For the adjunctive treatment of partial-onset seizures in patients aged 12 years and older

**ADD ON THE STRENGTH OF FYCOMPA® (perampanel)**

FYCOMPA is the first and only antiepileptic drug (AED) that targets glutamate activity at postsynaptic AMPA receptors

In three phase 3 clinical trials, FYCOMPA achieved a decrease in seizure frequency vs placebo.

**One daily dose at bedtime**

- Starting dose is 2 mg once daily in patients not taking enzyme-inducing AEDs and 4 mg in patients taking enzyme-inducing AEDs.
- Dose may be increased based on clinical response and tolerability by a maximum of 2-mg increments to a dose of 4 mg to 12 mg. Dose increases should occur no more frequently than at weekly intervals.
- A dose of 12 mg once daily resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once daily, but with a substantial increase in adverse reactions.

*Pooled results of 3 randomized, double-blind, placebo-controlled, multicenter trials of FYCOMPA. All trials had a 6-week baseline period followed by a 19-week treatment period (6-week titration and 13-week maintenance), and patients were required to have >5 seizures at baseline to be randomized. The intent-to-treat (ITT) population from Studies 1, 2, and 3 equals 1037 patients who received FYCOMPA and 441 patients who received placebo.
- The primary endpoint was the percent change in seizure frequency per 28 days during the treatment period as compared with the baseline period.

*More than 85% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation (VNS); approximately 50% were taking at least 1 enzyme-inducing AED.

*Patients from Latin American regions are excluded because of a significant treatment-by-region interaction due to high placebo response.

*The presence of concomitant enzyme-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin) increases the clearance of FYCOMPA.
Indication: FYCOMPA (perampanel) is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Important Safety Information

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA
- These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression
- Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA
- Closely monitor patients particularly during the titration period and at higher doses
- FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening

Serious Psychiatric and Behavioral Reactions

Hostility- and aggression-related adverse reactions occurred in 12% and 20% of clinical trial patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA-treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm, and/or any unusual changes in mood or behavior. Should suicidal thoughts or behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Dizziness and Gait Disturbance

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase.

Somnolence and Fatigue

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 7% of placebo-treated patients. Fatigue-related events were reported in 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 5% of placebo-treated patients. In the controlled Phase 3 epilepsy clinical trials, these adverse reactions occurred mostly during the titration phase. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

Falls

Falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients.

Withdrawal of AEDs

A gradual withdrawal is generally recommended with antiepileptic drugs to minimize the potential of increased seizure frequency.

Most Common Adverse Reactions

In clinical trials, the most frequently reported dose-related adverse reactions in patients receiving FYCOMPA 8 mg or 12 mg vs placebo (≥4% and at least 1% higher than the placebo group) included dizziness (35% vs 9%), somnolence (14% vs 7%), agitation (10% vs 5%), irritability (9% vs 3%), falls (7% vs 3%), ataxia (5% vs 0%), balance disorder (4% vs 1%), gait disturbance (4% vs 1%), vertigo (4% vs 1%), and weight gain (4% vs 1%).

Drug Interactions

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of FYCOMPA were decreased when administered with carbamazepine, phenytoin and oxcarbazepine. Concomitant use with strong CYP3A4 inducers such as St. John’s wort and rifampin should be avoided. Multiple dosing of FYCOMPA 12 mg/day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

Pregnancy Category C and Lactation

FYCOMPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to a nursing woman.

Hepatic and Renal Impairment

Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

Drug Abuse and Dependence

FYCOMPA is a Schedule III controlled drug substance and has the potential to be abused or lead to drug dependence.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on the next page.


To find out more information about FYCOMPA, speak to your representative or visit FYCOMPA.com/HCP.
FYCOMPA® (perampanel) tablets, for oral use, CII

**Warnings and Precautions**

- **Seizure Symptomatology:** Seizure symptomatology may worsen during the initial period of treatment with FYCOMPA. Patients should be monitored for new or aggravation of seizure symptomatology.

- **Psychiatric and Behavioral Reactions:** FYCOMPA can cause serious, new, or worsening psychiatric and behavioral reactions, including suicidal ideation and behavior, aggression, hostility, and other serious mental health disorders. If such reactions occur, dose reduction or discontinuation should be considered. Patients and caregivers should be instructed to report any psychiatric or behavioral symptoms to their healthcare provider.

- **Serious or Life-Threatening Psychiatric Reactions:** Patients receiving FYCOMPA should be closely monitored for suicidal ideation and behavior, aggression, hostility, and other serious mental health disorders. If such reactions occur, dose reduction or discontinuation should be considered. Patients and caregivers should be instructed to report any psychiatric or behavioral symptoms to their healthcare provider.

- **Suicidal Behavior and Ideation:** The risk of suicidal behavior and ideation is increased in patients treated with AEDs, including FYCOMPA. Patients should be monitored for new or worsening suicidal ideation or behavior, and if such symptoms occur, the dose should be reduced or the drug discontinued.

- **Other Psychiatric Reactions:** FYCOMPA can cause serious and new psychiatric reactions, including suicide ideation, behavior, aggression, agitation, hostility, and other serious mental health disorders. If such reactions occur, dose reduction or discontinuation should be considered.

- **Special Populations:** Elderly patients have an increased risk of falls compared to younger adults. Elderly patients have an increased risk of falls compared to younger adults.

- **Clinical Trials Experience:** In controlled clinical trials, the incidence of adverse events related to FYCOMPA was lower than placebo. In clinical trials, the incidence of serious adverse events was lower than placebo. The most common adverse reactions included somnolence, dizziness, agitation, and behavior changes.

- **Adverse Reactions in Pooled Clinical Trials:** In pooled clinical trials, the incidence of adverse events related to FYCOMPA was lower than placebo. The most common adverse reactions included somnolence, dizziness, agitation, and behavior changes.

- **Risk Management Program:** Patients and caregivers should be instructed to report any psychiatric or behavioral symptoms to their healthcare provider.

- **Additional Information:** Additional information is available in the package insert and the Warnings and Precautions section of the prescribing information.

**Table 1. Risk by indication for antiepileptic drugs in the pooled analysis**

<table>
<thead>
<tr>
<th>indication</th>
<th>Placebo Patients with Events per 1000 Patients</th>
<th>Drug Patients with Events per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence of Events in Placebo Patients</th>
<th>Risk Difference: Incidence of Events in Drug Patients/Incidence of Events in Placebo Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.3</td>
<td>4.3</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>1.75</td>
<td>2.05</td>
<td>1.18</td>
<td>1.15</td>
</tr>
</tbody>
</table>

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were smaller for the epilepsy and psychiatric trials. It is unknown whether FYCOMPA is associated with suicidal thoughts or behavior in patients with epilepsy.

**Table 2. Adverse Reactions in Pooled Double-Blind Trials in Patients with Partial-Onset Seizures (Exposure 2.2 to 6.5 mg per day in Clinical Trials and ≥4 mg per day in Open-Label Studies).**

<table>
<thead>
<tr>
<th>adverse reaction</th>
<th>placebo patients with events per 1000 patients</th>
<th>drug patients with events per 1000 patients</th>
<th>relative risk: incidence of events in drug patients/incidence of events in placebo patients</th>
<th>risk difference: incidence of events in drug patients/incidence of events in placebo patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2.8</td>
<td>5.1</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1.8</td>
<td>2.4</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.0</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8.0</td>
<td>15.0</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.1%</td>
<td>0.2%</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Weight gain

Weight gain has been observed with FYCOMPA use in adults. In the controlled Phase 3 epilepsy clinical trials, FYCOMPA-treated adults gained an average of 11 kg (25 lb) compared to an average of 0.3 kg (0.7 lb) in placebo-treated adults with a median exposure of 10 weeks. The percentages of adults who gained at least 7% and more than 15% of their baseline body weight in FYCOMPA-treated patients were 8% and 0.6%, respectively, compared to 4.5% and 0.2% of placebo-treated, respectively. Clinical judgment of weight monitoring is recommended. Comparison of Sex and Race No significant differences were observed in the incidence of adverse reactions. Although there were few non-Caucasian patients, no differences in the incidences of adverse reactions compared to Caucasian patients were observed.

OVERDOSAGE

Overdose

The administration of FYCOMPA tablets greater than 10 mg/kg/day by pediatric patients or 30 mg/kg/day in adults to healthy volunteers did not produce clinically significant changes in vital signs, electrocardiogram, or laboratory values. The concomitant use of FYCOMPA and CNS depressants including alcohol may increase the effects of FYCOMPA on the majority of measures (to ketamine 100 mg). In this group of subjects, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg and 36 mg was 37%, 46% and 46%, respectively, compared to alprazolam C-IV (1.5 mg and 3 mg), and oral ketamine C-III (100 mg) in recreational polydrug users. In a sub-therapeutic doses of oral FYCOMPA and 36 mg produced responses similar to ketamine 100 mg and alprazolam 3 mg.

Overdosage

The effects of FYCOMPA overdosage were generally mild to moderate in severity, with the most common effects being increased somnolence, asthenia, and anxiety. In overdosage studies, symptoms of tolerance, a number of subjects had missing data around Tmax of FYCOMPA. The above described data may represent an underestimate of FYCOMPA’s effects. The duration of effect of higher doses of FYCOMPA on the majority of measures was much greater than alprazolam 3 mg and ketamine 100 mg. In this study, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg and 36 mg was 37%, 46% and 46%, respectively, which was higher than alprazolam 3 mg (7%) but lower than ketamine 100 mg (85%).

In general, standard medical practice for the management of any overdose should be followed. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, for “Bad Drug Effects”, FYCOMPA 24 mg and 36 mg produced responses similar to ketamine 3 mg and greater than both doses of alprazolam tested. Of note, due to somnolence a number of subjects had missing data around Tmax of FYCOMPA. The above described data may represent an underestimate of FYCOMPA’s effects. The duration of effect of higher doses of FYCOMPA on the majority of measures was much greater than alprazolam 3 mg and ketamine 100 mg. In this study, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg and 36 mg was 37%, 46% and 46%, respectively, which was higher than alprazolam 3 mg (7%) but lower than ketamine 100 mg (85%).

 sings, symptoms, and Laboratory Findings of Acute Overdose in Humans There is limited clinical experience with FYCOMPA overdose. The highest reported overdose (approximately 264 mg) was intentional. This patient experienced severe adverse reactions of altered mental status, agitation, and aggressive behavior that resolved with management without sequelae. In general, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. Treatment for Management of Overdose of FYCOMPA The concomitant use of CNS depressants may cause additive effects when taken with FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be followed. In addition, the reactions at therapeutic doses with dizziness reported...
Mental Health Integration Easier Thought Than Done

By Frank Diamond

Start with the psychiatrist: a medical doctor by training who specializes in treating mentally ill patients. That’s integration of mental and physical health right there, but it may also be the highlight of that cooperation, as our cover story on page 22 makes clear. Contributing editor Joseph Burns lays out the benefits of mental health integration, which includes the possibility of lowering the medical costs of treating people with chronic diseases who also have behavioral health problems. That’s a combination that drives up medical costs, so if behavioral problems were dealt with as part of medical care, the cost of managing chronic disease might be a lot less.

Figuring out mental health care’s place in medicine was never easy, as practitioners for too long adhered to Sigmund Freud’s methods, most of which have been debunked. That’s tough to recover from. The effort to clearly diagnose conditions, as primary care physicians might do before treating, say, the flu, doesn’t satisfy skeptics either.

Theodore Dalrymple, MD, worked as a physician and prison psychiatrist in Birmingham, England, for years before turning to the craft that would make him famous: writing. In his book Admiraile Evasions: How Psychology Undermines Morality, Dalrymple argues that the over 300 categories in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, leads to overtreatment and undertreatment. Schizophrenics “are left to molder in doorways, streets, and stations of large cities, while untold millions have their fluctuating preoccupations attended to with the kind of attention that an overconcerned mother gives her spoiled child with more or less the same results.”

That mental conditions seem to spread “in proportion as they are known about” undermines not only the specialty, but also culture, Dalrymple argues. Even the many who disagree with him would have to admit that it’s difficult to imagine an oncologist disparaging cancer treatment in a similar manner.
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**Cover Story**

**End the Separation of Mental Health**
Integration of care would have clinical benefits and mean major savings, say some experts. The medical costs for people with chronic medical conditions who also have behavioral health problems are much higher than the medical costs of those without the combination.

**Let the Buyer Be There**
As transparency tools that illuminate the price and quality of care become more user friendly, a stubborn question persists: Will patients use them? Many still rely on advice from family and friends. Fewer than 20% of Americans fully trust quality information from insurers.

**A Q&A With Robert Wachter, MD**
One of the most influential physician executives in the country describes the bumpy road of health care IT in his new book. Meaningful use has served its purpose, he says, and he’d largely scrap phases 2 and 3.

**Original Research**

**How to Better Manage Cardiogenic Shock**
A retrospective comparison of readmission patients shows that percutaneous ventricular assist devices (pVADs) reduce risk of rehospitalization, as well as reduce costs and length of stay. Increased use of pVADs might help hospitals deliver greater value to payers.

**DEPARTMENTS**

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ANTICIPATED RETAIL AVAILABILITY MARCH 10
Quality-Adjusted Cost of Care Called New Measure for New Cures

The health care industry should take into account outcomes when weighing the cost of new treatments and technologies and make quality-adjusted life years (QALYs) part of the equation, say the authors of a study in the April issue of *Health Affairs*.

One needs only to look at how medications revolutionized the treatment of HIV in the 1990s, the authors argue, to see that cost entails more than just the acquisition cost of a treatment.

Antiretroviral therapy didn’t come cheap, but the longevity gains that resulted wound up being 9 times larger than the therapy’s cost, say the study’s authors. They have cooked up a formula (http://tinyurl.com/HA-cost-study) that will help government officials, health plan executives, and others see if they are getting their money’s worth.

The formula involves weighing cost against the “growth in value to patients, in terms of monetized gains” in QALYs, a result that they call the quality-adjusted cost of care (QACC). Darius Lakdawalla, PhD, is the lead author and a professor at the University of California who specializes in pharmaceutical development and regulatory innovation. He tells Managed Care that “when expensive but innovative treatments come on the market, the quality-adjusted cost of care provides a framework for pharmacy directors and health plans to determine whether additional costs incurred to cover these new medications provide good value to their enrollees.”

The *Health Affairs* paper looked at two diseases, colorectal cancer and multiple myeloma, through this lens.

Colorectal cancer is the fourth most common cancer and a disease that claims about 50,000 American lives each year. The baseline cost of treating this disease rose significantly between 1998 and 2005 because of new medications. In 1993, the standard treatment for colorectal cancer, a 24-week regimen of fluorouracil and leucovorin, was $121. By 2005, the average cost of treatment climbed to more than $35,000 because of the advent of drugs like oxaliplatin (Eloxatin) and bevacizumab (Avastin).

However, the improvements in patient health in terms of mortality and morbidity were equivalent in value to increasing the average lifespan by four months, the study states. “Using $100,000 as the value of a life year—a figure commonly used in health economics—the improvements in health increased by approximately $33,115,” Jason Shafrin, PhD, tells Managed Care. Shafrin is a senior research economist at Precision Health Economics and also one of the study’s authors.

The study breaks it down this way: “Thus, the quality-adjusted cost of care increased by only $1,377 during this time period. In this case, society got roughly what it paid for.” (Shafrin explains that $1,377 is the difference between the increase in cost between 1998 and 2005—$34,493, minus the $33,115 increase in value—rounded to the nearest dollar.)

When they turned to the second disease—multiple myeloma—the researchers looked at the differences between patients who used innovative treatments such as bortezomib (Velcade) and lenalidomide (Revlimid), introduced in 2003 and 2006 respectively, and those who used older therapies.

Shafrin says that “the cost of multiple myeloma treatment increased by $72,937, but the improvements in health over this time period were valued at $140,800 for all patients with multiple myeloma. Thus, the net cost of health actually decreased by $67,863.”

Meanwhile, the quality-adjusted cost of care for patients using the older therapies rose by $49,000 per patient by 2009.

The study points out that the examples of these two diseases document rapid cost growth, but they show how different the answers can be to the question of whether society is getting its money’s worth.

Pharma Management Keeps Getting Harder

Ivacaftor (Kalydeco) hasn’t been in the news quite as much as sofosbuvir (Sovaldi) and some of the oncology drugs, but priced at $300,000 per year, it’s also part of the trend of high-priced drugs that is sweeping American health care.

Approved by the FDA two years ago...
ago, ivacaftor targets a particular genetic mutation that affects about 4% of people with cystic fibrosis, so despite that stratospheric price, it hasn’t had the same effect on pharmacy budgets as the hepatitis C drugs like Sovaldi and cancer drugs have been projected to have.

One of Managed Care’s regular contributors, Krishna Patel, PharmD, wrote about ivacaftor in April (http://tinyurl.com/Krishna-article), and her takeaway is for payers to follow the guidelines for ivacaftor and not erect obstacles to people getting a drug that might make a huge difference in their lives.

The FDA is expected to approve a new medication some time this year that combines ivacaftor with another medication, lumacaftor.

Rather than working in a small percentage of people with cystic fibrosis, this new combination is expected to be effective in roughly half of those with cystic fibrosis who are ages 12 and older.

Kevin Bowen and Patrick Gleason of Prime Therapeutics, the Minnesota PBM, recently published some projections for what this new combination might cost. If they’re right, lifetime treatment with ivacaftor-lumacaftor for many people with cystic fibrosis might cost more than $10 million.

And, in Gleason’s view, it’s wishful thinking to believe the cost of the new combination will be offset by avoidance of medical costs, which can be extraordinarily high for cystic fibrosis because some people with the disease get lung transplants, says Gleason. “You can’t pay for this with medical cost avoidance.”

Bowen and Gleason started with the premise that the ivacaftor-lumacaftor drug combo will be roughly the same price as ivacaftor alone and, by looking at Prime Therapeutics claims, put a price tag of $367,000 per year on it, which includes medical and pharmacy costs.

They figure someone might be on the drug for 28 years if they start at about age 12 (the harsh truth is that people with cystic fibrosis face a limited life expectancy).

So the lifetime treatment cost can be estimated at $10.3 million ($367,000 x 28 = $10.3 million).

Then they looked at the medical costs of someone who got a lung transplant. Lung transplants are expensive. The total medical and pharmacy cost in the year of the transplant is $577,000 and, in subsequent years, $143,000 per year.

Cystic fibrosis care without a lung transplant or ivacaftor costs about $76,000 per year.

Bowen and Gleason didn’t do this math, but figuring that lung transplants are done as a last resort, it is reasonable to assume that a person with cystic fibrosis might have many years of care prior to lung transplant, then a transplant, followed by years of post-transplant care.

So the equation for lifetime treatment costs might look something like this: $1.368 million (18 years x $76,000) + $577,000 (the year of the lung transplant) + $1.287 million (9 years x $143,000 of post-transplant care).

That adds up to more than $3.2 million, which is about a third of the $10.3 million in lifetime treatment cost for the ivacaftor-lumacaftor combination.

These new drugs for cystic fibrosis are an advance. If they mean that the young people who are affected by a trying, life-shortening disease can live healthier and perhaps longer lives, they should be welcomed with open arms—and, at a practical level, with adequate insurance coverage so that families can afford them.

But at these prices how are we, as a society, going to pay for them?

Geisinger’s PCMH Garners Attention

Geisinger Health Plan is touting its patient-centered medical home (PCMH) effort, and with good reason. A recent study in Health Affairs (http://tinyurl.com/PCMH-Geisinger) notes that the insurer’s ProvenHealth Navigator shaved off 7.9% of total costs for more than 6,400 Medicare enrollees from January 2006 through June 2013.

The largest source of savings was acute inpatient care ($34, or 19% savings per member per month), which accounted for 64% of total estimated savings. Acute admission rates fell by 18% during the study period.

That’s impressive, but many experts say that the PCMH model works well only under certain circumstances, and cannot be widely replicated (http://tinyurl.com/Millenson-article).

For instance, Geisinger is an integrated system, with both insurance...
and provider arms. The researchers, most of whom are affiliated with Geisinger, note that the insurance arm has the advantage of being led by a systemwide programmatic leadership that focuses on the entire care process instead of a single episode.

They also say that the main goal of PCMHs is not to save money but to emphasize providing the right care earlier in the process through routine doctor visits, better care coordination, and preventive services. That said, savings continued to grow into the eighth year of the Navigator program, and it doesn’t seem to be a matter of the savings in acute care coming from shifts to costs in other areas of care.

The explanation from the Geisinger researchers is familiar: Cents spent on timely prevention can eliminate the need to spend dollars on treatment. How long can that last? They conceded that the law of diminishing marginal returns eventually will kick in.

Still, eight years is a long time, and the researchers say their findings suggest that the PCMHs can achieve cost savings in larger contexts.

**Briefly Noted**

“Generally accepted guidelines” might be tough to achieve in some instances. Take for instance the use of statins for people ages 17 to 21. Guidelines issued by the National Heart, Lung, and Blood Institute in 2011 would mean nearly 500,000 people in this age group on statins, according to a study last month in *JAMA Pediatrics*. No thanks, say the American College of Cardiology and the American Heart Association, which are sticking with guidelines that focus mainly on adults. Under those guidelines, about 80,000 young people would be issued statins. Some experts think that lifestyle changes should be the preferred treatment for younger people. Other experts point out that the effectiveness of statins have not been measured on this population, and maybe it’s time to do so. **One way to reduce** the chances of patients developing dementia is better management of diabetes, according to a meta-analysis in the *American Journal of Psychiatry*. “Other prognostic factors that are potentially manageable are pre-diabetes and the metabolic syndrome, neuropsychiatric symptoms, and low dietary folate,” the study states. Early dietary interventions could help, say researchers. …

**Enhanced recovery protocol reduces LOS**

Many who go under the knife probably wish surgeons wouldn’t starve them and cut off their water supply before surgery but accept the deprivation as necessary. For more than 15 years, hospitals in Europe have used a different technique, called an enhanced recovery protocol (ERP), which involves giving patients a drink a few hours before surgery that contains carbohydrates, electrolytes, minerals, and vitamins. Patients also receive painkillers before the operation, and epidurals placed during the surgery remain in place after the procedure. Patients are encouraged to walk soon after surgery and are usually discharged earlier.

Maybe that’s the reason more hospitals in the United States should consider the ERP approach, at least when it comes to colorectal surgery, suggest the authors of a recent study in the *Journal of the American College of Surgeons*. Researchers at the University of Virginia Health Center compared results of colorectal surgeries before (August 2012 to February 2013) and after (August 2013 to February 2014) trying the ERP approach.

The conventional method involves fasting, liberal fluid administration in the intraoperative period, the use of nasogastric tubes and opioid-centric pain measurement strategies, and plenty of bed rest.

Treatment for the ERP group (109 patients) cost nearly $800,000 less in total than treatment for the group (98 patients) treated in the conventional way. There was a substantial reduction in length of stay as well. Patient satisfaction also improved considerably during the study period.

**Length of stay for colorectal surgery patients relative to the medical center as a whole**

<table>
<thead>
<tr>
<th>Days</th>
<th>Median length of stay after implementation of ERP</th>
</tr>
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<tbody>
<tr>
<td>Aug</td>
<td>7</td>
</tr>
<tr>
<td>Sep</td>
<td>6</td>
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<td>Oct</td>
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<td>3</td>
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<tr>
<td>Jan</td>
<td>2</td>
</tr>
<tr>
<td>Feb</td>
<td>1</td>
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After implementation of ERP

<table>
<thead>
<tr>
<th>Median length of stay colorectal surgery patients (blue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median length of stay all patients (red)</td>
</tr>
</tbody>
</table>

Source: Thiele RH et al., *Journal of the American College of Surgeons*, February 2015

The share of people ages 65 and older who say that they’ve fallen in the last two years increased from 28% to 36% between 1998 and 2010—higher than what researchers expected—according to a study in *JAMA Internal Medicine* …

The first line of treatment for depression should take place in the primary care physician’s office, according to a study in the *Annals of Family Medicine*. PCPs can render effective treatment in face-to-face visits, say researchers.

—Frank Diamond and Peter Wehrwein
In a land where storms are rare, Blue Shield of California has found itself in the midst of two of them, and critics are hoping they will serve as a precursor to the type of public scrutiny that other not-for-profit Blues could face.

The first storm struck in August 2014, when the California Franchise Tax Board quietly revoked the state tax exemption for Blue Shield of California (BSC). Then, in December, BSC launched a bid to acquire Care1st Health Plan, a privately owned Los Angeles-based Medicaid and Medicare plan with 520,000 members in three states. Those fronts collided in March, when word of the tax board’s decision leaked out—for seven months it had gone unnoticed—and then a former BSC executive, Michael Johnson, started raising questions about BSC’s not-for-profit status.

Others have piled on since. State Insurance Commissioner Dave Jones said BSC’s tax exemption enabled it to evade $100 million in state taxes annually. Jones and others are questioning BSC’s considerable surplus.

“As a tax-exempt company with a surplus of $4.2 billion, Blue Shield was able to accumulate an enormous amount of money on which it did not pay state taxes by evading the tax on the premiums it collects,” Jones said in a statement (http://tinyurl.com/Jones-BSC).

Meanwhile, BSC spokesman Steve Shivinsky counters that the company did, in fact, pay $392 million in taxes in 2014.

Johnson, the former BSC director of public policy who went public with his criticisms after leaving the company, says BSC hasn’t lived up to its social welfare commitment as a not-for-profit organization. Legislators in Sacramento, as well as the state Department of Managed Health Care (DMHHC), which is reviewing the Care1st bid, have noticed. The department may yet call public hearings on the deal.

But the process is murky. The Los Angeles Times broke the story of BSC losing its tax exemption shortly after Johnson left the company. The tax board has hardly been transparent. When asked why the board pulled the exemption, spokesman Daniel Tahara replied, “I am unable to speak to that as it is not public information.” A tax board spokeswoman told the Times that audits aren’t available for public review.

As consumer groups and legislators push for public hearings on the Care1st acquisition, they would like to know the rationale behind the tax board’s decision. Julie Silas, a senior attorney for Consumers Union, the policy arm of Consumer Reports, asks, “Does that same thought pattern that was used by the Franchise Tax Board to make its decision have an implication on the not-for-profit status of Blue Shield of California?”

The tax board revoked Blue Shield of California’s exemption from state taxes, not its not-for-profit status per se, notes Shivinsky, and the company intends to continue operating as a not-for-profit. “The possible loss of state income tax exemption in no way threatens Blue Shield’s not-for-profit status,” he insists.

Exemption a holdover from the ‘80s

BSC and other not-for-profit Blues were 501(c) (4) tax-exempt entities under the Internal Revenue Service code until the 1980s, when Congress—bowing to lobbying from for-profit insurers—removed most of the federal tax exemptions the Blues had. Originally, all Blues were not-for-profit, but that started to change in the 1990s when Blue Cross of California and what today is Anthem, among other Blues, started to convert to for-profit companies. For the Blues that retained their not-for-profit status with the IRS—now known as 501(m) enti-
ties—states have honored their previous 501(c)(4) filings and granted exemptions for state tax purposes.

So what are a not-for-profit’s “social welfare” obligations? Don’t look to the IRS for an answer, as Henry J. Aaron of the Brookings Institution notes; 501(c)(4) organizations also include political action committees. “Given that some of the most egregious examples of political activism by people who do not want to divulge their names occur through 501(c)(4)s, it seems that there are precious few standards. The very idea that there might be some [standards] got officials at the IRS in a bunch of trouble,” Aaron has written.

BSC maintains it is entitled to the exemption and will appeal the tax board’s decision. Its defense will uphold the Care1st purchase as an example of its public commitment.

Shivinsky says that having Care1st will enable BSC to serve more Californians by giving it an entry into Medi-Cal, the name for Medicaid in the state. “Blue Shield has been criticized for not being in the Medi-Cal business, but entering the Medicaid market is quite difficult,” he says. More than a third of all Californians are covered by Medi-Cal.

Embarrassment of riches?
The capital for that Care1st acquisition, with a winning bid of $1.5 billion, comes from BSC’s $4.2 billion surplus. Silas at Consumers Union says the surplus far exceeds the state minimum and Blue Cross Blue Shield Association guidelines. In her view, BSC amassed that surplus trading on the goodwill of the Blue Shield name while not paying all the state taxes a for-profit plan pays.

Johnson, the ex-BSC employee, wants to see his former employer do more for the state with that surplus: “I wouldn’t want to prescribe what that should be, but it could be things like, instead of spending [$1.5] billion to increase market share, to use that money to subsidize coverage for people in need, or providing access to insurance in rural parts of the state that the for-profit companies aren’t serving.”

Providing coverage to people in need is precisely the idea behind acquiring Care1st, counters BSC’s Shivinsky. After the Care1st acquisition, the BSC surplus will drop to around $3 billion—a level that independent actuaries confirm is needed to maintain an “A” financial rating; that’s a rating that is necessary to insure large employers across the state as well as the huge California Public Employees’ Retirement System, according to Shivinsky. “A minimum level in a savings account is not something that we think would be financially prudent for a company that’s covering over 3 million Californians,” he adds.

Another defense BSC might use for its tax exemption is the $325 million it has funneled into its own charitable foundation in the past decade along with its net income cap of 2% of revenues. That cap resulted in $560 million in refunds to members and community contributions last year and $392 million in taxes paid in 2014, most of them federal but also $39 million in state franchise taxes because of the loss of its exemption, according to Shivinsky.

Consumer groups have questioned BSC’s spending on other things, including executive pay. The Los Angeles Times reported that BSC did not list any executives by name in its state filing for 2012, only saying its top three officials each made more than $1 million a year. Also raising eyebrows: The company’s contribution of $10 million in 2014 to defeat a ballot measure that would have regulated insurance rates and its expenditure of $2.5 million (Shivinsky noted that it was over 10 years) for a luxury box at the new stadium for the 49ers.

Johnson is marshaling his forces. He’s started an online petition at Change.org demanding that BSC disburse its profits to improve access to health care. He’s advocating a model along the lines of Blue Cross of California’s conversion to a for-profit entity in the 1990s, when two foundations, the California Healthcare Foundation and the California Endowment, received $3 billion in proceeds from the conversion to fund their endowments. The foundations aim to expand access to care for disadvantaged Californians. Johnson says if the Care1st sale is a yardstick, BSC would be worth about $10 billion in such a conversion. (Shivinsky calls this Johnson’s “guess-estimate ... that no one has attempted to validate.”)

Public hearings on the Care1st acquisition may give Johnson and others a chance to have their say, but they will also give BSC a platform from which to stage its defense with one mystery lingering in the background: Why exactly has BSC found itself in this position, fighting to regain its state tax exemption?
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Spending on Compounded Drugs Goes Sky High
Soaring prices and aggressive marketing fuel a buying frenzy for these specially made agents. The industry says it is meeting a need.

By Thomas Reinke

Compounding pharmacies are on a tear, blanketing the country with concoctions touted to cure what ails us. Changes in federal regulations and billing mechanisms have opened the door to high prices and pitchmen who promote miraculous treatments that seem like nothing more than new fangled snake oil.

The industry counters that it is creating products that wouldn't be available otherwise. Moreover, the compounders say that they are only dispensers, and that licensed providers are responsible for the prescriptions.

There's no disputing, though, that the recent growth in compounded drugs has been dramatic—and very expensive. They now sit as the third most costly drug category in Express Scripts' latest drug trend report. The company says the annual trend for compounded drugs was 128.4%, highest of the traditional therapy classes. The average cost per script was $1,164. From 2012 to 2014, the quarterly spend for compounded medications increased from $28 million to $171 million.

“We initially saw an increase in the prices of ingredients coming across on claims, but then we also saw an increase in the volume of claims,” says Jo-Ellen Abou Nader, an audit and fraud specialist at Express Scripts.

Express Scripts reports that much of the increase stems from the alignment of the increase in AWP for bulk powders with the increase billed by the compounding pharmacies. Another important factor is a billing regulation that requires the listing of all ingredients and their prices on claims. Previously, claims included just the primary ingredient and the total cost of the script.

David Ball, a consultant and spokesperson for the International Academy of Compounding Pharmacists, acknowledged in an email the effect of more detailed line item billing. “One of the reasons we know that costs have ’skyrocketed’ is because beginning in 2012, Express Scripts began seeing the real cost of each ingredient used in a compound,” Ball wrote. “Before, they had a single-line submission claim form that didn't take into account the complete picture.”

Ball says volume is increasing because there's a need for the compounded product: “There seems to be strong demand across the spectrum, including for hormone replacement therapy, ophthalmic drugs, and pediatric preparations, to name just three.”

Express Scripts says pain creams are the most common type of compounded medication, incorporating ingredients such as gabapentin, baclofen, cyclobenzaprine, progesterone micronized, and propylene glycol.

“The problem with compounded drugs is that there is no FDA approval process to say that these mixtures work, and there can be adverse reactions, overuse, and overdoses,” says Abou Nader.

Express Scripts says it has implemented a multipronged approach to rein in compounded drug costs that includes blocking payment for more than 1,000 bulk powders that it says do not provide a clinical benefit over traditional

### Per-member, per-year spending for the top 10 traditional therapy classes

| Condition                        | Spent
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<tbody>
<tr>
<td>Diabetes</td>
<td>$97.67</td>
</tr>
<tr>
<td>High blood cholesterol</td>
<td>$48.73</td>
</tr>
<tr>
<td>Compounded drugs</td>
<td>$46.04</td>
</tr>
<tr>
<td>Pain/inflammation</td>
<td>$45.98</td>
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<tr>
<td>High blood pressure/heart disease</td>
<td>$36.06</td>
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<tr>
<td>Heartburn/ulcer disease</td>
<td>$33.40</td>
</tr>
<tr>
<td>Asthma</td>
<td>$29.59</td>
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<tr>
<td>Attention disorders</td>
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<tr>
<td>Depression</td>
<td>$25.98</td>
</tr>
<tr>
<td>Mental/neurological disorders</td>
<td>$24.85</td>
</tr>
</tbody>
</table>

Source: Express Scripts 2014 Drug Trend Report
medications. The country’s largest PBM says its strategies will save its clients more than $1.9 billion in 2015. “Our clients want safety and many of them have opted in,” says Abou Nader. But Abou Nader says when the company limited the use of bulk powders, the pharmacies started to crush tablets and capsules: “We saw one claim for a pain cream for migraines with multiple ingredients, including tramadol and zolmitriptan, that had over 2,000 tablets in it.”

A new business model for compounding pharmacies is also contributing to costs. Compounding has expanded from the original practice of individual prescriptions for specific patients to large-scale manufacturing and aggressive nationwide marketing of standardized concoctions for the general public. Compounding pharmacies are promoting their products with direct-to-consumer telemarketing campaigns and DTC websites.

“We have received tips through the fraud hot line that patients are being called by telemarketers asking if they take pain medication and if so, they are told that compounds may be a better solution,” says Abou Nader.

In February, CBS aired a report about a patient who received a monthly supply of three compounded medications he did not authorize, costing $18,000.

Abou Nader adds there’s another possible fraudulent practice in the telemarketing campaigns. “If the patients are receiving cold calls that don’t fully disclose what is going on, they are likely to be suspicious and less likely to be paying their copays. Forgiving copays could be a fraudulent practice and we audit the pharmacies for compliance.”

Regulatory changes and safety issues

The aggressive marketing stems, in part, from federal regulatory changes. In 1997, Congress passed a law that recognized compounded drugs for the first time. Prior to that they were technically unapproved new drugs subject to FDA approval, but the FDA used its discretion in not requiring reviews, explains Michael Carome, MD, director of research at the FDA watchdog agency Public Citizen.

That law banned advertising of compounded products. It said a drug may be compounded “only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug class or type of drug.”

The ban was challenged by compounding pharmacies and struck down by the Supreme Court in 2002, and the 2013 Drug Quality and Security Act (DQSA) officially removed the 1997 ban on advertising.

That law includes new regulations for “outsourcing facilities”—the compounding pharmacies that manufacture and distribute large volumes of standard dose compounds. “In essence the DQSA legalized large-scale production of compounded products for sale to the public,” says Carome.

Carome says the 2013 law did not go far enough in controlling compounded drugs and there are serious safety and quality issues. “In our view,” he says, “the DQSA and FDA have created a tier of lower-quality drug manufacturers. They are required to adhere to good manufacturing practices but they are not required to comply with standards for traditional drugs such as safety, potency, and manufacturing consistency.” Ball, the spokesman for the international academy, has a different characterization of DQSA, noting that the law has meant that outsourcers can step forward and elect to be overseen, inspected, and regulated by the FDA.

Carome says only 52 facilities have registered as outsourcing pharmacies, but his group believes that is just a fraction of the number that are operating (Congress choose to make registration voluntary, notes Ball). Forty-three have been inspected, which has resulted in 42 receiving citations for deficiencies in their manufacturing practices. A dozen compounders have received warning letters. “There can be a significant lag of 8 to 10 months between an inspection and a warning letter so more may be in the works.”

The FDA is working at its own pace under its limited mandate for safety to improve compounding. It has issued several draft guidances for comments and formed an advisory committee. One initiative is focused on identifying ingredients that should be banned from compounds. Separately, Carome suggests that prior authorization is a reasonable next step for health plans and PBMs who are striving to manage compounded drugs. 
Diabetes diagnosis among Medicaid enrollees jumped by 23% in states that expanded the government program under the ACA, according to a study in *Diabetes Care* (http://tinyurl.com/Med-diabetes). In the states that did not expand Medicaid, the diagnosis among beneficiaries inched up by only 0.4%.

The study is based on data collected by Quest Diagnostics. The company’s researchers compared new diabetes diagnoses during the first six months of 2014, the period after Medicaid was expanded in 26 states and Washington, D.C., with new diagnoses during the first six months of 2013. Diabetes was defined as an ICD-9 diagnosis of 250.x or an HbA1c level of over 6.4%.

In the expansion states, the Quest researchers found that the number of new diagnoses in the non-Medicaid population actually decreased slightly, by –2.2%, between 2013 and 2014, in contrast to the big jump of 23.2% in the newly expanded Medicaid population. The number of new diagnoses overall increased by just 0.8%. The non-Medicaid population is about 7 times larger than the Medicaid population, so the big jump in diagnoses among Medicaid beneficiaries gets offset in the overall tally.

In the nonexpansion states, it was a different story. The number of new diagnoses in the non-Medicaid population increased by 3.3%, so the new diagnoses overall increased by 2.6%, which is a larger increase than in the expansion states.

One caveat: All of these numbers come from Quest Diagnostics, and while Quest has a huge database, it is still just one company. Other sources of data, for instance information from CMS or health insurance plans, were not included.

The Quest researchers noted that the Medicaid patients with newly identified diabetes will experience better management of their disease than if diagnosis had been made later—and that should lead to fewer complications.

Well, maybe.

William C. Knowler, MD, is the chief of diabetes epidemiology and clinical research at the National Institute of Diabetes and Digestive and Kidney Diseases. He tells the *New York Times* what the study also mentions. Some research has shown no mortality benefit from early diagnosis of diabetes that is the result of screening.

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### Change in number of patients with newly identified diabetes in Medicaid expansion states vs. nonexpansion states

<table>
<thead>
<tr>
<th>Expansion states</th>
<th>Nonexpansion states</th>
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<tbody>
<tr>
<td></td>
<td>Medicaid</td>
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<tr>
<td>Medicaid</td>
<td>+23.2%</td>
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<tr>
<td><em>Other</em></td>
<td>~</td>
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<tr>
<td><strong>Total</strong></td>
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<tr>
<td><strong>January–June 2013</strong></td>
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<tr>
<td><strong>January–June 2014</strong></td>
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*Other represents non-Medicaid patients.
Source: Kaufman HW et al., *Diabetes Care*, March 2015
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It turns out we’re doing mental health care all wrong, and we’ve been doing it wrong for decades. It also turns out there are flaws in the payment system that foster an inefficient and perhaps ineffective approach to caring for those with mental health and substance use problems. And, as with so many other problems in American health care, health plans and federal and state governments all need to reform payment and delivery for the situation to improve.

In the predominant form of care delivery today, mental health providers are separated from primary care physicians. Yet more than 80% of patients with behavioral health conditions first seek care in medical settings—and as a result, 60 to 70% of these patients get no treatment for their mental health disorders, notes Roger Kathol, MD, president of Cartesian Solutions, a consultancy near Minneapolis.

Matching this fragmented delivery system is an equally fragmented payment system, a legacy of the ‘90s push to control costs by carving out the management and payment of behavioral health care. Carve-outs often meant stingier coverage with high cost sharing, limits on visits, and special prior authorization requirements. Federal and state parity laws were supposed to address that problem by eliminating any differences between the coverage for mental health and other types of care. The implementation of parity, though, has been a grind—slow and prone to getting bogged down in details.

Besides, even at its best, parity can leave the actual delivery of mental health care stuck in a Plessy v. Ferguson stage of separate and—tragically, for those not getting the care they need—never fully equal.

Progressive provider organizations like Intermountain Healthcare are making good faith efforts to integrate mental health care into the rest of health care. The federal Substance Abuse and Mental Health Services Administration (SAMHSA) has given out grants of up to $500,000 annually to community mental health centers to integrate physical health care services, such as wellness programs, into their offerings. Medicaid programs—once backwaters but increasingly the laboratories for all kinds of health care innovation—are experimenting with better ways to coordinate physical and behavioral health. For example, last year, Florida became the first state to offer a Medicaid plan that is exclusively for people with serious mental illnesses such as schizophrenia. Isn’t that segregation and a throwback to when...
Health care for people with mental health problems was completely separate? The more optimistic view is that it will mean a focused approach that will combine physical and behavioral health care for people with serious psychiatric disorders.

Integration could save money
Eliminating the partition that separates physical and behavioral health might yield myriad clinical benefits, but it could also mean some major cost savings. Last year, Milliman actuaries prepared a report about the economics of integrating medical and behavioral health care for the American Psychiatric Association. They started with the premise, which is amply supported by research, that the medical costs of people with chronic medical conditions who also have behavioral health problems are much higher than the medical costs of those without behavioral health problems. By their reckoning, the layering of behavioral health problems on top of medical ones adds about $293 billion in health care costs for private payers, Medicaid, and Medicare. That’s a tenth of all American health expenditures and is $30 billion more than all the money Americans spend on prescription drugs each year. Integrating behavioral health into the rest of health would slice $26 billion and $47 billion off that $293 billion (9 to 16%), according to Milliman’s figuring.

This all sounds terrific, persuasive, even commonsensical. But at this point, integration straddles aspiration and reality, and the footprint in reality may be the smaller of the two. For one thing, providers who are working on integration note that there’s a big difference between what they are trying to accomplish and merely co-locating services, even if co-location is a step in the right direction. “Just because you have mental health practitioners in clinics doesn’t necessarily mean patients are getting team-based care that is centered on the whole person,” says Brenda Reiss-Brennan, PhD, the mental health integration director for the primary care clinical program at Intermountain. When Rand researchers examined the results of the SAMHSA community health grant program, they gave it a faint-praise grade of “mixed success,” noting the spotty results for getting people to participate in wellness programs and little improvement in obesity and smoking outcomes. The Medicaid experiments are impressive, but that’s what they are—experiments. No one knows whether they will work.

The hard truth is that integrating behavioral health will be an uphill battle against history, entrenched interests, and some legitimate skepticism that although integration sounds good, putting it into practice will be difficult.

In an article published last year in Health Affairs, David Mechanic, PhD, a prominent Rutgers medical sociologist, crafted an informative pocket-size history of behavioral health care in this country. Prior to the ’50s, most Americans with serious mental health problems were taken care of at large public mental hospitals, often for extended periods—years, if not decades. By some accounts, the introduction of antipsychotic drugs like Thorazine made it possible for people to leave these hospitals. Mechanic, however, says that deinstitutionalization was made possible primarily because of Medicare, Medicaid, and other safety-net programs. Regardless of the reason, the number of people in public institutions fell drastically, with day-to-day care shifting to community settings and hospital care for people with serious problems shifting to general hospitals, often in specialized psychiatric units. As Mechanic notes, many experts and advocates for the mentally ill see this 50-year history of treating people in a community setting as a well-intentioned but woefully executed policy that has resulted in jails and prisons taking the place of those emptied mental hospitals.

Enter the carve-outs
From a pure payer perspective, deinstitutionalization became a budget-busting nightmare, so as managed

“Just because you have mental health practitioners in clinics doesn’t necessarily mean patients are getting team-based care that is centered on the whole person,” says Brenda Reiss-Brennan, PhD, of Intermountain.

F for systems that integrate primary care with behavioral health services, the secret sauce is making the specialist part of the care team—and not just co-locating in the primary care practice.
care took off in the ’80s, mental health care costs were a target. Many insurers elected to carve out mental health benefits and turn them over to separate companies. These companies, sporting NCQA and other kinds of accreditation, assembled networks of providers and used utilization review and case management methods to rein in costs. Strict utilization made some sense when government officials and others believed that mental health professionals were abusing the system and when practice patterns varied widely. “In one part of the country there were people who had depression who were hospitalized for two years. A similar person with that same diagnosis in another part of the country might have been hospitalized for a couple of weeks or even treated as an outpatient,” says Kathol, the Minneapolis-area consultant. Carve-outs did work, at least in a limited sense. From 1986 to 2005, spending on mental health and substance abuse treatment decreased from 9.3% of the nation’s health bill to 7.3%. The catch is that although those costs were controlled, the effect on overall health care costs from carve-outs isn’t clear. Milliman’s analysis and other evidence suggest that it might have been a temporary, whack-a-mole kind of victory, with behavioral health costs popping up as added costs elsewhere in the health care system.

Problems with parity
One thing is clear: Carve-outs and restrictive utilization of mental health benefits engendered a backlash in the form of parity laws that are designed to erase any differences between coverage for behavioral health problems and other kinds of health problems. The first federal parity law was passed in 1996. A 2008 law plugged the holes in that law by prohibiting differences in treatment limits, cost sharing, and in- and out-of-network coverage, among other things. The ACA extended the 2008 law to health plans sold on the exchanges and also defined behavioral health as one of the essential health benefits that health plans must cover even if they are not sold on the exchanges. But leveling behavioral health coverage with other health coverage only goes so far, and it still leaves obstacles to actually getting behavioral health care. For one thing, a disproportionate number of Americans with mental health problems are covered by Medicaid, and nothing in the parity laws say that Medicaid

<table>
<thead>
<tr>
<th>PMPM Health Care Costs by Population and Presence of Behavioral Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commercial</strong></td>
</tr>
<tr>
<td>No MH/SUD</td>
</tr>
<tr>
<td>Non-SPMI MH</td>
</tr>
<tr>
<td>SPMI</td>
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<tr>
<td>SUD</td>
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<tr>
<td>Total</td>
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<tr>
<td><strong>Medicare</strong></td>
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<tr>
<td>No MH/SUD</td>
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<tr>
<td>Non-SPMI MH</td>
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<td>SUD</td>
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<td><strong>Medicaid</strong></td>
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<td>No MH/SUD</td>
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<tr>
<td>MH/SUD</td>
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<tr>
<td>Total</td>
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</tbody>
</table>

*Totals for Medicare do not reflect pharmacy costs.
Abbreviations: MH=mental health, PMPM=per-member, per-month, SUD=substance use disorder, SPMI=severe and persistent mental illness
More than 3 million prescriptions to date

real-world experience and counting†

Preferred for >75% of commercial and Medicare Part D lives†

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*Data on file. Based on TRx data sourced from IMS NPA and NSP databases, weekly data through 3/2/15.
†Approval from the Food and Drug Administration (FDA) was granted in March 2013.

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Many behavioral health providers won’t see people with Medicaid coverage because the reimbursement rates are too low, so Medicaid beneficiaries may be shut out of getting the care they need. The same is true for many Americans covered by private insurers that pay behavioral health providers at a low rate.

In Kathol’s view, promises to expand access by adding providers may not be fulfilled if the delivery of mental health is segregated, because so many people with mental health problems seek help in medical settings. “If you don’t have payment and delivery in the medical sector where all the patients are, essentially it’s like not providing mental health care,” he says. Partly because of the managed care carve-outs, more than 90% of behavioral health care professionals today practice in standalone mental health care settings, according to Kathol. There is an argument from the carve-outs that managing mental health benefits separately doesn’t preclude integrating the delivery of care (see “Don’t Blame Carve-Outs” on the next page).

### Impact of behavioral comorbidities on PMPM in a commercial population

<table>
<thead>
<tr>
<th>Condition</th>
<th>No mental health/substance use</th>
<th>Serious and persistent mental illness (SPMI)</th>
<th>Mental health diagnoses but not SPMI</th>
<th>Substance use disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>$7,000</td>
<td>$6,000</td>
<td>$5,000</td>
<td>$4,000</td>
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<tr>
<td>Asthma</td>
<td>$6,000</td>
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<tr>
<td>Cancer</td>
<td>$5,000</td>
<td>$4,000</td>
<td>$3,000</td>
<td>$2,000</td>
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<tr>
<td>Chronic kidney disease</td>
<td>$4,000</td>
<td>$3,000</td>
<td>$2,000</td>
<td>$1,000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>$3,000</td>
<td>$2,000</td>
<td>$1,000</td>
<td>$0</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>$2,000</td>
<td>$1,000</td>
<td>$0</td>
<td>$0</td>
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<tr>
<td>Chronic pain</td>
<td>$1,000</td>
<td>$0</td>
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</tr>
<tr>
<td>Arthritis</td>
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<tr>
<td>Chronic pain</td>
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<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Back pain</td>
<td>$6,000</td>
<td>$5,000</td>
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<tr>
<td>Headache</td>
<td>$5,000</td>
<td>$4,000</td>
<td>$3,000</td>
<td>$2,000</td>
</tr>
<tr>
<td>Diabetes (with complications)</td>
<td>$4,000</td>
<td>$3,000</td>
<td>$2,000</td>
<td>$1,000</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
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<td>$2,000</td>
<td>$1,000</td>
<td>$0</td>
</tr>
<tr>
<td>Hypercholesterolemia (with complications)</td>
<td>$2,000</td>
<td>$1,000</td>
<td>$0</td>
<td>$0</td>
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<tr>
<td>Hypercholesterolemia (without complications)</td>
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<td>$0</td>
</tr>
<tr>
<td>Hypertension (with complications)</td>
<td>$0</td>
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Don’t blame carve-outs

Brian Wheelan, executive vice president and chief strategy officer for Beacon Health Options, a managed behavioral health company in Boston, contends that the definition of integrated care and what it takes to achieve it is being oversimplified. “There’s a narrative that says, ‘Just put all your money for behavioral health and primary care in one place and you’ll magically integrate care,’” he argues. He contends that the realities of integrating care are actually more complex and vary substantially based on the population characteristics and types of behavioral health services that are being delivered.

“No one is arguing that individuals who have substance use problems and those with serious mental health conditions are actually better served in managed care programs that specialize in building and managing provider networks that include a variety of evidence-based behavioral health care services. Most primary care physicians (PCPs) will tell you, says Wheelan, that there are limits on whom they can effectively treat in their offices without dramatically disrupting their practices.

His analysis is useful even if you disagree with certain parts of it. Wheelan organizes people with behavioral health problems into different groups, and the relevance of integration varies with the group. One group, which typically includes about 4% of all members of a health plan, will have serious mental illness like schizophrenia, bipolar disorder, or a debilitating personality disorder. “For these individuals, the myth of integration breaks down because very few primary care practices are equipped to handle the challenges presented by their complex conditions. It’s a small group of people, but their care is costly,” Wheelan says.

A second group includes patients with substance use problems, such as addiction and alcoholism. Health plans struggle to care for this group because they may require detox and residential treatment. Oftentimes these patients require a separate license, according to Wheelan, and determining the medical necessity of treatment is challenging. “What do you do if this is a patient’s 11th referral to detox?” he asks. “You need specialty care for this group.”

A third group includes patients with mild to moderate depression, and it’s for these individuals that treatment in primary care is definitely the most effective and appropriate, if done well, he says. One problem, in his view, is that many PCPs often fail when attempting to co-locate behavioral health clinicians. Another is that health plans must guard against a tendency by PCPs to overprescribe psychotropic medications rather than access traditional outpatient therapies that evidence shows to be highly effective.

A fourth group includes patients being treated by specialists, such as cancer patients. “If you organize a practice around caring for patients with a high-cost condition and pay with bundled payment, much of the time, mental health care belongs in that payment,” says Wheelan. “You see this model in medical homes for oncology and diabetes and in headache or pain clinics.”

Lastly, there is a group of people with conditions like heart disease and obesity that have comorbid depression. In Wheelan’s opinion, PCPs in large group practices may have the staff and resources to care for these patients but perhaps not PCPs in more constrained circumstances. Even PCPs in large groups need to refer serious cases to full-time mental health professionals, he notes.

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case manager. Those with the most severe mental illness shift to a high level of specialist care.

Reiss-Brennan’s research has shown that integrated care gets checkmarks in both the quality and cost columns. In a study published in the Journal of Healthcare Management, Reiss-Brennan reported that the annual cost of taking care of a patient in an integrated mental health care setting was $667 less, on average, than the annual cost of care for a patient treated in non-integrated settings. This study was published in 2010, so the data are getting old, but the program has been enhanced by Intermountain’s patient-centered medical home efforts. Reiss-Brennan says Intermountain is planning to publish more recent data soon that will take into account the medical home organization and other changes in the way care is delivered.

Integrating mental health services into primary care was a natural extension of Intermountain’s culture of learning and quality improvement, says Reiss-Brennan. “Our primary care physicians asked us, ‘What do we do about all the depression and substance abuse and domestic violence patients we see in our practice?’” she says. The answer was to organize teams around primary care doctors that included mental health providers and to standardize work processes for behavioral health care, just as health plans and providers already do for patients with diabetes and asthma. The difference-maker is that mental health professionals are part of the primary care team and are not simply located within the practice.

Despite its success with this model, Intermountain still struggles to integrate financing for mental health. “We still have fee-for-service payment, and because mental health care is carved out, treatment for some mental health conditions is not paid for,” says Reiss-Brennan. Global payment would be more appropriate for health plans seeking to integrate mental health and primary care, she adds.

**Group Health’s approach**

Group Health’s approach to integration is to embed behavioral health specialists in primary care medical homes, says Larry Marx, MD, the plan’s medical director for behavioral health support services.

One health plan testing a global payment model for primary care, she adds.

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**Global payment for the whole person**

One health plan testing a global payment model for integrating mental health care into primary care is Rocky Mountain Health Plans in Grand Junction, Colo. For the past three years, 10 practices have been testing ways to integrate mental health and primary care. These practices include small independent primary care groups, large multispecialty groups, federally qualified health centers, and pediatric groups—and they serve a range of patients, including those covered by Medicaid, according to Patrick Gordon, the plan’s associate director.

Currently, the global payment covers costs for behavioral health and primary care, including personnel costs, information systems, infrastructure, and a budget for team-based care. “Our payment system allows the practices to hire or contract with their own behavioral health providers and to chart in their existing medical records in a fully integrated, team-based model of care,” says Gordon. “In this way, the primary care practice owns the behavioral health resources and is accountable for patient and population outcomes.”

This year, researchers from the University of Colorado and Denver are working with Milliman’s consultants to evaluate whether the program has cut costs and improved quality. So far, the costs of care in the practices where behavioral health care is integrated are running about 2% to 4% lower than the network average, says Gordon. Is that decrease the result of behavioral health integration or just a happy accident? Gordon hopes the Milliman and university researchers will provide an answer.

Group Health in Seattle is also pushing ahead with behavioral health integration by embedding behavioral health specialists in primary care medical homes, says Larry Marx, MD, medical director for behavioral health support services. When a patient arrives for care, the office staff administers the PHQ-9, a depression screen. This model of care is being tested in three medical centers. Depending on how it works, it may be expanded throughout the Group Health system.

Like Reiss-Brennan at Intermountain, Marx makes a point of drawing a sharp line between co-location and team-based, integrated care. “The challenge we’re facing is that we want to move in the direction of an integrated model of care, but we have the typical barriers that other health plans face including the financial barriers involved in trying to deliver integrated care when behavioral health management is carved out,” Marx explains.

Breaking through the financial barriers requires new payment models, according to Reiss-Brennan. Fee for service does not foster team-based care. “You need some form of global payment to incentivize practices to support the whole patient,” she says. Financial incentives for hitting quality targets are also needed.

“The concepts are still being sorted out in terms of the savings and the risk sharing,” notes Reiss-Brennan, “but when we do that, then we will be caring for the whole person. That’s the goal.”
Shopping for Health Care

Transparency tools that illuminate the price and quality of health are all the rage. But will Americans use them to find good deals?

By Thomas Reinke
Contributing Editor

It’s easy to comparison shop these days. In fact, it’s so easy we take it for granted. On Kayak, you can find the cheapest flight and easily filter by how many stops and time of day. Go to TripAdvisor or Yelp, and you can click away to find the most popular hotels or restaurants. And of course, you can read endless customer product reviews when you shop on Amazon.

This same sensibility and experience is now being applied to health care in the form of what the field has elected to call “transparency tools.” The name refers to the fact that until recently, information about prices and quality in health care has been largely hidden in arcane government datasets and private insurance claims. As has often been said, when third-party payers were picking up the tab or charging minimal copayments, Americans had little reason to fret about the price of the health care they were getting. With the advent of higher deductibles and less generous coinsurance, attitudes are changing fast.

Transparency tools—fast, intuitive, and increasingly available on your phone as apps—are being touted as the way to unleash the disruptive power of shopping for health care. They allow people to compare prices for procedures like colonoscopies and for imaging tests like MRIs. An increasing amount of quality data is also available—and comprehensible. For example, CMS’s Hospital Compare tool makes it easy to find out how your local hospital stacks up against others on readmission rates, how patients rated their experience at the hospital, and how it handled certain aspects of care. The information gets quite specific. You can find out, for instance, what percentage of outpatients with chest pains got aspirin within 24 hours of their arrival. In April, CMS added star ratings that summarize patient experience survey data to Hospital Compare so that comparison among hospitals is easy.

But some health plan executives—and the vendors selling these transparency tools—are waving them around like magic wands. There are still plenty of good reasons to be skeptical about how much they can accomplish. For one, providers have considerable influence over prices—and considerable power in referring patients to specific other providers and facilities, regardless of price. When it comes to quality, are we really measuring it or just what can be most easily measured? Perhaps most importantly, even though their own money is increasingly at stake, how many people are really going to be savvy health care shoppers, especially when it comes to sorting out difficult issues of quality?

Hunting for a good deal

Without question, transparency tools are in vogue. CMS has five tools, and 11 states have developed their own tools based on all-payer-claims databases. About
70% of the privately insured population had access to cost-transparency tools in 2013, according to the Government Accounting Office’s report Health Care Transparency: Actions Needed to Improve Cost and Quality Information for Consumers.

Clunky, vague versions are being replaced by ones that are slick and specific. “The transparency tools offered by health plans have made a significant step forward,” says Paul Ginsburg, PhD, a health care policy expert at the University of Southern California. “They now provide consumers with their exact out-of-pocket costs for services based upon their own copays and deductibles.”

Fueling the proliferation of price-transparency tools is the growing number of people with health savings accounts and other consumer-directed health plans (CDHP). By some counts, almost 1 in 4 Americans with employment-based health insurance has CDHP coverage. Chris Riedl, head of product strategy and management at Aetna, says that people with the company’s CDHP coverage, called Aetna HealthFund, go online to check prices two times more often than traditional health plan members. Riedl says the company’s transparency tools have had more than 5 million hits, with annual increases averaging 40% to 50%. Aetna has looked at 34 commonly used services and found that members saved on average $170 in out-of-pocket costs, while employers saved $610 in allowed costs.

Beliefs about high quality, high cost
Still, today’s transparency tools lack some important features, and consumers may not use them effectively. As Ginsburg points out, the current sweet spot is the routine test or procedure, for which quality may not vary much from provider to provider. When it comes to more complex and expensive services, higher prices are synonymous with higher quality in many people’s minds, even though that may not be the case—and people are more concerned about quality than price. Results from a 2014 survey about health care quality by the Associated Press-NORC Center for Public Affairs Research in Chicago bear this out. The survey found that 48% of Americans believe that higher quality health care costs more. That’s not terribly surprising, but it’s a bit of a reality check if you’re banking on transparency tools and people’s shopping acumen to bring down health care spending.

There’s no shortage of efforts to measure quality and present the data in a way that is average-person friendly. In addition to CMS, private groups like the National Committee for Quality Assurance and the Leapfrog Group have tools that make it easy to search and find quality data. Leapfrog’s Hospital Safety Score is especially easy to use. In the AP-NORC survey, 40% of respondents said they had seen information on the consumer ratings websites HealthGrades, Yelp, or Angie’s List.

Commercial insurers have taken steps to make sure their tools highlight the cost and quality of providers. Victoria Bogatyrenko, vice president of innovation at UnitedHealthcare, says physicians with its Tier 1 rating have met the company’s criteria for cost efficiency, and members who use the insurer’s cost estimator tool are more likely to use a Tier 1 physician than those who don’t. The program uses a variety of standards, including some developed by medical specialty societies, to evaluate physicians for quality and cost efficiency. The ratings are available online and through the Health4Me app, which has a “guest version” that provides cost information for more than 750 inpatient and outpatient services. Aetna takes a similar approach. Riedl says providers the company deems high quality and cost-effective are in Aetna’s Aexcel Network, and the transparency tool highlights them with a blue star. It is as if the Michelin Guide decided to branch out from rating restaurants and hotels.

Health plans have a trust problem
But health plans have a problem as raters of provider quality: People just don’t trust them. In the AP-NORC survey, fewer than 20% of Americans said they have a high level of trust in information about provider quality that comes insurers or state and federal agencies. As in many other areas friends and family are the most trusted sources. Physicians fall somewhere in the middle. The survey found that slightly fewer than 50% of respondents trust their regular doctor as a source for information about health care quality.
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**Flaws in quality measures**

But in fairness to health plans and all the other organizations developing quality measures, it's not easy to know exactly what should be measured—and further, how to make the results palatable to the shopping public. The AP-NORC survey found that people tend to focus on "soft" quality measures like the doctor–patient relationship and a doctor's personality traits. This emphasis is perfectly understandable. Those are the aspects of medical care that patients experience directly and that don’t require any special knowledge. It’s a classic example of the gap between experts and the public. “What may be defined as quality by experts from a clinical perspective could be very different from what a consumer defines as quality,” notes Riedl.

**Fewer than 20% of Americans have a high degree of trust about quality information from health plans.**

Jennifer Schneider, MD, chief medical officer at Castlight Health, a developer of third-party price-transparency tools, sees major room for improvement in quality measures. Most of the measures being used today are designed to drive performance in provider organizations, but they don’t resonate with consumers, in her opinion. “We need more robust and meaningful measures,” says Schneider. “What we have now doesn’t help consumers make choices at the doctor level.”

The National Quality Forum is running the Measure Applications Partnership (MAP), a multistakeholder initiative funded by CMS to develop more meaningful measures of quality, including measures that meet consumers’ needs, measures for the public reporting of quality, and measures for performance-based payment. The partnership includes consumers, businesses and purchasers, labor, health plans, clinicians and providers, communities and states, and suppliers. The NQF believes that “MAP’s careful balance of stakeholders’ interests ensures that the federal government will receive varied and thoughtful input on performance measure selection.”

However, three years into the process, the program seems to be suffering from analysis paralysis, and it shows just how slowgoing the development of measures can be. MAP released a report in March describing its effort to identify “measures that matter.” The report noted multiple viewpoints on what should constitute a measure that matters, with some stakeholders stressing the importance of process and others preferring structural measures. The program’s stakeholders did not reach a consensus on which measures are the most valuable in driving results.

Even if transparency tools improve so that Americans can become astute shoppers, buying health care will never be as simple as buying an airplane ticket. Often, we’re not free agents when it comes to health care purchases. Decisions about the need for additional care and recommendations about who will provide it are frequently made by clinicians during the course of an office visit or at the time of hospital discharge. Realistically, how are transparency tools and shopping for price and quality going to fit into that scenario? Transparency tools are available to physicians as part of decision-support modules. But as an article in JAMA’s issue on price transparency pointed out last year, these modules often lack the specific rates that a health plan pays each provider and may not incorporate a patient’s specific terms of coverage.

**Making the referral “shoppable”**

Brian Lobley, senior vice president for marketing and consumer business at Independence Blue Cross in Philadelphia, acknowledges the problem but sees today’s technology and cost shifting to individuals as changing this dynamic. Independence is in the middle of revamping its patient portal and transparency tools that will address what he calls the “shoppable referral.”

The goal is to create an app that allows easy cost comparison on a smartphone and real-time information about a member’s out-of-pocket costs, specific to his or her particular health plan. Text messages might remind members that the service they’re scheduling is in a shoppable category, with different prices depending on the facility and provider.

Lobley expects these handy and specific transparency tools to start useful discussions between doctors and patients: “They mean that I can now engage my doctor and say, ‘Hey, going to Dr. Smith is going to cost me $750 out of pocket. I am looking here and this data says that Dr. Jones really has the same or better outcomes and because of my health plan’s contracts, it is going to cost me zero dollars. Why am I going to Dr. Smith?’”

The health insurance industry is undergoing a transformation, Lobley explains enthusiastically, with members becoming active consumers who are keenly interested in getting a good price, just like for an airline ticket or hotel. “At the end of the day,” says Lobley, “I have a responsibility to our members to make sure they’re extracting the right value and experience out of the health plan. I want to protect their dollars as much as they want to protect their dollars. So I want to make sure that they have the information they need to help them save money.”

**MC**
A Conversation With Robert Wachter, MD

Reality Bytes: Medicine’s Bumpy Ride Into the Digital Age

Interview by Peter Wehrwein

Robert Wachter, MD, is a professor and associate chair of the Department of Medicine at the University of California–San Francisco. A prolific writer and blogger, his most recent book is *The Digital Doctor: Hope, Hype, and Harm at the Dawn of Medicine’s Computer Age*. In April, Wachter topped Modern Healthcare’s list of the 50 most influential physician executives in the country.

You’re often given credit for hospitalists becoming part of health care. When people say that, I say it sounds just like Al Gore invented the Internet. I coined the term, and I think people generally see me as the academic leader of the field.

In the mid-’90s in the managed care era, I had just been given a new job to run the medical service at UCSF, and my boss, a very thoughtful, strategic guy, said to me, “Come up with some new way of delivering care that’s better and less expensive and trains people better.” And I began sniffing around and found this new model emerging in early-adopter places, where you had a separate doctor in the hospital. Nobody had written about it; it didn’t have any standardized name.

As I was out there talking about the benefits of the model, many people yelled at me and said, “This is terrible! You don’t get it!”

What, according to them, didn’t you get? “You’re screwing up the doctor–patient relationship” or “My patients need me.” There were actually more complaints from doctors than from patients. I think patients accepted the notion that their primary care doctor was overwhelmingly busy and couldn’t be there for them all day long.

It was primary care doctors who said, “You’re saying we’re not good enough to take care of our own patients in the hospital.” And I said, “No, I’m not saying that.
What I’m saying is that the organizational model for hospital care, which may have made sense in the days of Marcus Welby, doesn’t make sense anymore. And it’s not that these new doctors are going to be any smarter; it’s just that they’re going to have the professional focus on hospital care in a way that you don’t.”

Is there anything comparable between the hospitalist and the computerization of health care that we’re seeing now? I think the IT transition is a much bigger issue because it’s much more ubiquitous and will ultimately have a much larger impact on the world.

But in other ways, they’re the same. These are big changes, and we always underestimate how hard they’re going to be, and we underestimate the push-back from people who, for various reasons, don’t want the change.

You mention several things that motivated you to write this book. What was the driving force? I think the driving force was disappointment, and the disappointment was because I’ve been doing work in patient safety for 15 years. We’ve been waiting for this day—when computers would finally enter health care and fix everything. We’ve come to believe that if you computerize something, it makes it better, faster, slicker, and cheaper—and it’s all good.

And then one day about two years ago, I was sitting in a meeting at UCSF and we were discussing this case where we gave a kid a 39-fold overdose of an antibiotic. In a completely wired system. As I began to hear about the nature of the case, my jaw dropped, and I realized that something fundamental had changed in the way we practice medicine, the way we talk to each other, the way we trust automation.

Nobody had written about it before. When I looked around for literature, it was either technical or too futuristic and hype-y for my taste.

You write about the loss of communication in medicine—the electronic siloing. The few times I’ve been a patient, when I’ve had younger doctors, I felt like they were getting sucked into the computer. The older doctors, not so much. Do you see the current era of electronic medicine as interfering with communication in a lot of different ways? Yeah, I don’t think there’s any question that it is. That doesn’t mean that we should pull out the plugs and go back to pen and paper. Some of it is just an extension of the rest of our lives. Is Facebook interfering with communication? Your kids used to learn to talk to you and their friends, and now social media is how they communicate. Is that a good thing or a bad thing? Who knows, but we’re not going to turn back the clock.

What struck me was the degree to which technology profoundly changed the way we communicate with each other—doctors to doctors, doctors to nurses, doctors to patients, patients to patients.

What we’re trying to do in health care these days is figure out how to deliver better, more satisfying, more patient-centric care—and do it at a cost that doesn’t bankrupt the country. Where are computers helping? Where are they not? When they are not, how do we mitigate that? Is it with different electronic tools? Is it a matter of making the ones we’ve already got better? Or is it something that’s pretty old school, where we’d say, “We’ve got to schedule meetings or informal gatherings that bring back person-to-person communication in an electronic environment.”

It seems like you would probably land on the last thing you said—more person-to-person communication in an electronic environment. You know, it’s interesting you say that, because I try to be thoughtful and open and a bit agnostic about where I’m going to land.

Computers are helpful but there are times when medicine is a human-to-human experience, and the machines can get in the way.

But let’s take the radiology department as an example. There’s no question in my mind that the decrease in interactions between the frontline clinicians taking care of the patients and the radiologists compromises the care of the patients and compromises the education of both parties.

I would approach the question pretty agnostically about how we fix that in the most cost-effective way. And it might be that we recreate old-style radiology rounds. Or we might then say, “Really? We’re going to make all these busy teams schlep down to another floor and wait for the prior team to go through?”

So maybe it shouldn’t be exactly as it was. Maybe, we teleconference, along with some fancy new tool that allows the radiologist to point to a spot on the film that we’re all looking at on our computers.

I don’t know the right way to do it, but I think sometimes the solution needs to be a new or better form of technology.

Let’s talk about the government’s role in health care and this IT transition. You’re pretty hard on meaningful use. Many people call it meaningless abuse!

You’re talking about phases 2 and 3, right? You think phase 1 was a good idea. I think the first phase was a politically astute and necessary act that served its purpose quite well. The adoption curve for health IT was unbelievably slow until the federal money kicked
in. You know, we were at 10% adoption in doctors’ offices and hospitals in 2008. We’re at 70% today.

If the economy had not imploded in 2008 and if there hadn’t been $700 billion in stimulus money, then there’s no way we would have found $30 billion for health IT adoption. We wouldn’t have found $3 billion. I’m not sure if we would have found $300 million.

**So is the EHR the Great Recession’s WPA?** There is an analogy there. It’s a public good that would not have happened on its own.

But the analogy—it’s a little tenuous because I think we would have gotten there eventually. With the ACA, with the pressures now on providers—clinicians and hospitals and health care systems—to deliver high-quality, safe care at a lower cost: Those pressures would have ultimately led to computerization. But there’s no way in a million years they would have gotten us from 10 to 70% adoption in five years.

**And the opposition?** The pushback—there are parts of it I agree with, there are parts that I don’t. One criticism is that the computer systems and the EHRs were not ready for prime time, so the federal government subsidized the adoption of mediocre systems. That doesn’t pass the sniff test because, I believe, the systems would have remained mediocre if nobody was using them. These systems only get better when you get to version 14.0.

But once the feds get deeply in the weeds in the world of technology, you have problems. Just think about if the feds were designing your iPhone. It can’t work. Not that they’re bad people. Even forgetting the politics of blue states and red states. It’s just not an appropriate role for the federal government. And that $30 billion put the government in a position where they created a pretty powerful regulatory apparatus. Of course, all the interest groups jumped in to have their say, which is a natural phenomenon.

During my research for the book, when I spoke to frontline doctors and nurses, or to CIOs or CMIOs trying to grapple with the federal regulations, or to vendors, they told me we are spending so much of our bandwidth now on just meeting the next meaningful use requirement. We could do better and more innovative stuff if these things got dialed back.

**Would you junk the second and third phase?** I would declare victory and then pull back massively on it. Not even call it “meaningful use” anymore. There’s no more money to give out. And now you’re talking about penalizing doctors for not having the right computer system.

I think the world in 2015 looks very different from the world in 2008. We now have incentives on value, so if you are a health care delivery system or a doctor’s office, and if you deliver good, quality, satisfying care at the lowest cost, you will do well—and if you don’t, you won’t. With those incentives in place, I don’t think you want the federal government intervening very much.

There are two exceptions where I think there is a role for the federal government. It has to intervene on privacy and security because nobody has figured this out yet.

The other is interoperability. It is a public good if all these systems talk to one another. And the federal government is the only entity that can bash people’s heads together and say, “Folks, either you link these systems together yourselves, or we will make sure you do it.”

**You end your book with the story of a patient in the ICU and turning off the machines. I think what you’re driving at is that at a certain point, we want machines out of the picture.** Yes, I think that’s right. There are times when the machines are helpful and wonderful, and there are times when medicine is a fundamentally human-to-human enterprise, and the machines can get in our way. We have to be thoughtful about when those moments occur and address them.

Despite all the problems, you’re upbeat about the future of medicine, EHRs, and digital communication. I interviewed nearly 100 people, and they each gave me very different views on a lot of stuff. But then I said, “What’s the end game here? After we figure out the policies and the politics and the new designs, what does this look like?” And they all pretty much painted the same picture, and it was pretty terrific.

**You sort of go all Eric Topol there.** Where I differ from Eric is I don’t think he places the advances in enough context or addresses the challenges well enough. I wrote *The Digital Doctor* partly in reaction to his first book, which I thought was kind of over the top. There are probably a few people in La Jolla who have sensors in their underwear or who wear gizmos on their head when they sleep. That’s all really fun. It has very little to do with the day-to-day practice of medicine.

**Do you think we’re at a point with health care IT where there’s all this friction, but like primary care physicians learning to accept hospitalists, people are recognizing that EHRs and computerization are going to work out?** I think the difference is that the complaining—it’s not just about losing something. It’s actually quite legitimate. I think what we’re hearing from many docs is that the systems are not very good, and they’re making it difficult for them to do their work. That doesn’t mean you turn back the clock. These systems just have to get better. I’m hoping the book makes a contribution to doing that.
Eleven recently- or soon-to-be-released biologics may hit blockbuster status within five years, according to Thomson Reuters’ annual “Drugs to Watch” report. The inclusion of 11 drugs in the 2015 report is notable, as only three made the list in 2014.

**Nivolumab (Opdivo)** tops this year’s list. Bristol Myers-Squibb’s anticancer agent could reach $5.6 billion in sales by 2019. **Alirocumab (Praulent)**, Regeneron and Sanofi’s monoclonal antibody to treat hypercholesterolemia and now under priority review at the FDA, comes in second at $4.4 billion. **LCZ-696**, a Novartis combination agent for chronic heart failure, rounds out the top three, with predicted sales of $3.7 billion by 2019.

Specialty drugs are driving the drug-dollar market, says Larry Whisenant, director of specialty pharmacy operations at McKesson Specialty Health. As more specialty products emerge, he adds, they will continue to be a main cost factor—about 20 to 60%—for payers and employers. Biosimilars will mitigate this trend, but the timing and impact remain to be seen. Whisenant says that 2016 “may be a little early, but certainly within the next two to three years, depending on level of acceptance.”

Another factor that will affect specialty drug spending, says Whisenant, is that PBMs and payers are consolidating in a big way, as with UnitedHealth Group’s acquisition of Catamaran. “What you see there is 75% of the market driven by three PBMs.” The effect of this consolidation of power is that as new specialty products become available and widen the market, PBMs are likely to drive harder bargains or offer more exclusive formularies.

**Here come the biosimilars**

On March 6, the FDA approved filgrastim-sndz, (Zarxio)—a biosimilar of Amgen’s Neupogen, which prevents infections in cancer patients—the first biosimilar to be approved in the United States under the 351k pathway. Hot on Sandoz’s heels is Apotex, whose filgrastim (Grastofil) biosimilar application is under FDA review. Experts see, though, a number of obstacles slowing biosimilars’ market penetration: Physicians who don’t understand the approval process, patient acceptance, litigation, and questionable cost savings, to name a few.

That didn’t deter Merck from saying at March’s Cowen Healthcare Conference that five biosimilars would be submitted for global approval this year and next. In the United States, Merck is taking aim at AbbVie’s Humira, J&J’s Remicade, Sanofi’s Lantus, Roche’s Herceptin, and Amgen’s Enbrel. Existing agreements, however, would prevent Merck from launching an Enbrel biosimilar in the United States.

**Clinical trial updates**

Bevacizumab (Avastin) plus chemotherapy improved overall survival (OS) by nearly five months compared with chemotherapy alone for women with platinum-sensitive recurrent ovarian cancer, according to data presented at the Society of Gynecologic Oncology’s Annual Meeting on Women’s Cancer.

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**In the rush to spend, queries give pause**

In the wake of fast-growing expenditures on biologic therapies, opinion leaders are raising questions about how biologics and other specialty drugs are evaluated and used.

Maurie Markman, MD, clinical professor of medicine at Drexel University in Philadelphia, asks whether the regimens in a phase 3 trial comparing FOLFOXIRI versus FOLFIRI plus bevacizumab (Avastin) as first-line treatment of metastatic colorectal cancer is justified when it is associated with an “impressive” risk of toxicities. Speaking on OncologyLive, Markman also questioned the propriety of a phase 3 trial that explored the use of erlotinib (Tarceva), an epidermal growth factor receptor (EGFR) inhibitor, as maintenance therapy for patients with ovarian cancer when clinical data have shown that EGFR is not a clinically relevant target.

Writing in Pain Medicine News, New York anesthesiologist S.J. Slavin argues that, in the long run, cost reduction and quality-of-life improvements cannot be attained together. More people in the United States “have better access to the care they would want than the people who can afford to purchase private insurance in England,” he says, and questions what, specifically, we should look for in health care quality.

On Scientific American’s blog, Harvard Med student Ilana Yurkiewicz asks provocative questions about why aren’t we making greater use of agents that studies have shown to work and be cost-effective. Yurkiewicz cites the evidence for hydroxyurea in sickle cell disease, the Lyme Disease vaccine, and tamoxifen or raloxifene for breast cancer prevention in high-risk patients.
The GOG0213 trial marked the first time a phase 3 study has shown OS improvements in this population. PCSK9 inhibitors were in the spotlight at the American College of Cardiology’s Annual Scientific Session. Monthly dosing of alirocumab (Praluent) reduced hypercholesterolemia in patients with high cardiovascular risk, according to data from the ODYSSEY CHOICE I and CHOICE II trials. At the same conference, Amgen presented one-year data from the phase 2 and phase 3 OSLER trials of evolocumab (Repatha). In open-label studies, evolocumab reduced adjudicated cardiovascular events. Results of both studies were published in the New England Journal of Medicine. Both agents are under review at the FDA.

The PERSIST-1 phase 3 trial examining pacritinib, an oral JAK2 multi-kinase inhibitor for treatment of patients with myelofibrosis, met its primary endpoint. Compared with best available therapy, pacritinib resulted in a statistically significant increase in patients achieving a 35% or greater reduction in spleen volume. Takeda will terminate the phase 3 MONET-A trial, which studied motesanib in patients with stage 4, non–small-cell lung cancer (NSCLC), after the oral angiokinase inhibitor failed to meet its progression-free survival endpoint.

Have you heard?

Sofosbuvir (Solvadi) and ledipasvir/sofosbuvir (Harvoni) got labeling updates after the FDA warned about postmarketing cases of bradycardia when either of the hepatitis C agents are co-administered with amiodarone. Genetic testing in metastatic NSCLC patients and subsequent molecular biomarker-guided therapy is cost-effective compared with a chemotherapy-treatment approach without molecular testing, according to a study published in the Journal of Thoracic Oncology. Now that the FDA has said that 23andMe can provide an alert about Bloom Syndrome in its genetic profiles to prospective parents, the company plans to begin developing drugs based on its massive genetic database. CEO Anne Wojcicki says engaging consumers in drug development could be an industry game-changer.

— Katherine T. Adams

All clinical studies mentioned in this article are phase 3 unless otherwise stated.

## 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>
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<tbody>
<tr>
<td>Feb. 23 (NDA)</td>
<td>Novartis</td>
<td>panobinostat (Farydak); oral</td>
<td>In combination with bortezomib and dexamethasone for multiple myeloma in patients who have received ≥2 prior regimens including bortezomib and an immunomodulatory agent</td>
<td>Histone deacetylase inhibitor carries a black box warning about severe and fatal cardiac ischemic events (4% of patients in clinical trials), arrhythmias (12%) and severe diarrhea (25%).</td>
</tr>
<tr>
<td>March 6 (BLA)</td>
<td>Sandoz</td>
<td>filgrastim-sndz (Zarxio); subcutaneous injection</td>
<td>All five indications for filgrastim (Neulasta)</td>
<td>First biosimilar approved in U.S. under 351k pathway. Zarxio achieved biosimilarity, not interchangeability.</td>
</tr>
<tr>
<td>March 10 (BLA)</td>
<td>United Therapeutics</td>
<td>dinutuximab (Unituxin); intravenous infusion</td>
<td>In combination with GM-CSF, IL-2, and 13-cis-retinoic acid in children with high-risk neuroblastoma with partial response to a prior first-line agent</td>
<td>GD2-binding monoclonal antibody carries a black box warning about severe neuropathic pain. IV opioids may be administered before, during, and after infusions.</td>
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### New indications of previously approved treatments

<table>
<thead>
<tr>
<th>Date (sBLA)</th>
<th>Manufacturer</th>
<th>Drug (trade) name</th>
<th>Indication</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>March 4</td>
<td>Bristol-Myers Squibb</td>
<td>nivolumab (Opdivo)</td>
<td>Metastatic squamous NSCLC with progression on or after platinum-based chemotherapy</td>
<td>Previously approved for unresectable metastatic melanoma.</td>
</tr>
<tr>
<td>March 25</td>
<td>Regeneron</td>
<td>aflibercept (Eylea)</td>
<td>Diabetic retinopathy in patients with diabetic macular edema</td>
<td>New indication based on 2 RCTs in patients age 23 to 87.</td>
</tr>
</tbody>
</table>

Sources: FDA, Fierce Biotech, and manufacturers’ package inserts.

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— Katherine T. Adams

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Operational Implications of Utilizing 2 Advanced Technologies for Rendering Short-term Hemodynamic Support to Patients Presenting With Cardiogenic Shock: A View Through the Lens of Hospital Readmissions

Dennis J. Scotti, PhD, MS, MBA; David A. Gregory, MPA; Theodore L. Schreiber, MD; Adhir Shroff, MD, MPA; Daniel R. Buck, MBA, MPH

INTRODUCTION
At an estimated cost to the American public of over $17 billion in 2010, hospital readmissions for Medicare beneficiaries represent a major national priority (Hickman 2012). A recent study showed that up to 20% of all Medicare beneficiaries are readmitted within 30 days of discharge (Bradley 2013). Moreover, although some of these readmissions are part of the course of treatment, the vast majority are unplanned and therefore represent an opportunity for cost savings (Jencks 2009). For example, a recent report by the Medicare Payment Advisory Commission (MedPAC) concluded that three quarters of readmissions within 30 days were preventable, representing $12 billion in additional Medicare spending during fiscal year (FY) 2005 (James 2013). Despite the need to reduce the cost of preventable readmissions, the 19% average rate for all-cause, 30-day readmissions (2007–2011) has remained intractably high (Gerhardt 2013).

Recognizing the need to reduce hospital readmissions, Section 3025 of the Affordable Care Act (ACA) added Section 1886(q) to the Social Security Act, establishing the Hospital Readmissions Reduction Program (HRRP). This section requires the Centers for Medicare & Medicaid Services (CMS) to reduce payments to Inpatient Prospective Payment System hospitals with excess readmissions, effective for discharges beginning on Oct. 1, 2012. The first three conditions the HRRP focused on were pneumonia and two of the most prevalent forms of cardiovascular disease, acute myocardial infarction (AMI) and heart failure (HF).

ABSTRACT
Purpose: Reducing hospital readmissions for critically ill patients is of concern to payers and providers alike. Patients in cardiogenic shock are often treated with devices to help support the functions of the heart while the patient undergoes treatment. This study compares the readmission experience of Medicare beneficiaries treated for cardiogenic shock (CS) using percutaneous ventricular assist devices (pVADs) vs. extracorporeal membrane oxygenation (ECMO), two types of advanced cardiac support devices. Hospital readmission is a surrogate for quality and cost.

Design and methodology: A retrospective comparison of readmission patterns of patients treated for CS using two advanced cardiac support devices during calendar years 2011 and 2012 was captured via the Medicare Inpatient Standard Analytic File (100% census file). A total of 649 eligible cases (pVAD, 517; ECMO, 132) with 90 days of follow-up documentation were included in this analysis. Baseline characteristics were compared, including demographics, admission type, and severity of illness, with the 2 groups generating clinically similar baseline profiles. Primary outcomes include 30- and 90-day readmissions, associated length of stay (LOS), and costs.

Results: At 90 days after initial hospitalization, the readmission rates in the pVAD and ECMO cohorts were 38.7% (200/517) and 53.0% (70/132), respectively. Overall, pVAD was associated with a 27.1% reduction in readmission ($P$=.004). With the use of pVAD, 90-day readmission costs were lower by $12,294 ($32,736 vs $20,442, a reduction of 37.6%, $P$=.02) and readmission LOS was shorter by approximately 8 days, (20.5 vs. 12.7 days, a 37.9% reduction, $P$=.002). Similar trends were observed at 30 days; however, only LOS was significantly reduced, by 7.0 days ($P$<.001).

Conclusion: In clinically comparable cohorts, pVADs were associated with reduced risk of rehospitalization, lower cost, and shorter LOS, resulting in cost savings for payers and providers. Increased adoption of pVAD, as a technology to support patients in cardiogenic shock, may help hospitals deliver greater value to both government and commercial payers.

(Key Terms) Hospital readmissions, costs, length of stay, cardiogenic shock, hemodynamic support, pVAD, ECMO, Medicare...
large commercial payers are taking action as well by requiring metrics from hospitals showing their rates of readmission for high-priority conditions. Major commercial payers, including WellPoint and Aetna, have announced payment initiatives encouraging hospitals to reduce readmissions.

Compelling logic underlies the selection of cardiovascular disease, especially HF and AMI, as a target for reducing hospital readmissions. Advanced HF is the leading cause for hospital readmissions among both Medicare and commercial insureds (Desai 2012). A review of the claims of over 11 million Medicare beneficiaries from the MedPAR database found HF to be the leading cause of hospital readmissions, with a 30-day rehospitalization rate of 26.9% (Jencks 2009).

A particularly challenging clinical complication of HF and AMI is cardiogenic shock (CS). CS is a state of end-organ failure and is the leading cause of death in patients experiencing an AMI (Maini 2014). In 2013, the annual incidence of AMI was projected to be 635,000 cases (Go 2013); approximately 7% to 10% of AMI cases are complicated by CS (Thiele 2007). Although AMI patients whose condition is complicated by CS constitute a relatively small group of hospital admissions, these patients frequently experience adverse clinical and economic outcomes and approximately 25% of these cases require hemodynamic support (Lloyd-Jones 2010, Whellan 2010, Thiele 2007).

**KEY POINTS**

- Cardiovascular disease is leading cause of hospital readmission among Medicare beneficiaries and people with commercial insurance coverage.
- Physicians are increasingly reliant on advanced technologies to treat patients in cardiogenic shock after less-costly conventional drug therapy and mechanical cardiac support prove unsuccessful.
- Previous studies have suggested that percutaneous ventricular assist devices (pVADs) are more cost-effective than extracorporeal membrane oxygenation (ECMO) devices for treating patients with refractory cardiogenic shock.
- This study, which focused on hospital readmissions, showed that 90 days after their initial hospitalization, the readmission rate for patients treated with pVADs was lower than those treated with ECMO devices (38.7% vs. 53%).
- Readmission costs were also lower ($20,442 vs. $32,736) and the readmission LOS were shorter (12.7 days vs 20.5 days) for those treated with pVADs compared with those treated with ECMO devices.
- With the exception of length of stay, many of the differences between pVADs and ECMO devices 30 days after initial hospitalization did not reach statistical significance.
addition to lengthy hospital stays with prolonged confinements in intensive care units, these hemodynamic support devices and their management are costly; all of these factors contribute to the overall costs of patients with cardiogenic shock. Accordingly, both payers and providers are searching for treatment options that improve quality and lower costs, which include reducing the incidence of hospital readmission (Jencks 2009).

Historically, intraaortic balloon pump (IABP) has been one of a limited number of mechanical hemodynamic support options when treatment of CS with inotropic and vasopressor drugs has failed. Although relatively inexpensive, IABPs have not made great strides in altering the clinical outcomes of CS patients (Romeo 2013, Thiele 2012). More advanced devices for rendering short-term percutaneous cardiac support — such as extracorporeal membrane oxygenation (ECMO) and more recently introduced percutaneous ventricular assist devices (pVADs) — may be used as an alternative to IABP or to escalate therapy for refractory CS.

pVADs, such as Impella 2.5 (Abiomed Inc., Danvers, Mass.) and TandemHeart (CardiacAssist, Pittsburgh), are minimally invasive, short-term mechanical pumps used to help hearts that no longer can pump blood effectively. These mechanical devices permit physicians to determine how much hemodynamic support is needed, ranging from 2.5 to 5.0 liters of forward blood per minute. Several recent studies have shown that these devices are effective in providing urgent, systemic circulatory support, thereby preventing additional cardiac and organ damage, expediting recovery time, and reducing subsequent major adverse events, including mortality (Liu 2013, Maini 2012, O’Neill 2014, Lemaire 2014). By comparison, ECMO also facilitates enhanced flow of oxygenated blood but has been associated with high rates of peri-procedural complications and mortality rates exceeding 50% (Zangrillo, 2013) when used to treat patients in CS. The devices and clinical terms referred to in this discussion are defined in the glossary.

In addition to its clinical utility, pVAD was dominant in a cost-effectiveness analysis during initial hospitalization when compared with other circulatory support systems (Maini 2014). Further, published budget impact models have linked use of pVADs with nominal per-member, per-month expenditures for payers and a reduction in costs over time after the initial hospitalization (Gregory 2013). As clinical practice patterns evolve, both physicians and managed care professionals need to better understand the economic consequences of reliance on advanced cardiac support devices as adjunct to or as substitutes for use of IABPs in the treatment of CS. This study provides a comparative economic analysis of readmissions stemming from the use of ECMO and pVADs as advanced technologies for providing mechanical hemodynamic support in the broad context of CS.

**METHODS**

**Study design**

This study was designed as a retrospective comparison of readmission dynamics related to patients surviving treatment for CS supported by two advanced cardiac assist devices during calendar years 2011 and 2012. Primary outcomes included 30- and 90-day readmissions and associated length of stay (LOS) and costs for...
all survivors of the initial CS event. Readmissions within 30 days of the initial (“index”) stay were included in both measures. As secondary analyses, these variables were examined in a subgroup of cases where CS was present on admission, and the relationship between readmissions and discharge disposition was explored.

**Data source and study population**

The primary source of data for this retrospective analysis is the Medicare Standard Analytic File (SAF) of inpatient fee-for-service claims. The SAF contains all such records collected by Medicare from institutions and noninstitutional providers and contains claim-level detail on diagnosis, procedures, diagnosis-related groups (DRGs), dates of services, reimbursement and cost amounts, providers, and patient demographic detail. Our study population was compiled from the SAF data sets ranging between Jan. 1, 2011, and Dec. 31, 2012.

Demographic and clinical information for the patients analyzed in this study were identified using the *International Classification of Diseases–Ninth Revision* (ICD-9) coding system. Eligible candidates for this study included all patients in the inpatient SAF file who were discharged alive and with at least one of the procedure codes of interest and at least one of the diagnosis codes of interest (ICD-9) appearing on a single claim. A total of 901 discharged patients (defined as the index hospitalization). Of these, 136 patients were identified as having the diagnosis of interest and at least one of the procedure codes across the 2 years of claims data. Of these, 136 patients with discharge dates after Oct. 1, 2012, were excluded from the sample given that insufficient time remained to measure 90-day readmissions within the study period. An additional 60 patients were removed because of the presence of multiple procedures (devices) of interest on a single date or claim. A total of 705 patients were eligible for inclusion.

In addition to the standard information contained in the SAF, we utilized *severity of illness* (SOI) and *service intensity weights* (SIW) from the All-Patient Refined DRG Classification System (APR-DRG, Version 29, 3M Co.) to assess clinical differences between the cohorts. Using claim-level detail, each APR-DRG is subdivided into four levels of illness severity: *minor* (level 1), *moderate* (level 2), *major* (level 3), or *extreme* (level 4), with a specific SIW assigned to each SOI level based on age and primary and secondary diagnoses. For purposes of this study, all procedure codes, including device-specific codes, were removed from the claim-level detail prior to APR-DRG and severity assignment to establish baseline clinical profiles of the cohorts prior to treatment intervention.

Upon preliminary examination of SOI characteristics, we identified 56 cases that mapped to APR-DRG 200 “Cardiac Congenital and Valvular Disorders,” 53 of which were categorized as extreme, with an SIW of 5.3761 (whereas others ranged from 0.7238 to 4.1402). Further examination revealed that these were predominantly scheduled/elective procedures. Clinical members of the research team agreed that the congenital and structural pathology of these cases was not clinically aligned with the typical CS profile. Therefore, all 56 cases were removed, resulting in 649 patients being included in the analysis. Of the 649 patients, 517 were treated with pVAD based on the presence of ICD-9 procedure code 37.68 upon index admission, while 132 were treated with ECMO on the basis of the presence of ICD-9 procedure code 39.65.

**Variables**

The claims containing the first instance of CS during the study period were considered the index hospitalization and served as the source for describing the baseline characteristics of research subjects (Table 1). Characteristics of the patients included in the study, including race, gender, age, and diagnoses present on admission (POA), were evaluated to assess the level of clinical comparability between the cohorts. For diagnoses POA, the ICD-9 appropriate diagnosis codes were extracted from each claim and the top 10 were compared across the pVAD and ECMO cohorts.

The type of admission at index hospitalization also was identified to assess the existence of noteworthy differences among these subgroups. As defined by CMS, inpatient admission types include, but are not limited to the following:

*Emergent:* The patient required immediate medical intervention as a result of severe, life threatening, or potentially disabling conditions. Generally, the patient was admitted through the emergency room.

*Urgent:* The patient required immediate attention for the care and treatment of a physical or mental disorder. Generally, the patient was admitted to the first available and suitable accommodation.

*Elective:* The patient’s presenting condition permitted adequate time to schedule the availability of suitable accommodations (this type was by far the least frequent admission type for this population).

For statistical analysis purposes, 30- and 90-day readmissions were treated as dichotomous (“yes” or “no”) occurrences. Patients with more than one readmission in each readmission category (30 and 90 days) were counted only once.
Readmission LOS was determined by taking the difference of the admission date for the rehospitalization and the discharge date. Admissions and discharges occurring on the same day were deemed as 1-day stays. Readmission cost was determined by calculating the total cost associated with the readmission claim as reported in the Inpatient SAF file. When patients had more than one readmission in either the 30- or 90-day timeframe, LOS for the visits were combined and an average cost was calculated for the readmissions.

Subgroup analyses included assessments of 30- and 90-day readmissions for patients who had an admission type of either urgent or emergent, reflecting index hospitalizations where inadequate time was available to schedule or plan for appropriate resources. For this subgroup analysis, these patients were combined into one group and all other patients were excluded (including elective, trauma, and other). We also conducted a subgroup analysis on only those patients with CS POA.

Additional descriptive analyses included evaluations of 90-day readmissions by discharge disposition, as well as a comparison of admitting and principal diagnoses at readmission. The SAF database assigns a patient’s discharge disposition to 1 of 13 distinct settings. Of these, five were combined and recoded as discharged to institutional care (293 patients), while two were combined and recoded as discharged to community care (315 patients). The six remaining discharge categories were thinly represented (comprising only 41 patients in total) and were therefore excluded from analysis. A comparison of admitting and principal diagnoses for patients rehospitalized at 30 and 90 days was performed by extracting the respective codes for each treatment cohort.

**Statistical analysis**

Tests of differences among discrete categorical variables were assessed using the Pearson’s chi squared or Fisher’s exact test, as appropriate. Differences for normally distributed continuous variables with adequate sample sizes were tested using the t test. Logarithmic transformation was used to normalize data where substantial departures from normality were detected and data were positively skewed. When logarithmic transformation was not appropriate, comparisons were performed using the Mann-Whitney test. Data distribution anomalies were identified by standard SPSS diagnostic tests. Statistical analyses were 2-tailed and a value of P<.05 was considered statistically significant. All analyses were performed using SPSS Version 20 (IBM SPSS Statistics, Chicago).

**RESULTS**

Table 1 (see page 46B) compares the baseline characteristics for the study cohorts. The highest percentage of patients in the pVAD cohort fell in the 65–69-year age category (pVAD=22.8%, ECMO=19.7%, P=.48), which is in contrast with the number of patients under age 65 observed in the ECMO cohort (pVAD=20.1%, ECMO=37.1%, P=.001). The ECMO cohort is therefore decidedly younger than the pVAD cohort and includes disabled beneficiaries under age 65 in this Medicare claims database. The age disparity between the two groups is statistically significant only in the under-65 category (P<.001), which disadvantages pVAD regarding its readmission parameters. There was no difference in gender, with approximately 59% men in the pVAD group as compared with 58% with ECMO. In terms of race, patients identifying themselves as white represented the highest percentage among the race categories of white, black, and other. The study cohorts were similar on race (white, P=.31, black, P=.08, and

<table>
<thead>
<tr>
<th>Measures</th>
<th>pVAD</th>
<th>ECMO</th>
<th>Change</th>
<th>% Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admissions (counts)</td>
<td>517</td>
<td>n/a</td>
<td>132</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>30-day readmissions (counts)</td>
<td>134</td>
<td>25.9%</td>
<td>45</td>
<td>34.1%</td>
<td>8.2%</td>
</tr>
<tr>
<td>30-day readmission LOS (days)</td>
<td>10.5</td>
<td>n/a</td>
<td>17.5</td>
<td>n/a</td>
<td>7.0</td>
</tr>
<tr>
<td>30-day readmission cost (dollars)$^{2,4}$</td>
<td>$28,159</td>
<td>n/a</td>
<td>$46,830</td>
<td>n/a</td>
<td>$18,671</td>
</tr>
<tr>
<td>90-day readmission LOS (days)</td>
<td>200</td>
<td>38.7%</td>
<td>70</td>
<td>53.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>90-day readmission cost (dollars)$^{2,4}$</td>
<td>12.7</td>
<td>n/a</td>
<td>20.5</td>
<td>n/a</td>
<td>7.8</td>
</tr>
<tr>
<td>90-day readmission cost (dollars)$^{2,4}$</td>
<td>$20,442</td>
<td>n/a</td>
<td>$32,736</td>
<td>n/a</td>
<td>$12,294</td>
</tr>
</tbody>
</table>

ECMO=extracorporeal membrane oxygenation, LOS=length of stay, pVAD=percutaneous ventricular assist device.

1. 2011–2012 Medicare SAF 100% sample file.
2. Cost data are limited to 2012 only due to data constraints.
3. Log transformations were performed to address data distribution anomalies identified by standard SPSS diagnostic tests.
4. Mann-Whitney nonparametric tests were used when justified by small sample sizes and/or nonnormally distributed measures.
5. Fisher’s exact tests were applied based on the dichotomous nature of the data.
other, \( P = .71 \) and gender (\( P = .80 \)) as well as all age groups over 65. Table 1 also shows that the study groups were not comparable in terms of relative frequency of CS POA. In the pVAD cohort, 58.3% of patients had CS POA compared with 41.7% of the patients in the ECMO cohort, a statistically significant difference of nearly 17% (\( P < .001 \)). Moreover, 1,143 patients who did not survive their index event were excluded prior to any additional analysis, reflecting an overall mortality rate of 56%. Of these cases ECMO was associated with a higher mortality rate (67.4%) when compared with pVAD (50.8%; \( P < .001 \)).

In addition to the key baseline characteristics, we compared the average SOI of our two study cohorts. The range of SOI values by study cohort and by inpatient admission type is shown in Table 2 (page 46B). Overall, the clinical severity was assumed to be similar due to the fact that the average SOI was not statistically significant between the study cohorts. Appendix A (page 46D) displays the top ICD-9 codes POA and their frequency of occurrence in both study cohorts. This clinical profile is offered to provide descriptive depth and was not used for matching purposes.

Table 3 reports results on the outcome variables of primary interest. Frequency of readmission, costs, and LOS were calculated and analyzed for the subgroups at both 30 days and 90 days post discharge. Although not statistically significant, the 30-day readmission rate was lower for pVAD when compared with ECMO (25.9% vs. 34.1%; \( P = .06 \)). The mean difference in cost of \$18,671 when compared with the ECMO cohort, where 59% were discharged to community care (either with or without medical support). This finding is in direct contrast to the ECMO cohort, where 59% were discharged to another institution, generating a statistically significant difference (\( P = .008 \)) in the rate of discharge to community settings for pVAD.

We also examined the relationship between aggregate 90-day readmissions and postindex discharge disposition (Table 7; page 46D). It is worth noting that, overall, 46.8% of patients who were discharged to an

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**PVAD vs. ECMO**

observed for CS patients readmitted within 90 days were similar to those observed at the 30-day mark (Table 3). The readmission rate was lower for pVAD when compared with ECMO (38.7% vs. 53.0%; \( P = .004 \)). The mean differences in cost and LOS at 90 days were statistically significantly lower for the pVAD cohort by \$12,294 (\( P = .02 \)) and 7.8 days (\( P = .002 \)).

The clinical reasons for readmission within 30 and 90 days (as defined by admitting and principal diagnoses) are presented for each cohort in Appendices B and C (pages 46E–46F). Patients in the pVAD cohort were most often rehospitalized with the admitting and principal diagnosis of subendocardial infarction, while patients in the ECMO cohort were most often readmitted with the admitting diagnosis of CS, coronary atherosclerosis, or shortness of breath, and a principal diagnosis of coronary atherosclerosis.

The readmission dynamics of the subset of patients whose index admission was classified as either urgent or emergent were examined, and the results are displayed in Table 4. As with the overall sample, the pVAD cohort had a lower frequency of admissions at both 30 and 90 days postdischarge when compared with the ECMO cohort. The average LOS and cost of the readmission at both 30 and 90 days also favored the pVAD cohort. The mean differences in the average LOS were statistically significant at 30 days postdischarge (17.1 vs. 10.6 days; \( P = .004 \)) and at 90 days postdischarge (20.9 vs. 14.5 days; \( P = .02 \)). The 90-day readmission mean difference in cost of \$13,950 was also statistically significant (\( P = .049 \)).

Because of the clinical importance of cardiogenic shock, a separate subgroup analysis was performed to evaluate differences in readmissions among patients with CS POA across the study groups (Table 5). At 30 days, the profiles of this subgroup revealed a 35.6% reduction in readmissions (pVAD, 24.6% [74/301]; ECMO, 38.2% [21/55]) and a 7.6-day reduction in average LOS between the pVAD cohort and the ECMO cohort (pVAD, 9.0 days; ECMO, 16.5 days), both of which were statistically significant (\( P = .046 \) and \( P = .02 \), respectively). Although not statistically significant, the average cost of a 30-day readmission in the ECMO cohort was \$51,260 compared with \$32,404 in the pVAD cohort, a 36.8% saving in the pVAD group (\( P = .15 \)). Trends in 90-day readmissions for this subgroup paralleled those found at 30 days. Patients treated with pVAD exhibited a 25.6% reduction in readmissions (\( P = .10 \)), a \$19,063 average savings in costs (\( P = .16 \)), and a 6.6-day reduction in mean LOS (\( P = .01 \)). While reductions in readmissions did not achieve statistical significance, we believe the magnitude of the observed reductions and average costs (and their respective \( P \) values) suggest the odds favor positive operational impacts associated with the use of pVADs at 90 days postdischarge for the CS POA subgroup.

To complete our analyses, we compared (post hoc) the differences in discharge disposition between the study groups subsequent to their index hospitalization (Table 6; pages 46D). Over half (54.5%) of the patients in the pVAD cohort were discharged to community settings for both 30 and 90 days postdischarge. As with inpatient readmissions, this finding is in direct contrast to the ECMO cohort, where 59% were discharged to another institution, generating a statistically significant difference (\( P = .008 \)) in the rate of discharge to community settings for pVAD.
institutional setting were readmitted within 90 days compared with 39.0% of patients who were discharged to home, approaching a statistically significant difference of nearly 8% \( (P=0.06) \).

**DISCUSSION**

In the present era of healthcare reform, there is increasing pressure to improve quality of care while reducing costs. Recently, federal policymakers have focused on reducing the large and often unnecessary costs of Medicare readmissions by instituting the HRRP as part of ACA. While well intentioned, so far the HRRP has done little to reduce the all-cause, 30-day readmission rate, which has remained at approximately 19% for the past 5 years. This rate has dropped just 0.6%, to 18.4% in 2012 (the first year hospitals were penalized for excess readmissions for certain medical conditions), illustrating the intractable nature of the problem (Gerhardt 2013).

The challenge of controlling readmission costs is not just a Medicare issue. According to an analysis by OptumInsight Inc. of 5.4 million commercial and 900,000 retired covered lives, the average readmission cost to commercial carriers is 37% higher than for the average initial hospitalization (Kilroy 2013). Value-based care organizations, such as ACOs, should put programs in place that will address inpatient readmissions.

Although CS represents a small percentage of all HF patients, the mortality rate can be well over 50% and the cost to treat these patients is often exorbitantly high, with readmission rates well above the all-cause rates for both Medicare and commercial populations. One of the principal methods for restoring hemostasis in CS patients is via mechanical hemodynamic support, which was traditionally achieved with IABP, or if necessary, ECMO. Recent studies have shown pVADs provide effective mechanical hemodynamic support when compared with ECMO, with fewer clinical complications and at a lower index cost.

Unlike previous studies that focused on the initial, or index, hospital stay, this study moved the timeframe of interest to postindex discharge and explored the effect that utilization of these two commonly deployed cardiac support devices (ECMO and pVAD) had on the frequency, cost, and LOS of 30- and 90-day readmissions. As the study results show, the use of pVAD during the index hospitalization was associated with reductions in readmission frequencies, cost, and LOS at both 30 and 90 days when compared with the use of ECMO. Moreover, most of these reductions were statistically significant and were derived from a pVAD study cohort that was decidedly older than the ECMO cohort and well matched in terms of clinical severity.

The use of pVAD was also linked to reductions in the frequency, costs, and LOS of 30- and 90-day readmissions in the subgroup analyses comprising only patients who had CS and were classified as emergent or urgent on index admission, lending to the durability and credibility of the results observed in the overall study population. Also of note is the finding that pVAD was used more often than ECMO in these patients who were classified as urgent/emergent or who presented to the hospital with CS, suggesting the performance of pVAD is preferred to ECMO when time to plan for appropriate resource deployment is not an option.

Although the results of this study were based on the Medicare population, previous studies of commercially insured beneficiaries have shown that the economic impact of pVAD use in younger CS patients was favorable during their index hospitalizations. The authors assume the economics associated with the use of pVAD after discharge may also be similar. Future research should employ a similar study design utilizing a commercial claims database to test this hypothesis.

Our study is not without limitations. The study cohorts were derived from the fee-for-service Medicare claims data contained in the Inpatient SAF file. Restrictions on age and the disproportionate prevalence of disabled beneficiaries in our dataset limit the generalizability of our findings to the total population of those with insurance. Moreover, unlike prospective clinical studies, claims data are limited to administrative coding, including diagnoses and procedure codes that may lack precision and limit the number of variables and measures available for interpretation and analysis. Also, planned readmissions, which are part of the follow-up care and standard treatment protocols for a given condition, could not be filtered out of the study. Additionally, because this is a retrospective analysis, it is more difficult to control for factors that may influence adequate matching cohorts and their associated outcomes.

Finally, all observational studies are subject to the influence of hidden biases beyond the knowledge and control of the investigators. Accordingly, the conclusions from our study are susceptible to variable interpretations, do not imply causality, and should be applied judiciously. We would, therefore, encourage further research to explore the relationship between pVAD deployment and readmission outcomes based on more tightly controlled study designs.

**CONCLUSION**

The present study examined the readmission profiles of two advanced mechanical devices (pVAD and ECMO) that are increasingly deployed to provide cardiac support in the broad context of cardiogenic shock. The re-
sults of this study show that the use of pVADs are linked with reduced cost and improved operational efficiency, not only during the index stay as previously reported, but also post-discharge. Specifically, pVADs were associated with statistically significant reductions in readmission rates, LOS, and hospital costs. Our study, while limited in scope, does suggest that pVADs may have downstream operational implications that work to the benefit of CS patients after discharge. This research offers providers and managed care professionals an opportunity to better understand the economic consequences of clinical decisions to utilize advanced technologies as they strive to optimize post-acute care, including hospital readmissions. In the current era of health reform, commercial insurers as well as government policymakers should consider these potential operational effects of pVADs, as they attempt to control cost while maintaining quality in this high-risk patient population.

REFERENCES


### APPENDIX

**TABLE 1**

**Baseline characteristics of the study population by treatment cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>pVAD (n=517)</th>
<th>ECMO (n=132)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age category²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>104</td>
<td>20.1%</td>
<td>49</td>
<td>37.1%</td>
</tr>
<tr>
<td>65–69</td>
<td>118</td>
<td>22.8%</td>
<td>26</td>
<td>19.7%</td>
</tr>
<tr>
<td>70–74</td>
<td>87</td>
<td>16.8%</td>
<td>20</td>
<td>15.2%</td>
</tr>
<tr>
<td>75–79</td>
<td>85</td>
<td>16.4%</td>
<td>16</td>
<td>12.1%</td>
</tr>
<tr>
<td>80–84</td>
<td>63</td>
<td>12.2%</td>
<td>12</td>
<td>9.1%</td>
</tr>
<tr>
<td>85+</td>
<td>60</td>
<td>11.6%</td>
<td>9</td>
<td>6.8%</td>
</tr>
<tr>
<td>Gender²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>213</td>
<td>41.2%</td>
<td>56</td>
<td>42.4%</td>
</tr>
<tr>
<td>Male</td>
<td>304</td>
<td>58.8%</td>
<td>76</td>
<td>57.6%</td>
</tr>
<tr>
<td>Race²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>428</td>
<td>82.8%</td>
<td>104</td>
<td>78.8%</td>
</tr>
<tr>
<td>Black</td>
<td>50</td>
<td>9.7%</td>
<td>20</td>
<td>15.2%</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
<td>7.5%</td>
<td>8</td>
<td>6.1%</td>
</tr>
<tr>
<td>CS/POA³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>301</td>
<td>58.2%</td>
<td>55</td>
<td>41.7%</td>
</tr>
<tr>
<td>No</td>
<td>216</td>
<td>41.8%</td>
<td>77</td>
<td>58.3%</td>
</tr>
</tbody>
</table>

CS=cardiogenic shock, ECMO=extracorporeal membrane oxygenation, POA=present on admission, pVAD=percutaneous ventricular assist device.

1. 2011–2012 Medicare SAF 100% Sample File.
2. Pearson's Chi Square was used due to the categorical nature of the data.
3. Fisher's exact tests were applied based on the dichotomous nature of the data.

Footnote: It is important to note that 1,143 patients who did not survive were excluded prior to any additional analysis. This resulted in an overall mortality rate of 56%. Of these cases, ECMO was associated with a higher mortality rate (67.4%) when compared to pVAD (50.8%) (P<.001). When stratified by gender, ECMO was associated with a higher mortality rate for both males (68.7% vs. 48.6%) and females (64.7% vs. 55.9%) (P<.001 and P=.03, respectively). Furthermore, at all age levels, ECMO was associated with a higher mortality rate, a statistically significant finding at age groups 65–69 (P<.001), 70–74 (P<.001), 75–79 (P=.004).

**TABLE 2**

**Severity of illness of the study population by treatment cohort and admission type**

<table>
<thead>
<tr>
<th>Admission type</th>
<th>SOI</th>
<th>n</th>
<th>%</th>
<th>SOI</th>
<th>n</th>
<th>%</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent</td>
<td>2.47</td>
<td>292</td>
<td>56.5%</td>
<td>2.54</td>
<td>57</td>
<td>43.2%</td>
<td>349</td>
<td>.40</td>
</tr>
<tr>
<td>Urgent</td>
<td>2.52</td>
<td>177</td>
<td>34.2%</td>
<td>2.58</td>
<td>55</td>
<td>41.7%</td>
<td>232</td>
<td>.49</td>
</tr>
<tr>
<td>Elective</td>
<td>2.31</td>
<td>46</td>
<td>8.9%</td>
<td>2.57</td>
<td>19</td>
<td>14.4%</td>
<td>65</td>
<td>.13</td>
</tr>
<tr>
<td>Emergent/urgent</td>
<td>2.49</td>
<td>469</td>
<td>90.7%</td>
<td>2.56</td>
<td>112</td>
<td>84.8%</td>
<td>581</td>
<td>.24</td>
</tr>
<tr>
<td>Other</td>
<td>1.03</td>
<td>2</td>
<td>0.4%</td>
<td>3.05</td>
<td>1</td>
<td>0.8%</td>
<td>3</td>
<td>.16</td>
</tr>
<tr>
<td>All admission types</td>
<td>2.47</td>
<td>517</td>
<td>100.0%</td>
<td>2.56</td>
<td>132</td>
<td>100.0%</td>
<td>649</td>
<td>.09</td>
</tr>
</tbody>
</table>

ECMO=extracorporeal membrane oxygenation, pVAD=percutaneous ventricular assist device, SOI=severity of illness.

1. 3M All Patient Refined DRG Classification System.
2. Students T-Test was used.
**TABLE 4**
Readmission dynamics in the cardiogenic shock population by treatment cohort (urgent & emergent admissions only)

<table>
<thead>
<tr>
<th>Measures</th>
<th>pVAD (n=301)</th>
<th>ECMO (n=55)</th>
<th>Change</th>
<th>% change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day readmissions (counts)</td>
<td>127 27.1%</td>
<td>38 33.9%</td>
<td>6.9 pct. pt.</td>
<td>20.2%</td>
<td>.16</td>
</tr>
<tr>
<td>30-day readmission LOS (days)</td>
<td>10.6 n/a</td>
<td>17.1 n/a</td>
<td>6.6</td>
<td>38.3%</td>
<td>.004</td>
</tr>
<tr>
<td>30-day readmission cost (dollars)</td>
<td>$28,706 n/a</td>
<td>$47,302 n/a</td>
<td>$18,596</td>
<td>39.3%</td>
<td>.08</td>
</tr>
<tr>
<td>90-day readmissions (counts)</td>
<td>186 39.7%</td>
<td>56 50.0%</td>
<td>10.3 pct. pt.</td>
<td>20.7%</td>
<td>.06</td>
</tr>
<tr>
<td>90-day readmission LOS (days)</td>
<td>14.5 n/a</td>
<td>20.9 n/a</td>
<td>6.4</td>
<td>30.8%</td>
<td>.02</td>
</tr>
<tr>
<td>90-day readmission cost (dollars)</td>
<td>$26,772 n/a</td>
<td>$40,722 n/a</td>
<td>$13,950</td>
<td>34.3%</td>
<td>.049</td>
</tr>
</tbody>
</table>

**ECMO**=extracorporeal membrane oxygenation, **LOS**=length of stay, **pVAD**=percutaneous ventricular assist device.
1. 2011–2012 Medicare SAF 100% Sample File.
2. Cost data are limited to 2012 only due to data constraints.
3. Log transformations were performed to address data distribution anomalies identified by standard SPSS diagnostic tests.
4. Mann-Whitney nonparametric tests were used when justified by small sample sizes and/or nonnormally distributed measures.
5. Fisher’s exact tests were applied based on the dichotomous nature of the data.

**TABLE 5**
Readmission dynamics in the cardiogenic shock population by treatment cohort (CS present on admission)

<table>
<thead>
<tr>
<th>Measures</th>
<th>pVAD (n=301)</th>
<th>ECMO (n=55)</th>
<th>Change</th>
<th>% Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day readmissions (counts)</td>
<td>74 24.6%</td>
<td>21 38.2%</td>
<td>13.6 pct. pt.</td>
<td>35.6%</td>
<td>.046</td>
</tr>
<tr>
<td>30-day readmission LOS (days)</td>
<td>9.0 n/a</td>
<td>16.5 n/a</td>
<td>7.6</td>
<td>45.8%</td>
<td>.02</td>
</tr>
<tr>
<td>30-day readmission cost (dollars)</td>
<td>$32,404 n/a</td>
<td>$51,260 n/a</td>
<td>$18,856</td>
<td>36.8%</td>
<td>.15</td>
</tr>
<tr>
<td>90-day readmissions (counts)</td>
<td>110 36.5%</td>
<td>27 49.1%</td>
<td>12.5 pct. pt.</td>
<td>25.6%</td>
<td>.10</td>
</tr>
<tr>
<td>90-day readmission LOS (days)</td>
<td>12.3 n/a</td>
<td>18.9 n/a</td>
<td>6.6</td>
<td>34.8%</td>
<td>.01</td>
</tr>
<tr>
<td>90-day readmission cost (dollars)</td>
<td>$29,462 n/a</td>
<td>$48,525 n/a</td>
<td>$19,063</td>
<td>39.3%</td>
<td>.16</td>
</tr>
</tbody>
</table>

**CS**=cardiogenic shock, **ECMO**=extracorporeal membrane oxygenation, **LOS**=length of stay, **pVAD**=percutaneous ventricular assist device.
1. 2011–2012 Medicare SAF 100% Sample File.
2. Cost data are limited to 2012 only due to data constraints.
3. Fisher’s exact tests were applied based on the dichotomous nature of the data.
4. Mann-Whitney nonparametric tests were used when justified by small sample sizes and/or nonnormally distributed measures.
### TABLE 6
Discharge disposition of the study population by treatment cohort (institutional care vs. community care)

<table>
<thead>
<tr>
<th>Discharge disposition group</th>
<th>Discharge disposition description</th>
<th>pVAD (n=486)</th>
<th>ECMO (n=122)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institutional care</td>
<td>Discharged/transferred to short-term general hospital</td>
<td>44 9.1%</td>
<td>9 7.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharged/transferred to a SNF</td>
<td>104 21.4%</td>
<td>23 18.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharged/transferred to an ICF</td>
<td>3 0.6%</td>
<td>2 1.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharged/transferred to an IRF</td>
<td>41 8.4%</td>
<td>19 15.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharged/transferred to LTCH</td>
<td>29 6.0%</td>
<td>19 15.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>221 45.5%</td>
<td>72 59.0%</td>
<td></td>
</tr>
<tr>
<td>Community care</td>
<td>Discharge to home or self care (routine discharge)</td>
<td>195 40.1%</td>
<td>32 26.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discharged to home under care of organized HHSO</td>
<td>70 14.4%</td>
<td>18 14.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>265 54.5%</td>
<td>50 41.0%</td>
<td>.008</td>
</tr>
</tbody>
</table>

HHSO=home health service organization, ICF=intermediate care facility, IRF=inpatient rehabilitation facility, LTCH=long-term care hospital, SNF=skilled nursing facility.

1. 2011–2012 Medicare SAF 100% Sample File.
2. Compares the differences in discharge rates to community care between pVAD and ECMO cohorts.
3. Fisher’s exact tests were applied based on the dichotomous nature of the data.

### TABLE 7
Aggregate 90-day readmission rates by discharge disposition (institutional care vs. community care)

<table>
<thead>
<tr>
<th>90-day readmission</th>
<th>Institutional care (n=293)</th>
<th>Community care (n=315)</th>
<th>Total</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>137 46.8%</td>
<td>123 39.0%</td>
<td>260</td>
<td>.06</td>
</tr>
<tr>
<td>No</td>
<td>156 53.2%</td>
<td>192 61.0%</td>
<td>348</td>
<td></td>
</tr>
</tbody>
</table>

1. 2011–2012 Medicare SAF 100% Sample File.
2. Fisher’s exact tests were applied based on the dichotomous nature of the data.

### APPENDIX A
Top diagnoses present on admission for each treatment cohort

<table>
<thead>
<tr>
<th>Diagnostic code</th>
<th>Diagnosis description</th>
<th>pVAD</th>
<th>ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>41401A,B</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>394 76.2%</td>
<td>59 44.7%</td>
</tr>
<tr>
<td>4280A,B</td>
<td>Congestive heart failure, unspecified</td>
<td>320 61.9%</td>
<td>69 52.3%</td>
</tr>
<tr>
<td>78551A,B</td>
<td>Cardiogenic shock</td>
<td>301 58.2%</td>
<td>55 41.7%</td>
</tr>
<tr>
<td>2724A,B</td>
<td>Other and unspecified hyperlipidemia</td>
<td>228 44.1%</td>
<td>33 25.0%</td>
</tr>
<tr>
<td>4148A,B</td>
<td>Other specified forms of chronic ischemic heart disease</td>
<td>198 38.3%</td>
<td>26 19.7%</td>
</tr>
<tr>
<td>4019A,B</td>
<td>Unspecified essential hypertension</td>
<td>178 34.4%</td>
<td>37 28.0%</td>
</tr>
<tr>
<td>41071A</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>172 33.3%</td>
<td>16 12.1%</td>
</tr>
<tr>
<td>25000A,B</td>
<td>Diabetes mellitus without mention of complication</td>
<td>148 28.6%</td>
<td>25 18.9%</td>
</tr>
<tr>
<td>51881A,B</td>
<td>Acute respiratory failure</td>
<td>129 25.0%</td>
<td>25 18.9%</td>
</tr>
<tr>
<td>42823A</td>
<td>Acute on chronic systolic heart failure</td>
<td>107 20.7%</td>
<td>20 15.2%</td>
</tr>
<tr>
<td>42731B</td>
<td>Atrial fibrillation</td>
<td>98 19.0%</td>
<td>28 21.2%</td>
</tr>
<tr>
<td>4254B</td>
<td>Other primary cardiomyopathies</td>
<td>81 15.7%</td>
<td>23 17.4%</td>
</tr>
</tbody>
</table>

ECMO=extracorporeal membrane oxygenation, pVAD=percutaneous ventricular assist device.

1. 2011–2012 Medicare SAF 100% Sample File.
2. Top 10 diagnosis code POA for the pVAD cohort.
3. Top 10 diagnosis code POA for the ECMO cohort.
### APPENDIX B

#### Top 10 admitting and principal diagnoses for readmissions at 30 days

<table>
<thead>
<tr>
<th>Diagnosis code</th>
<th>Diagnosis description</th>
<th>n</th>
<th>%</th>
<th>Diagnosis code</th>
<th>Diagnosis description</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>78650</td>
<td>Chest pain, unspecified</td>
<td>20</td>
<td>14.9%</td>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>38</td>
<td>28.4%</td>
</tr>
<tr>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>18</td>
<td>13.4%</td>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>14</td>
<td>10.4%</td>
</tr>
<tr>
<td>41091</td>
<td>AMI of unspecified site, initial episode of care</td>
<td>10</td>
<td>7.5%</td>
<td>41041</td>
<td>AMI of other inferior wall, initial episode of care</td>
<td>13</td>
<td>9.7%</td>
</tr>
<tr>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>8</td>
<td>6.0%</td>
<td>41111</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>8</td>
<td>6.0%</td>
</tr>
<tr>
<td>78605</td>
<td>Shortness of breath</td>
<td>7</td>
<td>5.2%</td>
<td>41001</td>
<td>AMI of anterolateral wall, initial episode of care</td>
<td>7</td>
<td>5.2%</td>
</tr>
<tr>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>5</td>
<td>3.7%</td>
<td>41091</td>
<td>AMI of unspecified site, initial episode of care</td>
<td>7</td>
<td>5.2%</td>
</tr>
<tr>
<td>4280</td>
<td>Congestive heart failure, unspecified</td>
<td>5</td>
<td>3.7%</td>
<td>42823</td>
<td>Acute on chronic systolic heart failure</td>
<td>7</td>
<td>5.2%</td>
</tr>
<tr>
<td>41041</td>
<td>AMI of other inferior wall, initial episode of care</td>
<td>4</td>
<td>3.0%</td>
<td>4271</td>
<td>Paroxysmal ventricular tachycardia</td>
<td>5</td>
<td>3.7%</td>
</tr>
<tr>
<td>4271</td>
<td>Paroxysmal ventricular tachycardia</td>
<td>4</td>
<td>3.0%</td>
<td>0389</td>
<td>Unspecified septicemia</td>
<td>3</td>
<td>2.2%</td>
</tr>
<tr>
<td>7802</td>
<td>Syncope and collapse</td>
<td>4</td>
<td>3.0%</td>
<td>41402</td>
<td>Coronary atherosclerosis of autologous vein bypass graft</td>
<td>3</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

**ECMO admitting diagnoses**

<table>
<thead>
<tr>
<th>Diagnosis code</th>
<th>Diagnosis description</th>
<th>n</th>
<th>%</th>
<th>Diagnosis code</th>
<th>Diagnosis description</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>78551</td>
<td>Cardiogenic shock</td>
<td>4</td>
<td>8.9%</td>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>5</td>
<td>11.1%</td>
</tr>
<tr>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>3</td>
<td>6.7%</td>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>5</td>
<td>11.1%</td>
</tr>
<tr>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>2</td>
<td>4.4%</td>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>3</td>
<td>6.7%</td>
</tr>
<tr>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>2</td>
<td>4.4%</td>
<td>42823</td>
<td>Acute on chronic systolic heart failure</td>
<td>3</td>
<td>6.7%</td>
</tr>
<tr>
<td>4240</td>
<td>Mitral valve disorders</td>
<td>2</td>
<td>4.4%</td>
<td>1623</td>
<td>Malignant neoplasm of upper lobe, bronchus or lung</td>
<td>2</td>
<td>4.4%</td>
</tr>
<tr>
<td>4280</td>
<td>Congestive heart failure, unspecified</td>
<td>2</td>
<td>4.4%</td>
<td>99683</td>
<td>Complications of transplanted heart</td>
<td>2</td>
<td>4.4%</td>
</tr>
<tr>
<td>42823</td>
<td>Acute on chronic systolic heart failure</td>
<td>2</td>
<td>4.4%</td>
<td>9971</td>
<td>Cardiac complications, not elsewhere classified</td>
<td>2</td>
<td>4.4%</td>
</tr>
<tr>
<td>78605</td>
<td>Shortness of breath</td>
<td>2</td>
<td>4.4%</td>
<td>0389</td>
<td>Unspecified septicemia</td>
<td>1</td>
<td>2.2%</td>
</tr>
<tr>
<td>78650</td>
<td>Chest pain, unspecified</td>
<td>2</td>
<td>4.4%</td>
<td>40391</td>
<td>Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease</td>
<td>1</td>
<td>2.2%</td>
</tr>
<tr>
<td>99683</td>
<td>Complications of transplanted heart</td>
<td>2</td>
<td>4.4%</td>
<td>41001</td>
<td>AMI of anterolateral wall, initial episode of care</td>
<td>1</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

AMI=acute myocardial infarction, ECMO=extracorporeal membrane oxygenation, pVAD=percutaneous ventricular assist device.

1. 2011–2012 Medicare SAF 100% Sample File.
**APPENDIX C**

Top 10 admitting and principal diagnoses for readmissions at 90 days\(^1\)

<table>
<thead>
<tr>
<th>pVAD admitting diagnoses</th>
<th></th>
<th></th>
<th>pVAD principal diagnoses</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis code</strong></td>
<td><strong>Diagnosis description</strong></td>
<td><strong>n</strong></td>
<td><strong>%</strong></td>
<td><strong>Diagnosis code</strong></td>
<td><strong>Diagnosis description</strong></td>
</tr>
<tr>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>32</td>
<td>16.0%</td>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
</tr>
<tr>
<td>78650</td>
<td>Chest pain, unspecified</td>
<td>27</td>
<td>13.5%</td>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
</tr>
<tr>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>14</td>
<td>7.0%</td>
<td>41041</td>
<td>AMI of other inferior wall, initial episode of care</td>
</tr>
<tr>
<td>41091</td>
<td>AMI of unspecified site, initial episode of care</td>
<td>13</td>
<td>6.5%</td>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
</tr>
<tr>
<td>4280</td>
<td>Congestive heart failure, unspecified</td>
<td>10</td>
<td>5.0%</td>
<td>42823</td>
<td>Acute on chronic systolic heart failure</td>
</tr>
<tr>
<td>78605</td>
<td>Shortness of breath</td>
<td>9</td>
<td>4.5%</td>
<td>41001</td>
<td>AMI of anterolateral wall, initial episode of care</td>
</tr>
<tr>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>7</td>
<td>3.5%</td>
<td>4271</td>
<td>Paroxysmal ventricular tachycardia</td>
</tr>
<tr>
<td>41041</td>
<td>AMI of other inferior wall, initial episode of care</td>
<td>6</td>
<td>3.0%</td>
<td>41091</td>
<td>AMI of unspecified site, initial episode of care</td>
</tr>
<tr>
<td>78659</td>
<td>Other chest pain</td>
<td>6</td>
<td>3.0%</td>
<td>42843</td>
<td>Acute on chronic combined systolic and diastolic heart failure</td>
</tr>
<tr>
<td>41090</td>
<td>AMI of unspecified site, episode of care unspecified</td>
<td>4</td>
<td>2.0%</td>
<td>0389</td>
<td>Unspecified septicemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECMO admitting diagnoses</th>
<th></th>
<th></th>
<th>ECMO principal diagnoses</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis code</strong></td>
<td><strong>Diagnosis description</strong></td>
<td><strong>n</strong></td>
<td><strong>%</strong></td>
<td><strong>Diagnosis code</strong></td>
<td><strong>Diagnosis description</strong></td>
</tr>
<tr>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
<td>5</td>
<td>7.1%</td>
<td>41401</td>
<td>Coronary atherosclerosis of native coronary artery</td>
</tr>
<tr>
<td>78551</td>
<td>Cardiogenic shock</td>
<td>5</td>
<td>7.1%</td>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
</tr>
<tr>
<td>78605</td>
<td>Shortness of breath</td>
<td>5</td>
<td>7.1%</td>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
</tr>
<tr>
<td>41071</td>
<td>Subendocardial infarction, initial episode of care</td>
<td>4</td>
<td>5.7%</td>
<td>42823</td>
<td>Acute on chronic systolic heart failure</td>
</tr>
<tr>
<td>78650</td>
<td>Chest pain, unspecified</td>
<td>4</td>
<td>5.7%</td>
<td>99683</td>
<td>Complications of transplanted heart</td>
</tr>
<tr>
<td>51881</td>
<td>Acute respiratory failure</td>
<td>3</td>
<td>4.3%</td>
<td>1623</td>
<td>Malignant neoplasm of upper lobe, bronchus or lung</td>
</tr>
<tr>
<td>99683</td>
<td>Complications of transplanted heart</td>
<td>3</td>
<td>4.3%</td>
<td>40391</td>
<td>Hypertensive chronic kidney disease, unspecified</td>
</tr>
<tr>
<td>41011</td>
<td>AMI of other anterior wall, initial episode of care</td>
<td>2</td>
<td>2.9%</td>
<td>4148</td>
<td>Other specified forms of chronic ischemic heart disease</td>
</tr>
<tr>
<td>4240</td>
<td>Mitral valve disorders</td>
<td>2</td>
<td>2.9%</td>
<td>4254</td>
<td>Other primary cardiomyopathies</td>
</tr>
<tr>
<td>4280</td>
<td>Congestive heart failure, unspecified</td>
<td>2</td>
<td>2.9%</td>
<td>4928</td>
<td>Other emphysema</td>
</tr>
</tbody>
</table>

AMI=acute myocardial infarction, ECMO=extracorporeal membrane oxygenation, pVAD=percutaneous ventricular assist device.
1. 2011–2012 Medicare SAF 100% Sample File.
New Eye Therapy Takes Aim At Limbal Stem Cell Deficiency

Studies of Holoclar—approved in Europe but not yet in the U.S.—show impressive results and give LSC patients new hope.

Thomas Morrow, MD

ext time you look into a mirror, look closely at one of your eyes. As you look at the clear portion, the cornea, then the white section, the sclera, have you ever wondered why there is such a clear line of demarcation? Have you ever thought about how the cornea, the only organ in your body without a blood supply, keeps itself transparent and healthy for decades?

The limbal stem cell (LSC) is the answer to these questions. The LSCs create a fine line of cells separating the sclera from the cornea. With a little help from the deep basement cells of the cornea (the cells deep within the clear part of the eye), they repopulate the cornea on a continual basis to maintain the health and transparency of the cornea.

About 30 people per million population develop a deficiency of the LSCs for a variety of reasons, including congenital diseases, inflammatory diseases, thermal and chemical burns (in particular alkali injuries), trauma from repeated surgical procedures, and chronic contact lens irritation. When there’s a shortage of LSCs, the barrier between the cornea and conjunctiva is more easily breached, so the white, opaque tissue from the conjunctiva can invade and, in some cases, cover the clear cornea. Symptoms include chronic irritation, photophobia, unstable tear film layer, erosion of the cornea, neovascularization of the cornea, cornea thinning and ulcers, blurring, and even blindness.

Current treatment strategies in the U.S. include removing any source of ongoing trauma, along with a variety of local treatments, such as topical steroids. Transplants of amniotic tissue have been used with varying degrees of success.

Another approach is to transplant LSCs from an unaffected area in the bad eye or from the opposite eye. But LSC transplants have typically required a rather large supply of LSCs, and the eye can be damaged at the donor site.

Some hospitals specializing in diseases of the eye have tried to create a “homebrew” approach to culturing and multiplying donor stem cells and transplanting them, but this approach has been limited to a few hospitals and lacks consistency.

All of this may change soon. Although not yet approved by the FDA, its European equivalent has just approved the first stem cell therapy for limbal stem cell deficiency. The treatment, called Holoclar, consists of a tiny transparent sheet of 300,000 to 1.2 million viable autologous human corneal epithelial cells expanded in cell culture and includes an average of 3.5% LSCs. It comes in a circular transparent sheet of tissue ready for transplantation onto the affected eye.

Thomas Morrow, MD, is chief medical officer of Next IT. He is the immediate past president of the National Association of Managed Care Physicians and has 24 years of managed care experience at the payer or health plan level. The views expressed here are his alone. Contact him at TMorrow@ManagedCareMag.com.
Holoclar replaces the damaged cornea and, according to the European Medicines Agency, “creating a reservoir of LSCs for continuous regeneration of the epithelium.” Holoclar is indicated for use in ocular burns regardless of whether the deep stromal area of the cornea is damaged. If deep stromal injury has occurred, keratoplasty (removal of damaged deep cornea tissue) may be required along with the Holoclar transplant. Holoclar was not approved for use in genetic disorders that result in LSC deficiency.

**Checking for tumorigenesis**

The Holoclar procedure involves taking a very small biopsy from the patient needing the transplant, stimulating proliferation of the cells contained in the biopsy specimen using cell-growth factor, and then preserving the “sheet” of tissue by cooling it to low temperatures so it can be stored and eventually transplanted. People talk a lot about new frontiers in medicine, but limbal stem cell transplantation truly is a breakthrough. One worry with stem cell technology is the tissue may have tumorigenic properties. As a safeguard, Holoclar’s developers tested the chromosomal characteristics of cells in the tissue for stability. Other tests proved that there was no significant immunogenicity, that the cells did not metastasize to other sites in the body, that the cells were not toxic in any sense of the word.

Holoclar was developed by an Italian company, Holostem Terapie Avanzate, a spinoff from the University of Modena. It was studied in 133 people in two studies that were neither randomized nor controlled. Because most of the people studied had limbal stem cell deficiency for many years (87% for more than five years), a pre-post analysis methodology was used to measure endpoints. The two studies differed slightly, but suffice it to say they both included subjects with moderate and severe corneal neovascularization, epithelial defects, corneal opacity of varying degrees, and a potpourri of symptoms. Their vision was poor and limited to counting fingers, detecting hand movements, or perceiving light.

Results were remarkable. Overall “success of transplantation” occurred in 72% of patients and in 92% of those who underwent repeated Holoclar treatment. One year after the procedure, corneal neovascularization changed from a score of “moderate-to-severe” to “moderate-to-none” in roughly 3 in 4 patients and epithelial defects were rated at the “trace or none” level in a large majority (84%).

The effects on vision were a little less impressive. Almost half of those who received the transplant said their vision improved. A subgroup analysis demonstrated a much larger percentage (83%) of those without stromal scarring reported improved vision, a finding that may eventually factor into coverage decisions.

The European regulators concluded that in most patients, Holoclar enabled restoration of a stable, intact corneal epithelium with resolution of epithelial defects and regression of corneal vascularization and absence of “conjunctivalisation”—the migration of cells from the conjunctiva into the cornea that can, in severe cases, lead to blindness. Vision and ocular symptoms also improved, and the chance for subsequent successful keratoplasty in patients with deep stromal scarring increased. The regulators noted that mild-to-moderate adverse drug reactions (ADRs) were common, although many were self-limited and some related to the ancillary topical steroid used after surgery to prevent swelling. Overall, the rate of serious ADRs was low, with only three serious ADRs being judged as related to Holoclar.

**U.S. market likely to be next**

Holoclar is eventually likely to find its way across the Atlantic. It could benefit thousands of Americans who have had corneal and conjunctival damage from burns or trauma.

Holoclar also demonstrates how our Old World colleagues can sometimes be a step ahead of us in the New World in creating Tomorrow’s Medicine! 

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Increasing colon cancer screening could save 200,000 lives by 2030

Increasing the colorectal screening rate to 80% would significantly reduce the incidence and mortality from the disease (http://tinyurl.com/colon-cancer-Outlook) and might even prove to be cost-effective.

In 2013, 58% of Americans in the screening age range of 50 to 75 were screened for colorectal cancer. Less-than-optimal screening rates inspired the National Colorectal Cancer Roundtable to launch the “80% by 2018” campaign. The roundtable, founded by the American Cancer Society and the CDC, is a coalition of about 60 public, private, and voluntary organizations that combat colorectal cancer.

A research team led by Reinier G.S. Meester of the Erasmus University Medical Center in Rotterdam calculated what meeting the 80% screening rate by 2018—and keeping it there—would mean compared with the status quo of a screening rate of about 60%.

Their predictions, reported recently in Cancer, are that incidence would go up initially by 20% because colorectal cancers would be found in Americans who hadn’t been screened. After that, however, it would go down, decreasing by 17% by 2020 and by 22% in 2030.

Their mortality-rate crystal ball shows a 19% decrease in colorectal cancer deaths by 2020 from the “80% by 2018” effort, and an impressive 33% decrease by 2030.

Those percentages translate into 277,000 fewer Americans being diagnosed with colorectal cancer from 2013 to 2020, and 203,000 fewer dying from the disease.

Barriers remain, however. “Underscreened individuals tend to have lower educational levels and income and to lack health insurance,” note Meester and his colleagues.

And, truth be told, the cost-cutting benefits of more screening—which weren’t calculated as part of this study—are somewhat speculative. Neither the potential overuse of screening nor the added expense of pushing screening rates all the way up to 80% have been factored into previous analyses adequately.

However, the increasing number of extremely high-priced cancer drugs may enhance the math that favors screening. As treatment costs go up, the avoided costs increase from cancers that are averted due to screening.

“We know from past studies based on Medicare reimbursement rates that screening can be highly cost-effective, or even cost-saving,” Meester tells Managed Care. “In those studies, prevented treatment costs balance or outweigh the screening costs.”