedules, which are lower compared with those of a private payer and therefore provide conservative cost estimates (Nguyen 2013).

There are no available head-to-head trials that compare linaclotide with lubiprostone; therefore, placebo-
adjusted estimates of relative efficacy were derived. For the definition of response based on SBM frequency, posthoc analyses of linaclotide clinical trial data were conducted using the same definition as lubiprostone to ensure comparability of response rates, given the inconsistent definition between the linaclotide and lubiprostone trials. Due to this data limitation, the definition of response for SBM was required to be \geq 4 per week (i.e., the primary efficiency endpoint in lubiprostone phase 3 clinical trials). A response definition of \geq 3 SBM per week would have been a more clinically relevant definition of response, given that Rome III criteria defines constipation as fewer than 3 defecations per week (Longstreth 2006).

Additionally, due to a lack of sufficient data from the publicly available FDA review of lubiprostone clinical trials, the global assessment of treatment satisfaction measure of response required curve-fitting techniques to impute the percentages of subjects who achieved the defined threshold of response for both linaclotide and lubiprostone, which may not exactly reflect the clinical trial results.

The results from the model are likely conservative given the response rate derived for linaclotide from the curve-fitting technique produced a lower OR of response compared to the OR calculated if response rates from the actual linaclotide clinical trial data were used. The model assumes that those patients who discontinue therapy incur costs for 1 month (4 weeks) of drug treatment, and that patients who respond take the medication once daily for the full time horizon of the model (4 weeks). In actual clinical practice, initial prescription days supplied could be shorter, and actual use of the treatments may be less frequent than daily.

Finally, the model is based on a homogenous clinical trial population and treatment protocol, which may not be representative of real-world clinical practice. Studies of the comparative effectiveness of linaclotide and lubiprostone through analysis of real-world data would be valuable.

CONCLUSION

In a model based on published clinical data, linaclotide was found to be a less costly treatment option with similar effectiveness for patients with CIC when compared with lubiprostone. The results of this study are intended to provide useful information for determining effective treatment options in the absence of direct head-to-head clinical or economic evaluations.

REFERENCES


The American Cancer Society's report last month that the cancer death rate has dropped 23% since its peak in 1991 did not set off any celebrations. The steady downward trend has been apparent for some time. Besides, cancer will continue to rack up grim numbers this year. The society’s annual report estimates that 1.7 million Americans will be diagnosed with the disease in 2016, and that 600,000 will die from it. That’s more than 4,600 new cancer diagnoses each day and about 1,600 deaths.

But optimists will see good news. Overall incidence rates are stable in women and have been falling for men. By the society’s reckoning, 1.7 million cancer deaths have been avoided since 1991. It credits declines in smoking rates and improvements in screening and treatment for the deaths averted but does not apportion that credit. Falling death rates for four major cancers—lung, breast, prostate, and colorectal cancer—are driving the overall trend. The report notes, for example, that death rates for female breast cancer are down 36% from its peak years. Bucking the favorable trends are upticks in the death rates rising for anal, liver, and pancreatic cancer.

The report delves into the racial and ethnic differences in cancer incidence and mortality; for example, the death rate for stomach and prostate cancer is 2.5 times higher for black men than it is for white men. Reasons for differences vary by the type of cancer and whether the difference is in incidence or mortality.