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Cover Story

Watch Your Step: Don’t Get Trapped by the ACA  22
Unfinished regulations, obscure reform mandates, and unintended consequences should give managed care plans pause as health reform comes into being. Here are five trouble spots to watch out for.

Q&A With Jonathan P. Weiner, DrPH  33
This health data expert heads a new center working to develop useful new health information technology, including improved EHRs.

Nearly Universal HIV Screening Arrives  38
Or does it? Despite the recommendation by the U.S. Preventive Services Task Force there are hurdles.

How an ACO Contract Holds Together  48
Though details will vary depending on the size, experience, and capacities of the providers involved, there are four basic components.

Focus on Biologics

Health Plans Tackle Biomarker Limitations  51
A more pragmatic approach to covering tests.

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open wide. When one is reaching for a metaphor to describe the Affordable Care Act’s effect on health care, that’s a good start, lending itself to an image of a python about to swallow something bigger than its esophagus, or a dentist with instruments of torture.

Insurers should be very concerned, as our cover story by Michael D. Dalzell on page 22 points out. It looks at five ACA trouble spots, but note the sidebar that cites five more that are not quite so dire, but still irksome. Lack of space made us focus on the main problems, and leave many others for later discussion. How many? Hard to say when you’re talking about a monster law that is 907 pages long, with regulations that go on for 70,000 more.

Health care lawyer Kathrin Kudner, displaying a talent for understatement, points out that “it’s not organized in a user-friendly way.”

The ACA reaches into all our lives, and inevitably it reaches into a few corners of this issue. For instance, accountable care organizations (ACOs) are a bulwark of health reform, and insurers need to be careful here, as well. Our story on page 48 explains the four basic elements every ACO contract should contain.

Meanwhile, the U.S. Preventive Services Task Force calls for nearly universal screening for HIV (page 38). It’s a grade A recommendation, meaning that plans must cover the service and patients need not pay anything out of pocket — another ACA provision.

Lest I be accused of being a noodge or even someone with a political ax to grind, let me quickly point out that everybody — and I mean everybody — agreed that something needed to be done to fix the system, and the ACA was a true compromise plan. In the end, the ACA might very well succeed, but not without some discomfort.

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Massachusetts Can No Longer Avoid Making Tough Decisions About Costs
A special panel hopes to push providers toward a global payment system that focuses more on outcomes

By John Carroll

S
even years ago, when Massachusetts passed its big health care reform bill aimed at universal coverage, lawmakers left out one very noticeable element. There was no effort to rein in prices. At the time, a number of industry observers noted that this part of the reform effort — a sure-fire controversy — would have to wait.

Striving for a more universal coverage of its citizens, state officials inevitably started to feel the rising tension brought on by surging insurance premiums. That in turn helped inspire Chapter 224 of the Acts of 2012, “An Act Improving the Quality of Health Care and Reducing Costs Through Increased Transparency, Efficiency and Innovation.”

There are no actual controls put in place to manage health care prices in Chapter 224. Instead, the state is investing more in electronic health records and creating a Health Policy Commission to help shine a light on what insurance companies, Medicare, and Medicaid are paying — and what providers are charging — for services.

If any medical groups or anyone else in the system are found to be hiking prices at a faster rate than the state has targeted, they may find themselves called on the carpet for a public chiding. Then they will be required to put together a plan to tell the state how they will do better.

Consumer protection

If they ultimately fail, and the commission says that rates are rising unreasonably fast, then the HPC can ask the attorney general’s office to step in and consider action to protect consumers.

Just as the state’s 2006 reform legislation helped pave the way to the national reform act put together by the Obama administration, a number of industry executives and policy players say that the state may once again be playing a pioneering role on health care reform. And some of the measures about to be put into place may migrate to other hard-pressed states, regardless of the political persuasion of the state legislature.

“In many ways, the law formalizes the recent period of intense public debate and scrutiny around health care costs, an environment that really pushed the system to make major changes,” says Anna Gosline, director of policy and research at the Blue Cross Blue Shield Foundation of Massachusetts and co-author of an in-depth analysis of the legislation.

The 3.6% solution

Under this new law, state officials can intervene in a proposed health care merger, such as a hospital buyout, if the state determines that the larger enterprise would lead to an uncompetitive situation that would trigger higher costs for consumers. Add it all up, and the state’s position is that it can persuade the health care system to keep costs rising at a modest pace — despite years of annual cost hikes that have significantly exceeded the general inflation rate.

In 2013 and 2014, the state is looking to cap the growth of health care costs at 3.6 percent for each year. By next year and the year after, says Gosline, the state should start to see hard data on how it’s doing. That gives the HPC time to push providers further away from fee-for-service health care — Medicaid and the health plan for state employees are required to push that agenda — toward a new system of alternative payments that focuses more on quality and outcomes.

And accountable care organizations (ACOs) and patient-centered medical homes — widely viewed by reformers as key tools in the push for
cost containment — will have a chance to deepen their roots in the state health care system.

“We’ve seen private payers make huge moves toward permanent change,” Gosline says. Blue Cross Blue Shield of Massachusetts, the dominant insurer in the market, she notes, has already persuaded 86 percent of its specialists and 82 percent of primary care doctors to voluntarily operate under a global payment contract intended to pay for better quality and outcomes instead of volume.

“We agree and insurers agree that when you pay more for doing stuff, what you get is more stuff,” says Harvard University economist David Cutler. “If you pay for more efficient care you get more efficient care.

“One big thing [Chapter 224] does is provide a lot of exposure and transparency for consumers when they can use it,” says Cutler, who helped shape the legislation. By October the state should have a significant amount of quality and price data on hand, helping provide some real transparency in gathering rates.

“How can the industry ever get better if no one knows what it’s doing?” asks Cutler. And insurers have been supportive.

5 years in front

“This is the first step,” notes Lora M. Pelligrini, the CEO of the Massachusetts Association of Health Plans. “Public scrutiny can be very effective in the board room.”

It’s true, Cutler says, that there are no major penalties associated if the system fails to hit the 3.6 percent inflation rate laid out by the new regulations. On the other hand, that’s the key number that now guides all the parties engaged in negotiating rates. Insurers will focus on that figure, as will providers.

“We’re about five years ahead of the rest of the country,” Pelligrini says. But the underlying forces that brought the issue to a head in Massachusetts can only grow in all states. “Costs are going to continue to be an issue, particularly as we recover from the recession.”

The Affordable Care Act will put more pressure on state governments as the country achieves wider health care coverage, and employers and individuals are going to pay close attention to premiums along with all the other health care costs they face.

But now that the Health Policy Committee has begun to do its work, the association wants to help mold the way Chapter 224 will work, she adds. Of particular concern for health plans, is the added incentive the provider groups have to merge as ACOs gain steam.

Under the existing legislation, the HPC can delay any merger while it undertakes a review and the attorney general’s office can be called in to consider opposing it.

But the association wants new legislation that “puts the onus on the attorney general to approve it. One of the problems is that the AG reviews antitrust issues,” says Pelligrini. “Some of these merger issues, though, are not antitrust but anticompetitive.”

The association is concerned that providers could create a few large groups not to be more efficient, but to simply negotiate higher fees from managed care companies, and it wants the AG’s office to be acutely aware of those concerns.

“We have a very aggressive rate review here, with some of the most efficient health plans in the country, with a 90 percent medical loss ratio,” says Pelligrini. “We don’t have high rates because of profits, but because of high costs.”

Cutler says that “It is a very big guide to what other states will think about, and not just blue states. The red states are going to be even more interested. No state government can run a deficit, so you have to do something about health care.”

Many of these states are going to find raising taxes anathema, so using payment reform and transparency efforts to make the market work will be attractive to everyone.

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JUNE 2013 / MANAGED CARE 5
Physician Misdiagnosis Flies Under the Radar

Erroneous diagnosis might be one of the most intransigent problems in health care, but it’s one that gets little attention, according to a study and commentary on the matter. “Health care leaders assume their physicians should be responsible for ensuring reliable diagnoses, but most physicians seem to believe they are doing just fine,” says a commentary in the Sept. 26, 2012 issue of the Journal of the American Medical Association. The authors — Mark L. Graber, MD, Robert M. Wachter, MD, and Christine K. Cassel, MD, MS — argue that misdiagnosis has been overlooked by experts trying to improve quality and safety (http://tinyurl.com/diagnosis-viewpoint).

They point out that in To Err Is Human, the groundbreaking study by the Institute of Medicine, the phrase “medication error” is used 70 times while “diagnostic error” occurs only twice.

“Through malpractice suits, physicians are well aware of diagnostic error, but there is a general tendency to perceive that such errors are made by someone else, someone less careful or skillful,” the viewpoint states.

Nobody appears to be doing much about this, either.

“Moreover, whereas errors such as wrong-site surgery and wrong-dose medication errors seem amenable to systems solutions (time-outs, computerized order entry, etc.), diagnostic errors seem intensely personal: The ‘system’ appears to be the physician, and his or her own knowledge, skills, values, and behaviors.”

Through a chart review, researchers associated with the Houston Veterans Administration Medical Center looked at 190 misdiagnoses related to primary care. The most common were pneumonia (6.7 percent), decompensated congestive heart failure (5.7 percent), acute renal failure (5.3 percent), cancer (primary) (5.3 percent), and urinary tract infection or pyelonephritis (4.8 percent).

The study was published in the online edition of JAMA Internal Medicine (formerly Annals of Internal Medicine) on Feb. 23, and the results were alarming (http://tinyurl.com/Texas-diagnosis). Most of the errors involve some sort of process breakdown or miscommunication between the primary care physician (PCP) and the patient.

“Process breakdowns most frequently involved the patient-practitioner clinical encounter (78.9 percent) but were also related to referrals (19.5 percent), patient-related factors (16.3 percent), follow-up and tracking of diagnostic information (14.7 percent), and performance and interpretation of diagnostic tests (13.7 percent),” says the study, “Types and Origins of Diagnostic Errors in Primary Care Settings.”

Hardeep Singh, MD, MPH, the lead author of the study tells MANAGED CARE, “We are just now uncovering the underlying complexity of the problem, so anything I say today is likely to change down the road.”

He adds, “There are strategies health plans can use now, such as building reliable follow-up and tracking systems, which would be very useful. Because diagnosis evolves over time, I would encourage the clinician executives to explore how they could use their data to measure missed or delayed care especially in ambulatory settings.”

The study says that it is “not surprising that the primary care setting is vulnerable to medical errors.... However, data about the most frequent misdiagnosed conditions are scarce, and little is known about which diagnostic processes are most vulnerable to breakdown.”

The editorial by Graber, Wachter, and Cassel says, “We are unaware of any health care organization that is currently collecting specific data on diagnostic error or engaged in a systemwide campaign to decrease the frequency or consequences of diagnostic error.”

PCMH Creation Boosts Quality

Physician practices being transformed into patient-centered medical homes (PCMH) might be able to do so while improving quality of care for at least two HEDIS measures — blood pressure control over two years and breast cancer screening over three, according to a study in the Journal of General Internal Medicine.

The study looks at quality and efficiency in practices making the transition into PCMHs. The study group included 18 intervention practices with 43 doctors and the control group consisted of 14 practices with 24 doctors.

The best results are seen in intervention practices that were redesigned (for example, those that use electronic health records more effectively) and were staffed with nurse care managers.

Those practices were also put on a revised payment plan that includes pay-for-performance incentives of up to $2.50 per member per month for improvement in clinical quality.

“In a randomized trial, we observed that some indicators of quality and efficiency of care in general adult primary care practices transitioning...
to PCMH status can be significantly, but modestly, improved over two years, although most indicators did not improve and there were no cost savings compared with control practices,” says the study, “Quality and Efficiency in Small Practices Transitioning to Patient Centered Medical Homes: A Randomized Trial.”

“For the most part,” the study adds, “quality and efficiency of care provided in unsupported control practices remained unchanged or worsened during the trial.”

The blood pressure and breast cancer screening indicators are 2 of 11 HEDIS indicators that are measured.

The nurse care managers kept in contact with high users of emergency departments, “which contributed to the significant reduction in ED visits per episode of care among intervention physicians’ patients,” the study states.

However, “Despite these improvements, we did not observe significant cost savings, and ED costs continued to rise over time, even with the significant reduction in visits observed.”

The reduction in ED visits was modest and outweighed by the increase in costs of visits.

**Many Guidelines Skirt Cost Issue**

In an era when, some argue, much of medical management is being shifted toward the provider, a study shows that nearly half of physician professional societies still do not consider costs when developing guidelines.

This comes from a study, “Cost Consideration in the Clinical Guidance Documents of Physician Specialty Societies in the United States,” in the May 6 issue of JAMA Internal Medicine. It cites the Choosing Wisely initiative (which we’ve reported on http://tinyurl.com/Choosing-Campaign) as a possible movement toward greater cost awareness among physician societies. It also reports on stiff resistance to that movement.

“Opponents of explicit cost consideration, however, believe that

### Patients like condensed drug information

Boiling down the complex and often dense (at least to laymen) medical information that’s distributed with prescriptions into one page of easily understood data seems to encourage patient engagement, according to a study by Catalina Health, a health care communications company. The study is the result of an improvement effort by Catalina and the Engelberg Center for Health Care Reform at the Brookings Institute.

Catalina distributed a patient medication information (PMI) form* in August 2012 to about 3,200 patients through Rite Aid stores in California and Michigan for three medications. It then polled by telephone to see how well the one-page format fared.

The form is part of a quality improvement effort by Catalina and the Engelberg Center for Health Care Reform at the Brookings Institute under an agreement with the FDA.

* The form was developed by a workgroup that includes Catalina, the Medical Cognition Laboratory at Duke University, Emory University School of Medicine, the Feinberg School of Medicine at Northwestern University, GlaxoSmitKline, Janssen, Pfizer, Purdue University College of Pharmacy and the Regenstrief Center for Healthcare Effectiveness Research.

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**What respondents did with the written medication information**

<table>
<thead>
<tr>
<th>Read and kept the information</th>
<th>Threw it away after reading it</th>
<th>Kept it but did not read the information yet</th>
<th>Never read it and threw it away</th>
<th>Do not remember</th>
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<tbody>
<tr>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
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<tr>
<td>42%</td>
<td>40%</td>
<td>34%</td>
<td>33%</td>
<td>2%</td>
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**How useful was the information?**

<table>
<thead>
<tr>
<th>Very useful</th>
<th>Somewhat useful</th>
<th>Not very useful</th>
<th>Not useful at all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>68%</td>
<td>63%</td>
<td>26%</td>
<td>30%</td>
</tr>
</tbody>
</table>

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Source: Patient Information Quality Improvement Survey Results, Catalina Health
NEWS & COMMENTARY

physicians should place individual patient needs ahead of societal needs, regardless of cost,” the study states. “Critics fear that the introduction of costs into clinical decision making at any level will ultimately lead to bedside rationing and cause a rift in the physician-patient relationship that will foster public mistrust of the medical community.”

The study’s authors looked at clinical guidelines for 30 specialty societies and found that 17 explicitly include cost in the discussion.

While nine of the societies use a system in which cost influences the strength of the recommendation, eight are “inconsistent in their approach or failed to mention the exact mechanism for considering costs.”

The authors offer the societies some advice. “In our analysis, the most common way to use cost in justifying a recommendation was to state that an intervention was recommended because it was as effective as other options but less costly.”

In an accompanying editorial, Joseph P. Drozda Jr., MD, sees hope that more attention will be paid to costs.

“It is safe to say that these societies will continue to address the appropriate use of medical interventions in their clinical guidance documents,” writes Drozda.

“It is probably also safe to say that the growing trend of formally addressing costs in guidance documents will continue as well.”

Savvy Patients Could Drive Costs Up

The renewed hope that shared decision making might finally fulfill its promise and lower costs (see our April cover story http://tinyurl.com/Burns-shared) just hit some static. Patients who participate in their medical decisions spend more time in the hospital (0.26 of a day) and raise the cost of their stay by an average of $865, according to a study in JAMA Internal Medicine.

Researchers at the University of Chicago surveyed about 21,750 patients at the university’s medical center between July 1, 2003 and August 31, 2011. Ninety-six percent of the patients wanted more information about their treatment, while about 29 percent expressed a strong preference for shared decision making.

The authors say, “This contrasts with the expectation that patient participation in care decisions might decrease costs and suggests that it is important to evaluate efforts to increase patient engagement in decision making with respect to their effects on outcomes and costs.”

The study, “Association of Patient Preferences for Participation in Decision Making With Length of Stay and Costs Among Hospitalized Patients,” extrapolates the costs.

The authors say that “when multiplied by the approximately 35 million annual hospitalizations in the United States, the 28.9 percent of patients who somewhat or definitely disagreed with delegating decisions to their physician would represent about 10 million hospitalizations, for which an additional 0.26 day and $865 per hospitalization would total 2.6 million hospital days and about $8.7 billion in costs.”

Another red flag: The authors say that older patients, people with government sponsored insurance, and African Americans are less inclined to participate in care decisions.

“This could cause efforts to make physicians more responsive to medical decision preferences to increase health disparities by having little effect on utilization for these less empowered groups while increasing utilization among more empowered groups, who are already more likely to receive medical care.”

One of the study’s authors, David Meltzer, MD, says, “Patients who want to be more involved do not have lower costs. Patients, as consumers, may value elements of care that the health care system might not.”

Briefly Noted

Last year, for the first time in over 50 years, America spent less on health care than it had in the previous year, according to a study by the IMS Institute of Healthcare Informatics. The price tag was still hefty — $325.8 billion — but it was 1 percent below 2011. Per capita, we spent $898, down $33 from 2011. Experts cite the expirations of patents for such blockbuster drugs as Lipitor and Zyprexa.... Wellness programs take a hit in a new Rand report, Reuters is reporting. Such programs have only modest success, according to the report, which collected data from about 600 employers with at least 50 workers. Al Lewis, founder of the Disease Management Purchasing Consortium, tells Reuters that the most motivated employees tend to sign up, making it impossible to gauge success. Lewis was more blunt when he talked to Managed Care in March, describing the wellness industry as made up..... Testicular cancer rates are on the rise, with the increase seen mostly among Hispanic men, according to new research. The information comes from a national epidemiology database. Researchers tracked testicular cancer rates from 1992 through 2009. The incidence of testicular cancer appears to be increasing very slowly but steadily among virtually all groups that were studied, Scott Eggener, MD, an associate professor of surgery at the University of Chicago tells HealthDay News. “The novel finding is that the most dramatic increase is in Hispanic men.” He does not know why that is.... Black and Hispanic women diagnosed with breast cancer are likely to wait longer to get treatment than white women, according to researchers at the University of California–Irvine. They can’t really say why it happens, as is also true for numerous other studies pointing to disparities in treatment along racial and/or ethnic lines. Researchers analyzed the records of 8,860 women age 15 to 39 who were diagnosed with breast cancer between 1997 and 2006. Eight percent of white women waited six weeks before getting treatment; 15 percent of black and Hispanic women waited the same amount of time.

— Frank Diamond
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A1C Reductions vs Sitagliptin

INVOKANATM 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (P < 0.05)

Difference from sitagliptin†: –0.37%

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
100 mg: 3.6%; 300 mg: 3.0%; placebo: 2.6%

With metformin and a sulfonylurea over 52 weeks:
INVOKANATM 300 mg: 43.2%; sitagliptin 100 mg: 40.7%

Difference from placebo†: –0.3%

Convenient Once-Daily Dosing

Recommended starting dose: INVOKANA™ 100 mg

Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥ 60 mL/min/1.73 m² and require additional glycemic control

The most common (≥ 5%) adverse reactions were:

- Female genital mycotic infection
- Urinary tract infection
- Increased urination


Learn more at INVOKANAhcp.com/journal
IMPORTANT SAFETY INFORMATION (continued from first page)

DRUG INTERACTIONS

**UGT Enzymes: Inducers**: Canagliflozin may decrease the exposure to canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, and UGT2B7, by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital) is started, some form of glucokinase should be considered increasing the dose to 300 mg once daily if patients are currently receiving INVOKANA™ 300 mg once daily, have an AUC greater than 60-fold/μM/mL, and require additional glucokinase control. Consider using a glucokinase inhibitor in patients with an AUC of 40 or less to 60-fold/μM/mL receiving concurrent therapy with a UGT inducer and requiring additional glucokinase control.

**Dose Ratio**: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin 200% and 30%, respectively, when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

**Pregnancy Category C**: There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at 20.3 times clinical exposure from a 1000 mg dose. These outcomes occurred with drug exposure during periods of normal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues**: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.

**Diabetes**: Diabetic ketoacidosis (DKA) has been reported in patients with type 2 diabetes. Although no cases of DKA were reported in clinical trials, DKA should always be considered in the differential diagnosis of any patient with ketoacidosis treated with INVOKANA™. DKA may be more likely to develop in patients with other metabolic or endocrine abnormalities, and in patients with coronary artery disease or heart failure.

**Hepatic Impairment**: Canagliflozin is secreted in the human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

**Overdosage**: There was no reports of overdose during the clinical development program of INVOKANA™. In an event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin is negligibly removed during 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**ADVERSE REACTIONS**

**Most Common (25%) Adverse Reactions**: Genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥10% of patients were: male genital mycotic infections, vulvovaginal pruritus, throat, nausea, and constipation.

**Summary of Full Prescribing Information**: See also Boxed Warning and Contraindications. See prescribing information for INVOKANA™ tablets.
WARNINGS and PRECAUTIONS

Immunologic Tests: INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hyperkalemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².

Hyperkalemia: INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.

Genital Mycotic Infections: INVOKANA™ increases the risk of genitourinary infections. Patients with a history of genitourinary infections and uncontrolled males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment. These reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™, treat per standard of care and monitor until signs and symptoms resolve.

Increased in Low-Density Lipoprotein (LDL-C): Discontinued increases in LDL-C occur with INVOKANA™ treatment. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antihyperglycemic drug. Clinical studies establishing conclusive evidence of microvascular risk reduction have been established.

Hyperkalemia: More frequent monitoring of renal function is recommended in patients with an eGFR below 60 mL/min/1.73 m².

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antihyperglycemic drug.

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Increased in Low-Density Lipoprotein (LDL-C): Discontinued increases in LDL-C occur with INVOKOKANA™ treatment. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antihyperglycemic drug.

Drug Interactions: INVOKANA™ co-administration with canagliflozin, a nonselective inhibitor of several UGT enzymes, including UGT1A9, UGT2B7, decreased canagliflozin area under the curve (AUC) by 15%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60mL/min/1.73 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 40 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

Drug Interactions: INVOKANA™ was used in the development of the drug as in vivo and in vitro methods. The efficacy and safety of INVOKANA™ have not been established in pediatric patients under 18 years of age. The most common (≥5%) adverse reactions were female genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation. Please see Brief Summary of full Prescribing Information on the following pages.

Hyperkalemia: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin). In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient’s clinical status. Canagliflozin is negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥5% of patients were: male genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.
These data reflect 26-week placebo-controlled trials. In one trial INVOKANA was used as trial. The data reflect exposure of 1987 patients to INVOKANA and a mean duration of exposure to

**CONTRAINDICATIONS**

- Hypersensitivity: INVOKANA causes intravascular volume contraction. Symptoms indicative of hypovolemia can occur after initiating INVOKANA (see Warnings and Precautions). Therefore, a lower dose of insulin or insulin secretagogues may be required to maintain the rate of insulin injections with INVOKANA.

- Hypertension: INVOKANA can lead to hypokalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium secretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia (see Warnings and Precautions).

- Use of Concomitant Use with Insulin and Insulin Secretagogues: Use of INVOKANA with insulin or insulin secretagogues is known to cause hypoglycemia.

**INDICATIONS AND USAGE**

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are intolerant to or unable to achieve adequate glycemic control with a sulfonylurea, a thiazolidinedione, or metformin and pioglitazone.

**ADVERSE REACTIONS**

The types and frequency of common adverse reactions observed in the clinical trials are included in Table 1.

**Drug Interactions**

Drugs that interfere with the renin-angiotensin-aldosterone system and other antihypertensive (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or patients with low systolic blood pressure). Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

In a Renal Function: INVOKANA increases serum creatinine and decreases GFR. Patients with moderate renal impairment who are taking medications that interfere with potassium secretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Continue INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hyperglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Hyperglycemia with concomitant use with insulin or insulin secretagogues may be required to maintain the rate of insulin injections with INVOKANA.

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Hyperglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Hyperglycemia with concomitant use with insulin or insulin secretagogues may be required to maintain the rate of insulin injections with INVOKANA. Continue INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m², the mean baseline eGFR of 30 to less than 50 mL/min/1.73 m² (mean baseline eGFR 38 mL/min/1.73 m²) [see Clinical Studies (74) in full Prescribing Information], episodes of hypoglycemia were detected in 3.1%, 3.3%, and 3.4% of patients treated with placebo, 100 mg with INVOKANA 100 mg, and 3.3% with INVOKANA 300 mg, respectively. In the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 0.9% with INVOKANA 100 mg, and 8.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse reactions were 0.5%, 1.4%, and 2.7% for placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. 18/76 patients (23.1%) on INVOKANA (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event with a low glucose value was obtained). In individual clinical trials, severe hypoglycemia was defined as an event (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was detected in 3.1%, 3.3%, and 3.4% of patients treated with placebo, 100 mg with INVOKANA 100 mg, and 3.3% with INVOKANA 300 mg, respectively. In the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

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† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was observed).

Laboratory Tests: Increases in Serum Potassium-Dose-related, transient Increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 2 weeks) in a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information) in this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 11%, 14%, and 21% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. More severe elevations i.e., greater than or equal to 6.5 mEq/L occurred in 1%, 2%, and 5% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. In patients with moderate renal impairment, increases in potassium were more common in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers (see Warnings and Precautions).

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo-controlled trials, the mean change in serum phosphate levels were 0.3%, 0.7%, and 1.3% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), the mean serum phosphate levels increased by 1.2%, 3.0%, and 3.9% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. The mean baseline phosphate levels were 4.5 mg/dL (N=115), serum phosphate levels increased by 26.0 mg/dL (N=113), and 23.2 mg/dL (N=566) with placebos and with metformin + pioglitazone, and metformin + pioglitazone + canagliflozin (N=279). Patients 65 years and older had a higher incidence of adverse reactions compared to younger patients; more prominent increase in the incidence was seen in patients with moderate renal impairment, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers (see Warnings and Precautions).

Increases in Inhoneophyptid Cholestrol: Non-high-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, the mean change in serum non-HDL-C levels was greater than 4.0 mg/dL at week 26, compared to 4.8% with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), mean serum non-HDL-C levels increased by 12.6%, 14.0%, and 16.1% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively, compared to 6.9% with placebo. Increases in non-HDL-C levels occurred in 30%, 38%, and 47% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in non-high-density lipoprotein cholesterol (non-HDL-C) were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum non-HDL-C levels was greater than 2.0 mg/dL at week 26, compared to 4.8% with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), the mean serum non-HDL-C increased by 12.6%, 14.0%, and 16.1% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. More severe elevations i.e., greater than or equal to 6.5 mg/dL occurred in 1%, 2%, and 5% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. In patients with moderate renal impairment, increases in non-HDL-C were more common in those with elevated non-HDL-C at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers (see Warnings and Precautions).

Quantitative increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively.

Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C of normal.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C) are increased in patients with severe hepatic impairment and is therefore not recommended (see Clinical Pharmacology (12.3) in full Prescribing Information).

Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. More severe elevations i.e., greater than or equal to 6.5 mg/dL occurred in 1%, 2%, and 5% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. In patients with moderate renal impairment, increases in LDL-C were more common in those with elevated LDL-C at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers (see Warnings and Precautions).

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was greater than 1.0 mg/dL at week 26, compared to 4.6 mg/dL with placebo. In a trial of patients with moderate renal impairment (see Clinical Studies (14.2) in full Prescribing Information), serum mean magnesium levels increased by 0.1%, 2.6%, and 7.4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively.
INVOKANA™ (canagliflozin) tablets

OVERDOSE
There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Instruct female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms [see Warnings and Precautions]. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice [see Warnings and Precautions].

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [see Warnings and Precautions].

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium
Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778
Manufactured for:
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Titusville, NJ 08560
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- Eliquis® (apixaban) tablets
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- INVOKANA™ (canagliflozin)
- JAKAFI® (ruxolitinib) tablets
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- LINZESS™ (linaclotide) capsules 145 mcg - 290 mcg
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- PREVNR® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
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- RAVICTI™ (glycerol phenylbutyrate)
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- Teflaro® (ceftaroline fosamil) for injection 600 mg · 400 mg

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The bacterium Clostridium difficile (C. difficile) causes antibiotic-associated diarrhea, colitis, other serious intestinal conditions, and death in severe cases. C. difficile infection (CDI) occurs most often in individuals who have had one or more antibiotic courses, which can suppress normal colonic microbiota. This allows C. difficile to proliferate and release toxins that inflame and damage the gastrointestinal (GI) tract mucosa.

In the past decade, CDI incidence and severity have increased significantly in health care settings; more than 500,000 cases are reported each year. A 2012 Weekly Morbidity and Mortality Report from the U.S. Centers for Disease Control & Prevention reported that “the incidence, mortality, and medical care costs of CDIs have reached historic highs.” When CDI is confirmed, physicians typically discontinue treatment with the inciting antibiotic and prescribe oral metronidazole for mild or moderate CDI, or oral vancomycin for severe CDI. Yet, up to 35% of patients have a CDI recurrence within two months after therapy.

The first recurrence is typically treated with the same regimen as the initial episode, or with a relatively new antibiotic, fidaxomicin (Dificid). To treat a second recurrence, physicians often use tapered or pulsed doses of vancomycin; however, up to 65% of patients develop a third recurrence after this therapy. These recurrences are costly to treat and place patients at risk for serious morbidity and sometimes mortality.

Transplantation

Fecal microbiota transplantation (FMT) involves using one of several methods to introduce saline-diluted fecal matter from a healthy donor into the patient’s GI tract to recolonize the colon with healthy bacteria. Potential benefits of FMT include lower cost than several courses of antibiotics and hospitalization; faster treatment and resolution than achieved with several weeks of antibiotics; mild to no side effects; and reduced risk of antibiotic-associated resistance.

Gastroenterologists using this treatment typically recommend that donors be healthy family members or spouses/significant partners who have common genetic and/or environmental factors. To ensure a donor is healthy, clinicians prescreen them through interviews and laboratory testing before obtaining stool for transfer. Published reports describe different methods of preparing donated stool; however, the FMT Workgroup recently published a standard protocol for donor stool preparation.

The gastroenterologist can accomplish FMT using a nasogastric tube, a nasoduodenal/jejunal tube, an upper tract endoscope, a colonoscope, a retention enema, or combined upper and lower approaches. The procedure takes 5 to 25 minutes. The scarce reported cost data range from a few hundred to several thousand dollars per procedure, depending on the FMT preparation and administration method.

Treatment success is typically defined by symptom resolution without relapse within eight weeks of FMT. Regular checkups for CDI are required up to a year after FMT.

Key questions and findings

1. Does FMT for recurrent or relapsing CDI result in short-term and long-term CDI resolution?

Evidence from seven case series that reported
short-term (≤3 month follow-up) data on 190 patients indicates that FMT results in high rates of CDI resolution (72.5% to 100%). There is evidence from three of these case series that suggests some patients not responding to FMT initially benefit from a second FMT.

Evidence from six case series that reported longer term data (>3 month follow-up) on 201 patients indicates that FMT results in high rates of CDI resolution (76.8% to 100%).

2. How does the efficacy of FMT compare to other treatments for recurrent and relapsing CDI (i.e., various vancomycin regimens, metronidazole, fidaxomycin, pooled intravenous immunoglobulin, monoclonal antibodies)?

One randomized controlled trial (RCT) (known as the FECAL trial) was halted early because of superior efficacy after an interim analysis found FMT to be significantly more effective than vancomycin alone or vancomycin plus bowel lavage. Most FMT patients (81.3%) had CDI resolution after a single FMT; 93.8% achieved resolution with a second FMT.

In contrast, only 30.8% of the vancomycin group and 23.1% of the vancomycin plus bowel lavage group had CDI resolution (p <0.001 for between group comparisons with FMT group).

3. What adverse events (AEs) have been reported in studies of FMT and how do AEs from FMT compare to AEs from antibiotic therapy?

In studies, FMT was generally well-tolerated. Eight of the nine FMT case series that assessed AEs reported that no AEs occurred among 290 study patients. The remaining study (43 patients) found that about one-third of patients noted irregular bowel movements and excessive flatulence the first two weeks after the procedure.

In the RCT (FECAL trial), patients reported very short-term symptoms (resolved within three to 24 hours of FMT): diarrhea in most patients, abdominal cramps in about a third of patients, and belching in a few patients.

FMT diffusion has been tempered by the U.S. Food and Drug Administration’s (FDA) announcement in May 2013 that FMT must be treated as a drug or biologic requiring clinicians to submit an Investigational New Drug (IND) application to perform the procedure. ECRI Institute identified about 42 institutions in the United States, Europe, and Canada that offered the procedure as of January 2013, some as part of ongoing clinical trials and some on an exceptional case basis.

Physicians performing FMT have reported that patients with recurrent CDI are receptive to FMT because they are very ill with poor quality of life. Health care facilities offering FMT would need to create dedicated laboratory facilities to test and safely process donor stool and facilitate safe administration to patients. Centers also should provide patient counseling.

Excerpted with permission from ECRI Institute’s database of Emerging Technology Evidence Reports. To download the full report, visit www.ecri.org/managedcare.

For inquiries about this report or membership in ECRI Institute’s Health Technology Assessment Information Service, e-mail htais@ecri.org.
Express Scripts, the mega PBM, reports that the 2012 drug trend for traditional medications declined in 7 of the top 10 traditional classes. In part that decline stems from patent expirations for blockbuster medications like Lipitor and a rising generic fill rate.

Diabetes medications are a top 10 class and they enjoy a unique position vis-à-vis the other top 10 drug classes. They didn’t lead costs downward; instead they bucked the trend with a huge expenditure increase. Expenditures for antidiabetic agents increased by 11 percent. Utilization increased by 1.5 percent and prices by 9.5 percent.

Antidiabetic agents are a complicated treatment category for health plans and PBMs. There are new combination medications, diabetes is a high priority disease, and there is an intense focus on improving adherence, all of which drive up costs.

Health plans have been unable to control the cost of antidiabetes. Drug manufacturers exploit the importance of these medications with price increases. In most cases, health plans and PBMs are required to provide easy access to the medications and support concerted efforts to improve adherence.

Other contributing factors to skyrocketing costs include volume shifts in different subclasses of agents, a trend toward extended release variants, the introduction of new combination agents, and, most significantly, the use of pens for altered insulins.

While health plans and PBMs need to focus on controlling costs, poor adherence and glycemic control remain a huge problem. That places them in the difficult position of trying to hold down expenditures while simultaneously improving outcomes. The availability of new medications and new ways of administering insulin may lead to better glycemic control that may in turn hold down downstream costs associated with the complications from disease progression.

**Pens**

Insulin pens are the primary driver of increased expenditures in diabetes. These compact preloaded injectors are much simpler to use than vials and syringes.

From 2009 through 2012, the total volume of diabetes prescriptions increased by 4.6 percent while the number of prescriptions for insulin pens grew by 23.2 percent, according to projections based on data from IMS Health.

In the same period, total expenditures for insulin pens increased by 129 percent, from $1.7 billion to $3.9 billion.

For insulin as a subclass, the volume trend has been an increase in long-acting and rapid-acting analogs over human insulins and the use of pens over vials. The most popular long-acting insulin — Lantus Solostar — grew by 143 per-

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**Though Costly, Insulin Pens Facilitate Better Adherence**

Studies suggest that U.S. physicians are hesitant to put patients on insulin therapy, but these pens may offer value by improving control

By Thomas Reinke

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**Adults with diabetes receiving treatment with insulin or other therapies, United States, 2007–2009**

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes, no medication</td>
<td>16%</td>
</tr>
<tr>
<td>Insulin only</td>
<td>12%</td>
</tr>
<tr>
<td>Insulin and other medications</td>
<td>14%</td>
</tr>
<tr>
<td>Oral medication only</td>
<td>58%</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention

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cent from 2009 through 2012, going from 3.3 million to 8 million prescriptions. Expenditures increased from $700 million to $2.1 billion. The average cost of a 30-day prescription was $273 in 2012.

The two most popular rapid-acting pens — Novolog Flexpen and Humalog Kwikpen — grew 139 percent from 2.3 million to 5.4 million prescriptions. Total expenditures increased from $600 million to $1.7 billion.

“We looked at the use of pens in patients over 18 years old, and found that about two thirds of the insulin prescriptions we fill across our company are for insulin pens,” says Debbie Hiller of Kerr Drug, a North Carolina pharmacy chain. Hiller manages Kerr’s diabetes programs.

“New starts on insulin generally prefer pens over vials and syringes, while long time insulin patients may choose to stay with the vials — it’s sort of a ‘don’t fix what isn’t broken’ philosophy for them,” says Hiller.

Diabetes is an important business line for retail pharmacies that see many revenue opportunities in diabetes, such as glucose meter sales and front-of-store sales when patients come in to pick up their prescriptions. Some retail pharmacies offer formal diabetes education classes which are paid for by Medicare and occasionally by private payers.

Cost vs. control

There is little that health plans and PBMs can do to control diabetes costs. “Diabetes is a priority, and health plans have to provide access to the medicines,” says F. Randy Vogenberg, RPh, PhD, an industry consultant. “There isn’t much opportunity to control costs through tiering or utilization management. Health plans are trying to assure their customers that they are negotiating costs. They are playing the manufacturers against each other for the best contract price and higher rebates.”

The latest drug benefit report from the Pharmacy Benefit Management Institute, voice of the pharmacy benefit management industry, says that pharmacy benefit plan sponsors are controlling their costs by reducing the use of copayment waivers for antidiabetics, stemming from questions about the value of reducing copayments. PBMI says several studies have challenged the assumption that copayment waivers increase medication adherence or contain overall health care costs.

In other situations where health plans found it difficult to control expenditures, they switched their attention to providing value through other means, such as limiting downstream costs or improving outcomes.

Delayed insulin use

“There are some data that patients have elevated HbA1c levels for 1 to 5 years before they get started on insulin. But to the extent that a patient moves to insulin when they need it, that’s better health care delivery,” says Robert Ratner, MD, chief scientific and medical officer at the American Diabetes Association.

A major reason for the delay, Ratner says, is a lack of time and resources in physicians’ offices to teach patients about all of the techniques involved with the use insulin vials and syringes. He says pens allow physicians an easier way to start patients on insulin.

The Diabetes Attitudes, Wishes, and Needs (DAWN) study found both provider and patient barriers to timely initiation of insulin therapy. The multinational study found that U.S. physicians and nurses were more likely to delay starting insulin therapy than providers in most other countries. The resistance to insulin therapy among doctors stemmed from a concern that insulin would not improve glucose control.

Ratner says insulin pens can improve self-management. “Everyone says pens are simpler to use than vials and syringes, but I hate that comment. Pens go far beyond that: They help patients take their medicine regularly.”

He says pens improve accurate dosing and increase patients’ confidence in injecting themselves.

“If you’re dialing a pen to the appropriate dose, you have much better accuracy and reproducibility each day compared to a vial and syringe. There’s simply no way that patients can draw up a dose as accurately with a vial.”

The bottom line for health plans and PBMs is that they need to continue to demonstrate value by managing costs, and in diabetes, consider promoting timely switching to insulin therapy plus ways to improve patient education in self-management.
5 Trouble Spots You Could Face In Implementing the ACA

With the Affordable Care Act taking effect in just six months, unfinished regulations, obscure reform mandates, and unintended consequences create a potential minefield for payers.

By Michael D. Dalzell
Senior Contributing Editor

Ask people “What’s the most incomprehensible thing you’ve ever read?” and you’ll get a lot of different answers. *Finnegan’s Wake.* Your bundled phone-and-cable bill. Anything by Eckhart Tolle.

Craig Garner, a Santa Monica, Calif.-based lawyer and health care consultant, has a favorite: “It’s 907 pages long, with 70,000 pages of regulations — and it’s not done!” That would be Public Law 111–148, aka the Patient Protection and Affordable Care Act. Dwarving our Constitution by 66 million words, the ACA “is a complicated law, and it’s not organized in a user-friendly way,” says Kathrin Kudner, member of the health care practice at Dykema. She is based in the firm’s Ann Arbor, Mich., office.

Now that just six months remain before the bulk of the ACA is implemented, clarity becomes more critical with each passing day. And yet the law’s complexities, obscure provisions, and unwritten regulations are rife with unintended consequences and create ambiguity for payers about how to move forward.

Missteps can be costly. Here are five areas to watch for trouble:

1. **WHY HEALTH PLAN ACTUARIES CAN’T SLEEP**

   Cost uncertainties top everyone’s list of ACA worries. In a system dependent on widespread participation, one X factor is how many people will disregard the individual mandate. “In the commercial market, 3 or 4 percent of the population accounts for two thirds of the cost,” says Bill Copeland, national industry leader of Deloitte’s Life Sciences and Health Care Practice. “If we don’t get everyone to sign up, costs are going to be a lot higher than what everyone projects.”

   The Congressional Budget Office expects more than 4 million people to forgo health insurance and pay the penalty for violating the individual mandate. The effect of age rating, which is expected to make coverage costlier for the young, prompted America’s Health Insurance Plans to warn that many more young healthy adults will look at the price — and pass. Moreover, 78 percent of uninsured Americans who qualify for commercial subsidies or expanded Medicaid coverage don’t know it, according to White House polling, and states like Florida and Texas that have stiff-armed health care reform are doing little to encourage participation.

   Add in the fact that a survey by HealthPocket.com in March found that only 2 percent of plans available to consumers today cover the ACA’s essential health benefits — and payers have an expensive ramp-up coming to comply with minimum essential coverage.

   “Payers have to be worried about how to price the benefit packages correctly,” says Kudner.

   It’s hard to price the unknown, but experience in Massachusetts may be instructive. A weak individual mandate and guaranteed-issue encourage people to take and drop coverage as their needs change. Caps on premium increases caused a Massachusetts Division of Insurance official in 2010 to rail about a possible train wreck if nothing is done in parallel to address health care costs. Today,
Massachusetts struggles with per-capita costs 15 percent above the national average.

The ACA inches toward cost containment through Medicare payment reforms, and the Centers for Medicare & Medicaid Services hopes the commercial market will follow its lead. Medical loss ratios present a barrier, however, says Mark Lutes, a lawyer in the health care and life sciences practice at Epstein Becker Green, in Washington. "Designing payment reforms involves administrative costs, which plans have to watch. There’s no incentive for them to do it."

Blue Cross Blue Shield of North Carolina President Brad Wilson told a group of brokers in March that he wouldn’t be surprised to see premium hikes of 50 percent for 2014. Copeland thinks increases could be even higher in some states, owing to the elimination of exclusions and limitations and the addition of actuarial value requirements. “Individual and small group products today, by and large, pay out about 50 percent of actuarial value,” he says. Raising them to 60 percent — bronze level — and higher drives costs, with implications for take-up.

PROVIDER INFO TECH STUCK IN 20TH CENTURY

In many ways, it’s a corollary of the cost problem: How to manage the risk associated with members entering the system with fragmented or no claims histories. Guaranteed issue can lead to adverse selection, so the ACA builds in risk-adjustment provisions. But health plans could be leaving risk-adjustment money on the table if their providers’ electronic health record (EHR) capabilities are subpar.

The historical difficulty of EHR systems not talking to one another stems, in part, from the design of each provider’s EHR being unique. “When you try to extract data from those EHRs, you quickly find it’s difficult to do at the population level,” says Michael Gleeson, senior vice president for product strategy at Arcadia Solutions in Burlington, Mass. “It requires a certain amount of remediation to make sure there are standards across the board for how care is delivered.”

That has obvious implications for accountable care organizations (ACOs), but for health plans, the concerns are similar. "If you have access to EHR information, you can affect the delivery of care,” says Gleeson. “There are not many more ways to look at claims data, but if you can integrate clinical data, you get a more accurate picture of each of those patients.”

Health plans have the information technology experience to help providers manage populations effectively. Engaging providers can pay for itself almost immediately, Gleeson says, by improving risk-adjustment premiums — “which is not only beneficial to Medicare Advantage plans, but also to commercial plans that operate in the new exchanges, where each plan’s premium will be adjusted for risk.

There’s also an opportunity to shave administrative costs, he adds, because electronic access to clinical data eliminates the need for chart audits.

Providers that don’t adopt technology to drive cost-efficient care may find themselves marginalized. “Some bigger self-insured companies are going to need to take matters into their own hands because they spend a significant amount on health care. You’ll start to see those organizations provide tiered networks of providers,” Gleeson predicts. Preferred providers, he says, will show they are clinically integrated and capable of measuring the quality of their care.

Be forewarned, however: Forced EHR compliance can alter market dynamics. “Arguably, that has put a lot of cost on individual and small group providers, pushing them into the arms of larger groups and hospital systems. That creates concentration in markets that didn’t previously exist,” says Lutes.

EXCHANGES STILL WORKS IN PROGRESS

Whether the exchanges will operate effectively on October 1 is an open question. “Will they be able to handle the volume, answer people’s questions, give the data properly to health plans?” asks Copeland at Deloitte. “Will they be able to handle the flow of money, subsidies, all of the complications around

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rules of eligibility, including all of the Medicaid eligibility laws? It couldn’t be more complex.”

Eligibility determinations require input from multiple agencies, including Social Security, Homeland Security, the Treasury, the Internal Revenue Service (IRS), CMS, and state agencies. The feds are still working out the bugs.

Technical challenges aside, “What are the rules?” asks Copeland. “We [Deloitte] are constantly finding nuances, either in the work we do with states to build their exchanges or the work we do with health plans in building their readiness to work through the exchanges.”

Uncertainty over who will run some exchanges creates opportunity for missteps. “In our state [Michigan], we did not know for a long time what kind of exchange would be implemented,” says Kudner, at Dykema. “Plans had to make decisions based on assumptions and without a great deal of knowledge about what the exchange would look like and what requirements would be imposed.”

State-run exchanges still can impose requirements in addition to the statutory requirements, though not all have outlined what those additional obligations may be. Lack of clarity about competitive standards is particularly vexing.

“Plans are going to have to balance participation in the exchange with their Medicare Advantage, Medicaid, and commercial business outside the exchange,” says Kudner. “States have the option of...”
limiting plan access to the exchange. So if you’re a small plan, there has to be some concern about being excluded and what that means for business.”

Competitive balance is a multifaceted concern. Regulating the small-group market “creates a less attractive market to insure from the payer’s perspective,” says Lutes at Epstein Becker Green, a national law firm. “Therefore, you’ll have everyone gravitating toward self-funding as far down as possible. That changes the ability to create a small-group marketplace balance between exchange and non-exchange products.”

The District of Columbia Health Benefits Exchange Authority has taken a controversial approach to this issue. Worried that it won’t have the critical mass it needs to encourage competition within its exchange, the D.C. board proposed that all individual and small-group market plans sold in D.C. go through the exchange. Unhappy small businesses have taken their concerns to the D.C. City Council, which has the last word.

On the positive side, the exchanges present an opportunity to cultivate a vibrant individual market. “We don’t truly understand the individual market today,” says Copeland, noting that the health insurance industry is built on employer-focused products. “What makes an employer buy things and what drives an individual to buy things are completely different.”

Smart exchanges, he says, will create a feedback loop that collects information on what customers value so that plans can learn about individual buying behavior and what engages members in their health care.

“All of those things feed back into the system and should make it work a lot better. At some point we’re going to see health plans focus on the employer side or the individual side, [creating] a divergence in what heath care financing really looks like.”

IS MEDICAID AN OPPORTUNITY OR A ‘GOTCHA’?

Democratic Arkansas Gov. Mike Beebe’s strategy for persuading a Republican legislature to accept Medicaid expansion hinged on a waiver allowing Medicaid beneficiaries to shop in the exchanges. Lutes thinks this and other recent waivers amount to the first steps in turning Medicaid into a block grant program, which may be an opportunity for Medicaid plans.

“It could mean a lot more resources get poured into the process of working with state programs, rather than plans merely taking a capitation and delivering services,” he says. In this scenario, Medicaid plans would have an opportunity to develop their vision for a cost-effective care management program, rather than simply responding to an RFP.

Medicaid expansion in any state, though, is rife with challenges. Foremost among them: Of the 15 million uninsured people soon to become eligible for Medicaid, most won’t have had any sustained experience with the health care system.

“I don’t believe this area is well thought out yet from a federal, state, and health plan perspective,” says Copeland. “Health plans recognize they’re going to have to take on a heavy burden educating their members about the role of the ER and picking a doctor and so forth, but there is a significant larger role explaining to people what their benefits will be and how they can access them.”

Educating newcomers about how to use the system could require a lot of high-touch customer service, which runs up administrative costs. Automating the process to make it as self-serve as possible is one option for keeping expenses down.

Past Medicaid expansions released pent-up demand. Lessons can be drawn from California, where Medi-Cal embarked on an ambitious expansion in 2010, only to find that physicians weren’t willing to accept Medicaid rates, which were 56 percent of Medicare. The federal payment bump, temporarily matching Medicare rates in 2013 and 2014, had little effect. The resulting provider shortage made it difficult to hold plans accountable to a rule that new patients be seen within 30 days.

Medicaid expansion’s biggest risk for managed care plans? Early adopters, like California, “have been living off of bonus money — quality assurance fee funding where the federal government matches state money, state health department money — all these ways of funding the system,” says Garner, the
INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena™ (aripiprazole) for extended-release injectable suspension

INDICATION
Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.

» Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.
FOR THE TREATMENT OF SCHIZOPHRENIA

A new option to help protect your members from relapse

Introducing once-monthly Abilify Maintena: demonstrated to significantly delay the time to relapse vs placebo for up to 1 year* (P<0.0001).

Visit AbilifyMaintena.com for product information and Formkit.com for formulary information.

*Based on a Phase 3, double-blind, randomized clinical trial in patients with schizophrenia; Abilify Maintena (n=269) vs placebo (n=134).

IMPORTANT SAFETY INFORMATION (continued)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including Abilify Maintena. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Continued on next page.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on the following pages.
IMPORTANT SAFETY INFORMATION for Abilify Maintena™ (aripiprazole) for extended-release injectable suspension (continued)

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

» **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

» **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).

» **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

**Orthostatic Hypotension:** Aripiprazole may cause orthostatic hypotension. Abilify Maintena should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

**Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

**Seizures/Convulsions:** Abilify Maintena should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

**Potential for Cognitive and Motor Impairment:** Abilify Maintena may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain Abilify Maintena does not affect them adversely.

**Body Temperature Regulation:** Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

**Dysphagia:** Esophageal dysmotility and aspiration have been associated with Abilify Maintena; use caution in patients at risk for aspiration pneumonia.

**Alcohol:** Advise patients to avoid alcohol while taking Abilify Maintena.

**Concomitant Medication:** Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the Abilify Maintena dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

**Most commonly observed adverse reaction:** The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs placebo, respectively, was:

» **Akathisia** (8% vs 4%) in adult patients with schizophrenia.

**Injection Site Reactions:** In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena-treated patients.

**Dystonia** is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

**Pregnancy/Nursing:** Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on adjacent pages.

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ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension, for intramuscular use

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Full prescribing information and Medication Guide. 

See full prescribing information for complete boxed warning.

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (median duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of these trials, the overall number of patients exposed to drug in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

• Although the causes of death were varied, most of the deaths were attributed to cardiovascular causes, including myocardial infarction. In the OROS Methylphenidate trial, the death rate in patients treated with OROS Methylphenidate was lower than that in placebo-treated patients (mean age: 64 years; range: 17-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with haloperidol and haloperidol succinate. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., tachycardia, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic uncertainty of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal symptoms and EPS. Other important considerations in the differential diagnosis include central anticholinergic heat, stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive supportive treatment and medical monitoring of all concomitant medical problems that might contribute to the NMS syndrome. Treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential for recurrence of antipsychotic drug-induced neuroleptic malignant syndrome (NMS) should be kept in mind. It is not known whether the risk of recurrence of NMS is higher or lower than the risk of NMS in patients treated with atypical antipsychotics.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential for recurrence of antipsychotic drug-induced neuroleptic malignant syndrome (NMS) should be kept in mind. It is not known whether the risk of recurrence of NMS is higher or lower than the risk of NMS in patients treated with atypical antipsychotics.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, may also cause or worsen tardive dyskinesia. If a patient develops signs and symptoms of tardive dyskinesia, it should be noted whether the tardive dyskinesia is associated with this increased risk. Precise risk estimates for tardive dyskinesia are not available. In some patients, tardive dyskinesia has resolved when the antipsychotic was discontinued; however, some patients require continuation of anti-psychotic treatment despite discontinuation of the antipsychotic drug.

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+2.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+3.2 mg/dL; median exposure 22 days; N=799).

Table 1 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose levels at baseline (mean exposure 25 days; median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients (+2.2 mg/dL; median exposure 42 days; N=42) was not significantly different than in placebo-treated patients (+5.0 mg/dL; median exposure 42 days; N=42) (p=0.24).

Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (+6.1 mg/dL; median exposure 25 days; N=1050) and LDL Cholesterol (+6.4 mg/dL; median exposure 25 days; N=1050) were significantly different than in placebo-treated patients (+3.7 mg/dL; median exposure 25 days; N=799), respectively; and at 24 weeks, Total Cholesterol (+9.6 mg/dL; median exposure 25 days; N=1050) and LDL Cholesterol (+9.6 mg/dL; median exposure 25 days; N=1050) were significantly different than in placebo-treated patients (+5.0 mg/dL; median exposure 25 days; N=799), respectively.

Weight Gain: Weight gain has been observed with antipsychotic use. Clinical monitoring of weight is recommended. In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1872) compared to 0 kg (N=1100) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was −1.5 kg (N=137) compared to −2.0 kg (N=468) in placebo-treated patients.

Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

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Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its 

α1and α2-adrenergic antagonist activity. Orthostatic hypotension occurred in 4/375 (1.1%) patients treated 

with ABILIFY MAINTENA during the stabilization phase, including abnormal orthostatic blood pressure 

(1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension 

(1/576, 0.2%). In the stabilization phase, the incidence of significant orthostatic change in blood pressure (defined 
as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 

when comparing standing to supine values) was 0.2% (1/576).

Leukopenia, Neutropenia, and Agranulocytosis: Class Effect: In clinical trials and post-marketing 

experience, leukopenia and neutropenia have been reported temporarily related to antipsychotic 

agents, including oral aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leucopenia/neutropenia include pre-existing low white blood cell count 

(WBC) and history of drug-induced leukenopa/ neutropenia. In patients with a history of a clinically 
significant low WBC or drug-induced leukenopa/neutropenia perform a complete blood count 

CBC) within two to four months of the therapy. In such patients, consider discont 

uation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence 
of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection 

and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA 
in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC 
counts until recovery.

Seizures: As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients 

with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower 

the seizure threshold may be more prevalent in a population of 65 years or older.

Parkinson’s disease and, more rarely, akinetic seizures, are rarely observed with the oral 

formulation. In patients who tolerated and responded to treatment with oral aripiprazole 

for at least 720 days.

ABILIFY MAINTENA 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult 

patients with schizophrenia, with approximately 1,281 patients-years of exposure to 

ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 

180 days (at least 7 consecutive injections) and 620 patients treated with ABILIFY MAINTENA had 

at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and 

open-label studies. The safety profile of ABILIFY MAINTENA is expected to be similar to that of 
on oral aripiprazole. These data are from trials of the safety data presented below and are derived from trials with 

the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and 

single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA 
or placebo under double-blind conditions, the incidence of adverse reactions was similar 

between the two treatment groups.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole: Adverse Reactions 

Assessment of Dose-Related Effects: Aripiprazole was evaluated for safety in 16,114 adult 

patients who participated in multiple-dose, clinical trials in schizophrenia. For the purposes of 

this analysis, the oral formulation was considered identical to the injectable formulation. Adverse 

reactions which had an incidence equal to or less than placebo.

Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients 

Treated with Oral Aripiprazole

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Oral Aripiprazole (n=1843)</th>
<th>Placebo (n=1166)</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Vision</td>
<td>3</td>
<td>2</td>
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<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Neusea</td>
<td>15</td>
<td>11</td>
<td></td>
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<tr>
<td><strong>Nervous System</strong></td>
<td>Constipation</td>
<td>13</td>
<td>7</td>
<td></td>
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<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td>Vomiting</td>
<td>11</td>
<td>6</td>
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<td></td>
<td>Dyspepsia</td>
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<td></td>
<td>Dry Mouth</td>
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<td></td>
<td>Gastroesophageal Reflux Disease</td>
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<td></td>
<td>Abdominal Discomfort</td>
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<td></td>
<td>Stomatitis</td>
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<td><strong>Fatigue</strong></td>
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<tr>
<td><strong>Pain</strong></td>
<td>3</td>
<td>2</td>
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<td></td>
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<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Muscle Spasm</td>
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Dose-Related Reactions of Oral Aripiprazole: Dose response relationships for the incidence of 
treatment-emergent adverse events were evaluated from four trials in adult patients with 

schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 

15 mg/day, 20 mg/day, and 35 mg/day) to placebo. This analysis, stratified by study, indicated that the only 
adverse reaction to have a possible dose response relationship, and then most prominent 

only with 30 mg, was somnolence (including sedation); incidences were placebo, 7.1%, 10 mg, 8.5%, 

15 mg, 9.3%, 20 mg, 9.5%, 30 mg, 12.5%.

Injection Site Reactions of ABILIFY MAINTENA: In the open-label, stabilization phase of a study 

with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any 
iputative adverse reaction was 4% for ABILIFY MAINTENA-treated patients. The 

mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably 
painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the injection 

site to the opening of the injection site (4.1 vs 8.3).

In a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively 

collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesia). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.8% placebo, 10.9%).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively 
collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesia) did not show a difference between aripiprazole and placebo.

Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, 
may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Whi

ese symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in 

males and younger age groups.

Adverse Reactions in Long-term, Double-blind, Placebo-controlled Trials of Oral Aripiprazole: The adverse 

reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo 
in patients with schizophrenia were generally consistent with those reported in the short-term, 

placebo-controlled trials, except for a higher incidence of tremor (8% [1253]) for oral aripiprazole 

compared to placebo (3% [370]). In this study, the majority of the cases of tremor were of mild intensity 

(8/12 mild and 4/12 moderate), occurred early in therapy (8/12 <4 weeks), and were of limited duration (7/12 <10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (42/853) for oral aripiprazole.

An examination of population subgroups did not reveal any clear evidence of differential adverse 

reaction profiles in the 2 age, gender, and race.

Adverse Reactions of ABILIFY MAINTENA: In the open-label, stabilization phase of a study 

with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any 

adverse reaction was 4% for ABILIFY MAINTENA-treated patients. The 

mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably 
painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the 

site to the opening of the injection site (4.1 vs 8.3).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent or mild (0% to 12% of subjects following the first injection and 77% to 96% of subjects following the last injection. 

Extrapyramidal Symptoms of Oral Aripiprazole: In short-term, placebo-controlled trials in 
schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-

related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for 

EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale 

(4% somnolence) for oral aripiprazole-treated patients. In this study, the majority of the cases of tremor were of mild intensity 

(8/12 mild and 4/12 moderate), occurred early in therapy (8/12 <4 weeks), and were of limited duration (7/12 <10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (42/853) for oral aripiprazole.
Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole: Following are events that reflect adverse drug reactions reported by clinical investigators during oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 12,543 adult patients. All events assessed as possible adverse drug reactions have been included in this table. In addition, medically-considered likely or non-Medically-considered likely adverse drug reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of Adverse Reactions, Clinical Pharmacology (12.2), Precautions (15), or Overdosage (30) have been excluded.

Adverse Reactions Observed During Premarketing Evaluations of Oral Aripiprazole</p>
Santa Monica lawyer. “When that ends it will be a significant issue for providers, and I do not know if the system is sustainable without these funds.”

Opportunity may be richer in states like Arkansas, which amounts to privatized Medicaid. “That would be a coup of the ACA,” says Garner. “For all the criticism that the ACA is socialized medicine, Arkansas’s compromise with Medicaid expansion moves the ACA toward the private sector.

“In some ways, I kind of get it,” he laughs. “The whole post office thing has not worked out too well, but FedEx did.”

SELF-FUNDED PLANS NEED A ROADMAP

While employers are trying to keep up with the ACA, self-funded companies have a doubly difficult task. “The Department of Labor has never issued definitive guidance that says, ‘These are the rules that apply to self-funded plans, and these are the rules that apply to fully funded plans,’” says Bonita Hatchett, a partner in Barnes & Thornburg, a Chicago-based law firm.

As the ultimate fiduciary, the employer — not its third-party administrator — is responsible for operation of the plan. So self-insured companies have to be up on the ACA’s lesser-known provisions, such as notifying employees who have exceeded lifetime limits that they again qualify for coverage and mandates for self-reporting rule violations.

Hatchett is concerned that people don’t grasp the urgency.

“We’re only six months from the penalty phase, and I don’t see the type of interest and aggression these employers should have in putting their policies and procedures in place and making sure their plans are compliant.”

Maybe that’s because the government once enabled complacency. No more. The Department of Health and Human Services (HHS) and the Internal Revenue Service plan to add 15,000 agents to enforce these provisions. “The agencies are really going to start focusing on this stuff,” says Hatchett.

“In the past, nobody did. No one did discrimination testing for self-funded plans. People just thought they could skid under the radar and the agencies really didn’t care.”

For now, employer focus seems concentrated on who qualifies as a full-time employee to be offered benefits. The ACA defines full time as an average of 30 hours per week. That gets tricky for industries with employees who work variable hours.

“If one week they work more than 30 hours but the next week they work below 30, that kind of fluctuation could inadvertently trigger a fine,” says Amy Christen, member of the employee benefits practice at Dykema’s Bloomfield Hills, Mich., office. Employers can opt to track and average employee hours over a longer defined period. “If, during that measurement period, variable hour or seasonal employees average below 30 hours a week, then the employer minimizes its risk of triggering a fine.”

Christen says some industries are exploring the tactic of “changing their employment structure to not permit [part-time] employees to work more than 30 hours,” thus eliminating them from the play-or-pay pool.

Manipulating employee eligibility, however, could be risky. “There might be some ERISA-based [liability] because the employer is making decisions for the sole purpose of making you ineligible for benefits,” says Hatchett. “We’ve seen litigation when an employee has been ill and the employer would do all sorts of scheduling to make sure that employee was not eligible for coverage.”

Costs and regulation could change the benefit paradigm altogether. Companies that see their costs increasing might decide that it’s cheaper to pay the penalty and get out of health care. “I don’t have any employers that are looking at that option because the exchanges are not far enough along,” says Christen. If the exchanges are going strong by 2016, employers might start to send employees there.

Hatchett’s got another take: “If you think about the amount of manpower it takes internally to follow the rules, it’s significant. You could have a whole department that does nothing but health care reform compliance. Is that a good use of payroll?”

Michael D. Dalzell is a former managing editor of Managed Care.
A Conversation With Jonathan P. Weiner, DrPH

Information Technology Required
A heath data pioneer launches a center at Johns Hopkins to develop new ideas for population health

Johns Hopkins University’s Jonathan P. Weiner, DrPH, has always supported managed care. He teaches perhaps the longest-running and largest university class on the topic in the country.

Today, with the United States investing hugely — and successfully, he says — in information technology and the creation of accountable care organizations, he has a newfound optimism, and a new research center aimed at achieving long-held goals in population health. He is asking his colleagues and his students to think about information technology and population health in different ways, such as whether electronic medical records can help us create clinical care and outcomes measures that are more detailed and more relevant than the ones we have today.

Weiner has been breaking ground in the use of data for years. With his late colleague Barbara Starfield, MD, MPH, he developed the Johns Hopkins ACG Risk Adjustment/Predictive Modeling Software System, which is used across the United States and in more than 15 other countries to help manage the care of more than 80 million people. He is now director of the newly established Johns Hopkins Center for Population Health Information Technology and a professor at Johns Hopkins University’s Bloomberg School of Public Health and its medical school’s division of health sciences informatics. He is a member of the CMS Meaningful Use and HITECH Clinical Quality Measures technical expert panels and a member of several advisory committees related to quality and health information technology for national organizations.

He is a reviewer and has served on editorial boards at the New England Journal of Medicine, JAMA, Health Services Research, and Health Affairs and he is on the editorial board of this publication, Managed Care. Before joining Johns Hopkins in 1981, Weiner was a consultant with Medicus Systems Corp. and a computer systems analyst at the University of Massachusetts Health Services-Valley Health Plan HMO. He earned a bachelor’s degree in human biology at the University of Pennsylvania, a master’s in health administration at the University of Massachusetts, and a doctorate in public health at Johns Hopkins University. He spoke recently with Managed Care editor John Marcille.

MANAGED CARE: You have been involved in managed care and health informatics for more than 30 years, but recently you began to call yourself evangelical on the topic of health information technology and population health. What is different today?

JONATHAN P. WEINER, DrPH: That’s easy. We’ve been talking about using electronic medical records and other consumer information technology for years, and it is only now that they are available. We’ve gone from about 5 or 10 percent
of doctors having an EMR to an astounding figure of close to 80 percent of all office-based doctors having them. We’ve gone from a relatively small percentage of people using smartphones and the Internet for health communications to an era where most of us envision that it will be completely ubiquitous. As a field, we must embrace digital information. The ideas have been around for a while, but a tipping point has been reached.

MC: Physicians may have EMRs, but many still don’t like them.

WEINER: The Office of the National Coordinator for Health Information Technology gets my award for the most effective government health care program in the last five years. The whole meaningful use thing is really a smart way of getting a computer on a doctor’s desk. On the other hand, there really aren’t a lot of meaningful users out there yet. But it will happen. Our young medical students wouldn’t practice any other way. In fact, at Johns Hopkins, we had to put a policy in place to keep medical students focused on studies and not developing smartphone apps and other information technology programs. We have about five successful technology spinoffs from medical and public health students. So it will change, even if those who are in established practice are having challenges today.

MC: You also mentioned that more patients are using smartphones and computers with Internet access.

WEINER: Communication between medical providers and patients is way behind other service industries in terms of embracing digital technology. Once the impediments of fee-based care and the old 15-minute, four-times-a-year model of patient interaction are overcome, a whole new communication framework will happen. It may take a generation, but it will happen.

MC: I want to have an e-mail conversation with my physician, but his office says it can’t be done. Is HIPAA one of the biggest impediments?

WEINER: It can be done. Kaiser Permanente and others do it. Patients have to sign all kinds of waivers, and I understand risk management and lawyers watching out, but there is no question that it has to happen. When organizations do embrace it, everybody is pleased. People forget that HIPAA was meant to put standards in place to free the data. If someone abuses data, he should be put in prison or fined, but HIPAA was never meant to be an impediment to communication.

MC: What about the lack of interoperability between systems? Isn’t that slowing us down?

WEINER: We have made great advances in standardization in the last couple of years, and vendors are very sensitive to making sure that organizations can communicate with one another. But we have a long way to go. There have not been strong enough regulatory controls. The feds have backed off. You don’t have to fully participate with a health information exchange to get meaningful use money. So we are still trying to get that right. It’s obvious from banking and other industries that it can be done, even if health care information is more complex.

MC: You’ve pointed out that the Affordable Care Act and accountable care organizations give us a solid place to start for population health.

WEINER: The ACA is the biggest thing in health care since Medicare and Medicaid, as imperfect as it is. The ACA is really about getting people an insurance card, and that’s essential. Accountable care organizations were an afterthought, but a great afterthought.

More than half of information in the EMR is unstructured…. We’ve brought in our computer science faculty colleagues to do natural language processing.

MC: What do you think of the design of ACOs?

WEINER: I am pessimistic about some of the specifics, the lack of teeth, but I am 100 percent supportive of the general concept. A health care system has to have a budget, it has to have a population, and it has to have information technology. All else is negotiable. The ACO has most of those things. Is it the strongest population health system we could design? Not exactly. They don’t all have health care IT, but the smart ones are really jumping on board. The answer is to view the end game as keeping the population healthy and let the provider design the most efficient system.

MC: You work quite a bit overseas. Can our system be better?

WEINER: In many other countries, the electronic health record is ubiquitous, but they have not
always been able to bring it all together to benefit population health. In the United Kingdom, for example, all of their general practitioners have EMRs, but for some political reason, they are not keen on sharing their data. Israel has an HMO-style system, an EMR, and population health. I do believe a public-private partnership is the way to go. A private insurance plan is going to see a population as beginning and ending with enrollment, so the government must play a role to ensure a community focus and to maintain continuity as members switch in and out of health plans.

MC: Have you seen examples of that?

WEINER: There are some really neat innovations being funded by the CMS Innovation Center. They are helping several states, like Oregon, Minnesota, and Vermont, blend the ACA and private health plans, with health information technology as a centerpiece.

MC: Are the advantages of health information technology clearly being realized now in improved outcomes, lower costs, and improved experiences, or is most of this still to come?

WEINER: Most of it is in the future. Today, the greater part of our health care information technology is used to make sure doctors and health systems get paid or are meeting federal regulations. I call that the "money or mandate focus" that is prevalent in most everything we do in health care. We certainly have enough smarts to make HIT systems useful for improving health outcomes, but this takes time.

MC: So you do believe the use of health information technology will enable us to better measure care and outcomes?

WEINER: I have been working with some wired organizations to think about new ways to develop e-measures, but this has not been easy. Even after many years of EMR use, most organizations have their hands full making sure that they effectively use their IT to treat the patient. I believe there’s a sort of “Maslow’s hierarchy” of EMR use in an organization: The first priority is, don't hurt the patient. It’s true that for every one mistake the EMR might cause, the computer catches three, but every so often the system fails. Second, just make it through the day. Doctors and nurses have a lot to do, and especially when it’s new, technology can mess up their workflow. Third, realize the return on investment in terms of enhanced billing or other ways to capitalize on the EMR’s cost. Fourth, use it to improve one at a time patient care efficiency. And fifth, after the other four goals have been achieved, comes the type of things I am talking about here. For example applying the EMR for population health, research, and outcomes measurement. There are probably only a few dozen organizations in the country that have achieved the highest level of my EMR “hierarchy of needs.”

MC: Can you give us some examples of organizations that have successfully exploited this?

WEINER: We can’t turn the whole fee-for-service world, particularly Medicare, into Kaiser Permanentes or integrated delivery systems like Intermountain Healthcare or Geisinger Health System, but they are our models for ACOs. Kaiser Permanente has shown that when you move away from fee for service and the doctors are able to communicate with their patients using a Web portal, it saves in terms of utilization and leads to happier patients. There is still more to be done on overall ROI, but unquestionably, when systems are put in place, there are many upsides.

MC: Does the patient-centered medical home show the same potential?

WEINER: Health IT is at the medical home’s core, as with ACOs. Group Health Cooperative’s medical home is fully wired and has shown some ROI.

MC: Is the Center for Population Health Information Technology working on creating ways to capitalize on health IT at the higher levels you described?

WEINER: Yes. One day, everything that happens in the health care system will be documented — not just medical care, but also interactions with the patient, outcomes, functional status, and biometrics. All of that can lead to new types of measures, including new process measures, new outcomes measures, and new consumer measures. It is essential that those of us interested in managed care and quality of care use these tools to create new approaches to measurement that couldn’t have been done with just claims data or paper records.

MC: Can you give us an example?

WEINER: With a paper record, an organization could manually collect information such as blood pressures and body mass indexes for a whole
population. It would be a lot of work, but you could do it. The EMR is very helpful for that, but still, we could have done it before. What we could not know without the EMR is: When did the doctor learn the results? When did she take an action? Did she incorporate the computer’s ability to help her choose a drug? When did the patient open the results on the Web portal? When did the patient start the medication? Those are data that we could use to create new types of measures.

**MC:** Does having the data result in these new measurements, or are these measurements we would like to have, and therefore we will collect the data?

**WEINER:** Yes and yes. It’s a chicken and egg. If the data aren’t there and it’s not feasible and cost-effective to collect the data, that’s one point. But it ultimately has to have value. We’re back to money or mandates. We either have to truly show that it will save somebody money or we have to make it a centerpiece of our regulatory framework.

**MC:** And the patient involvement you mentioned, that’s important?

**WEINER:** On one side, we have doctors and ACOs, and on the other side are patients and communities. We really have to remember that even patients with multiple conditions and multiple doctors will only have contact with the health care system for a half a percent of their time in the year, but capturing health information about the other 99.5 percent of their lives is the next frontier. Think about biometrics: In Asia, they have developed new sensor technology that people can wear, and it’s really very cheap.

**MC:** We are going to end up with a lot of data.

**WEINER:** Yes the term Big Data is really apropos. We will have more and more structured data, but we are also going to have tons of unstructured data. In fact, more than half of information in the EMR is unstructured. At our new “See-Fit” Center — The Johns Hopkins Center for Population Health IT, or CPHIT — we’ve brought in our computer science faculty colleagues to do natural language processing. They are helping us mine the text to figure out how to help health plans and public health agencies. We are working on a project right now using EMR notes to do a better job of helping outreach nurses find high-risk moms early on in their pregnancy.

**MC:** How are physicians going to manage it all?

**WEINER:** Today doctors have to use their right brain and their left brain, the communicative side and the side that houses all of the science they learn in medical school. What is going to happen is a big shift to the right brain — the more humanistic side — because the machine will always be smarter than the doctor in terms of the science, the technology, and all of the data. Increasingly, the patient won’t need the doctor for all of that. There are going to be more and more phone apps and e-health programs, and they are going to get better and better. The doctors — or maybe the nurse practitioners, health coaches, or others — are going to have to help the patient in human terms. The communication part — taking massive amounts of data and bringing it down to simple-to-use solutions — is going to be part of the challenge.

**MC:** How is health care information technology going to affect population health in the next ten years, big picture?

**WEINER:** Health IT alone will not lead our health care system to becoming population-health-focused, but we cannot have a population-health-focused system without health IT. Financial incentives, regulatory incentives, and organizational mission and structure are what motivates providers. Some organizations are doing a good job, but when someone loses health insurance, so much for the population. That’s a tough nut to crack. I was at a meeting recently at the American Public Health Association, where the health officers were trying to embrace ACOs and managed care, but they were validly concerned about what happens when someone loses coverage. Because they have way more resources, the best managed care plans are able to do a better job of outreach than most public health agencies, but the instant someone leaves the health plan, they are no longer a part of the population. Without interoperable EMRs to provide cross plan continuity, we can’t possibly address that concern.

**MC:** Ultimately, each patient’s data will be available to practitioners and researchers around the country. Are you concerned about data security?

**WEINER:** I am involved in a grant project in which I am the only public health person; the others are all engineers and IT encryption and security experts who mainly work outside of health care.
If we can create systems that are good enough for homeland security, good enough for all the banks, then secure and interoperable EMR systems can and should also happen.

**MC:** I’m sure you appreciate the potential for research.

**WEINER:** All of us in the evidence-generation field are going to have to completely change how we do business, and that is very positive. If all of the care that doctors and nurses provide to a patient is in the EMR, and all of the outcomes and outputs are in the system, and then we bring in the data from phone apps so people can tell us how they are doing, think of all the research possibilities. The Institute of Medicine calls this the Learning Healthcare System. Will we still need randomized clinical trials? I think so, but not as often. And while it is important to keep investing in genomics research, the value for society from an investment in the Learning Healthcare System would likely be far more rapid.

**MC:** There’s a general belief that health plans are not exploiting the data they have for research purposes. Is there a difference between the investments being made by for-profit and not-for-profit organizations?

**WEINER:** Some of the smartest, best health plans in America are for-profit. On the other hand, it is really discouraging to see them focus on one quarter at a time and do things that don’t always benefit the collective good. Many not-for-profit plans aren’t necessarily better. The Blue Cross system, which is still majority not-for-profit, could do far more in sharing its data for research purposes. Whose data is it anyway? The data belongs to the employers and consumers and taxpayers of America. I am very disappointed and discouraged that most payers don’t do more to translate the data to value for society.

**MC:** Any positive examples?

**WEINER:** A collective of several Blue Cross plans recently shared data on bariatric surgery and other types of obesity care with me and my colleagues at John Hopkins, no strings attached. The national Blue Cross & Blue Shield Association facilitated it, and I was grateful. We published about 30 peer-reviewed articles adding to science. They didn’t provide a penny to us; they just provided the data. It hadn’t happened before, and it hasn’t happened since. Kaiser Permanente does excellent research, and the Patient-Centered Outcomes Research Institute is looking for collaborations of health systems and payers. So there are pockets of opportunity, but we’ve only gone a tenth of the way toward what is possible.

**MC:** The amount of outcomes research we do for the public good in our health care system is nowhere near what we need to do.

**MC:** What is the vision?

**WEINER:** The amount of outcomes research we do for the public good in our health care system is nowhere near what we need to do. I would like to free the data for the next generation of researchers. We need HIPAA-compliant research reviewed by ethics boards that is accessible to universities and other research institutes. At most turns, for-profit organizations are more concerned about value for shareholders, and a lot of the leading not-for-profit organizations have followed suit. Because they know their data are valuable, leading wired organizations and health plans are selling their data to pharmaceutical companies and others. I guess this goes back to my “money or mandate” premise. They are not going to make money by helping science and for now there is no government mandate to share. The other part of the problem is that if one does it and the other one doesn’t, then it feels unfair. I would like to see more consortiums and a certain amount of EMR budget set aside for research purposes.

**MC:** It’s up to private payers?

**WEINER:** I am a big supporter of managed care, but they need to do more in this regard. The great majority of important outcomes research done in this country is done with Medicare data and not managed care data. CMS does a great job of sharing HIPAA-compliant data with all researchers.

**MC:** Right, but their patients are not representative of the general population.

**WEINER:** Exactly. And with all of the challenges in rolling out the ACA, the government has backed off from some of its claims and EMR data sharing plans. But as our nation collects more electronic health care data, we have to figure out how to use it for the benefit of society.

**MC:** Thank you.
Universal HIV Screening Rule Reinforces Insurers’ Approach

The U.S. Preventive Services Task Force renders a Grade A recommendation, but there are some questions on how to proceed

By Frank Diamond
Managing Editor

The U.S. Preventive Services Task Force played against type at the end of April and still garnered attention. Instead of saying “fewer” — as in fewer mammographies, fewer PSA tests (just two from a growing list) — the task force called for more screening for HIV. Nearly universal screening, in fact. In doing so, it echoes something that the Centers for Disease Control & Prevention had been saying since 2006.

Preventive benefit

“The recommendations are not exactly the same,” says Virginia Moyer, MD, USPSTF chairwoman. “They’re never going to be exactly the same. But they’re essentially the same.” (For example, one slight difference: the CDC wants screening for patients from 13 to 64; the task force’s range is 15 to 65.)

Don Liss, MD, the vice president for medical and quality management at Independence Blue Cross, says that he’s glad and a bit surprised. “This is a reasonably bold step.”

Robert McDonough, MD, the head of clinical policy, research, and development at Aetna, says that health plans should be able to implement the recommendation fairly easily since it “doesn’t require anybody to have any particular diagnosis or risk factor, so it’s removed that particular complication.”

Moyer agrees. “You’re being screened because people get exposed without even knowing it.” It does, however, extend screening to “younger adolescents and older adults who are at increased risk.”

Because of the way that health care reform laws are established,” Liss says, “this is considered a preventive benefit, which has no out-of-pocket exposure for the patient, so it’s got to be covered 100 percent in most circumstances by health plans. That may be the most profound impact of the recommendation in terms of the health insurance aspect.”

The Accountable Care Act (ACA) states that preventive services given a grade A recommendation by the task force must be covered in this manner.

By 2014, says Liss, all plans will have to be compliant. Screenings involve administering a fairly inexpensive blood test — Medicare pays $12 for it.

“It would be part of your regular checkup,” says Moyer. “Whether it needs to be annual, we didn’t say; we simply don’t have the answer to that question. But somebody at higher risk would certainly be screened more frequently than someone who’s at low risk.”

This lack of specificity could be a problem, says Liss. “It isn’t entirely clear, and the task force doesn’t specify, what the interval of testing should be.”

The recommendation says that “One reasonable approach would be a one-time screening of adolescent and adult patients to identify persons who are already HIV-positive, with repeated screening of those who are known to be at risk for HIV infection.... Routine rescreening may not be necessary for individuals who have not been at increased risk since they were found to be HIV-negative.”

Complicated

Conceivably, someone could be screened at age 15 and not have to be screened again, says Liss. “That makes it even more complicated for the clinician. It’s not like a vaccine that, perhaps, you get once and you’re done, or even a hemoglobin HbA1c test in a diabetic, where you know it’s twice a year, every year. So it creates confusion. For example, if somebody saw a doc 10 years ago and had it, do you know that they had it? Do you accept that as reported by the patient?
“There are clearly lots of places where people get HIV screening other than their primary care doc’s office. Certainly, physicians have universally screened pregnant women for years now. It’s a little bit more complicated than some of the standard preventive services that physicians are used to managing out of their family practice or even their pediatrics or internal medicine practice.”

McDonough says that “Our policy at Aetna going back as far as 2001 is to just simply cover routine HIV testing. Even before the changes and [the task force’s] recommendations in 2005 to recommend testing based on risk factors, there wasn’t any easy way to code it or ask a patient whether he either had been exposed to HIV or was at risk for infection.”

As a result, “We did not limit coverage of HIV testing only to persons with any specific reported risk factors. So it hasn’t really changed the way that we’ve been covering this HIV testing.”

The insurer covered the test, but now there is pressure to make sure the test is performed as often as necessary.

Clinician executives at health insurance plans can help by creating systems that reinforce the recommendation, says Moyer. “When you’re a solo doc working in a rural area with no particular support, you’ve got to remember this stuff yourself. If you’re working in a big system, the system can help you. The system, for example, can determine if the patient hasn’t been screened within a specified length of time.”

**Checklist**

Doctors don’t like being overwhelmed with reminders, but there are other approaches that should be explored. It took about 20 years from the first credible evidence of the benefit of using beta blockers after a first heart attack to the time when 95 percent of such patients were reliably prescribed a beta blocker. That still bothers many in health care.

“When I do a well-child visit, the visit is set up in checklist format,” says Moyer, a pediatrician, “so that we remember to do all of the things that are routine. It just would go on the checklist. This is an opportunity for simple system changes that make the right thing to do an easy thing to do.”

Health care has learned from the beta blocker debacle, Liss insists. “There have been major, major, major advances in the way everyone gets information.” The amount of time from the discovery of breakthrough technology to its use in clinical practice has shortened, he says.

“Health plans will include HIV information in the same guidelines that we put out for all preventive services,” says Liss. “If the U.S. Preventive Services Task Force recommends it, we recommend it to our provider network.”

Still, the health insurer can do only so much: Physician buy-in is crucial. “We allow the physician to use his own discretion in terms of the interval of frequency,” says McDonough. “We don’t have any edits in the claims system to limit the frequency of retesting.”

Liss says that “We hope that physicians are

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**Clinical tests deemed accurate; cost-effectiveness analysis sketchy**

One of the reasons the U.S. Preventive Services Task Force decided to support nearly universal screening for HIV is the accuracy of the repeatedly reactive immunoassay followed by confirmatory Western blot or immunofluorescent assay, according to the task force’s recommendation. The test is accurate 99.5 percent of the time, with lab results returned within two days.

The recommendation also states that rapid HIV testing “may use either blood or oral fluid specimens and can provide results in 5 to 40 minutes. The sensitivity and specificity of the rapid test are also both greater than 99.5 percent; however, initial positive results require confirmation with conventional methods.”

**No comparison**

The tests are inexpensive (Medicare pays $12), according to experts, but just how they pay off in the long run has yet to be nailed down.

The recommendation states that the task force’s “deliberations on grade recommendations for the effectiveness of clinical preventive services do not include cost or cost-effectiveness considerations. For policy context, however, the USPSTF reviewed some cost-effectiveness analyses published since a review in 2005. These analyses, which include downstream costs, support the cost-effectiveness of HIV screening in settings with low or average HIV prevalence. No studies directly compared universal versus targeted screening in low-prevalence populations or explicitly considered the potential long-term cardiovascular harms of antiretroviral therapy.”
getting such information from the professional societies, from the periodicals that they read, and other sources.”

**Infected, but unaware**

About 1.2 million people in the United States currently have HIV, with 50,000 additional cases annually. Nearly 600,000 people have died of AIDS since the first reported incidents in 1981. It’s estimated that between 20 and 25 percent of people with HIV are unaware that they have it.

One main driver of the update is recognition that introduction of antiretroviral therapy before symptoms emerge (when CD4 counts are between 0.200 and 0.500 x 10^9 cells/L) greatly reduces the progression to AIDS as well as mortality rates.

“New information became available about the effectiveness of treatment,” says Moyer, “particularly the effectiveness of treatment in people who are less likely to know that they have it.”

In addition, the tests for HIV are now highly accurate, limiting the psychological harm from a false-positive finding. The new guidelines more fully reflect “advances in HIV management, congruent with treatment guidelines that were moving toward earlier antiretroviral initiation,” according to an editorial by Moupalii Das, MD, MPH, and Paul Volberding, MD, published online April 30 in the *Annals of Internal Medicine* (http://tinyurl.com/screening-editorial). The editorial discusses the recommendation by Moyer on behalf of the USPSTF: http://tinyurl.com/HIV-study-screening.

The recommendation states that now “false-positive test results are rare; reported rates of such results with conventional testing are 1 in 250,000 tests in low-prevalence populations. Evidence about potential consequences of receiving a false-positive HIV test result (for example, anxiety, psychological distress, or labeling) is limited and largely anecdotal.”

Moyer says that while the recommendation is clear, there’s room for flexibility. “There’s no bright line underneath anyone’s birthday,” but the guideline has to state some age range. “That doesn’t mean close your eyes when a 14-year-old comes in and close your eyes when a 66-year-old comes in. What it means is it should be routine between 15 and 65.”

The USPSTF previously recommended risk-based screening focusing on certain populations, notably men who have sex with men, users of illicit injectable drugs, and all pregnant women. This all reflects “a movement from risk-based to population testing that had begun with a similar Institute of Medicine report recommendation in 1998 that was later endorsed by the American College of Obstetrics and Gynecology,” according to Das and Volberding.

Moyer emphasizes that the screening be done with the patient’s knowledge and consent. “We always discuss things with our patients.” It helps, too, that treatment has advanced over the years. “There’s less of an attitude that the diagnosis of HIV infection is a death sentence,” McDonough says. “There’s more of an attitude that HIV infection can be managed over time. It’s more along the lines of other conditions you can think of like diabetes or hypertension or COPD — conditions that you manage as opposed to illnesses that are invariably terminal. Those changes in attitudes have also increased acceptance of the idea of screening asymptomatic people to detect the disease earlier on.”

Moyer says, “If you go back to the early days of AIDS, when treatment was 30 or 40 pills a day taken on different schedules, that was just impossible. You really couldn’t expect that to work. We’ve simplified it so that now some people can take medications only one time a day. That’s doable.”

**Increasing consensus**

Das and Volberding ended their *Annals* editorial on a hopeful note. “Informing all infected persons of their status may well reduce ongoing transmission-risk behavior in and of itself, and if antiretroviral therapy is also accepted and successful, further spread will be substantially reduced and perhaps even eliminated. Now, with an increasing consensus on population-wide screening, a growing belief in universal treatment, and the goal of near universal access to medical care under the Affordable Care Act, we may have ultimately awakened from the nightmare of the HIV/AIDS epidemic.”

**There’s a lack of specificity regarding how often the HIV screening test should be given to people who are not at risk**

Don Liss, MD, the vice president for medical and quality management at Independence Blue Cross.

There’s a lack of specificity regarding how often the HIV screening test should be given to people who are not at risk, says Don Liss, MD, the vice president for medical and quality management at Independence Blue Cross.
Indications

Rheumatoid Arthritis: HUMIRA is indicated, alone or in combination with methotrexate or other non-biologic DMARDs, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Juvenile Idiopathic Arthritis: HUMIRA is indicated, alone or in combination with methotrexate, for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older.

Psoriatic Arthritis: HUMIRA is indicated, alone or in combination with non-biologic DMARDs, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.

Ankylosing Spondylitis: HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn’s Disease: HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis: HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine. The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to anti-TNF agents.

Plaque Psoriasis: HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

† First patient dosed April 1997.

Please see Brief Summary of full Prescribing Information on the last pages of this advertisement.
99% of health plans cover HUMIRA on formulary as a first choice targeted immunomodulator†

‡ In-depth analysis of medical policy and formulary position from data on-site from The Zitter Group, PATT Tool, October 2012. The Zitter Group PATT is a summary of utilization management techniques for 202 plans making up more than 197 million lives. First choice refers to a preferred or parity formulary.

Safety Considerations†

Serious Infections
Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies
Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions
Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Please see Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the following pages.
IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapolumary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA in patients with an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- Consider the risks and benefits of treatment in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection, patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.
- Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.
- Drug interactions with biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.

- Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.

- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.

- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.

- Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

Anaphylaxis and angioedematous edema have been reported rarely following HUMIRA administration.

- If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.

- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.

- Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.

- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.

- Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.

- Exercise caution when considering HUMIRA for patients with these disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g., thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.

- Consider stopping HUMIRA in patients with significant hematologic abnormalities.

CONGESTIVE HEART FAILURE

- Worse or new onset congestive heart failure (CHF) may occur.

- Exercise caution in patients with CHF and monitor them carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.

- Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.

- It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.


Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.

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**PROFESSIONAL BRIEF SUMMARY**

**CONSORT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**HUMIRA® (adalimumab)**

**WARNING: SERIOUS INFECTIONS AND MALIGNANCY**

Infections that may be opportunistic include aspergillosis, histoplasmosis, blastomycosis, coccidioidomycosis, legionellosis, and tuberculosis. Infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic pathogens, including legionellosis, lassa fever, and tularemia, have been reported in patients treated with HUMIRA. Discontinue HUMIRA in patients with serious infections and malignancy.

**WARNINGS: SERIOUS INFECTIONS AND MALIGNANCY**

**Serious Infections**

Patients treated with HUMIRA are at increased risk for developing serious infections, including opportunistic infections. These infections may be opportunistic and include aspergillosis, histoplasmosis, blastomycosis, coccidioidomycosis, legionellosis, and tuberculosis. Infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic pathogens, including legionellosis, lassa fever, and tularemia, have been reported in patients treated with HUMIRA. Discontinue HUMIRA in patients with serious infections and malignancy.

**HUMIRA® (adalimumab)** is a member of the tumor necrosis factor (TNF) alpha blocker group containing infliximab, etanercept, and adalimumab. All these biologic products is not recommended in the treatment of systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, and other chronic inflammatory diseases, particularly those with high active disease and/or chronic exposure to immunosuppressant therapy or psoriasis patients with a history of NMSC prior to and during TNF blocker treatment.
Liver Enzyme Elevations
Liver enzyme elevations were reported in 0.9% of patients treated with HUMIRA. In controlled trials, increases in alanine aminotransferase (ALT) levels of ≥3 x ULN occurred in 0.9% of HUMIRA-treated patients, compared to 0.2% of placebo-treated patients. The ALT elevations were generally mild to moderate in severity and no patients discontinued treatment due to ALT elevations. In patients with CD, the rate of antibody development was 3%.

The proportion of patients with decreased serum creatinine clearance who had ALT elevations ≥3 x ULN was greater in HUMIRA-treated patients than in placebo-treated patients (4% vs. 1%). In patients with CD, the rate of antibody development was 3%.

Immunogenicity

Adalimumab antibodies were detected in 12% of patients receiving HUMIRA monotherapy and in 7% of placebo-treated patients. In the first 48 weeks of treatment, the rate of antibodies to adalimumab after retreatment with HUMIRA was similar to the rate observed prior to retreatment.

In patients with RA, the rate of antibody development in patients receiving HUMIRA monotherapy was compared to patients with RA treated with placebo, methotrexate (MTX), or infliximab. Patients treated with HUMIRA had a greater proportion of patients with antibodies to adalimumab compared to placebo (20.7% vs. 1.8% of control-treated patients). In patients with CD, the rate of antibody development was 3%.

In patients with CD, the rate of antibody development with HUMIRA monotherapy was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab detected only when the drug is administered systemically to the patient. The rate of antibody development was based on the percentage of patients who had an antibody titre of ≥1.5 x ULN. The rate of antibody development with HUMIRA was 3%.

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juvenile idiopathic arthritis (JIA) have not been established.

Safety and efficacy of HUMIRA in pediatric patients for uses other than drug to the mother.

or to discontinue the drug, taking into account the importance of the potential for serious adverse reactions in nursing infants from immunoglobulins are excreted in human milk, and because of absorbed systemically after ingestion. Because many drugs and It is not known whether adalimumab is excreted in human milk or

Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile idiopathic arthritis

In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <10 kg. The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions [see Adverse Reactions].

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA [see Warnings and Precautions].

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 70 years of age and older, received HUMIRA in clinical studies RA-1 through W. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Dosages up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA “Medication Guide” to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

• Infections

Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

• Malignancies

Counsel patients about the risk of malignancies while receiving HUMIRA.

• Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

• Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Commercial payers can be a little reluctant to get into a lot of details about their accountable care organization (ACO) contracts, not wanting competitors to know too much. It’s also true that contracts vary according to the size, experience, and capacities of the provider. “We are meeting them where they are,” says Jill Hummel, vice president for innovation at WellPoint.

Still, there’s a basic framework on which most ACO contracts are built. Here are four of the main parts.

**Shared savings**

Shared savings are what make the ACO wheels go round, and they are the chief mechanisms that bring the payer and provider into financial alignment. Cost targets are set for the year, based on formulas that include past experience, projections, and comparisons with similar patients. Typically, physicians continue to get paid fees for services, but at the end of the year, if spending by the provider is lower than the target for that year, the provider and the payer share the difference between the medical expenditure and the target. The split varies. A 50–50 split is most common, but it can skew so 80 percent goes to the provider, 20 percent to the payer. Some contracts include a risk corridor so providers don’t start sharing savings until a certain threshold — say, 2 percent of the cost target — is met.

The notion is that there may be some random variation in spending that has nothing to do with the provider’s efforts, so the shared savings shouldn’t kick in with the first dollar. In addition, the provider’s share of the shared saving money may be capped at between 5 and 15 percent of the cost target.

Typically, contracts will exclude high-cost outliers from the shared-savings calculations. This is seen as a way to remove insurance risk from the contract and focus on medical spending that a provider can control. The threshold for high cost varies, but between $100,000 and $200,000 is common. Some services, such as organ transplants, may also be excluded from the shared-savings calculations.

**One- or two-sided risk**

ACO contracts come in two basic models, one- and two-sided risk. Sometimes one-sided risk is called gainsharing (bonus-only) and two-sided risk (bonus-penalty). In a one-sided risk contract, the provider gets a chunk of the unspent money if spending is below the cost target for the year, but has no exposure to the risk if spending exceeds the target. The risk is only upside. With two-sided contracts, the providers are on the hook if spending goes over the cost target. In exchange for taking on that downside possibility, in two-sided risk contracts, providers usually stand to get a larger percentage — 60 percent or so — of the shared savings.

Initially, the federal government’s Centers for Medicare & Medicaid Services (CMS) proposed that all of the organizations in its Shared Savings program move from one- to two-sided risk contracts by their third year of participation. But there was a hue and cry about this and many other aspects of CMS’s proposed rules for its ACO contracts. So when the final rules came out in October 2011, organizations were allowed to stick with one-sided risk contracts, which some experts worry will dilute the influence ACOs will have on health care spending overall.

For the most part — and not unexpectedly — large physician groups and hospital-led organizations are the entities signing two-sided risk contracts. Allina Health in Minneapolis and Partners
Healthcare in Boston are among the heavyweights participating in CMS’s Pioneer program, which features two-sided risk contracts. In the third year of that program, organizations that beat cost targets in each of the first two years can move to per-beneficiary, per-month capitated payment instead of fee for service.

**Quality measures**

Quality measures (or, if you prefer, quality metrics) are often set up as a gate to the shared savings: If providers don’t meet them, they lose out on any money they might have received by beating cost targets. The reason is obvious: Quality measures have some real bite when there is a strong financial incentive to meet them.

Furthermore, a gate system is supposed to keep providers from cutting corners in order to control costs. Quality measures are also being used as a ladder: The higher the score on a quality report card, the larger the percentage of shared savings a provider might receive. The Medicare Shared Savings program uses a system that determines the percentage of shared savings an ACO receives by a point total based on the number of quality targets it meets.

Some payers keep a separate eye on “resource metrics” like hospital readmissions and emergency department visits that not only reflect quality — presumably some acute care services can be avoided with better care management — but also have a direct bearing on spending and cost. In some cases, quality measures are used as the gate to shared savings and resource metrics (also called utilization measures) as a ladder.

The quality measures used in ACO contracts vary. Scott Sarran, MD, chief medical officer for Health Care Service Corp.’s government programs, says his company has 20 measures, borrowed from HEDIS and weighted by importance.

CMS initially proposed a boggling array of 65 measures in five domains but settled on a simpler scheme of 33 measures in four domains. In the CMS Shared Savings program, the participating organizations need report only their performance on the 33 measures to pass muster and possibly get a chunk of the shared-savings money. How well they do doesn’t matter. But in the second and third year, performance on the measures starts to count. How the quality measures are graded also varies.

Some payers use a sliding scale of benchmarks: The tougher the benchmarks met, the larger the provider’s share of savings.

**Attribution**

Attribution, also referred to as assignment, is the masterstroke of the ACO in many ways. Attributing beneficiaries to organizations based on utilization patterns allows the creation of organizations that can be held accountable for cost and quality without having to overhaul traditional Medicare or go against the grain of the preferred provider organizations and their fairly loose networks. It also takes advantage of the increasingly fast and reliable retrieval and analysis of beneficiary data.

So how does it work? In broad strokes, a beneficiary is attributed to an ACO if over one to two years she has received most of her primary care services from a physician in that ACO.

Where she most recently received services is sometimes factored in. If a beneficiary hasn’t seen a primary care physician, then services provided by specialists might be used instead.

CMS uses a system that attributes patients based on past utilization patterns to start out with. As the year goes on, it informs the ACOs quarterly about utilization patterns and the beneficiaries they are responsible for.

At the end of the year, there’s a look back to see where a beneficiary actually ended up getting primary care. If it wasn’t from the ACO’s physicians, then that patient won’t be attributed to that ACO.

It’s all very ingenious and elegant. But there are devils in the details.

“It is important to understand attribution fully before walking into a shared-savings agreement,” says Mike Englehart, president of Advocate Physician Partners, a 4,000-physician group in the Chicago area.

“You need to know you are going to handle tie-breakers when a patient may be seeing your primary care physician and a specialist from another system. What are the minimal number of contacts needed for attribution?

“We didn’t realize how complicated attribution would be,” he says. “It took some time to sort out.”

Peter Wehrwein is a freelance writer in Newton, Mass.
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Health Plans Tackle Biomarker Limitations

Some insurers and PBMs are experimenting with a pragmatic approach to covering testing

Thomas Reinke
Contributing Editor

Pharmacotherapy biomarkers — those that predict drug response — and their related pharmacogenetic (PGx) tests are seen as the pathway to personalized medicine in cancer and other diseases, but their uptake has met resistance. Often they are supported by poorly designed, small, or biased clinical studies.

“There aren’t good ways for purchasers to assess analytic and clinical validity or clinical utility,” says Lee Newcomer, MD, senior vice president at UnitedHealthcare. “Here is the issue: Is the test dependable enough that a physician can rely on it to determine therapy? The only tests where we have solid information about those three measures are the biomarkers that have gone through the FDA approval process with a new drug.”

Newcomer refers to the three universally recognized criteria for PGx tests:

- Analytic validity — ability to accurately measure an analyte biomarker
- Clinical validity — the marker measured is linked to the target disease; and, most important
- Clinical utility — solid evidence that targeting the marker will improve patient outcomes

Health plans have been especially concerned about clinical utility.

“There is almost a gold rush out there to find biomarkers for cancer and other diseases,” says Newcomer. “People are not slowing down and doing the research that is necessary to demonstrate clinical utility. The lab companies and test developers are saying that it is expensive and it takes time. In response, the health plans are saying, We can’t afford for you not to do that. If we have resources being expended and bad treatment decisions being made, that is a lose-lose for the patient, health plan, and sponsor.”

Health plans cover the genetic tests mandated on drug labels and many plans will add a few additional tests that they have studied and determined to be beneficial. Generally, large health plans will have coverage policies for about 20 tests, experts say.

The prospects for credible biomarkers and wider coverage of PGx tests are improving. Some health plans and PBMs are experimenting with a pragmatic approach to covering testing. Advances in clinical studies will simplify marker and test development, and a new coding structure for identifying and billing genetic tests (See “Coding, billing process” on page 53) should help to control costs and utilization.

Despite limited coverage, genetic testing is expanding rapidly. “At UnitedHealthcare, we are now paying more for molecular diagnostics than we are for chemotherapy,” says Newcomer. That includes pharmacogenetic tests and other categories, such as genetic screening for heritable disease. National expenditures for genetic testing are expected to reach $6.2 billion in 2014, according to one source.

High prices

“Genetic tests cost from $80 to $1,400,” says David Lassen, PharmD, chief clinical officer at Prime Therapeutics. Some health plans contract with specific labs for certain tests and are able to negotiate prices. The list price can be much higher: The sticker price for the Oncotype DX multigene diagnostic assay from Genomic Health is $4,125 according to its Web site.

The industry says a four-digit price is justified by...
the years of work it takes to discover and complete clinical trials needed to provide evidence of the test’s validity and utility.

Flexible approach
Prime Therapeutics and certain of its Blue Cross owners are rolling out a pragmatic approach to evaluating and covering PGx tests in a cost-effective way.

“Genetic testing is gradually improving and we work to identify appropriate opportunities where we may want to facilitate testing,” says Lassen. “We have created a framework for thinking about where and how to rationally apply pharmacogenetic testing in ways that ensure quality and clearly improve outcomes and total cost of care.”

Prime’s approach includes requiring clinical utility and then goes beyond it.

“We start by digging deep into the evidence supporting a test and its ability to improve value and outcomes,” says Lassen. If reasonable evidence exists, Prime looks at other factors.

“The first question we ask is whether or not testing is the standard of care,” says Lassen. That question is important because in many cases there is controversy regarding the value of a test or its testing methods. Lassen cites HER2 gene testing for Herceptin in breast cancer. About 1 in 5 patients has the gene, and testing is complicated by the existence of two different tests. Immunohistochemistry measures gene over expression while the fluorescence in situ hybridization (FISH) test measures gene amplification.

The American Society of Clinical Oncology and the College of American Pathologists have recommended either test. So the incidence of the HER2 mutation and the possibility of expensive testing present a management challenge to health plans. “We have evaluated this situation and believe that health plans are already managing it well in terms of the appropriate standard of care,” says Lassen.

“The next question we ask is, Is the test administratively feasible? There are situations where testing can be administratively impractical — an example is testing for sensitivity to warfarin,” says Lassen. “The guidelines state that for new warfarin starts, sensitivity testing should be done within five days, but the chances are the results won’t be back in time to know how the patient is responding.” Simpler International Normalized Ratio (INR) lab tests are the most common approach to monitoring warfarin therapy.

“The third question is whether there is a potential for positive return on investment. If the answer is yes then we will move ahead,” he says.

Prime is testing its new framework. “In cardiology we are facilitating the testing for mutations in the gene CYP2C19 that identifies poor metabolizers of clopidogrel. The objective is to identify patients who are using brand-name antiplatelet therapy and if they are poor metabolizers of the medicine where there is limited value to therapy, then we can recommend to the prescriber to consider using generic clopidogrel.” This savings from the generic provides the return on investment that Prime is looking for.

“The other area we are looking at is oral oncology, specifically Tarceva and the EGFR test in lung cancer. We are looking for EGFR-positive patients who have been shown to respond to therapy,” says Lassen.

An important step in Prime’s program is rapid engagement with prescribers for new starts in therapy. “When we see a claim that indicates a new start, within 24 hours we reach out to inform the prescriber of the opportunity to test.

“Our lab partners will give us quick turnaround,” says Lassen. Prime has contracted with a few labs that it has evaluated to provide high quality tests quickly.

UnitedHealthcare uses a similar approach. “The FDA mandates testing for 17 or 18 agents,” says Newcomer. “We are looking at coverage of other biomarkers, primarily based upon how much activity we are seeing — for example, a specific test billed frequently by one lab. We are using that approach with the BRCA1 and BRCA2 tests for the risk of breast cancer.”

Testing laboratories
Both health plans are similar in another way. Both work with specific testing laboratories that they have evaluated for consistent quality in their
new coding and billing system for genetic tests may help to resolve the tug of war between laboratories and payers on payment rates and coverage issues.

At present, over 3,000 tests are billed under a limited set of the American Medical Association's Current Procedural Terminology (CPT) codes. That means health plans often do not know what they are paying for because many different tests are billed with the same code. In many cases it is impossible to track utilization of covered and noncovered tests. The coding limitation also makes prior authorization impractical.

In 2012 the AMA expanded the number of codes to facilitate more accurate reporting of tests, says Robert Musacchio, PhD, who heads up the AMA's CPT code development. However, the expanded code set still identifies categories of tests, not individual tests.

Separately, McKesson, which provides reagents, lab, and medical supplies to genetic testing companies, developed a coding structure for individual tests, called Z-Code Identifiers. Labs and testing companies register their tests in the McKesson diagnostics exchange by describing their tests in detail, and they receive a Z-Code Identifier for each test — unique codes for unique tests and the same code for identical tests from multiple labs. The AMA will use the detailed test information to assign a CPT code to a test, where appropriate.

"The Z-Code Identifiers are intended to allow laboratories to differentiate their tests, and allow payers to discern different tests from different labs," says Matt Zubiller, vice president for decision support products at McKesson.

The new map reference product with Z-Code Identifiers and CPT codes will be available from the AMA for payers to use in early 2014, says Zubiller.

The process is an enhancement of one currently used by Palmetto GBA, a Medicare administrative contractor that began using the diagnostics exchange and requiring Z-Code Identifiers to identify specific tests. The program is intended to identify and establish coverage and payment for molecular diagnostic tests. The Palmetto program originally met resistance from providers and the industry. Originally, a criticism was that using Z-Code Identifiers could raise questions under HIPAA regulations.

"Now we think, but we are not absolutely sure, that we have a HIPAA-compliant way to ask for what specific test is being performed and billed," says Newcomer.

In addition to bolstering billing, the new coding system could be used to facilitate prior authorization of tests — and evaluate the performance of specific labs.

Zubiller says prior authorization can be smarter under the new system. "This is a very granular system; it will allow payers to avoid blanket prior authorization of all tests. Instead they can work with labs and use smarter policies that target tests that are of interest."

"Clearer identification of tests will enhance transparency for physicians, hospitals, laboratories, and payers when it comes to diagnostics and treatment selection," says Zubiller. "Greater clarity will bring health care stakeholders one step closer to the collaboration needed to assess these tests."

The tandem Z-Code Identifiers can also be used in payment reform programs such as episode-of-care payment programs, which require tight control and tracking of all services, Zubiller says. The map using CPT and Z-Code Identifiers has one major deficiency: It does not currently provide information for use in determining payment rates. Most other CPT codes have been assigned a relative value by the Centers for Medicare & Medicaid Services (CMS), which Medicare and private payers use in setting payment rates. The relative value units (RVUs) provide a consistent framework for determining the complexity of a service. Payers then apply a dollar multiplier to set the actual payment rates.

Payment for PGx tests is open to wide variation in payment because no one has assigned RVUs to the CPT codes. Newcomer points out that health plans cannot get together on this because that would violate antitrust rules. "Everyone looks to CMS," he says.

The assignment of RVUs is handled by an AMA committee called the RVS Update Committee. RVS means relative value scale.

"The CPT editorial process that established the new CPT codes is separate from the RVU assignment process," says Musacchio. "At this point there has not been a focus on creating RVUs."

One thing holding that up is that the AMA is said to be considering another very large expansion of the CPT codes for genetic tests.

While progress has been made in clearly identifying genetic tests for payment purposes, there is still a long way to go.
work, capacity, turnaround time, and prices. For example, UnitedHealthcare has a longstanding relationship with Genomic Health for its Oncotype DX gene array expression test that identifies patients who are at risk for recurring breast cancer.

“Our relationship with Genomic is unique because we require the laboratory to prescreen the request for appropriate patients as part of the contract,” says Newcomer. “I believe that was a first for laboratory contracting.”

Proof of clinical utility

The strategies of Prime Therapeutics and UnitedHealthcare reflect a real-world approach to PGx testing, but they do not eliminate the need for stronger evidence in pharmacogenetics.

“We need universally accepted criteria about how much testing is needed to get a test approved and covered. The science that verifies there is a statistically significant correlation between a gene and a disease trait is not keeping up with the development of markers,” says Newcomer.

Retrospective studies are commonly used for marker validation, but they can have inherent biases, and there is no agreement about what makes a good retrospective study.

“It is not important whether the criteria are set by the FDA or another agency; we need standards for studies that attempt to demonstrate clinical validity and clinical utility,” Newcomer says.

The National Comprehensive Cancer Network (NCCN) has taken one step forward in evaluating the amount of evidence that underlies cancer biomarkers. In December 2012, it released a biomarker compendium that ranks the strength of evidence for more than 900 biomarker uses that appear in the NCCN clinical guidelines.

The NCCN describes the compendium as a tool to guide the appropriate use of biomarkers to screen, diagnose, monitor, and provide predictive and prognostic information for the treatment of patients.

The compendium was compiled by panels of experts in a process similar to the one that the NCCN uses for its treatment guidelines. The strength-of-evidence statement uses the NCCN categories of evidence and consensus.

- Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B: Based on lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Category 3: Based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

There is another step forward in PGx testing. “The assessment and validation of biomarkers is becoming easier because of changes in the ways drug studies are conducted,” says Sumithra Mandrekar, PhD, professor of biostatistics at the Mayo Clinic.

“Phase 2 trials are becoming much larger. We are using phase 2 trials to get maximum answers about the drug marker interactions. The attitude is that it is worthwhile to spend a little extra time and enroll more patients and to use phase 2 data to really refine your question, the population, your treatment, and any marker,” says Mandrekar. She says the data from phase 2 trials are being examined more closely, such as questioning the clinical validity of a biomarker, and whether the drug works selectively in a certain subset of patients.

Phase 3 studies are also facilitating marker development.

“Researchers are starting to realize that there is value in obtaining tissue specimens in phase 3 trials for possible later use, even if those specimens are not studied as part of the original drug trial,” she says.

“For example, the original study may have assessed a drug in the overall population or within a marker-specific subgroup for late stage cancer. It is then possible to use this phase 3 trial to discover a new marker or a cutpoint and also to refine the marker and perhaps assess its use in a new setting, such as EGFR and ALK mutations in early stage lung cancer,” says Mandrekar.

Rich resource

There are other uses of these specimens. “They can be used to evaluate the assay methodology, reproducibility, or cutpoint for positive versus negative marker status. Specimens from phase 3 trials have associated clinical follow-up data, so they are a rich resource,” says Mandrekar.
The gaggle of multiple sclerosis therapies jockeying for Food and Drug Administration approval was evident at this spring’s American Academy of Neurology meeting, where Teva, Genzyme, and Biogen Idec all reported phase 3 trial data. But underlying the stream of manufacturers’ news releases was a sense that with next-generation MS drugs hitting the market, established players are concerned about protecting their franchises.

Teva’s best hope for holding on to the market share it built over the years with glatiramer acetate (Copaxone) rests with laquinimod. In an open-label extension of its ALLEGRO study, Teva presented data showing that patients who started laquinimod therapy early were less likely to experience disease progression than those who did not. Genzyme, which introduced oral teriflunomide (Aubagio) last year, rolled out data from a 1-year extension of its phase 3 trials of its infusible MS candidate, alemtuzumab (Lemtrada). The open-label extension demonstrated sustained response. And Biogen Idec, which may be positioned to command the market following FDA approval of BG-12 (Tecfidera) (table), tied up loose ends by touting reductions in 1-year relapse rates in patients given peginterferon beta-1a (Plegridy). Tecfidera approval or no, interferon beta-1a (Avonex) is Biogen’s cash cow, and Plegridy — viewed as a longer-acting version of Avonex — may help to retain Avonex prescriber loyalty with its less-frequent dosing.

Other trials of note

Talimogene laherparepvec, a virus engineered to kill advanced melanoma cells, provided a durable response after six months in 16 percent of patients injected with the virus, versus 2 percent of those given subcutaneous granulocyte-macrophage colony-stimulating factor. Overall survival data will be presented later this year.

Oral, interferon-free sofosbuvir grabbed the spotlight at the International Liver Conference. Gilead, which presented positive data from several studies involving patients with various hepatitis C genotypes, touted higher cure and time-to-cure rates versus standard therapies.

The National Institutes of Health ended a phase 2b study of an HIV vaccine after results showed it didn’t work. After 24 months, 41 of the 1,250 people who received the study drug developed HIV, while infection occurred in 30 of the 1,244 volunteers given a placebo. The study involved men and transgender people who have sex with men.

Did you hear?

An FDA approval based on a 12-person study? Sarepta Therapeutics is banking on accelerated approval of eteplirsen for the treatment of Duchenne muscular dystrophy. Phase 2b results involving 12 boys were strong, but the FDA wants Sarepta to prove the clinical relevance of the data before deciding whether additional study is
European regulators rejected Pfizer’s rheumatoid arthritis tablet, tofacitinib (Xeljanz), unconvinced about its efficacy data and concerned about side effects. Xeljanz received FDA approval last November. ... Fears of a new bird flu are sweeping Asia, with 127 deaths reported in China through early May. Chinese officials expect to have an H7N9 vaccine ready in six months, but Novartis says it has the technology to have a vaccine ready in 6 to 8 weeks.

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**SELECTED FDA BIOLOGIC AND SPECIALTY DRUG APPROVALS, MARCH 16–MAY 3, 2013**

<table>
<thead>
<tr>
<th>Date (type)</th>
<th>Manufacturer</th>
<th>Drug (trade name); administration</th>
<th>Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 27 (NDA)</td>
<td>Biogen Idec</td>
<td>Dimethyl fumarate (Tecfidera); oral</td>
<td>Relapsing forms of multiple sclerosis</td>
<td>Strong efficacy data in trials vs. placebo and with a comparator arm of glatiramer acetate (Copaxone), minus the safety tradeoff associated with powerful MS drugs, equals high sales expectations — “on the order of a Lipitor,” one analyst said. Cost is expected to be similar to other new MS oral drugs, about $50,000 per year.</td>
</tr>
<tr>
<td>April 29 (BLA)</td>
<td>CSL Behring</td>
<td>Prothrombin complex concentrate (human) (Kcentra); IV infusion</td>
<td>Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (e.g., warfarin) therapy in adult patients with acute major bleeding</td>
<td>Quick-acting product reverses effects of warfarin, but not those if novel anticoagulants such as dabigatran (Pradaxa) or rivaroxaban (Xarelto).</td>
</tr>
<tr>
<td>April 30 (NDA)</td>
<td>Raptor Therapeutics</td>
<td>Cysteamine bitartrate (Procysbi) delayed-release capsules</td>
<td>Management of nephropathic cystinosis in adults and in children age 6 and older</td>
<td>Nephropathic cystinosis affects about 500 people in the United States. This delayed-release version of cysteamine (Cystagon) allows for less-frequent dosing and avoidance of GI side effects. Procysbi will cost $250,000 per year, vs. $10,000 for Cystagon, on the market since 1994.</td>
</tr>
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**SELECTED FDA-RELATED ACTIVITIES, MARCH 16–MAY 3, 2013**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Drug (trade name)</th>
<th>Type of drug</th>
<th>Proposed use</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Gilead Sciences</td>
<td>Elvitegravir and Cobicistat</td>
<td>Elvitegravir is an integrase inhibitor that blocks the ability of HIV to integrate into the genetic material of human cells. Cobicistat inhibits cytochrome P450 3A (CYP3A), a metabolic enzyme, and acts as a boosting agent.</td>
<td>Elvitegravir and cobicistat are two of the four agents in Gilead’s Stribild, which the FDA approved last year. Gilead is seeking NDA approvals for elvitegravir and cobicistat as stand-alone agents for use as part of HIV treatment regimens.</td>
<td>FDA issued complete response letters April 29 for elvitegravir and cobicistat, citing deficiencies in documentation and validation of quality testing procedures and methods. The denials do not affect the FDA’s approval or continued use of Stribild.</td>
</tr>
<tr>
<td>Aveo</td>
<td>Tivozanib</td>
<td>Oral once-daily, investigational tyrosine kinase inhibitor</td>
<td>Advanced renal cell carcinoma</td>
<td>An FDA advisory panel voted 13–1 against approval, concerned about “an adverse trend” in OS despite a PFS benefit. The panel recommends another phase 3 trial. A final FDA decision is due by July 28.</td>
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</tbody>
</table>

BLA=biologics license application, IV=intravenous, MS=multiple sclerosis, NDA=new drug application, OS=overall survival, PFS=progression-free survival.


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FDA approval last November. ... Fears of a new bird flu are sweeping Asia, with 127 deaths reported in China through early May. Chinese officials expect to have an H7N9 vaccine ready in six months, but Novartis says it has the technology to have a vaccine ready in 6 to 8 weeks.

— Michael D. Dalzell

All clinical trials described in Drug Track are phase 3, randomized, controlled studies unless otherwise specified.
Overall drug spending increases 2.7 percent

Despite the continued rapid uptake in specialty and biologic drugs, overall drug spending across commercial, Medicare, and Medicaid managed care plans increased just 2.7 percent last year over 2011.* The effect of specialty drug costs was mitigated by the first decrease in traditional drug spending in more than 20 years, according to Express Scripts.

The traditional-drug spending trend was driven by higher generic-drug utilization, thanks to the arrival of the patent cliff. As managed care plans provided members with incentives to switch from brand-name pharmaceuticals to generic alternatives, utilization for 8 of the top 10 traditional therapy classes actually increased. Unit-cost decreases in 7 of those classes, however, more than compensated for the demand.

Specialty drugs continue to be a different story. Specialty-drug spending increased more than 18 percent over 2011, the strongest increase since 2004. Hepatitis C, respiratory, and cancer drugs led the way, each with spending increases of more than 25 percent. Biologics for inflammatory conditions represented the highest per-member, per-year spend — $50.62.

— Michael D. Dalzell

*Based on Express Scripts’ book of business. Express Scripts is the largest PBM in the United States.
What health plans will spend on traditional drugs is falling, caused by the wave of patent expirations for blockbuster drugs. Express Scripts, a pharmacy benefit manager, reports that spending for traditional drugs will decline through at least 2015. In its 2013 Drug Trend Report, the company expects spending to be –1 percent in 2013, –1.7 percent in 2014, and –1.4 percent in 2015. Utilization is expected to remain stable, but insurers will see even more savings as patents expire for Cymbalta (duloxetine) and Lidoderm (lidocaine).

Three traditional drug classes, however, merit watching: diabetes agents, agents that treat attention deficit disorders, and antidepressants.

The report says that for the second year in a row, medications used to treat diabetes were the most expensive therapy class per member, per year (PMPY). And while spending is expected to increase over the next few years, the magnitude of change is expected to slow. The report identifies new dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP1) competitors, and new insulins, including dulaglutide, still experimental, with once-weekly dosing that has shown promise in clinical trials, as possible new causes of spending increases.

Attention deficit disorder agents as a class had a drug expenditure increase of 14.2 percent in 2012, driven by increased utilization among adults and by shortages. That number is expected to be only 4.4 percent this year as the market stabilizes and generic competition increases. By 2014, however, expect an increase of 10 percent and then 8.6 percent in 2015. Express Scripts expects an increase in utilization among young and middle-age adults.

In contrast to these two classes, antidepressant spending should decrease. The report expects a 4.7 percent decline with the expiration of the Lexapro patent. Although there are some new drugs in the pipeline, like levomilnacipran and edivoxetine, they are expected to compete with existing drugs of the same type rather than to dramatically change utilization of existing drugs. Expect spending on antidepressants to be down 8.7 percent in 2014 and down 6.5 percent in 2015.

Amid falling drug expenditures generally, exceptions to the rule

Source: Express Scripts, Drug Trend Report 2013
In the past 10 years, no single disease has received as much attention in “Tomorrow’s Medicine” as multiple sclerosis. This group of patients, whose disease causes severe lifestyle disruption and eventual death, had no definitive therapy until the FDA approved interferon beta-1-b in 1993.

The hallmark of the disease is a constant pattern of relapsing and remitting neurologic disruption, although some patients experience rapid progress in a more linear fashion. The loss of the insulating myelin sheath surrounding the nerves is a dramatic autopsy finding and leads to progressive loss of function over decades until many people are wheelchair-bound.

MS, first described in 1868 by Jean-Martin Charcot, affects about 400,000 in the United States. A majority are women; many are stricken in their 20s.

This autoimmune disorder has been the focus of intense research for much of the last century leading to some remarkable therapies. The first approved drugs, including interferon beta-1-b, interferon beta-1-a, glatiramer acetate, and mitoxantrone, as well as the later arrival natalizumab required injection or infusion therapy. All have significant adverse events.

Last year, two oral compounds were approved: fingolimod and teriflunomide. They, too, have significant adverse events, and despite some impressive efficacy results in the clinical trials, there are still unmet needs because of the difficulties associated with these compounds.

**Tecfidera**

On March 27, the FDA announced the approval of a third oral product, dimethyl fumarate, sold by Biogen Idec under the name Tecfidera and “indicated for the treatment of patients with relapsing forms of multiple myeloma.” Tecfidera is a delayed-release tablet given as a maintenance dose of 240 mg orally, twice per day after an initial dose of 120 mg bid for one week.

**Tolerable side effects**

Compared to many other drugs for MS, this one has relatively tolerable side effects. It does not have a black box warning. The main warning is that Tecfidera may decrease lymphocyte counts by a mean of 30% during the first year of therapy but then the levels remain stable. The lymphocyte count improves after ceasing therapy but does not return to baseline. Six percent of patients taking Tecfidera develop a lymphocyte count lower than 500, dangerously low.

Performing an annual blood test to determine the lymphocyte count is recommended.

The most common adverse event is flushing which occurred in 40% of patients and resulted in 3% of patients stopping therapy.

The second common adverse set of events is gastrointestinal — nausea, vomiting, diarrhea, abdominal pain and dyspepsia — collectively resulted in an additional 4% of patients who discontinue therapy.

Other adverse events include hepatic transaminase elevations that occurred primarily in the first 6 months of therapy and were not associated with a significantly increased cessation rate as compared to placebo.

This compound is one of a family of compounds that have a rather simple structure and have found numerous uses in other industries. One common use was as a sofa and shoe treatment used to prevent mold during transport.

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Thomas Morrow, MD, is the immediate past president of the National Association of Managed Care Physicians. He has 24 years of managed care experience at the payer or health plan level. Contact him at TMorrow@ManagedCareMag.com.
and storage. Because of skin irritation that made headlines in Europe, it was banned for these uses.

The mechanism of action is unknown but is thought to be related to its ability to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. The Nrf2 pathway is involved in the cellular response to oxidative stress. The actual compound, dimethyl fumarate, is rapidly converted to the active metabolite monomethyl fumarate prior to entering the systemic circulation by esterases in the gastrointestinal tract, blood and tissue.

Further metabolism occurs through the tricarboxylate acid cycle, with the end result being carbon dioxide that is ultimately eliminated through the lungs.

The Tecfidera metabolism does not involve the cytochrome P450 system, which is significant because this important metabolic pathway metabolizes many drugs. Physicians are cautious when prescribing numerous drugs that involve this metabolic pathway because of the risk of drug-to-drug interactions.

**Efficacy**

Tecfidera was studied in two randomized, double-blind, placebo-controlled studies that collectively enrolled 1,529 patients with an overall exposure of 2,244 person-years. Both studies selected the primary endpoint of “proportion of patients relapsed at 2 years.”

Additional endpoints included the clinical endpoints of annualized relapse rate and time to disability progression. MRI findings were also included in the secondary endpoints and consisted of the number of new or newly enlarging T2 hyperintense lesions, the number of T1 hypointense lesions, and the number of gadolinium-enhancing lesions.

The trials demonstrated a relative reduction in the relapse rate of 49% and 34%, respectively, in Trial 1 and 2. The proportion with disability progression was 16% and 13% in study 1 and 2 as compared to 27% and 17% progressing in the placebo arms of the two studies.

MRI studies also demonstrated positive results with 2.6 and 5.1 new or newly enlarging lesions in the Tecfidera arms of study 1 and 2, respectively. This compared very favorably with 17 and 17:4 in the placebo groups.

Obviously these trials compared Tecfidera with a placebo. The competing oral drugs Aubagio and Gilenya have not been compared to Tecfidera in a clinical trial. Comparing the pivotal trials for these two (remembering the exact conditions and trial designs were not exactly alike) resulted in Tecfidera demonstrating somewhat better raw results than Aubagio. Gilenya appears to have somewhat better efficacy but is associated with side effects that require more clinical monitoring and are a bit more problematic.

**Managed care implications**

The price of Tecfidera has been announced at $55,000 per year, compared to $60,000 for Gilenya and $48,000 for Aubagio. Matthew Herper, staff writer for *Forbes*, wrote that Tecfidera will “become the most commonly used multiple sclerosis drug, taking share from not only the newer pills but also from older, commonly used injections....”

Although Tecfidera does not completely arrest MS, its addition opens the door to a rather broad choice for clinicians and patients in this rapidly expanding world of Tomorrow’s Medicine.

The author is a director in the value-based health department at Genentech. He has had no other industry affiliations in the past three years. The views expressed in Tomorrow’s Medicine are the author’s alone.
Cadillac has got a wheel in the ditch

The so-called Cadillac tax, an Affordable Care Act provision that is to begin in 2018, will very likely make many employer-sponsored health plans, not just the ones tailored for high-earners, too expensive, predicts a report by the Bipartisan Policy Center (http://tinyurl.com/Cadillac-Tax).

Cadillac plans cost above $10,200 per individual and $27,500 per family per year. Insurers offering such benefit packages will pay a 40 percent tax on any amount above that threshold — and that’s the rub.

The study, A Bipartisan Rx for Patient-Centered Care and System-Wide Cost Containment, says that employers and employees may wind up bearing the burden. If premiums increase 5.7 percent annually (the rate that is projected from national health expenditure data and one that is lower then historical growth), “the Cadillac tax would effectively prohibit half of today’s employer-sponsored health plans by 2029.”

But as we pointed out a few years ago, the reasons a plan might exceed the threshold are varied, and may have nothing to do with luxury benefits (http://tinyurl.com/Diamond-Cadillac).

The authors of the Bipartisan Policy Center report propose replacing the Cadillac tax with a plan that limits the income tax exclusion for employer-sponsored insurance (ESI) at the 80th percentile in 2015.*

This would be indexed to GDP per-capita growth through 2023, and GDP per-capita growth plus 0.5 percentage points thereafter. This would slow down bracket creep, but not eliminate it, so as to keep some pressure on.

* The study states that “Under current law, employer contributions to employee health benefits, including ESI [employer-sponsored insurance] premiums and various tax-advantaged health care spending accounts, are excluded from an employee’s taxable income. Employee premium contributions are also paid with pre-tax dollars in most cases. The ESI tax exclusion is the single largest tax expenditure, reducing annual federal income tax and payroll tax revenue by about $250 billion — which necessitates higher marginal tax rates on everyone, and it also reduces revenues for state governments.”

Source: Bipartisan Policy Calculations, assuming that ESI premiums grow at the same rate as national health expenditures, as projected by the CMS Office of the Actuary.