NovoPayerLink works behind the scenes to help put you at the forefront of diabetes management

At Novo Nordisk, we’re committed to supporting payers in the complex management of diabetes. That’s why we created NovoPayerLink.com, a Web site that offers exclusive diabetes tools, resources, and videos just for you. Contact your Novo Nordisk Account Executive for access today.
Our cover story on page 18 talks about private-label health plans in which Aetna offers large providers stake in the insurance side of the business. Aetna — and other health plans that might try this — hopes that working with the dominant local provider in an area will increase market share in places where they’re either running behind or out of the running.

I suspect this to be one of the early ripples before a tsunami of unforeseen consequences — both good and bad — of the Affordable Care Act.

A private-label health plan offers an alternative formula for competition to providers who do not want to join an accountable care organization (ACO), whether for operational or financial reasons. It comes down to this: Cost-cutting is not a growth strategy for hospitals, but becoming a plan sponsor might be a way to come to terms with the new methods of payment.

And some of our ideas about where to cut costs may be wrong.

A study in the *Journal of the American Medical Association* last month notes that trying to avoid emergency department care for the costliest Medicare patients by treating them in physicians’ offices instead won’t save as much as some experts had hoped.

Karen Joynt, MD, MPH, the lead author, tells Reuters Health, “It’s a more complicated problem than we thought.” But isn’t it always.

Answers to such vexing dilemmas might be found anywhere, maybe even across the vast Atlantic Ocean. Which brings us to our new department — The Wider View — on page 11. Our man in London (I always wanted to say that), Robert Royce, PhD, will report on how health care fares in the old world. Or doesn’t fare, as the case may be. Now an independent consultant, Robert has had a strong career in health care in the United Kingdom, most recently as director of strategy at Barking, Havering and Redbridge University NHS Trust in greater London.
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**Better-Functioning Offices Make PCPs Work Enjoyable**

Using “joy” and “primary care physician” in the same sentence can be downright provocative these days, as the authors of a study that does just that point out. “We set out in search of joy. What we found were pockets of professional satisfaction.”

Specifically, the authors — who include Thomas Bodenheimer, MD, a member of Managed Care’s Editorial Advisory Board — focus on 23 high-performing primary care practices to find out “how these practices distribute functions among the team, use technology to their advantage, improve outcomes with data, and make the job of primary care feasible and enjoyable as a life’s vocation.”


“We question why young people would devote 11 years preparing for a career during which they will spend a substantial portion of their workdays, as well as much of their personal time at nights, on form-filling, box-ticking, and other clerical tasks that do not utilize their training,” the study states.

They also question whether patients are being optimally served by this situation.

The study’s authors shadowed physicians for a day and also met with administrators and clinical leaders.

The study looks at seven methods that make practices more efficient. They are:

- Reducing work through pre-visit planning and pre-appointment laboratory tests
- Adding capacity by sharing the care among members of a team
- Eliminating time-consuming documentation through collaborative documentation and nonphysician order entry
- Saving time by ordering medications for an entire year in some cases
- Reducing unnecessary physician work by having a nurse or physician assistant passing on to the physician only information that specifically requires a doctor’s expertise
- Improving team communication through huddles and more formal meetings
- Improving team functioning by, for instance, having a medical assistant and physician sit side by side

The study notes, “No single practice has solved every issue; each practice still struggles to overcome its own set of constraints.”

Case studies illustrate the effectiveness of different approaches. For instance, six of the practices have nurses or medical assistants enter the orders and follow up with the patient.

“At the Cleveland Clinic Strongsville, primary care physicians work with two medical assistants or one medical assistant and one registered nurse.”

They take notes while the physician talks to and examines the patient.

“After one year of the new model, average daily visits increased from 21 to 28, thereby improving access and continuity.

“Revenue was up 20% to 30%, which has exceeded the cost of the additional medical assistant or nurse.”

**ED-to-ICU Transfer Sees Huge Increase**

Admissions to intensive care units (ICUs) from emergency departments (EDs) rose by nearly 50% between 2002 and 2009, according to a study in the May issue of Academic Emergency Medicine.

The authors of “National Growth in Intensive Care Unit Admissions from Emergency Departments in the United States from 2002 to 2009” add that nonwhites and Medicaid enrollees are over-represented:

“Higher rates of general ED and ICU use in these groups may be a symptom of less access to primary care and preventive services, contributing to both increased use of the ED and increasingly higher severity presentations requiring ICU-level care.”

Researchers used data from the National Hospital Ambulatory Care Survey, a national sample of hospital-based EDs. They looked at 4,267 patients who moved from the ED to the ICU, a sample representing over 14.5 million ED encounters during that time.

“Over the study period, ICU admissions from EDs increased from 2.79 million in 2002/2003 to 4.14 million in 2008/2009, an absolute increase of 48.8% and a mean biennial increase of 14.2%,” the study states. “By comparison, overall ED visits increased a mean of 5.8% per biennial period.”

The most frequent reasons for admission were chest pain, shortness of breath, and abdominal pain. The most frequent diagnoses were chest pain, congestive heart failure, and pneumonia.

“Despite this, the top 10 complaints and diagnoses [made up only] 50% and 35%, respectively, of all ICU admissions. This demonstrates the
heterogeneity of critically ill patients cared for in ED settings, further underscoring the need for critical care training in emergency medicine residency and beyond.

Another issue is that patients admitted to the ICU from the ED also underwent more tests, especially CTs and MRIs “which increased from 16.8% in 2002/2003 to 37.4% in 2008/2009, a 6.9% mean biennial increase.”

Patients making such a transfer spend an average of five hours in the ED, the researchers find. “This finding may suggest that delays in transfer from ED to ICU may be more dependent upon the availability of ICU beds than the level of resource utilization in the ED.”

**Mental Disorders In Children Soar**

The number of children diagnosed with mental disorders is increasing, bringing with it a $247 billion annual bill, according to a report by the Centers for Disease Control and Prevention.

“A total of 13%–20% of children living in the United States experience a mental disorder in a given year, and surveillance during 1994–2011 has shown the prevalence of these conditions to be increasing,” says the report “Mental Health Surveillance Among Children — United States, 2005–2011” (http://tinyurl.com/CDC-mental-report).

Attention-deficit disorder was the most prevalent parent-reported diagnosis among children aged 3–17. Behavior or conduct problems were second (3.5%), followed by anxiety (3%), depression (2.1%), and autism spectrum disorders (1.1%).

Mental disorders are among the most costly problems to deal with in children, and the authors of the study — published as a supplement to the May 17 edition of the CDC’s Morbidity and Mortality Weekly Report — cite other studies to make the case. “[One] included insurance claims from approximately 20% of the privately insured U.S. population aged 6 to 17 treated for an emotional or behavioral disorder in 2008,” the report adds.

**Patient safety not solely nurses’ job**

Hospital executives seem to be sending contradictory messages regarding patient safety in a survey by American International Group (AIG), the huge insurance company. Every staff member in the hospital is responsible for patient safety, according to 98% of hospital C-suite executives. But then 52% say that nurses “own it.” The survey report adds, “Interestingly, these executives see nursing staff turnover as one of the least influential items on overall hospital risk, including patient safety, regardless of the fact that they place the onus of patient safety on nurses.”

The authors counter that everyone in the hospital must own patient safety: doctors, nurses, administrators, support staff. “Everyone who touches a patient is equally responsible for patient safety. Anyone who identifies an issue with patient safety must feel free to discuss that issue for the benefit of patient safety without fear of retribution.”

**Hospital administrators assign responsibility**

<table>
<thead>
<tr>
<th>Most responsible for patient safety</th>
<th>52%</th>
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<tr>
<td>Nursing/clinical staff</td>
<td></td>
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<tr>
<td>Hospital executives</td>
<td>19%</td>
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<tr>
<td>Risk managers</td>
<td>11%</td>
</tr>
<tr>
<td>Everyone on staff</td>
<td>7%</td>
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<tr>
<td>Medical staff</td>
<td>4%</td>
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<tr>
<td>All the above</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
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<tr>
<td>Don’t know</td>
<td>1%</td>
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**Most responsible for overall hospital risk (including patient safety)**

<table>
<thead>
<tr>
<th>Most responsible for overall hospital risk (including patient safety)</th>
<th>74%</th>
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<tr>
<td>Patient safety dept.</td>
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<tr>
<td>Hospital executives</td>
<td>64%</td>
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<tr>
<td>Medical staff</td>
<td>63%</td>
</tr>
<tr>
<td>Risk managers</td>
<td>59%</td>
</tr>
<tr>
<td>Patient safety culture</td>
<td>50%</td>
</tr>
<tr>
<td>Board of trustees</td>
<td>41%</td>
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<tr>
<td>Nurse turnover</td>
<td>38%</td>
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<tr>
<td>Financial dept.</td>
<td>29%</td>
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<tr>
<td>Legal dept.</td>
<td>24%</td>
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Note: The data were generated by a 15-minute, computer-assisted telephone survey of 250 hospital executives conducted from Nov. 13 to Dec. 20, 2012.

Source: Patient Safety; Hospital Risk: Perspectives of Hospital C-Suite and Risk Managers, AIG, March 2013.
<65 years with private insurance and weighted the data to reflect a national estimate. This study reported a 24% increase in inpatient mental health and substance abuse admissions among children during 2007–2010, as well as increases in use and cost of these services and psychotropic medications for teenagers specifically over the same period (http://tinyurl.com/children-report).

The study addressed the vexing problem of just how mental disorders among children can or should be measured. “Substantial but not insurmountable challenges to surveillance of mental disorders in children exist... Criteria for mental disorders are subjective, are based on a symptom count instead of a biologic measure, might require assessment by different persons or in different settings, and might change over the course of development.”

More Docs, Hospitals Get EHR Payments
In one of the most dramatic comebacks in health care, 80% of hospitals and over 50% of doctors’ offices will receive incentive payments this year for installing electronic health record systems that meet government meaningful use standards, according to the Department of Health and Human Services.

It was only a few months ago that the New England Journal of Medicine warned that doctors and hospitals were very behind in their EHR upgrades (http://tinyurl.com/standards-blog-item).

This is something HHS also notes. In 2008, only 17% of physicians and 9% of hospitals were eligible for incentive payments.

“We have reached a tipping point in adoption of electronic health records,” says HHS Secretary Kathleen Sebelius.

There are 15 core objectives that must be met in order for the government to underwrite up to $44,000 in new technology spending per physician.

As of May 1, more than 291,000 health care professionals, mostly physicians, and over 3,800 hospitals have received incentive payments.

“In four years, they’ve made more progress then in the previous 20 years,” Farzad Mostashari, the national coordinator for health information technology at HHS, tells USA Today.

The incentive payments are part of the American Recovery and Reinvestment Act of 2009 (“the stimulus”). HHS in its announcement notes that “Health IT systems give doctors, hospitals, and other providers the ability to better coordinate care and reduce errors and readmissions that can cost more money and leave patients less healthy.”

All well and good, but some experts wonder how much the Affordable Care Act, which fosters EHR use, might bump into other laws.

“They worry that HIPAA and state confidentiality laws are getting in the way of efforts to coordinate care across sites of service.

“I respect patients’ need for privacy, but do you really care if someone knows that you broke your arm and went to the hospital?” Craig Garner, a lawyer and health care consultant, told us last month in our cover story on problems with ACA implementation. “Historically our country has cut back rights in times of war. If we really are in a war on health care, let’s get rid of HIPAA and HITECH. They’re obstacles to health care reform.”

Briefly Noted
In what’s being called one of the first instances of a group using the Affordable Care Act to contest an insurer’s benefit package, a women’s advocacy group says that a beneficiary should not have to pay for a dependent’s pregnancy costs. The Wall Street Journal on June 4 reports, “The complaints are rooted in a health law provision requiring employers to allow workers to keep dependents up to 26 years old” on coverage plans.... The Supreme Court ruled last year that states could opt out of Medicaid expansion, and so far 14 have done so, according to a report in the June issue of Health Affairs. This saves the government about $8.4 billion a year, but ensures that 3.6 million more people will be without insurance. The states not participating, though, are likely to see an increase in spending in the short run because they’ll have to spend more on uncompensated care.... CareFirst BlueCross BlueShield’s foray into the world of patient-centered medical homes has paid off handsomely. The health plan, with 3.4 million covered lives in Maryland, Washington, D.C., and northern Virginia, reports that it saved $98 million last year with its patient-centered medical home. It saved $36 million in 2011. Some experts worry that medical home savings will dwindle over time as doctors run out of obviously wasteful methods to eliminate. Most of CareFirst’s savings came from lower drug spending, less use of emergency departments, and fewer hospital admissions.... COPD hits women hardest, a report by the American Lung Association reaffirms. Women are 37% more likely to have COPD then men. About 7 million women are known to suffer from the disease, and millions more have it but have not been diagnosed.... We spend $200 billion each year, mostly in unneeded hospitalizations and doctor visits, thanks to the improper use of prescription drugs, according to a study by IMS Health’s Institute for Healthcare Informatics. The study, released June 19, says too many patients take the incorrect drug or dose. There is often inadequate oversight when patients are taking more than one medication. The study also cites the misuse of antibiotics. The authors say that financial incentives included in the ACA for better care coordination may help reduce the amount of waste.... Men are much more likely to develop health care related infections than are women, according to a study in the Journal of General Internal Medicine. Men have a 60% higher risk of developing bloodstream and surgical site infections. — Frank Diamond
Tests that search for individual genetic biomarkers to guide drug therapy in cancer are giving way to a game-changing technology. Instead of looking for one specific genetic alteration, tumor profiling tests are using both first and next generation sequencing systems to race through millions of DNA base pairs in an entire tumor genome to identify all of the alterations that exist in a cancer patient’s tissue sample.

A tumor profile test may encompass a panel of more than 200 genes. It looks for all alterations that have been associated with any solid tumor cancer. For example a tumor-profiling test may identify the presence of HER2, KRAS, or EGFR alterations in cancers outside of the one where they are well established. Profiling tests also attempt to identify a slew of lesser-known alterations.

“Cancer has long been defined by the tissue of origin, in part because that is all the diagnostic tools allowed us to do,” says Mike Pellini, MD, CEO of Foundation Medicine. “Now, we understand there are underlying molecular pathways that are not specific to any one tissue and new technologies that allow us to look for all pathways that are turned off and on.”

Tumor profiling is a leap forward, providing new insight to the genomic drivers and even the heterogeneity of tumors, and its use is skyrocketing. It has captured the attention of academic researchers, drug companies that use it to identify new targeted therapies, upstart clinical labs that market direct to consumers, and physicians who are looking for information to guide their treatment decisions.

About 30% to 40 percent of the tests are ordered for late stage disease. This may suggest the initial treatment is no longer working,” says Pellini. "Another bucket is comprised of uncommon or rare cancers, like small-bowel cancer or uncommon diseases that lack clear treatment options — where the oncologist may be looking for a rational approach to therapy. A third example is where only a small tissue sample is available and the physician is concerned that there might not be enough tissue to run a series of individual molecular tests.”

There is a risk that tumor profile reports may overload physicians with a complex list of possible causes of a cancer. The frequency of many of these alterations is generally low but it has become a common practice for profiling labs to suggest that the results may guide treatment. Test reports often say some of the alterations may be "potentially actionable targets." Some reports also list the drugs that could be used.

Crux of the problem

Therein lies the problem for clinicians and health plans. Not all molecular profiling is backed by solid evidence from gold standard clinical trials. Yet clinicians face the real-world problem of finding treatment options for tough cancers like those with acquired drug resistance. Health plans face the challenge of meeting their coverage benchmarks of cost effectiveness and clinical utility. “The insurance industry is somewhat cautious; we like evidence from scientific peer-reviewed literature, and these tests are still in the evaluation stage,” says Aetna’s Ira Klein, MD. A recent meeting of the American Society of Clinical Oncology included several abstracts of molecular profiling studies that showed the ability of these assays to identify new alterations, but most studies so far have shown insight only to the genetic basis of different cancers.

“We are concerned about who will be able to give the most reliable test,” says Klein. Many companies are developing assays with unique gene panels, and there is no specific regulatory
Early results of molecular monitoring

The June meeting of the American Society of Clinical Oncology highlighted several molecular profiling study abstracts. Many did not represent rigorous research, but they did provide some very interesting results.

Non-small-cell lung cancer is a frequent target for molecular profiling research. Lung cancer patients with EGFR mutations initially respond to tyrosine kinase inhibitors (TKIs), but then commonly develop drug resistance, and there is great interest in finding the genetic drivers of that acquired resistance.

Researchers at the University of California–San Francisco presented a study aimed at identifying possible additional drivers of acquired resistance. In the pre-treatment patients, next-generation sequencing with a 263-gene panel confirmed the presence of the EGFR L858R mutation in 95% of the DNA samples. The assay also discovered a concurrent BRAF V600E mutation in about 6% of the samples.

In patients who acquired TKI resistance after three months of treatment, the frequency of the BRAF V600E mutation increased to approximately 60%.

They abstract session concluded that the BRAF mutation can be an additional oncogenic driver.

The chosen labs are Med Fusion and Foundation Medicine. Med Fusion already has close business ties with U.S. Oncology as a clinical reference lab. Foundation Medicine has developed a tumor assay that is used in several academic medical centers. It encompasses 236 genes covering all solid tumor cancers.

A key component of the initiative is a data system for ordering all types of tests and for receiving lab results including genetic profiles in a consistent electronic format.

“It used to be that from a pure scientific perspective the treatment of NSCLC was one of the least interesting cancers. Now it has become one of the most interesting because a number of mutations have been identified that may lead to the use of targeted drugs,” says Neubauer. “Lung cancer has become an example of how molecular diagnostics may affect real-world patient care.”

The U.S. Oncology Network is known for its work on oncology pathways. Neubauer says that when sufficient profiling evidence is developed, it will work its way into those pathways.

The U.S. Oncology Network has laid out a clear plan for how it will take advantage of molecular profiling. With a few rare exceptions, the official stance of most health plans on molecular profiling is that it is experimental and not medically necessary. That strategy may work for now, but Foundation Medicine’s Pellini says, “It is not a question of ‘if’ molecular profiling will be covered — it is a matter of when.”

“NSCLC ... has become one of the most interesting [cancers] because a number of mutations have been identified that may lead to the use of targeted drugs,” says Marcus Neubauer, MD, medical director of oncology services for McKesson Specialty Health.

It’s an attempt to have an organized approach to how we handle precision medicine,” says Marcus Neubauer, MD, medical director of oncology services for McKesson Specialty Health, the parent organization of U.S. Oncology.

Klein says that another big concern. “The practical application of profiling results and the results of application are not yet known. It is still unclear how and when to use test results to guide therapy.

“At this point physicians do not understand the significance of all of this data,” Klein continues. “Data overload could prompt doctors to order more tests to narrow results, or it may lead to inappropriate treatment decisions.

“One really important aspect of this is that providers do not have the data infrastructure to translate all of the information in a report into outcomes. We need to build data libraries and maintain the data to determine where there are measurable results.”

Working toward a solution

In May, the U.S. Oncology Network announced a personalized medicine initiative aimed at incorporating molecular profiling and other genetic tests into clinical practice. Its new approach addresses many of the issues Klein identified.
Over the past few years hospitals around the country have been steadily snapping up physician practices to help bolster their business. The trend has drawn the scrutiny of Medicare’s Congressional watchdogs at MedPAC, who say that the consolidation of medical practices has spurred a migration of services to hospital outpatient centers, which charge significantly more than the practices ever did for the same services, and resulted in sharply higher prices on dozens of services which are still delivered at the doctors’ offices they bought.

Now they’re asking lawmakers to flatten those fees in a one-price-fits-all approach that’s likely to benefit private insurers who complain of suffering from the same bite.

The move by MedPAC has triggered a ground war on Capitol Hill with the American Hospital Association, which says any reduction in these fees would just further bleed hospitals that are already losing money on many of the services they provide Medicare beneficiaries. The hospitals also have to contend with critics who say that many of their members are being repeatedly gouged by the physician practices that were bought up by hospitals, and who then added fees for no good reason.

America’s Health Insurance Plans has been jabbing back as well. In a letter to the Senate Finance Committee at the end of May, Executive Vice President Carmella Bocchino made it clear that any comprehensive look at reforming Medicare’s physician payment system, a perennial hot topic in Washington, D.C., has to nip this particular trend in the bud.

“Modernization of the fee schedule should completely eliminate site of service differential reimbursement,” Bocchino wrote. “Specifically, revisions to the fee schedule should address the current disparity in payments for identical services delivered in a physician’s office versus a hospital outpatient facility.”

All things aren’t equal between outpatient departments (OPDs in MedPAC lingo) at a hospital and a doctor’s office, MedPAC concedes in its recent annual report to Congress. Hospitals, for example, maintain idle space so they can handle a sudden influx of patients — one of many hospital practices that justify higher prices for many of the hospital services Americans depend on.

But MedPAC zeroed in on dozens of services it says can be done just as safely and effectively in an outlying practice as at a hospital, and it divided them between the services that should warrant a flat fee along with another group of fees that should be only narrowly higher at hospitals.

If you do that, says MedPAC, the agency and beneficiaries would save a combined $900 million, helping to rein in annual costs while cutting outpatient revenue at hospitals by 2.7%. Just restricting the practice to cardiac imaging services would produce the lion’s share of those savings — $500 million. And for hospitals that provide a disproportionate level of services to the elderly who don’t have a primary care doctor to see, they could cap the cuts to prevent unduly punishing those hospitals.

Upgrades

There have been a variety of studies underscoring the rapid-fire acquisition of medical practices in recent years. One in particular from the American College of Cardiology found that the percentage of cardiologists employed by hospitals had grown from 11% of rank-and-file specialists to 35% between 2007 and 2012. For physicians, the sale of their practice can allow a hospital to come in and pay for an upgrade in electronic medical record technology while
guaranteeing a reliable income. For hospitals it’s a chance to develop their own steady flow of referrals. MedPAC concluded that many of the services that had been provided in the doctor’s office were also moving to the more expensive hospital setting.

**AHA mounts counterattack**

“From 2010 to 2011 … the share of evaluation and management office visits provided in OPDs … increased by 9%, the share of echocardiograms provided in OPDs increased by 15%, and the share of nuclear cardiology tests in OPDs increased by 22%,” noted MedPAC. “If these three types of services continue to migrate to OPDs at the same annual rate from 2011 to 2021, Medicare spending would be $2.3 billion higher per year by 2021, and beneficiary cost sharing would be $590 million higher per year.”

The report adds that “As an example of payment differences in 2013, Medicare pays 141% more in an OPD than in a freestanding physician’s office for a level II echocardiogram (counting the professional fee and facility fee). In addition, in 2013, Medicare pays 70% more in an (outpatient facility) than in a freestanding office for a 15-minute evaluation and management (E&M) office visit.”

Not surprisingly, the American Hospital Association fired a preemptive shot against the move back in March in an effort to stop MedPAC from including the recommendation in its report. In a detailed letter to Glenn Hackbarth, the chairman of the committee, the AHA did its own math and came back with a much deeper financial wound, estimating that the prospective deduction for the services would carve $2 billion from the books of “the chronically underfunded Medicare outpatient system.”

Rick Pollack, the executive vice president of the AHA, noted that “Given the complexity involved in crafting a site-neutral payment policy, the disproportionate impact that even small methodological decisions have on the analytical outcome and on hospital payments, and the many remaining unanswered questions about the underpinning analysis, the AHA position is that an increased level of transparency regarding the commission’s methodology and a more robust analysis of impact is absolutely necessary before this issue is committed to a published chapter.”

Those Level II echocardiograms that MedPAC was so concerned about, added Pollack, shouldn’t even be part of the discussion because they occur in emergency departments more than 20% of the time and the commission had agreed to consider only those items that take place in the ED less than 10% of the time. And anyway, he added, the association couldn’t replicate MedPAC’s financial analysis, raising questions about its accuracy. The vast majority of the tests still take place in physicians’ offices and besides that, notes Pollack, coding changes over the last several years may well have skewed the data anyway.

The AHA insists that if Medicare lowers these outpatient rates, the agency will essentially be undermining the hospital’s emergency medical capability, underfunding the idle capacity many hospitals maintain to handle sudden spikes in demand, which can happen in the wake of crises like the Boston bombing.

But the higher prices aren’t just charged for the services they provide in the hospital. Hospitals are also routinely charging insurers’ members a much higher rate for the services their employed physicians provide in their offices outside the hospital. MedPAC cited one case, reported in the *Boston Globe*, in which a patient was charged $1,525 for hospital and facility fees after having three precancerous skin patches removed at his doctor’s office. The patient — who never went to the hospital — was billed $678.91 for his share of the bill, and he’s been protesting it ever since after finding out that it wasn’t the result of a billing error.

In cost-sensitive Massachusetts, which has been trying to rein in health care expenses, it’s proven to be a lightning rod issue.

**Asking insurers for help**

“My position is that if you are visiting a doctor in a hospital and you go to a different room and get some procedure done, then it’s fair to charge for the facility. But otherwise it’s not, and I have refused to pay for a facility charge,” says Dolores Mitchell, who helms the Massachusetts Group Insurance Commission, which negotiates with insurers for coverage on over 410,000 state employees, retirees, and their family members. She’s been asking the insurers who provide coverage to her members to help put a stop to it.
THE WIDER VIEW

Health Coverage Lessons From the Greek Meltdown

The country’s catastrophic economic situation shrinks coverage, closes hospitals, and cuts physicians’ salaries — and that might be just the beginning

By Robert Royce, PhD

London — The financial crisis that engulfed much of the world from 2008 onward had a significant impact on Europe, to the point where it can be regarded as the dominant issue for most health care systems. It has affected — in some cases fundamentally — the ability to pay for current services, both public and private.

Whereas in the United States (which has also had to cope with a deep recession) the focus appears to be on efforts to arrest continued growth in health care prices and total expenditure while increasing insurance coverage, some parts of Europe are looking to significantly reduce all three. This article focuses on the experiences of Greece because its catastrophic economic situation has had a similarly extreme impact on its health system.

Cuts, job losses, closures

The scale of the cuts can be gauged by reports of hospital budgets being reduced by 40%, accompanied by severe shortages of staff, medical supplies, and even food for patients as companies fed up with not being paid stop delivery of goods. Job losses are accompanied by recruitment freezes (commonly only one job post can be recruited for every five lost), while those who remain in work have to accept significant pay cuts — when they eventually get paid.

For example physicians’ wages have seen a 25% reduction. Alongside the job cuts have been closures of hospitals, specialist units, and bed reductions. The aim is to reduce the number from 133 hospitals to 83.

In 1983, Greece established a national health service; however, social funds, linked primarily to employment, have always played a significant role in covering the costs of certain types of care — ambulatory care in particular. Patients who depend purely on the public health system increasingly find that the care they require is not available, or at best they face significant delays.

This has gotten significantly worse as Greece’s social sector accounts for 33% of government spending and therefore the austerity measures forced upon the country by its perilous debt position have fallen heavily on the health system. The conditions attached to the bailout by the International Monetary Fund, the European Commission, and the European Central Bank (collectively known as “the troika”) are as eye-watering as the Greek debt level (170% of GDP in 2011). The troika has insisted that public spending on health not exceed 6% of GDP and so health care spending, both public and private, is declining. As a result, the focus is squarely on significant cost reductions and their consequences.

The funding of the Greek health system is a complex mix of public sector, social funds, and private health insurance. To this can be added a significant and growing “black” economy of informal payment directly to the caregiver, reflecting the large difference between official payment rates and what providers actually charge.

A 2008 survey in the journal Health Policy, using a sample of 4,738 people, noted that 36% of those treated in a hospital reported at least one informal payment to a doctor. Of these, 42% reported that the payment was given because of the fear of receiving substandard care and another 20% claimed that the doctor demanded a payment. No doubt if the surgery were repeated the situation now would be worse.
Historically, Greece had an unusual distribution of clinical staff in that it had a very high ratio of specialists to inhabitants compared to EU countries but also manages to have a low ratio of primary care physicians. One might therefore be unsurprised to learn that the Greek health system has always allowed direct access to specialists without reference to a primary care doctor. The relative weakness of the primary care sector is just one of a number of areas where health care reform is widely regarded as being required. However, Greece has a problem with implementing reform programs that transcend health care.

The formal private sector has also suffered badly as the economy has shrunk. Private hospital admissions are down while public hospital admissions are growing — which is further increasing the waiting lists for publicly funded treatment. Private hospital admissions are dropping while those in public hospitals have increased by 24% in 2010 compared to 2009.

A similar pattern of goods disappearing from the formal market can be found with drugs. There has been downward pressure on drug prices and Greece has secured lower prices for a lot of generic drugs. However, drug shortages are common as companies seek markets offering higher prices and quicker settlement of bills. Pharmacies are getting customers to pay up front for drugs because paying the pharmacies is taking so long.

User charges, with some exemptions, have also gone up from €3 to €5 (about $6) and apply to primary care and outpatient care. This may not seem that significant, but needs to be seen in the context of the average Greek’s low income. In addition, 25% of the costs of drugs are met by the patient, although there are exemptions including those with chronic illnesses. Likewise, a number of other services, such as laboratory tests, also have a copayment. What people pay depends on their economic status and what social fund, if any, they belong to.

**Impact on health**

How is all this affecting the health of the people of Greece? Despite a relatively low GDP per capita of $21,750, the life expectancy of the 11.2 million inhabitants is one of the highest among countries in the Organization for Economic Co-operation and Development (OECD) at 77.8 years for males and 82.5 years for females. Some negative public health implications are already becoming visible, but generally speaking, public health is marked by long time gaps before effects are measurable — if they are measured at all. Moreover the impact of an economic recession on health status is not necessarily all negative. For example, a reduction in traffic accidents has been recorded in many countries as a result of people switching to other means of transport and/or traveling less.

Academics speculate that the degree to which negative public health outcomes will result from a recession are in part a factor of the degree to which social cohesion and support networks, formal and informal, are maintained — and perhaps even strengthened.

In Greece a number of negative health consequences are already evident. Suicides are up, mental health indicators are worsening, and self-reported general health indicators are deteriorating. One wonders what the long-term implications will be on the population if Greece’s economic troubles continue. The unemployment rate among 15- to 24-year-olds currently stands at 56.6%, and Greece’s jobless rate has almost tripled since September 2009. The current complaints about the health care impacts of the recession may prove to be merely the start of a wholesale reversal in health indicators in the coming years.

All of this sets a sobering context for the continued debate about the need for, and direction of, health care reform, both internationally and in the United States.

**For further reading**


The National Community Pharmacists Association (NCPA) asserts that “pharmacists are underappreciated, judging by the design of many public and private sector prescription drug plans” (http://tinyurl.com/Doseblog).

Adam J. Fein, PhD, author of the Drug Channels blog (http://tinyurl.com/Feinblog), begs to differ. “Are pharmacists undervalued?” he asks. “Not if money equals appreciation.”


Pharmacist salaries grew 2.6% from 2011 to 2012, when the average gross salary for pharmacists at retail, mail, and specialty pharmacies was $117,000. Meanwhile, salaries for all “health care practitioners and technical occupations” (a classification in the government’s Standard Occupational Classification System) grew by only 1.1% in 2012.

It looks as if buying medications at such places as Walmart is also having an effect. “For the first time, pharmacists at mass merchants had the highest average pharmacist salaries,” says Fein. “Pharmacists at mass merchants, who also saw the biggest pay jump, now earn a full-time average of $117,990 (+3.8%).”

When evaluating pharmacy dispensing fees, pharmacy directors at health insurance plans should realize that salaries are a retail pharmacy’s biggest expense, says Fein. “Payroll is about 70% of a pharmacy’s operating costs.”

### Pharmacist employment and salary, by dispensing format, 2012

<table>
<thead>
<tr>
<th>Dispensing format</th>
<th>Total employment</th>
<th>% change vs. 2011</th>
<th>Average annual salary</th>
<th>% change vs. 2011</th>
</tr>
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<tbody>
<tr>
<td>Mass merchants with pharmacies</td>
<td>31,870</td>
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<td>$116,980</td>
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<td>3,110</td>
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<tr>
<td>Total</td>
<td>180,410</td>
<td>2.6%</td>
<td>$116,288*</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

* Weighted average.  
Data include only pharmacists employed in retail, mail, and specialty pharmacies.  

### Pharmacy revenue growth slowdown

That’s not the only shift that occurred in the pharmacy business last year. Fein reports, “For the first time, revenues at U.S. pharmacies and drugstores declined … in 2012.” The orange line tracks the data; the straight line averages the data.

Source: Pembroke Consulting analysis of Bureau of Census data.  
Data are not seasonally adjusted.  
Aetna Joins With Providers In Private-Label Health Plans

A partnership with a respected hospital system or large physician practice could increase a health plan’s market share

By Thomas Reinke
Contributing Editor

One of the troubling aspects of accountable care organizations (ACOs) in the eyes of providers is the long-term business model. Hospital administrators and physicians are accustomed to revenue increases from Medicare and private payers that they use to expand their services and reputation, but ACOs emphasize saving, making it difficult for providers to see a path to increased revenue.

“One of the limitations of ACOs is that their target for savings is based on historical costs, but that model has very little upside,” says Paul Ginsburg, PhD, president of the Center for Studying Health System Change.

Forward-thinking providers have rationalized the ACO model and payment reform by finally accepting that the current volume-oriented fee-for-service approach is past its prime and that managing population health is the future of health care. But that doesn’t solve the fundamental problem of a pathway that offers financial and market share growth.

Aetna has come up with an answer that may make sense for some providers. As part of its ACO strategy, it is working with large health systems to form private-label health plans — local market plans jointly marketed with the insurance company. “Health care is a local business and we are working with local collections of doctors and hospitals to turn them into an integrated whole that will allow them to have their own products and rewards in their local marketplace,” says Charles Kennedy, MD, head of Aetna’s accountable care business. A private-label health plan may be a new source of revenue and profit for providers.

He says that by acting as part of the system, providers will be able to participate in shared savings. The private-label health plan provides another source for both providers and Aetna — new revenue from an increase in market share. “In some cases, providers have a stronger local reputation and relationships with employers than a health plan, and that can aid the sale of health insurance coverage,” says Kennedy. “We use provider partners on sales opportunities. Employer groups have the opportunity to hear from the doctors who will be taking care of their patients. It provides a rich set of interactions that traditionally has not happened.”

What it is

In its basic form, Aetna’s private-label health plan is a limited or tiered network benefit plan where Aetna holds the insurance license and performs its traditional insurer functions while the health system acts as the leading in-network provider. Private-label plans are intended to capitalize on the characteristics of limited network plans. “We use traditional benefit design strategies and steering mechanisms such as copayment differentials to financially reward the individual for staying within the network,” says Kennedy.

Aetna is looking to form private plans with the dominant health systems or physician organizations in a market. “We attempt to pick a pro-

Private label?

The term “private-label health plan” derives from the common retailing practice in which a well-known manufacturer — perhaps a clothing manufacturer — allows a retailer to sell its product under a label selected by the retailer.

“Hospitals may make less profit on hospital services but they can be made whole through income that is achieved as an owner of the health plan,” says Charles Kennedy, MD, at Aetna.
vider that an employer would buy,” says Kennedy.

The plan will use pricing to encourage that purchase.

“We are sensitive to the market expectations for pricing so we attempt to reach a market-leading price on the plan’s premium,” says Kennedy. “Given the importance of price in most markets, if you can come up with a credible network and achieve a market-leading price point, sales should be good.”

Aetna will also attempt to ensure success by bringing its national accounts to the local or regional private plans. Health plans owned entirely by local providers cannot do that; generally they compete for the local employer market.

Providers may also venture into insurers’ territory on their own. “Some providers who already are fairly efficient see very little financial opportunity in ACOs and they are starting to realize there may be advantages to forming their own health plan, sometimes in conjunction with an insurer,” says Ginsburg.

“Providers need to accurately assess their internal capabilities and readiness before deciding to become private-label health plans, says Glenn Tobin, senior vice president of the Advisory Board.

Inova Health System in Falls Church, Va., joined with Aetna to form a private plan in the Washington, D.C. area. Inova claims its service area covers 2 million people. It has five hospitals with more than 1,700 licensed beds and 16,000 employees.

The venture actually goes one step further than Aetna’s standard model. “Inova is a joint venture. There is a new entity called Innovation Health Plan and we are joint owners,” says Kennedy.

“The joint venture will hold the insurance license. It will be a company just like Aetna itself, or Anthem, or anyone else who operates in Virginia.

“This is the highest degree of health plan integration: Aetna and Inova are 100 percent aligned. A joint venture creates the most durable source of competitive advantage. Its downside is that it is more costly and time consuming, it is more complicated, and it is limited in the number of markets where it is feasible.”

Although Inova is Aetna’s only joint venture, Aetna has jointly marketed health plan products in other markets. For example, its first was Aetna Whole Health Plan, in Virginia. Carilion Health System in Roanoke, Va. is the local partner.

Kennedy says Aetna will work with physician organizations and hospital-centered health systems.

Tobin says that many providers are still developing their stance on accountable care models and that there are options to consider other than provider plans. “Our firm sees a tremendous amount of variety in how organizations are approaching accountable care and other reform topics,” says Tobin. “In many places, providers are considering how to take broader downloaded risk, such as partial or full capitation. These providers may be hesitant to start their own plans because of concern about competing with other payers in their market and the potential for being cut out of other networks, but still want to have incentive to reduce total health care costs.

“Across the country, three or four different accountable care payment reform models may emerge, and in terms of private-label health plans, full capitation may be a simpler alternative with similar financial rewards.”

Ginsburg. Providers may be motivated by the upside offered through the health plan profits, he says.

“You have a number of providers looking over Medicare ACOs and saying we would be better off getting into the Medicare Advantage business,” says Paul Ginsburg PhD, president of the Center for Studying Health System Change.

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“You have a number of providers looking over Medicare ACOs and saying we would be better off getting into the Medicare Advantage business,” says Ginsburg. “That is a new opportunity for providers and we’re going to see some plans formed by providers.”

The Advisory Board, a large consultancy for providers, is also seeing early signs of health system interest in forming Medicare Advantage plans. “The most advanced and most forward-leaning organizations are trying to think it through,” says Glenn Tobin, senior vice president.

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“Across the country, three or four different accountable care payment reform models may emerge, and in terms of private-label health plans, full capitation may be a simpler alternative with similar financial rewards.”
Will it work?

“Private-label health plans, whether developed by insurers and providers together or independently by providers, are likely to be very similar to health plans of the 1990s,” says Ginsburg.

Many of the 1990s plans failed because providers did not have the experience or systems to manage financial risk, coordinate care, or control utilization. Others failed because of the HMO backlash against restricted choice of providers. Private-label plans and ACOs have characteristics similar to HMOs.

Despite the possibility that history may repeat itself, private-label plans may have a better chance this time around.

“One very good reason for a health system to form a health plan is that it can offer an extensive network of providers,” says Ginsburg. “There is growing interest in limited and tiered network products and that will really accelerate when the insurance exchanges come into being.

“The individuals and families using the exchanges are likely to be much more sensitive to premiums than employers, and tiered networks are the vehicle for reduced premiums.”

Kennedy says Aetna’s private-label plans are likely to be offered through insurance exchanges. They are being sold directly to local small and large employers through brokers.

A private-label plan co-owned by Aetna and a health system might be named “Burname University Health System Health Plan” but not have the Aetna name in the title, as is the case with private-label AARP products backed by UnitedHealthcare.

In some markets, Aetna will be competing with its private-label plans, but in many markets it is a minority player, and a jointly marketed plan will be an opportunity to expand market share.

Two major characteristics that did not exist

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Physician groups, too, may sponsor private-label health plans

A private-label health plan need not be a partnership between a hospital and an insurer. Aetna is willing to establish private-label health plans with physician organizations. Charles Kennedy, MD, responsible for Aetna’s accountable care products, explains why.

“All indications are that it is going to be increasingly difficult for physicians to be successful in fee-for-service medicine. All of the payment reforms that seek to reward efficiency and effectiveness, such as shared savings, bundled payments, and capitation, will be increasingly demanded by the federal government.”

Kennedy says that physicians will realize that they will need new tools and patient management strategies to cope with the changes that are beginning to occur. Kennedy expects physicians to be interested in private-label plans. “They will be a way for physicians to participate in the changes. Plus they offer physicians a new way to expand their practices and give them a stronger position in relation to hospitals and other components of the delivery system.”

For an insurer, allying with physicians can make more sense than allying with hospitals.

In many markets, it will be very difficult for physicians to work with an insurer on a private-label plan because they are not organized into a large enough organization and because of long-standing mistrust between physicians and insurers. “Physician organizations generally don’t have the capital to do this on their own and insurers would not be the first place they would look for that capital,” says Glenn Tobin, senior vice president at the Advisory Board. “Becoming a health plan is also a very different business model that requires considerable organizational and operational changes.”

Paul Ginsburg, PhD, of the Center for Studying Health System Change, sees parallels between physician-centered private-label plans and ACOs that could make the private plans successful. “Physician-led ACOs are more attractive to health plans than hospital ACOs for two reasons. One, if the physicians have a capable organization, their ability to succeed as an ACO is higher because they don’t need to hesitate when it comes to reducing hospital admissions. But most do not have such organizations at present.”

“Hospitals will be a major source of savings in post-reform health care; we believe that hospital utilization will continue to trend downward,” says Kennedy. “The other reason that insurers should prefer physician-led private plans or ACOs is that they keep the marketplace more competitive. The greatest consolidation in a market is in the hospital sector and physician-led ACOs can maintain competition by choosing among hospitals for inpatient admissions. They can choose the hospitals with the highest quality and value.”
in the 1990s give private-label plans a chance for success.

“Health systems with elaborate networks are much more sophisticated than those of the 1990s, particularly those with widely implemented EHRs,” says Ginsburg. That gives them a better shot at managing care and controlling costs.

The other factor is a trend toward closer working relations between the providers and health plans, says Tobin. “Providers themselves are making investments to help them transition to risk management without being dependent on payers or others to do so. Some are seeing themselves being able to do it more effectively.”

Kennedy says, “At launch there are very few things providers have to do differently. Aetna will still be performing 90 percent or more of its traditional health plan functions, such as provider contracting and network management, actuarial work, and claims payment.”

Kennedy says Aetna’s private-label plans will use approaches to care management that it is also using in its ACO arrangements. “Aetna’s care management program is intended to make care more convenient, increasing the value of staying within the provider network.” He mentions a smartphone app that facilitates the choice of network providers and simplifies online appointment scheduling.

As a private plan gains experience, Kennedy says, his company will help the partner move into population health management and toward a long-term goal of changing physician practice patterns to obtain more efficient care.

**Plodding regulators**

The pace of state insurance department approval could tarnish private-label plans. Kennedy says in one state Aetna and a delivery system worked very hard to cut costs and produced a benefit plan that had a 10 percent premium advantage. However, when that product was reviewed by the state insurance department it took 14 months to receive approval. Kennedy says some states do not have well-thought-out policies dealing with providers entering into financial risk arrangements.

Kennedy is enthusiastic about private-label plans and has detailed explanations of how and why they will work, but other perspectives exist.

The Advisory Board’s Tobin says that private-label health plans do not have widespread and long-term track records of success. He points out that a central factor in the success of these ventures is the nature of the working relationship between the parties.

“We see that trust-based relationships need to exist between health plans and providers in order for them to collaborate closely to take on risk or other new payment relationships,” says Tobin. “Many traditional payers do not have that relationship with health systems today.”

He provides an example: “Many care management activities that payers are involved in are much more naturally located within the delivery system itself. New provider-payer linkages require a rebalancing of activity to the most effective and economical point of service.

“How willing payers will be to let those functions go remains to be seen. We see health systems seeking to build their own capabilities so that they can capture the benefit of cost reduction, rather than pass it on to the insurer.”

Ginsburg cautions that private-label plans are not for all providers. “Health systems that venture into this should already have a track record of being efficient. If they are not more efficient than their local market, and need to undergo the huge undertaking to change clinical operations, they would do better under an ACO contract, which would reward them for improvement.”

Tobin provides an example. “Many steps are required. Providers need to accurately assess their internal capabilities and readiness. You have to align the interests of the physicians and the hospitals. This may require changes in the details of contracts with physicians.”

Another reason for caution by health plans and providers is the possibility that a private-label health plan could create turmoil among highly competitive delivery systems.

“You might see markets with several private-label health plans; it’s hard to predict,” says Kennedy. “It will be a dynamic that plays out in different ways in different markets.”
The Affordable Care Act is health insurance market reform, not health care reform, says Peter Kongstvedt, MD, a managed care consultant and educator. “It’s one leg of a three-legged stool. Nothing was done on the provider side or the manufacturer side — whether it is pharmaceuticals or devices — other than some minor twiddling around the edges, like allowing for generics. That is small potatoes compared to what the ACA did on the payer side.”

He’s not complaining and he understands the politics behind it, but he sees a growing unrest about high provider and manufacturer prices, both in the industry and in popular opinion. “The ACA will accelerate the need for us to start looking at those other sectors.”

Kongstvedt is a faculty member at George Mason University, where he teaches a graduate-level course on managed care, and is the author of two books on the topic: The Essentials of Managed Health Care (2012), and Managed Care: What It Is and How It Works (2008). A frequent speaker at trade group conferences and a regular blogger on his Web site, www.kongstvedt.com, he is the founder of P.R. Kongstvedt Co., a consulting firm, and Kongstvedt Learning Solutions, an online employee training company. He previously was a partner at Ernst & Young and was associated with CapGemini and Accenture. Earlier he worked in the insurance industry, where he held a series of positions, including executive vice president and chief operating officer of Blue Cross Blue Shield of the National Capital Area.

A licensed physician and a fellow in the American College of Physicians, Kongstvedt earned his bachelor’s degree and his medical degree at the University of Wisconsin, where he also completed a residency in internal medicine. He spoke recently with Managed Care Editor John Marcille.

**MANAGED CARE:** Do you see any changes taking place in your consulting practice?

**PETER KONGSTVEDT, MD:** I used to focus equally on strategy and operations. It’s more on strategy now, at the board level as well as senior management level.

**MC:** Strategically, then, what concerns you most about the present state of the industry?

**KONGSTVEDT:** You can’t ignore the Affordable Care Act in answering that question. It’s a big law.
One concern is, will the changes be implemented well or properly? They don’t have to be perfect, but they do have to provide for information, enrollment, and access to coverage, or at least put that in motion. The biggest fear I have in all that, particularly in those states that are holding their breath, stamping their feet and threatening to turn blue before they do anything, is the information exchange requirements. There is a ton of information that has to get exchanged between insurance exchanges, states, Medicaid, the IRS, the federal government, and the health plans. That’s hanging over the entire system, at least for those who will participate in the insurance exchanges.

MC: How do you feel about accountable care organizations?

KONGSTVEDT: We are seeing lots of things called ACOs and patient-centered medical homes, but it is sort of like saying “bird” because each one is really, really different from another. Often half of all the revenue that goes into a hospital is from Medicare. You have to get Medicare ACOs right. It’s baked into the law; it’s not there as a pilot. Congress enshrined an experimental concept in law, which is always a good idea, right?

MC: Are you saying that the concept won’t fly well?

KONGSTVEDT: I don’t know. It may fly perfectly well. They are not stupid over there. ACOs are going to get adjusted a lot, but by putting it in the law, it will happen. We won’t dither around and take forever to get it implemented. But there’s plenty of room for pretty serious provider revenue shortfalls if we don’t do it right.

MC: What about on the insurance side?

KONGSTVEDT: My guess is that over the long term, the medical loss ratio restrictions will be fine, but I don’t know that. I worry the most about new risk-bearing health plans that have sprung up — you know they don’t call it risk for nothing. In the early days of HMOs and even PPOs, plans were springing up like dandelions and a lot of them went under because they didn’t know how to manage risk financially, much less medically. Fortunately, I think every state has enough large, stable payers that if new plans do go under, the state could simply divvy members up to existing plans. So I am not that worried on behalf of consumers.

MC: What are you worried about outside of the ACA?

KONGSTVEDT: The first, second, and third place problems go to provider consolidation and its effect on pricing. I can’t overstate what a big deal this is, what a problem it is for us.

MC: Please elaborate.

KONGSTVEDT: We’ve seen an astonishing consolidation that began in the 1990s — facilities combining to form these mega, hegemonic systems with true market power in the sense that economists use it: the ability to command prices. Most of these dominant systems got together ostensibly to save money and be more efficient, but that market power sure didn’t translate into payers or employers saving any money. On the other hand, health systems do have their own arms race to deal with.

MC: Arms race?

KONGSTVEDT: Hospitals make nearly all of their margin from procedures, and little from non-procedural medical care. But procedures can be moved, especially those for healthy patients that provide the highest margins. Hospitals are in competition with their own surgeons frequently or with other facilities that entice surgeons with the world’s most fancy hyper-turbo quantum sub-atomic laser scalpel. To compete, you need one too, or buy the physician’s practice, both of which are happening.

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MC: Yet you said many can command prices.

KONGSTVEDT: If you have market power, you can boost your chargemaster by 10, 11, or 12 percent and tell your health plans that you would be losing money on a new contract based on your new chargemaster. Then it goes back and forth, and at some point, if the hospital has enough market power, the parties come to an agreement, but from the plan’s perspective it is certainly not a happy agreement. In the process of updating my textbook recently, I talked to a lot of health plan executives involved in network negotiations, and a surprising number of health plans were getting double-digit increases every year. Every year. And as I teach my students, chargemasters are like snowflakes: No two are alike. There is some relationship to cost, but it
is kind of vague. And prices almost never go down. Even if a procedure gets simpler or less costly to do, the price doesn’t go down. By the way, we shouldn’t use terms like reimbursement — because it’s not, it is payments.

MC: I hate the term reimbursements. I don’t reimburse my mechanic for working on my car.

Kongstvedt: I hate it, too. I actually have a whole speech built around payment models, and that’s the first point I make. You have to understand that it is payment and not reimbursement — which is a kinder and gentler term implying fairness, as though you submitted your travel voucher to your boss.

MC: Is the problem getting worse?

Kongstvedt: It has been getting worse for quite a while, but is getting worse faster because of the employment of physicians. Having market power when you have all of the facilities is one thing, but if you also employ a huge number of physicians, especially primary care or high-volume specialties, that brings you even more premiums. Plus it brings you another hidden goodie: If certain procedures are done in a physician’s office, they are paid at one rate, and if they are done at the hospital, they are paid at a higher rate. When physicians are employed, they are more or less told to use the facility’s services for everything.

MC: Is physician ownership of equipment and self-referral a big problem, too?

Kongstvedt: Yes, but it is a very different problem. The problem with the physician ownership version of self-referral is the effect on utilization. By the way, I am pretty sure that most physicians who steer patients toward their services are doing it subconsciously. Most docs want to do the right thing. It’s not that they want to do more procedures for strictly craven reasons.

MC: But we talk ourselves into things that are in our interest, don’t we?

Kongstvedt: Yes. In another example, I have been reviewing a fair amount of research on this topic, and there are examples where some treatment is found to be really useless, except under certain circumstances, and it still gets done plenty often. It is not until payers and Medicare really put their foot down and say, “We will only pay for it under these circumstances,” that it slows or even stops.

MC: What is going to make a difference?

Kongstvedt: It really takes organizational efforts and pressure. Laws help, but the self-referral thing is a tough nut. It is so tough that in Medicare, Congress passed laws against it, which they have slowly pulled the teeth out of. You could drive a truck through the so-called in-office exemption, which allows physicians to self-refer for stuff that is in their offices. Their office could cover a square block, but it is under one roof, so it is exempt.

MC: Are fixes in those laws, or other laws that will deal with this, on the horizon?

Kongstvedt: The next piece that I think will happen — and we are starting to hear rumbles about it in Maryland and Massachusetts — is price control for facilities. Maryland already has a form of price control called an all-payer setting, which means the state sets the payment terms and all of the insurers use it. It is not single payer, and they don’t pay everybody the same. They have a lot of factors that they apply to it, but it is the state setting those rates. They still have to contend with the chargemaster and the incredible number of things that have fees attached to them, but there is some evidence that it does slow the rate of rise in facility costs. Other countries do it routinely, by the way. Maryland is also starting to talk about budgetary control. In Massachusetts, there is some discussion about this, too. The state would actually set payment caps. That would be getting a lot closer to Quebec in Canada. In their all-payer system, they also set budgets, and every quarter when the money runs out, facilities don’t get paid. That drops utilization fast.

MC: Will we get to that point?

Kongstvedt: I don’t know if or when those states will go to that, but it does point out that it is no longer completely out of the question to start to discuss it. I think that eventually we are going to end up with some form of price control or rate control on the facility side.

MC: And what about for the third category you discussed, the manufacturers?

Kongstvedt: We are the only nation that doesn’t have price controls for manufacturers. Medicare and Medicaid do for some things, though there are examples of its being deeply flawed. But we don’t have anything in the private sector. Sure, other countries that control pricing experience health inflation, too, but you just can’t escape the fact that we are so far out of bounds and have been for so long. We have willfully ignored this part of
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**INDICATION**

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).

**SELECT SAFETY INFORMATION**

The recommended dose of Synagis is 15 mg/kg of body weight given monthly by intramuscular injection. The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season.

Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a significant hypersensitivity reaction occurs with Synagis, its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays.

**Please see accompanying Brief Summary of Prescribing Information for Synagis on the next page.**

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INDICATIONS AND USEAGE

Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).

The following point should be considered when prescribing Synagis:

1. The safety and efficacy of Synagis have not been established for treatment of RSV disease.

The data described below reflect exposure to Synagis (n=1639) compared with the clinical trials of another drug and may not reflect the rates observed in practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions.

ADVERSE REACTIONS

The most serious adverse reactions occurring with Synagis are anaphylaxis and other acute hypersensitivity reactions.

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below reflect exposure to Synagis (n=1639) compared with placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) who were less than or equal to 35 weeks gestational age

In Trials 1 and 2 combined, fever and rash were each reported more frequently among Synagis than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively. Adverse reactions observed in the 153-patient crossover study comparing the liquid and lyophilized formulations were comparable for the two formulations, and were similar to those observed with Synagis in Trials 1 and 2.

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low level reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (n=1124) in Trials 1 and 2 above. The rates of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay.

The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

An electrochemical luminescence (ECL) based immunogenicity assay, with a higher tolerance for palivizumab exposure compared to the ELISA, was used to evaluate the presence of anti-palivizumab antibodies in subject samples from two additional clinical trials. The rates of anti-palivizumab antibody positive results in these trials were 1.1% and 1.5%.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Synagis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count less than 50,000 per microliter)

General Disorders and Administration Site Conditions: injection site reactions

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of children in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators, or corticosteroids were similar and no incremental increase in adverse reactions was observed among children receiving these agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: Synagis is not indicated for adult usage. It is not known whether Synagis can cause fetal harm or could affect reproductive capacity when administered to a pregnant woman.

Animal Data

Animal reproduction studies have not been conducted.

Pediatric Use

The safety and effectiveness of Synagis in children greater than 24 months of age at the start of dosing have not been established.

OVERDOSAGE

Overdoses of doses up to 70 mg per kg have been reported in clinical studies and post-marketing experience with Synagis, and in some cases, adverse reactions were reported. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

PATIENT COUNSELING INFORMATION

The healthcare provider should discuss the potential benefits and risks of Synagis with the parents or guardians of Synagis recipients. Parents or guardians should be informed of the possible side effects of Synagis and of the signs and symptoms of potential allergic reactions and should be advised of the appropriate actions. Parents or guardians should understand the dosing schedule and the importance of compliance with the full course of therapy.

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U.S. License No. 1799
1-877-633-4411

Revision Date: April 2013
Component No.: 10423A

RAl-SYNW16
it. We are willfully ignoring it now when we say that health care cost inflation is due to all of these baby boomers retiring into Medicare. But their costs don’t change all that much from the day they were not eligible to the next day when they are. This hasn’t been dealt with in the popular press, but in the academic world, there’s a reasonably good acceptance that the aging of the population is not having as big of an impact as other things.

MC: But we need medical devices.

KONGSTVED: Yes, and I for one am glad for their existence. But the prices of the devices are completely irrational. In certain procedures, the price of the device is half the price of the admission.

MC: So you think we’ll end up with price controls for manufacturers?

KONGSTVED: I think that is what we are slowly going to move to. I don’t expect to see it for a while, but I think the ACA is going to accelerate it.

MC: Ten or fifteen years?

KONGSTVED: Maybe. It’s actually very hard to really know what the effect of high health costs is on our economy because the other side of the equation is that it employs a huge number of people. If you cut health care costs by 5 percent, unemployment would go up. That’s not something you do without thinking about it, at least. In speeches, I sometimes employ a sort of trick on the audience. I show a picture of a cover of Time magazine that reads “Medical Costs: Seeking the Cure” over a picture of a physician wearing a surgical mask made with a dollar bill. And up in the corner it says, “The Politics of Gas.” I say, “You’ve seen this Time magazine recently, right?” And people will nod and say, “Yeah.” And then I blow out the date: 1979. The article makes the comment that health care costs are over 8 percent of our GDP now [1979], which is higher than any other nation on the planet, and if we get into double digits, we are doomed.

MC: But we weren’t, were we?

KONGSTVED: No, we weren’t doomed at all. In fact, we boomed. We didn’t lower health care cost inflation in the mid ’90s, as a lot of people think we did, but mostly our economy boomed, and so it kept pace. Then, when the economy started to flatten off and HMOs were backlashed, health care cost inflation started to accelerate again, especially compared to the regular GDP. And we are still chugging along. We talk about the cost of health care and how much it is crippling us, but it’s actually pretty hard to point to how or how much that is actually happening. The cost of wages and benefits for labor is higher, but when you have electronics and auto manufacturers moving back to the U.S., that tells you something. Health care diverts money in directions that don’t go into wages. On the other hand, it pays wages to people who are in health care.

MC: Changing the topic, your online program trains people in managed care, saying, “The more you know, the better you’ll do your job.” What is most important for medical and pharmaceutical executives to know?

KONGSTVED: They don’t necessarily need to know everything, but it helps to know how the pieces fit together if they want to improve the quality of the work that they do. For example, medical directors just coming from full-time practice are going to need to focus first on utilization management, quality management, and network management and recruiting. It is also very important for medical directors to understand payment methodologies. They can also play a role in marketing and sales.

MC: How are they most effective in that capacity?

KONGSTVED: Large employers and benefits management consultants want to know what is going on inside the medical management function. It’s one thing to read a description of it; it’s another thing to talk to a person who is charge of it. That can be a very powerful element of the marketing and sales process. It’s also important to be involved in new product design because sometimes you will see a benefit design that might sell well, but people didn’t really think through the implications of actually trying to administer it. But sales is where you really see a medical director’s involvement paying off.

MC: They go along for the pitch?

KONGSTVED: Yes, but sales is not just the initial sale. It is every single day, and keeping in touch with your largest customers can be a very good way to bind them a little bit closer. Ask them their input, what is important to them, what they are hearing about from their employees, that type of thing. Medical directors can often see that through a different lens than somebody who is not trained clinically. In one case, I suggested that a company’s medical directors talk to regulators and build up more of a relationship.

MC: Thank you. MC
If there is one trend that epitomizes the overconsumption of health care, it’s executive physicals. These in-depth half-day examinations, which often include extensive scanning, almost always reveal something, whether it’s truly there or not. I’ll let our colleague David McCann, editor of CFO Magazine, tell a story. You want to listen to this guy.

A good friend of mine underwent a “full-body screening” and a few suspicious cells were detected in his lung. So he had surgery, during which a hunk of one lung was removed. It was a difficult surgery, as you would imagine, and it took him a long time to recover. There was, of course, no cancer. Meanwhile, I had talked to my brother, who’s a radiologist, who literally smacked himself in the forehead when he heard the story and said, “Every single person has suspicious cells. These full-body screenings and the surgeries they lead to are a shameful scam.”

Far from being a rarity, findings like these — which often lead to surgeries like his — are so common that radiologists even have a disparaging name for them: “incidentalomas.” Doctors can’t ignore them — someone could sue if they truly turn out to be cancerous. Hence the finding itself creates the need for the surgery. Further, Overdiagnosed: Making People Sick in the Pursuit of Health by H. Gilbert Welch, Lisa Schwartz, and Steve Woloshin describes how the steady increase in imaging resolution is creating a parallel steady increase in these incidentalomas. For this and many other reasons, I strongly recommend against executive physicals, especially those involving scanning.

This article is taken from a chapter in the new book Cracking Health Costs: How to Cut Your Company’s Health Costs and Provide Employees Better Care by Tom Emerick and Al Lewis. It is printed with the permission of John Wiley and Sons Inc. ©2013. It has been modified slightly for continuity.

Tom Emerick, president of Emerick Consulting, was with Walmart for many years. One of his duties involved managing benefits for over 1.3 million employees. Al Lewis is the president of the Disease Management Purchasing Consortium. Earlier he taught economics at Harvard, held management positions at Interqual and Bain Capital, and was an analyst at Lehman Brothers.
of which would need to be followed up with doctors and possibly diagnostics and treatments. The bank’s spokesperson, in an understatement worthy of induction into the Wellness Ignorati Hall of Fame, observed: "It’s still too early to see financial savings."

Via Christi’s spokesperson was a bit blunter, admitting that these screens and follow-ups "offer another source of income" for the hospital.

The equivalent of the half-day executive physical for those of us in the “99 percent” is the biometric screen. Companywide screens are one of the many things that doctors are by and large opposed to (see the Wall Street Journal, Feb. 20, 2013), the federal government eschews (the National Heart, Lung and Blood Institute recommends only once every five years for healthy working-age adults) but that the ignorati seemingly can’t get enough of.

The good news about those screens is they will identify people at high risk for diabetes, one of the two diseases they most often target, and get them into a program well before they develop diabetes. The bad news (among other things) is that the evidence indicates that there is no difference in outcomes between people at high risk for diabetes who get screened and get early intervention and those who don’t.

Renowned British medical journal *The Lancet* published a major study in November 2012 showing results of screenings followed by 10 years of follow-up on more than 20,000 people. This study was conducted according to tight academic specifications (requirements include having a hypothesis to be tested, statistically significant samples, a control, blinding, and so forth), as opposed to wellness industry specifications (requirements include owning a laptop). And because Britain has a national health system, follow-up was relatively straightforward.

The results were unequivocal: There was zero health benefit to early screening in people without actual diabetes, if, like most diabetics, they received usual care for the next 10 years.

This result justifies the U.S. Preventive Services Task Force’s 2008 recommendation to restrict diabetes screening in the under-65 population to just those people with increased blood pressure. However, it doesn’t justify the section heading that too much health care is hazardous to your health (with full-body screens being a major exception), just that screening isn’t necessarily helpful to your health. Read on.

Along with diabetes, the other major focus of these biometric screens is heart disease. Heart disease is no doubt a killer, and there are sobering statistics somewhere about the number of people experiencing preventable heart attacks every year. Fortunately, “sobering” is not a synonym for “correct,” and if a statistic about preventable heart disease strikes you as sobering, it is probably because it’s wrong.

Here is the rather nonsobering actual statistic: the annual rate of heart attacks in the commercially insured working-age population is only about 1 in 500. Next, let’s add some educated guesswork. Feel free to substitute your own guesses — they won’t change the overall answer:

- If you omit the people with known risk factors or pre-existing heart disease — people who don’t need the screening because they already know they are at risk — that number falls to about 1 in 2,000.
- If you then count only the people who could have their heart disease detected via a rudimentary screen, thereby eliminating those whose subsequent heart attacks are not readily predictable, that number falls further, possibly to about 1 in 4,000. This ratio in reality is probably even more unfavorable, as cholesterol, particularly the “bad” cholesterol, turns out to be a very primitive marker for heart disease, both overinclusive (leading to much more treatment) and underpredictive (many people with acceptable “bad” cholesterol nonetheless have heart attacks).†

So a $40 biometric screen will find at best one avoidable heart attack in every 4,000 people ... at a cost of $160,000. Add in, for instance, $200 in incentives and $20 in time off from work to persuade

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people to participate, and you’ve now created the million-dollar heart attack screen.

And keep in mind that find is not the same as avoid. I don’t think anyone has statistics on what proportion of potential heart attacks are avoided. If we generously assume that fully half of avoidable heart attacks can indeed be avoided, the cost per avoidable heart attack that actually is avoided becomes $2 million.

You might say at this point: “Well, maybe I can’t justify spending $2 million in purely economic terms to prevent an employee from having a heart attack (which typically costs five figures to treat and recover from, including follow-up and lost work time). But a heart attack entails a human cost of pain, suffering, and possibly even risk of death, as well. And I would happily spend 2 million bucks to avoid that cost.”

A well-intentioned thought, to be sure. But the trouble is that you don’t know which one of the people being screened as being high-risk is going to be that 1 in 4,000. And that’s where the “too much health care can be hazardous to your health” part comes in. Two to three percent of the people screened — about 1 in 40 — will be instructed to follow up with their doctors. Follow the arithmetic here: 1 in 40 means that 100 people will get referred. However, only one of the people receiving this advice would actually have a heart attack if he or she failed to do so (and may even have one anyway, despite that follow-up care). But those other 99 will get extra doctor visits, prescriptions, and possibly cardiologist referrals. And cardiologists almost always order further testing, since their professional risk of doing nothing is quite high.

What is the result of “almost always ordering further testing”? According to Overtreated author Shannon Brownlee, invasive cardiac testing and procedures are performed almost 2 million times a year. To put this in perspective, the number of babies born in the United States is only about twice that. So at current rates of testing and procedures, half of all people will eventually have an average of one invasive test or procedure. Are our hearts so fragile or ill-evolved that such a massive proportion of our population needs (at a minimum) dye injected into them to make sure they are pumping correctly? Take a look at your own company’s heart attack rates — that 1 in 500 figure won’t be far off — and then decide if reducing that overall 1-in-500 annual chance to perhaps 1-in-1,000 is worth sending half your employees for invasive testing at some point. (Ad-
mittedly, that statistic is a little misleading because many of those employees wouldn’t get the invasive test until after they retire.)

And here are your chances of success: Once the substantial countrywide decline in heart events is taken into account, no company or health plan ever measured covering more than 100,000 people — about the level at which you can be sure of a result — has ever reduced that rate by half once the secular decline in heart attacks is taken into account, even over 10 years.

You might be thinking, “Especially considering the small chance of success, that sounds like a lot of inappropriateness.” But I haven’t even gotten to the inappropriate part yet. With the exceptions of cardiac procedures actually being done in the throes of a heart attack (U.S. medicine at its best: timely, responsive, and effective) and a few other clearly delineated cohorts, there is no clear evidence that these procedures actually help people to avoid heart attacks, as Overtreated shows at length. Among other pieces of evidence, there is no correlation between the rate of cardiac testing and procedures in a given geography and the rate of heart attacks.

Many primary care doctors know this. Paul Levy, who formerly ran Beth Israel Deaconess Hospital in Boston, recalls the time he needed a stress test as a requirement for participating in an ocean kayaking trip in Patagonia. His PCP refused to order it. She said: “Because he knows who you are, the cardiologist will be especially attuned to any odd peculiarity about your heartbeat. He will then feel the need, because you are president of the hospital, to do a diagnostic catheterization. Then, there will be some kind of complication and you will end up being harmed. But the reality is that whatever peculiarity he finds has probably existed for decades. There is no history of heart disease in your family. You cycle 100 miles per week and play soccer for hours every week, and you have never had a symptom that would indicate a circulatory problem. Therefore, I will not authorize a stress test.”

Also, the literature is quite clear that stenting people without unstable angina has no better outcomes than the diet-and-exercise solution. But because a stent is “doing something” and (see first section) basically free, many if not most people will follow the doctor’s recommendation and have stents inserted.

Still, the doctor is the professional, and he has all the data in front of him and is working on your employees’ behalf. So he wouldn’t recommend an invasive procedure unless it was truly indicated... or would he? He just might. MC
So many innovative efforts in care delivery double back to the decades-old problem of physician buy-in. That’s true even as the Affordable Care Act moves from law to reality, or some version of reality (talk to us in 2015). There’s much discussion about the team approach to providing health care, which is fine until you recall how most physicians are trained.

“Physicians are taught to be independent,” says Kenneth Hertz, a consultant with the Medical Group Management Association. “As you come through the system as a physician, you make it on your own. You don’t have a lot of people that are helping you get there.”

He adds, “The command-and-control concept that may have been very prevalent in the past is slowly disappearing. It’s a significant change in health care, so will it happen overnight? Probably not. But it is happening.”

Old habits die hard, and a metaphor used often by clinician executives in the early years of managed care comes to mind: herding cats.

“I do think you’re really on to something,” says Margaret E. O’Kane, president of the National Committee for Quality Assurance, which branched out over 10 years ago from measuring just health plans to assessing physician performance as well.

“In the airlines there’s a convention that if anybody sees something that seems unsafe, they’re ethically bound to challenge the other person no matter what position he is, no matter what position you are.”

Most experts say that the top-down culture in medicine is changing; in fact it has to change to adapt to the realities of health reform. The problem, as Hertz says, is that most of the evidence for this shift is anecdotal, and comes with caveats and qualifications.

An article titled “Red Flags That Represent Credible Threats to Patient Safety” in the journal *Patient Safety & Quality Healthcare* lays out the problem this way: “The hierarchical nature of patient care and the autonomy with which health care professionals have been taught to practice set the stage for a culture that does not respond well to even the slightest queries about possible problems with patient care, particularly from subordinates.”

It adds that “there’s a less obvious but no less dangerous risk related to the culture that often goes unnoticed until a serious adverse event happens: staff do speak up about potential concerns, but they are too easily convinced that their concerns are unfounded... [I]t is natural and often reasonable for people to defer final judgment to those who they perceive to be more ‘qualified.’”

**Betsy Lehman case**

Amy C. Edmondson, PhD, the Novartis professor of leadership and management at Harvard Business School, says, “This is both true and helpful, for the most part. There is an important qualification — deferring final judgment to experts is smart, so long as they have all the relevant information. People who might see themselves as less qualified still have an obligation to check, to test, if they are unsure about something.”

Edmondson, whose book *Teaming: How Organizations Learn, Innovate and Compete in the Knowledge Economy*, was released last year, continues that “It goes without saying that a nurse or technician is not equipped to guide the surgeon’s detailed procedure. However, any surgeon who does not want...
an OR surgeon is neither wise nor safe if he doesn’t want people to speak up if they see something amiss, says Amy C. Edmondson, PhD, the Novartis professor of leadership and management at Harvard Business School.

An OR surgeon is neither wise nor safe if he or she sees that the surgeon is about to do something in error — wrong site, leave an instrument behind — is neither wise nor safe.”

Edmondson cites the Betsy Lehman case. Lehman, a health reporter for the Boston Globe, got breast cancer in 1993 and participated in a clinical trial in which higher-than-normal doses of cyclophosphamide were administered. However, because of a clerical error, Lehman received much more than the dose recommended for the trial. The nurses saw that but did not speak up, because they assumed it must be part of the experiment. “After all, the doctors know what they’re doing,” says Edmondson.

Lehman died of an overdose.

Edmondson says “That one got a lot of attention….. It’s old news, but the phenomenon is not old news.”

Environment

The 2011 study “The Silent Treatment: Why Safety Tools and Checklists Aren’t Enough to Save Lives” notes that “Nurses today are voicing their concerns nearly three times more often than they did just five years ago. This improvement suggests that speaking up is becoming easier and more accepted within health care organizations.”

OK, but that doesn’t necessarily mean that physicians are listening. Health plans need to pay attention to this, says Ramón Lavandero, RN, MA, the senior director for the national staff at the American Association of Critical-Care Nurses (AACN). The study was sponsored by the AACN, the Association of Perioperative Registered Nurses (AORN) and the vendor VitalSmarts.

Lavandero says that health plan clinician executives have always asked: “Are people properly educated, properly credentialed, properly certified? What happens in terms of the outcomes in health care? What’s the level of the quality? What happens in terms of error when those factors aren’t in place? Clinician executives are already involved in that part. “The part that they may well start paying attention to also is the environment in which care is provided. More and more studies now are showing that the quality of the work environment itself affects the outcome,” Lavandero continues.

Not incidental

“Health plan executives are missing a huge part of the equation by thinking perhaps that this is incidental stuff, this is soft stuff — that having good communication skills, having genuine collaboration among health officials, having good decision making models are nice, but we have more important things to look at.”

“The Silent Treatment” notes that caregivers “are often unable to speak up and resolve their concerns about dangerous shortcuts, incompetence, and disrespect. More than 4 out of 5 nurses in this study have these concerns, more than 1 in 4 have seen either shortcuts or incompetence lead to patient harm, and more than half say disrespect from others has undermined their ability to take action. Yet, less than a third of these nurses spoke up in an effective way about their concerns.”

Amy Gibson, RN, MS, is the chief operating officer of the Patient-Centered Primary Care Collaborative (PCPCC), a multistakeholder organization dedicated to building effective patient-centered medical homes. Gibson says that physician reluctance to involve other providers has a lot to do with fee for service. If you’re paid based on the number of patients you see, then what’s the financial sense in including, say, a dietician when examining a diabetic? “It’s really hard to bring in those other members of the team when you can’t financially support that as part of the practice,” say Gibson.

Financial restraints

Michael S. Barr, MD, MBA, the senior vice president of the division of medical practice at the American College of Physicians, says, “As opposed to a hierarchical approach with
top-down commands, we encourage the development of appropriate job descriptions, training and cross-training, and routine team-meetings/discussions. Discussions about issues — clinical, operational, financial — should be based on mutual respect and collaboration while recognizing that some members of the team may have specific skills and knowledge appropriate to the task or issue at hand.... We encourage our members [internists] to recognize that it is now impossible for a physician to carry all of the day-to-day responsibility for patient care.”

The morning huddle

Hertz says that evolving practice policy forces everyone in the office to speak up — and physicians to listen. “For example, we talk about a morning huddle where the doctor gets together with the receptionist or a nursing assistant and they go through the schedule of patients. They talk about what needs to be done with each patient.”

Meetings can waste time, so more practices encourage huddling up to focus on a particular problem. “People want to get in and get the work done. By avoiding chairs and tables, the agenda can be kept short, to the point, and you can get on with the day.”

Patient-centered medical care, so much a bulwark of health reform, is all about communication, Hertz adds. “Not about health information technology. Not about billing systems. Not about electronic medical records. It’s all about communication,” says Hertz. “It goes to respecting each other and the knowledge skills and abilities that each of us have. It’s exactly about communication. It’s no longer about command and control only.”

“Physicians want to be practicing in the way that they were trained,” Gibson says. “They’re not trained to practice in this team environment. But they also are very frustrated with the care that they are trying to provide to their patients in this more comprehensive, holistic model that we talk about in the medical home. And they can’t do it alone.

“The ones who are really trying to embrace this idea of medical home, really trying to change the way their practice operates, really want to be practicing at the top of their licenses — they want to be the ones who are dealing with those patients with difficult diagnoses.”

Watch hospitals

Those doctors don’t necessarily want to make referrals, coordinate care, or contact community-based services. “That’s not the best use of a physician’s time,” says Gibson.

Watch what happens in the hospitals, O’Kane says. “It’s really going to matter a lot now that hospitals have to become safe or they’re going to be out of business. The other thing that’s hopeful is that many of the medical boards require some kind of survey of peers or other people that work with the person. So they’ll be getting feedback about team play as part of maintenance and certification.”

Physicians are willing to change for self-preservation, says Hertz, in a world where they see increased overhead and declining pay. “So you have two options: One is let’s do what we’ve been doing the way we’ve been doing it and hope it’s going to get better. The other is let’s take a look at doing this in a different way. I’m finding that we’re looking at different ways to do this.

“We’re looking at different ways to increase access and so when we try to do that we pull together a doctor, nurse, receptionist. Enlightened doctors are open to this.”

Phrases that might spell trouble

Timothy Lesar, PharmD, of Albany Medical Center, years ago compiled a list of pat phrases that should be red flags. They are often used by doctors in response to concerns voiced by other health care providers.

- The attending told me to order it that way.
- The patient says that’s how he takes it at home.
- It was published in.... (But not giving a reference.)
- This is a special case.
- The patient’s been titrated up to that dose.
- The patient is on protocol. (But not citing the protocol.)
- The dose is the same as listed on the patient’s old chart.
- That’s the way the dose is written in the progress notes.
- It’s on the list of medications the patient gave me.
- We always give it that way.
The pressure on employers to manage the rising costs of health care is increasingly focused on the pharmacy benefit plan. Within the pharmacy benefit, there is a significant expenditure differential between specialty and traditional drugs. In 2012, traditional drug expenditure actually decreased by 1.5%, while specialty drug expenditure increased by 18.4%. Oral chemotherapy on the pharmacy benefit grew over 25% in this period.

As a class, cancer now ranks third in overall specialty pharmacy drug spending, and it can be expected to continue to rise throughout this decade. The routine approval of new medications for cancer comes with a price — a price that is gaining the attention of health plans, PBMs, and employer benefit managers. In the 2012 Genentech Oncology Trend Report, managed care organization respondents identified quantity-limit programs as the number one strategy for specialty pharmacy providers to create oncology-related cost savings. While there is much activity and interest related to these quantity-limit programs, plan sponsors and benefits managers may have unrealistic expectations regarding cost avoidance associated with this strategy.

Oral oncology limits
Oral oncology quantity-limit programs, presented under different names such as cycle-management, short-fill, or split-cycle programs, are designed to avoid costs associated with unused oral chemotherapy and are most often focused on the first month or cycle of treatment. In most quantity-limit programs, the first treatment cycle is split into two equal shipments. The patient is contacted several days into treatment and given an assessment by a clinical representative of the specialty pharmacy. In the event that the patient cannot continue treatment for any reason, the remainder of the medication is not shipped, avoiding patient or plan sponsor liability for several thousands of dollars of unused oral chemotherapy. It can be expected that because of the mid-cycle intervention by a pharmacist or nurse from the specialty pharmacy, patients may actually see an improvement in treatment adherence, a very valuable side effect of this

Do the Numbers Add Up for Oral Oncology Quantity-Limit Programs?

Despite their attraction, these cost-control programs don’t always deliver

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Tom McCann is vice president for strategic services at Hobart Holdings, a pharmaceutical marketing agency solely focused on payer strategy. Before joining Hobart, he was vice president for oncology marketing and market access at Accredo Health Group. He has over 20 years of experience in pharmaceutical sales, marketing, and managed care. He holds a master’s degree in human resource management from Troy University and a bachelor’s degree from the United States Military Academy at West Point.
In 2013, there are approximately 27 oral oncology medications available. While this number continues to grow, not all of these medications can be dispensed in durations appropriate for a quantity-limit program. Many are subject to risk evaluation and mitigation strategy (REMS) programs that restrict change in quantity dispensing, while other medications may have dosing variability or complexities that can introduce a level of risk that is inappropriate for limiting quantities. Of oral oncology drugs that may be appropriate for quantity-limit programs, most will have limited use due to the low incidence of treatment.

The four most commonly used oral oncology drugs based on total quantity dispensed in 2009 (excluding medications that are subject to REMS requirements) account for more than 86% of total oral chemotherapy volume (Figure 1). They are Gleevec (48%), Tarceva (22.2%), Sutent (9.5%), and Nexavar (6.4%).

While utilization is not always limited to FDA-approved indications, the most common cancers treated by these four oral chemotherapies are leukemia (chronic myeloid leukemia or CML), lung, and kidney. Publicly accessible data on new start rates for these medications is limited, but can be estimated using information from the United States Cancer Statistics published by the Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute Web-based report (Table 1, below). These sources report cancer incidence rates per 100,000 lives, providing a baseline of understanding for a payer population’s exposure to specific types of cancer.

In a commercial population, only about 22% of patients diagnosed with the most common types of cancer will receive chemotherapy of any kind (oral or infused) in any year. Lung cancer patients are treated with chemotherapy approximately 50% of the time at some point during a year-long period, while leukemia and kidney cancer patients are less likely to be treated with chemotherapy. Pharmacy benefit managers and specialty pharmacy providers that manage oral oncology drugs routinely report discontinuation rates for these four medications at less than 30%, and even less for extremely well tolerated drugs like Gleevec. When projecting incidence rates for the most common types of cancer that can be treated with oral chemotherapies, discounting those patients not on chemotherapy and isolating only patients who discontinue therapy on the first treatment cycle, actual drug-cost avoidance per 100,000 lives can be

<table>
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<th>TABLE 1</th>
<th>Cost avoidance per 100,000 lives for oral oncology market share leaders using quantity-limit programs</th>
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<tbody>
<tr>
<td>Oral oncology market leader</td>
<td>Tarceva</td>
</tr>
<tr>
<td>Cancer site (a)</td>
<td>Lung</td>
</tr>
<tr>
<td>Rate per 100K lives</td>
<td>77.1</td>
</tr>
<tr>
<td>% Patients receiving chemo</td>
<td>50%</td>
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<tr>
<td>Cost avoidance potential/NRx</td>
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<tr>
<td>% Drop off rate</td>
<td>13%</td>
</tr>
<tr>
<td>Avoided shipments (d)</td>
<td>5.1</td>
</tr>
<tr>
<td>Cost avoidance total (e)</td>
<td>$9,129</td>
</tr>
</tbody>
</table>

(a) Data not shown for kidney cancer. Default value of 22% used from “average for all cancers”
(b) Data shown is for CLL and used to represent CML as default value
(c) Average of Sutent and Nexavar
(d) Avoided shipments = (rate per 100K lives) x (% patients receiving chemo) x (% Drop-off rate)
(e) Cost Avoidance Total = (Cost avoidance potential/NRx) x (Avoided Shipments)
expected to be less than $13,000 (Table 1). Considering that total specialty spending for a commercial population of 100,000 lives is approximately $24.6 million, direct savings from a quantity-limit program can be as little as 0.18% of total specialty spending.

Clearly, there are additional oral oncology drugs that can now be included in quantity-limit programs. However, these four oral oncology drugs represent a significant percentage of oral oncology utilization that is appropriate for a quantity-limit program. Gleevec, in particular, is typically the leading oral oncology drug in terms of total market share and is often the target of oral oncology quantity-limit programs. While Gleevec does command a significant portion of oral oncology spending, this is a reflection of the chronic use of this medication and is not due to the frequency of diagnosis of CML. Furthermore, pharmacy benefit managers report Gleevec adherence rates of much greater than 90%, significantly reducing the potential of direct savings associated with avoidance of drug shipments.

Greater clinical oversight

Beyond cost-savings promises, quantity-limit programs typically offer greater clinical oversight during the onboarding of the "new to treatment" patient. Many who discontinue their oral oncology treatment, especially in the first treatment cycle, do so for avoidable reasons. The mid-cycle intervention of a specially trained clinical representative of a specialty pharmacy can help manage side effect or dosing concerns that may lead to noncompliance with treatment or even lead to unnecessary hospital or emergency room visits.

A shrewd benefits manager may conclude that any saving is worth pursuing and, as new drugs are introduced into the program, saving will increase. While this is true, it is important to understand that these are not risk-free savings. Quantity-limit programs are designed to manage waste at the outset of oral chemotherapy treatment. For a newly diagnosed cancer patient or an existing cancer patient with progressive disease, starting oral chemotherapy can be daunting. Coordination with antiemetic therapy, changes in diet, side effects, and more can significantly affect adherence to treatment. Adding an additional administrative drug delivery in the initial treatment cycle — either in a retail or home delivery scenario — can add adherence risk for no clear clinical value. Without an overwhelming clinical or even financial justification, benefits managers will need to carefully weigh the value of these quantity-limit programs in terms of real cost avoidance, improvements in adherence, and potential disruptions in treatment due to product delivery or care coordination errors.

In the balance, quantity-limit programs offer some hope in addressing the growing costs associated with cancer care. However, the direct effect of these programs may come more from increased clinical interactions and less from direct drug cost avoidance. Prior to implementation, benefits managers should require rigorous modeling of oral oncology quantity-limit programs in order to fully understand the cost savings and the effect on their populations.

For further reading


CVS Caremark Oral Oncology Drug List (effective 10/1/2012).


Conflict of interest statement

This article is based solely on the author's personal experience, was not commissioned or influenced by any pharmaceutical manufacturer, and was not a billable effort.
The amount of research published in health care is astounding. Thousands of studies are disseminated each year on research ranging from personalized genetic-based drug therapies to promising biotech prescriptions for cancer. But the problem with all this great information is that it often takes more than a decade from when a best practice is published in a clinical study until it is broadly adopted.

For health plans seeking to meet increasing quality and reporting demands, this lag between publication and implementation means they must find more effective and efficient ways to communicate a wide range of data. Developing optimal approaches to delivering data that meet an organization’s goals for quality, growth, and sustainability is crucial to succeeding in the dynamic and demanding health care marketplace today.

Poor provider engagement

One reason there’s such a long time between publication and implementation is that as an industry, we haven’t always done an adequate job of disseminating the research we have to providers or encouraged them to adapt the relevant findings quickly.

For health plans seeking to meet increasing quality and reporting demands, this lag between publication and implementation means they must find more effective and efficient ways to communicate a wide range of data. Developing optimal approaches to delivering data that meet an organization’s goals for quality, growth, and sustainability is crucial to succeeding in the dynamic and demanding health care marketplace today.

Delays and gaps in adopting best practices have led to significant regional, socioeconomic, and even institutional quality chasms. Some estimates put the costs of such poor quality care at about $500 billion annually.

Costly delays

Recognizing that these costs must come down, health plan medical directors, pharmacy directors, and administrators are seeking better ways to educate and engage providers by requiring them to more fully comply with HEDIS, pay-for-performance (P4P), and other quality measurement initiatives. More than 90% of health plans incorporate HEDIS-based performance standards. Similarly, the federal Centers for Medicare & Medicaid Services asks health plans to raise their star ratings in the Medicare Advantage program.

Therefore one of the biggest challenges health plans face is how to disseminate information, guidance, and performance data among providers. Examples of information that must be communicated include:

- Relevant comparative effectiveness research
- Up-to-date HEDIS quality metrics
- Star ratings for Medicare payment
- Internal data on performance and outcomes benchmarked to peers and national standards
- Evidence-based guidelines
- Formulary guidelines

Just knowing what kind of information needs to be communicated today is not enough. Health plans also face barriers when implementing the typical provider engagement program. For instance:

- Physicians are overloaded with information from a wide range of sources, including payers themselves, pharmaceutical manufacturers, the media, and even patients. Historically physician education has been didactic, static, and often highly rigid, all of which discourage doctors from asking questions out of fear of peer ridicule.

By Barry Patel, PharmD

For centuries, the problem in medicine was too little information. Now there’s too much, and doctors need help coping.
Physicians simply lack the time to read meaningful journal articles and fully explore their implications. Studies show the average physician has no more than a few hours per week for such reading.

Health plans have limited resources. Many know what the organization needs to communicate — and to whom — yet they simply lack the ability to deliver the in-depth level of outreach providers require.

Communication failures exist between providers and health plans, stemming from misconceptions about and mistrust of education programs. For years, providers have perceived quality guidelines as being designed primarily to save the health plan money.

To receive optimal value from education programs, health plans first must recognize that educational efforts need to be meaningful, relevant, and include data specific to their patients.

One of the key clinical areas health plans target is care for patients with diabetes. Typically, these patients have high costs and, until recently, physicians’ adherence to quality metrics has been low. In the 1990s, when HEDIS scores showed that many physicians were not checking hemoglobin levels, health plans began educating providers on the importance of measuring patients’ blood sugar levels.

Not up to standards

Although some 90 percent of all providers do hemoglobin testing today, many providers are not performing up to standards for microalbumin testing. Microalbuminuria is an early and easily detectable sign of diabetes.

Steps to consider when developing physician-education programs

Choosing among many options to educate physicians can be challenging for health plans. There are several steps they can follow when developing provider outreach and education programs.

- **Identify barriers.** The ideal first step is to understand the perceptions of any current educational outreach programs and how these perceptions may have affected participation in education efforts in the past.
- **Review procedures in place for education.** Some organizations use e-mail newsletters or include updates on research with monthly checks. This may work sometimes, but often the information gets overlooked or never reaches the physician.
- **Target providers by specialty, recognizing that different approaches will appeal to different providers.** Health plans can identify which physicians are likely to respond through surveys and by reviewing past participation rates. Some physicians will need intensive face-to-face outreach, some will respond well to virtual programs, and some will be incorporating best practices already and need only passive interventions.
- **Consider outsourcing.** Messages involving education sometimes gain wider acceptance when they come from a credible outside source rather than from the health plan itself.
- **Measure results over time.** By measuring participation rates and results, health plans can expand successful programs and revise those that do not produce desired results.

Next, health plans should analyze the data they have on provider performance to identify gaps in care, using standards from the National Commission for Quality Assurance, the Joint Commission and other standard-setting organizations. Almost all health plans use the NCQA’s HEDIS to measure physicians’ performance. In the past several years, NCQA also has addressed performance of accountable care organizations, patient-centered medical homes, and patient-centered specialty practices to ensure that the providers in these organizations meet quality standards.

Plan data

In addition, plans have their own data they can use to identify physicians who are not meeting certain guidelines. Using this data, they can develop education programs targeting those physicians and highlighting best practices. Health plans should also analyze results over time, report back to providers, and do follow-up education as needed.

Once a successful education program is developed, health plans can develop initiatives designed to serve their specific populations.

If a health plan has a large population at-risk for diabetes, for example, an important initiative would be to ensure that proper prevention and testing programs are being employed.

Continuous improvement of any and all education initiatives will ensure that these programs will help maintain a level of quality that is best for members and allows providers to reach goals incorporated in P4P or other financial-reward programs.
able marker of renal damage. Only 30% to 40% of diabetic patients routinely get their microalbumin level checked, chiefly because providers mistakenly assume that checking creatinine levels is adequate for detecting early disease.

To improve testing of key indicators, including microalbumin levels for patients with diabetes, a health plan in the Midwest launched a comprehensive member and provider education program that included incentives to encourage better care. Within two years, scores improved significantly, enabling the plan to expand the program to other therapeutic categories.

**New approaches**

Using incentives to foster change often is successful, but health plans also are finding success with other methods of engagement, such as:

- Peer-to-peer outreach, in which physicians receive education from other clinicians
- Interactive workshops with peers, which are highly successful but costly and time consuming
- Practice-based learning, which is a critical evolution in teaching that emphasizes learning by doing

Social networking also is increasing among physicians of all ages. While busy physicians often do not have time to read numerous clinical journals, many will take time to read an excerpt or more from articles colleagues share in discussion groups or in professional associations. To share research on medical information, 24% of physicians use social media, such as Facebook, Twitter, and LinkedIn, on a daily basis, according to a recent study published in the *Journal of Medical Internet Research*.

Another important education method effective for disseminating evidence-based information to providers is academic detailing. Traditionally this approach has focused on changing prescribing patterns for targeted medications. In recent years, however, it has been expanded to target adherence to evidence-based medicine guidelines and has shown considerable promise.

For many years, the NCQA has run the Diabetes Physician Recognition Program (DPRP) cosponsored by the American Diabetes Association (ADA). DPRP is a voluntary program for physicians or physician groups that provide care to patients with diabetes. The program assesses adherence to key measures designed to improve patient outcomes.

Recognizing the importance of participation in such an initiative, a national health plan analyzed provider performance and discovered it had 40 providers in two key markets with low DPRP performance scores. After instituting a P4P program to improve scores, only one practice achieved the desired results.

Working with a consultant, the health plan then developed an academic detailing program for physicians. Each practice was evaluated on how well it managed blood glucose, blood pressure, and cholesterol levels; eye exams; nephropathy and smoking status assessments; and giving smoking cessation advice or treatment.

One-on-one, peer-to-peer education was implemented in all practices. A chart review conducted in 20 practices six months after the program began found that 17 (85%) of the practices achieved the 75 points needed for DPRP recognition, a marked improvement from the initial single practice achievement.

**Academic detailing**

The DPRP program provides two important lessons. First, it shows that when health plan education includes comparisons of a clinician’s own quality data with that of national and local benchmarks, performance is likely to improve. Second, the benefits of having peers communicate one-to-one with physicians using the principles of academic detailing are significant.

**The AHRQ approach to education**

Recently the federal Agency for Healthcare Research and Quality launched programs to engage and educate providers about comparative effectiveness research, and more specifically about the medical evidence that has direct implications for day-to-day practice. Physicians caring for large populations of patients with diabetes or heart disease receive education, through a multitude of approaches, including peer-to-peer outreach in one-on-one or small group presentations. Continuing medical education is also an important component of AHRQ’s approach to dissemination of research findings.
Virtual education outreach
This second lesson has emerged recently as part of a new approach to academic detailing called virtual education outreach. In this approach, physicians and other providers are connected via Web cams to trained clinician educators, such as medical doctors, doctors of pharmacy, and advanced-practice nurses, who provide one-on-one evidence-based education. These programs focus not only on education regarding evidence-based outcomes studies, but also on dynamic data reporting relevant to the provider’s specific population.

There are many benefits to combining what works in academic detailing with an approach that is cost-effective for health plans and that allows providers to schedule these sessions at their convenience.

The cost of these programs can range from $300 to $500 per provider. Considering the work that goes into analyzing data, scheduling appointments and delivering education via a trained clinician, these programs are comparable to, or cost less than, many other education and outreach efforts.

Early interest in such programs is promising. Recently, a large national health plan launched a pilot online education tool with providers with commercial or Medicare members with diabetes that enables physicians to schedule virtual meetings with clinicians.

The clinicians update doctors on their patients’ profiles and on the latest medical research in diabetes care. This information is tailored to the specific health concerns of the physician’s patients, giving physicians personalized and actionable treatment information.

Such virtual academic detailing can be used to give physicians the latest research and insights into quality performance and other data health plans need to communicate to physicians. Providers can get information about which patients need certain tests or other follow-up care, for example.

Such dynamic reporting, enabled through virtual academic detailing and presented by a clinician, allows providers to use specific clinical and quality information immediately for their patients. Another benefit of these virtual programs is that they help health plans reach providers dispersed across large rural areas, thereby ensuring more consistent adoption of best practices systemwide.

In addition, the virtual approach provides peer-to-peer education in a cost-effective and convenient manner because physicians can schedule their education when and where they want.

Typically, about 20% to 25% of eligible physicians participate in these voluntary virtual academic detailing programs, rates that are considerably higher than the industry average for traditional education programs. Some health plans are moving to require physicians to participate and others offer financial incentives to encourage physicians to participate.

Improvements
Once health plans have enough providers participating in these educational initiatives they are likely to see a reduction in the time from when research demonstrates a best practice to when it is incorporated into care delivery. At that point, plans should begin to see improvements in patient outcomes; the ultimate goal of physician education.

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Molecular Monitoring of Response In Patients With Chronic Myeloid Leukemia

Kathryn S. Kolibaba, MD, hematologist-medical oncologist, Northwest Cancer Specialists, Vancouver, WA

Abstract

Purpose: To discuss the importance of regular, consistent use of molecular testing to monitor treatment response and minimal residual disease in patients with chronic myeloid leukemia (CML), as recommended in established practice guidelines.

Design: This review outlines the efficacy of BCR-ABL1 tyrosine kinase inhibitors (TKIs) in eliciting significant treatment responses in patients with CML; describes the positive effect of achieving molecular responses on long-term outcomes; discusses the importance of regular, consistent molecular monitoring in CML; and highlights issues critical to the implementation of molecular monitoring in routine practice.

Methods: Published literature pertaining to molecular monitoring of the response to BCR-ABL1 TKI therapy for CML was searched and reviewed.

Results: BCR-ABL1 TKI therapy for CML can reduce the disease burden to a level detectable only by molecular methods. Although practice guidelines recognize the importance of molecular monitoring of disease as a means to optimize long-term patient outcome, standardization of methods and appropriate use of molecular monitoring in routine clinical practice are not ideal.

Conclusions: Without accurate, reproducible methods to measure treatment response, the clinical course of disease cannot be adequately monitored during treatment, leaving open the potential to miss patients who might benefit from a change in their treatment plan.

Introduction

The last decade has witnessed a paradigm shift in the treatment of patients with chronic myeloid leukemia (CML). The approval of imatinib, a BCR-ABL1 tyrosine kinase inhibitor (TKI), for CML marks one of the earliest successes of rational drug design based on knowledge of a specific underlying molecular defect. Imatinib — and the newer BCR-ABL1 TKIs nilotinib, dasatinib, bosutinib, and ponatinib — reduce the disease burden in CML so effectively that highly sensitive techniques are needed to adequately monitor treatment responses and minimal residual disease. Evidence is mounting that the achievement of a reduced disease burden early in treatment with TKIs predicts a favorable long-term outcome, and that patients who show suboptimal responses to TKI therapy may benefit from treatment modifications. Therefore, the consistent use of accurate and reproducible techniques to monitor treatment response becomes a critical component of care in the management of patients with CML. Efforts are now focused on the standardization of monitoring techniques and methods, as standardization is expected to affect both the use of health care resources and long-term patient outcome.

This review discusses the rationale behind the current need for standardized methods to measure accurately and reproducibly the level of response to TKI treatment, and addresses the...

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>alloHSCT</td>
<td>Allogeneic hematopoietic stem cell transplant</td>
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<td>AP</td>
<td>Accelerated phase</td>
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<td>BC</td>
<td>Blast crisis</td>
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<tr>
<td>CCyR</td>
<td>Complete cytogenetic response</td>
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<td>CML</td>
<td>Chronic myeloid leukemia</td>
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<td>CMR</td>
<td>Complete molecular response</td>
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<td>European LeukemiaNet</td>
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<td>MCyR</td>
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<td>Major molecular response</td>
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<td>National Comprehensive Cancer Network</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>Ph+</td>
<td>Philadelphia chromosome-positive</td>
</tr>
<tr>
<td>qRT-PCR</td>
<td>Quantitative reverse-transcription polymerase chain reaction</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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Although this practice can optimize long-term patient outcomes, it is not routine in clinical practice

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Disclosures: Novartis Pharmaceuticals Corp. provided financial support for manuscript development.
Introducing a **NEW** approach in type 2 diabetes treatment...
Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition.

**A1C Reductions as Monotherapy**

INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks.

**A1C Reductions vs Sitagliptin**

INVOKANA™ 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:
- INVOKANA™ 300 mg: 43.2%
- Sitagliptin 100 mg: 40.7%

**Effect on Weight**

Statistically significant weight reductions vs placebo at 26 weeks (P < 0.001).

- Difference from placebo†:
  - 100 mg: –2.2%
  - 300 mg: –3.3%

**Impact on Systolic Blood Pressure (SBP)**

Statistically significant SBP lowering vs placebo at 26 weeks (P < 0.001).

- Difference from placebo†:
  - 100 mg: –3.7 mm Hg
  - 300 mg: –5.4 mm Hg

INVOKANA™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

**Contraindications**

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR < 30 mL/min/1.73 m²), end stage renal disease, or patients on dialysis.

**Warnings and Precautions**

- Hypotension: INVOKANA™ causes intravascular volume contraction, symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR < 60 mL/min/1.73 m²), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™, patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Please see additional important safety information and brief summary of full prescribing information on the following pages.

**References**

Introducing INVOKANA®—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition.

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INVOKANA® is not indicated for weight loss or as antihypertensive treatment.

References:

Learn more at INVOKANAhcp.com/journal
WARNINGS and PRECAUTIONS

**Hypoglycemia:** The risk of hypoglycemia is increased when INVOKANA™ is co-administered with insulin or insulin secretagogues. Hypoglycemia may occur in patients on INVOKANA™. It is important to educate patients and healthcare providers about the increased risk of hypoglycemia with INVOKANA™ and recommend that they take appropriate measures to avoid this risk.

**Renal Impairment:** The effects of renal impairment on the pharmacokinetics and pharmacodynamics of INVOKANA™ have not been fully evaluated. The manufacturer recommends caution when using INVOKANA™ in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) and careful dose adjustment in patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²). In patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m²), renal function should be monitored closely.

**Hypersensitivity Reactions:** Hypersensitivity reactions are a potential risk with INVOKANA™. Symptoms may include rash, pruritus, fever, and other signs of hypersensitivity. If a hypersensitivity reaction occurs, the drug should be discontinued immediately.

**Hepatic Impairment:** The effects of hepatic impairment on INVOKANA™ have not been studied. Patients with hepatic impairment may be more susceptible to the adverse effects of INVOKANA™.

**Overdosage:** There were no reports of overdosage during the clinical development program of INVOKANA™. In the event of an overdose, the usual supportive measures should be employed. The drug should be discontinued, and the patient should be monitored closely.

**Drug Interactions:** INVOKANA™ can interact with other drugs, particularly those that increase the risk of hypoglycemia or hyperkalemia. It is important to monitor for these interactions and adjust the dosing regimen accordingly.

**Geriatric Use:** Elderly patients are at increased risk for adverse reactions related to INVOKANA™. It is important to monitor elderly patients closely and adjust the dosing regimen as needed.

**Pregnancy:** INVOKANA™ is not recommended for use in pregnant women due to the potential for fetal harm. In patients who require treatment during pregnancy, the benefits of INVOKANA™ should be weighed against the potential risks.

**Lactation:** INVOKANA™ can be excreted in human milk. It is recommended that women on INVOKANA™ avoid breastfeeding or use alternative methods of feeding.

**ADVERSE REACTIONS**

**DRUG INTERACTIONS:**

**Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Adverse reactions in patients who are taking INVOKANA™ concomitantly with insulin or insulin secretagogues may include hypoglycemia.

**Hypersensitivity Reactions:** Hypersensitivity reactions occurring with INVOKANA™ may include rash, pruritus, fever, and other signs of hypersensitivity. These reactions should be managed appropriately with the use of antihistamines or glucocorticoids as necessary.

**Hepatic Impairment:** The effects of hepatic impairment on INVOKANA™ are not well studied. It is recommended that patients with hepatic impairment be monitored closely for adverse reactions.

**Pregnancy:** The effects of INVOKANA™ on fetal development are not known. It is recommended that pregnant women avoid the use of INVOKANA™.

**Lactation:** INVOKANA™ can be excreted in human milk. It is recommended that women on INVOKANA™ avoid breastfeeding or use alternative methods of feeding.

**Geriatric Use:** Elderly patients are at increased risk for adverse reactions related to INVOKANA™. It is important to monitor elderly patients closely and adjust the dosing regimen as needed.

**Pregnancy:** INVOKANA™ is not recommended for use in pregnant women due to the potential for fetal harm. In patients who require treatment during pregnancy, the benefits of INVOKANA™ should be weighed against the potential risks.

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Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.
**WARNINGS and PRECAUTIONS (continued)**

**Hypovolemia:** INVOKANA® can lead to hypovolemia. 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 hypovolemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hypovolemia 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™.

**Hypersensitivity Reactions:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncontrolled males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

**Hyperuricemia:** Hyperuricemia reactions (eg, generalized urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis) were reported with INVOKANA™ treatment. These reactions generally occurred within hours to days after initiating INVOKANA™. Hypersensitivity reactions occur, discontinue use of INVOKANA™, treat per standard of care and monitor until signs and symptoms resolve.

**Increases in Low-Density Lipoprotein (LDL-C):** Statin-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

**Macrophage Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular role reduction with INVOKANA™ or any other antidiabetic drug.

**Renal Outcomes:** The incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, vasodilatory syncope, and dehydration), particularly with the 300-mg daily dose, was compared to younger patients; more prominent increases in the incidence was seen in patients who were ≥85 years of age. Small reductions in haemoglobin with INVOKANA™ relative to placebo were seen in older (>65 years and older: -0.72% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.52% with INVOKANA™ 100 mg and -0.67% with INVOKANA™ 300 mg relative to placebo).

**Insulin Secretagogues:** When used with concomitant insulin or an insulin secretagogue, canagliflozin results in a decrease in mean fasting plasma glucose. If the dose of insulin or insulin secretagogue is not decreased, hypoglycemia may occur. If hypoglycemia occurs, discontinue use of INVOKANA™ and treat appropriately.

**Potassium:** The efficacy and safety of INVOKANA™ have not been established in patients with severe hepatic impairment and it is therefore not recommended.

**Lactic Acidosis:** There have been no reports of lactic acidosis 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 (≥25%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥10% of patients were male genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation.

Please see Brief Summary of full Prescribing Information on the following pages.
INVOKE™
(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

CONTRAINDICATIONS

• Hypersensitivity to canagliflozin or any of the other excipients

WARNINGS AND PRECAUTIONS

Hypoglycemia: INVOKANA dosages of the trial

Hypertension

• INVOKANA: transient intravascular volume contraction.

ADVERSE REACTIONS

The table below summarizes the incidence of adverse reactions observed in clinical trials. Adverse reactions were not generally dose related, but were more frequent at higher doses. The incidence of adverse reactions was similar in patients treated with INVOKANA or placebo.

Table 1: Adverse Reactions from Pool of Four 26-Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>1.5%</td>
<td>2.2%</td>
<td>2.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.9%</td>
<td>1.8%</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Thirst#</td>
<td>0.2%</td>
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<td>3.6%</td>
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* The following important adverse reactions are described below and elsewhere in the labeling:

• Hypoglycemia
• Impairment in Renal Function
• Hyperkalemia
• Increased Urination
• Hypersensitivity Reactions
• Increases in Low-Density Lipoprotein (LDL-C)

Macrolide Antibiotics: There have been no clinical studies establishing effectiveness of INVOKANA in combination with macrolide antibiotics.

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• Increases in Low-Density Lipoprotein (LDL-C)

Macrolide Antibiotics: There have been no clinical studies establishing effectiveness of INVOKANA in combination with macrolide antibiotics.
In INVOKANA™-treated patients, the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration) was increased compared to placebo. An increased incidence was observed in patients with moderate renal impairment on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, a low glucose value (any glucose value below or equal to 70 mg/dL), and dehydration. An increased incidence was observed in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) and age 75 years or older. In individual clinical trials, volume depletion-related adverse reactions occurred at a higher rate when INVOKANA was co-administered with sulfonylureas (3.5% with sulfonylurea compared to 2.3% with placebo) or metformin (2.2% with metformin compared to 1.0% with placebo) and more commonly in concomitant use than in any other concomitant use combination.

In a trial carried out in patients with moderate renal impairment, the incidence of renal-related adverse reactions was defined as an eGFR 30% lower than baseline, was 0.9% with placebo, 1.0% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 2.5% with INVOKANA 300 mg had a significant renal function decline, defined as an eGFR 30% lower than baseline. A significant renal function decline was experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 0.9% with placebo, 1.0% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 2.5% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=106) with baseline eGFR of 30 to less than 60 mL/min/1.73 m², the overall incidence of these events was lower than 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 1.6% with INVOKANA 300 mg. Discontinuations due to renal-related adverse reactions occurred more commonly in concomitant use than in any other concomitant use combination.

In the dedicated trial, the incidence of adverse effects on the 300 mg dose was 1.4% with INVOKANA 300 mg had a significant renal function decline. 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 1.6% with INVOKANA 300 mg. Discontinuations due to renal-related adverse reactions occurred more commonly in concomitant use than in any other concomitant use combination.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 60 mL/min/1.73 m², baseline eGFR of 30 mL/min/1.73 m² (see Clinical Studies (74) for full prescribing information), the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 0.9% with placebo, 1.0% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 2.5% with INVOKANA 300 mg had a significant renal function decline.

In the pool of four placebo-controlled trials, male genital mycotic infections occurred more commonly in concomitant use than in any other concomitant use combination. Male genital mycotic infections occurred in 0.9% of men treated with placebo, 1.0% of men treated with INVOKANA 100 mg, and 0.6% of men treated with INVOKANA 300 mg. Male genital mycotic infections occurred more commonly in concomitant use and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents (see Warnings and Precautions).

Phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis. Phimosis was reported in 0.4% of uncircumcised male patients treated with placebo. Male genital mycotic infections occurred more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents (see Warnings and Precautions).

In the pooled population of four placebo-controlled trials, male genital mycotic infections occurred more likely to experience recurrence on INVOKANA compared to placebo. Male genital mycotic infections occurred more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents (see Warnings and Precautions).

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Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

<table>
<thead>
<tr>
<th></th>
<th>Overall [N (%)]</th>
<th>In Combination [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>INVOKANA 100 mg</td>
</tr>
<tr>
<td></td>
<td>3 (2.6)</td>
<td>3 (2.7)</td>
</tr>
</tbody>
</table>

*Number of patients experiencing at least one event of hypoglycemia based on either biochemical documentation or an episode or severe hypoglycemia event in the intent-to-treat population.

†Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover (not consciousness) or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was observed).
INVOKANA™ (canagliflozin) tablets

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, 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.

Inform 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 infections 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:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
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16282400
K02CAN13080B

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- BRILINTA® (ticagrelor) tablets
- Eliquis® (apixaban) tablets
- FORTESTA® (testosterone) Gel
- INVOKANA™ (canagliflozin)
- JAKAFI® (ruxolitinib) tablets
- KOMBIGLYZE™ XR ( saxagliptin and metformin HCl extended-release) tablets
- LINZESS™ (linaclotide) capsules 145 mcg - 290 mcg
- Onglyza® (saxagliptin)
- PREVNAR® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
- Quillivant XR™ (methylphenidate HCl) for extended-release oral suspension, CII
- RAVIDCTI™ (glycerol phenylbutyrate)
- SYMBICORT® (budesonide/formoterol fumarate dihydrate)
- Teffaro® (cetfaronol fosamil) for injection 600 mg · 400 mg

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P&T Community
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CML disease background and current standard of care

CML is a myeloproliferative disorder characterized by the unregulated growth of myeloid cells in the bone marrow and their accumulation in the blood. CML is caused by the constitutive expression of an aberrant fusion gene, BRC-ABL1 (also referred to as BCR-ABL), that is formed through a reciprocal translocation between chromosomes 9 and 22 (the Philadelphia chromosome [Ph]) (Bernards 1987; Nowell 1960). It has been estimated that 5,920 new cases of CML will be diagnosed in 2013 and that 610 people will die from the disease (American Cancer Society 2013). Without treatment, CML typically progresses from an initial chronic phase (CP) to the advanced accelerated phase (AP) within 4 to 6 years, and then to a final, fatal phase — blast crisis (BC) — within 1 year (Kalidas 2001).

In CML, treatment response is measured on several levels: hematologic response, cytogenetic response, and molecular response (Table 1) (National Comprehensive Cancer Network 2012). In terms of detecting minimal residual disease in CML, monitoring molecular responses by measuring BRC-ABL1 expression offers the highest degree of sensitivity compared with monitoring hematologic or cytogenetic responses (Radich 2009). Current standard first-line treatment for CML includes TKI therapy with imatinib, nilotinib, or dasatinib (National Comprehensive Cancer Network 2012), all of which are effective in eliciting molecular responses through the inhibition of BRC-ABL1 expression.

Imatinib was the first TKI to be approved for Ph-positive (Ph+) CML, based on the findings of the phase 3 International Randomized Study of Interferon and STI571 (IRIS), in which imatinib significantly improved the rates of major (MCyR) and complete (CCyR) cytogenetic responses, and the rate of freedom from progression to AP or BC compared with interferon-a (IFN-a) plus cytarabine (O’Briene 2003). Continued follow-up of the IRIS study confirmed the efficacy and safety of imatinib over 8 years of treatment (Deininger 2009; Druker 2006; Hochhaus 2009).

Four newer TKIs more potent than imatinib have been approved: nilotinib and dasatinib for first-line and second-line treatment of Ph+ CML (Saglio 2011; Rumi 2012), and bosutinib and ponatinib for second- and third-line treatment (O’Brien 2012; Iclusig 2012). Two- and 3-year follow-up of the phase 3 Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study confirmed initial findings that nilotinib 300 mg twice daily (BID) was significantly more effective than imatinib in improving the rates of CCyR (87% vs. 77%, respectively; \( P < .0001 \)) (Kantarjian 2011; Saglio 2010), major molecular response (MMR; 85% vs. 64%; \( P < .0001 \)), and complete molecular response (CMR; reported as MR4.5; 32% vs. 15%; \( P < .0001 \)) at 3 years ( Larson 2012), and in reducing the number of progressions to AP or BC (2 vs. 17; \( P = .0003 \)) by 3 years ( Larson 2012). A 4-year follow-up report on the ENSThnd trial further supported the efficacy of first-line nilotinib (Kantarjian 2012). Two-year follow-up of the phase 3 Dasatinib vs. Imatinib Study in Treatment-Naive CML Patients (DASISION) also showed that dasatinib significantly improved the rates of CCyR (86% vs. 82%; \( P = .0002 \)), MMR (64% vs. 46%; \( P < .0001 \)), and CMR (17% vs. 8%; \( P = .002 \)), and resulted in a lower rate of transformation to AP or BC (2.3% vs. 5%), compared with imatinib (Kantarjian 2010; Kantarjian 2012). Three-year follow-up data from the DASISION trial showed durable responses with dasatinib over time (Hochhaus 2012).

The advent of BCR-ABL1 TKI therapy represents a major advance in the treatment of CML. That TKI therapy can significantly reduce the frequency of progression of CML to advanced stages is important because the median overall survival (OS) of patients who progress to CML-AP/BC while being treated with imatinib or nilotinib is short (10.5 months) (Larson 2012). CML-AP/BC is considerably more difficult to treat than is CML-CP, and few effective therapeutic options are available (National Comprehensive Cancer Network 2012). Although allogeneic hematopoietic stem cell transplant (alloHSCT) — considered a potentially curative treatment for patients with CML — is standard treatment for patients with advanced disease, those with CML-AP/BC fare much worse following alloHSCT than do patients with CML-CP; 3-year OS rates after alloHSCT were 91% and 59% for patients with CML-CP and CML-AP/BC, respectively (Saussele 2010). The ability of TKIs to elicit response rates that are markedly higher than previously reported rates has driven the use of more rigorous clinical endpoints and has made it necessary to modernize the methods needed to measure treatment response. The end result has been updates to clinical practice guidelines that include expectations for milestone responses and that reflect the use of current technologies.

Guidelines for molecular monitoring of treatment response

Because TKI therapy for CML has the potential to reduce the disease burden to below the threshold of
detection of hematologic and cytogenetic testing, molecular monitoring using quantitative reverse-transcription polymerase chain reaction (qRT-PCR) is the method best suited to discriminate among degrees of response. Guidelines issued by the National Comprehensive Cancer Network (NCCN) (National Comprehensive Cancer Network 2012) and by the European LeukemiaNet (ELN) (Baccarani 2009) recommend molecular monitoring of BCR-ABL1 expression using qRT-PCR to monitor treatment response. Notably, both

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Hematologic, cytogenetic, and molecular response criteria (Baccarani 2009);* (Faderl 1999);b (National Comprehensive Cancer Network 2012)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of testing</td>
<td>Technique</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Blood cell count using blood sample</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>Karyotyping or FISH analysis using bone marrow aspirate</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td>qRT-PCR using blood sample or bone marrow aspirate</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; IS, International Scale; NCCN, National Comprehensive Cancer Network; Ph+, Philadelphia chromosome-positive; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; WBC, white blood cell


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sets of guidelines recommend reporting levels of BCR-ABL1 expression on the International Scale (IS), which uses a standardized baseline that was meant to be applicable across laboratories. Both the NCCN and ELN guidelines also establish response milestones — responses expected within specified timeframes — for first-line (Baccarani 2009; National Comprehensive Cancer Network 2012) and second-line (Baccarani 2009) TKI treatment (Tables 2 and 3). The two sets of guidelines have considerable overlap as well as differences with respect to treatment-response milestones. Nevertheless, it is important that the ELN guidelines be considered in the management of patients with CML in the United States because the ELN response milestones form the foundation for the response criteria and clinical endpoints used in modern clinical studies of CML (Guilhot 2012).

**Achievement of molecular response and improved long-term outcomes**

Evidence supports the concept that the achievement of an optimal response — that is, a level of response that meets or exceeds response milestones defined by the ELN or NCCN guidelines — within the first 18 months of treatment with imatinib significantly predicts favorable long-term outcomes. Applying ELN-defined criteria for treatment response, one study found that patients achieving optimal treatment responses at 6, 12, and 18 months had significantly higher rates of CCyR and MMR, and lower rates of disease transformation to AP or BC, after 24 and 48 months of treatment, compared with patients who failed treatment (Alvarado 2009). Another study found that treatment failure (as defined by ELN criteria) at 3, 6, 12, or 18 months correlated significantly with a lower 5-year probability of CCyR, OS, and progression-free survival (PFS) (Marin 2008).

Studies that designate a specific level of response — not necessarily tied to ELN or NCCN criteria — as a milestone have also found significant correlations between the achievement of a treatment response and long-term outcome. One such study found that CCyR at 3, 6, or 12 months correlated with improved 3-year event-free survival (EFS) and OS (Jabbour 2011). An analysis of the IRIS study showed that achievement of MMR by 12 and 18 months of imatinib therapy correlated significantly with a higher rate of EFS at 7 years (Hughes 2010). With respect to PFS, however, achievement of MMR at 12 and 18 months in patients with CCyR did not significantly improve the rate of 5-year PFS, compared with patients who had achieved only CCyR (Druker 2006). An analysis of the German CML IV study showed a significant correlation between MMR

**TABLE 2**
Summary of recommended treatment modifications according to NCCN Guidelines,* based on response to first-line treatment with imatinib (white rows) or to nilotinib or dasatinib (gray rows) (National Comprehensive Cancer Network 2012)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Favorable response</th>
<th>Time on therapy</th>
<th>Unfavorable response</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue same dose</td>
<td><strong>BCR-ABL1 (IS) ≤10%</strong></td>
<td>3 months (IM)</td>
<td><strong>BCR-ABL1 (IS) &gt;10%</strong></td>
<td>• Evaluate for adherence and drug interactions</td>
</tr>
<tr>
<td></td>
<td><strong>BCR-ABL1 (IS) ≤10%</strong></td>
<td>3 months (NIL or DAS)</td>
<td><strong>BCR-ABL1 (IS) &gt;10%</strong></td>
<td>• Conduct mutational analysis</td>
</tr>
<tr>
<td></td>
<td><strong>CCyR</strong></td>
<td>12 months (IM)</td>
<td>≤PCyR or cytogenetic relapse</td>
<td>• For patients with PCyR at 12 months, increase imatinib dose up to 800 mg, as tolerated, if patient is not a candidate for other TKIs</td>
</tr>
<tr>
<td></td>
<td>≥PCyR</td>
<td>12 months (NIL or DAS)</td>
<td>≤mCyR or cytogenetic relapse</td>
<td>• Switch to another TKI</td>
</tr>
<tr>
<td></td>
<td><strong>CCyR</strong></td>
<td>18 months (IM)</td>
<td>≤PCyR or cytogenetic relapse</td>
<td>• Evaluate for allogeneic HSCT</td>
</tr>
<tr>
<td></td>
<td><strong>CCyR</strong></td>
<td>18 months (NIL or DAS)</td>
<td>≤PCyR or cytogenetic relapse</td>
<td>• Consider enrollment in clinical trials</td>
</tr>
</tbody>
</table>

*Please refer to NCCN Guidelines for more detailed description of treatment recommendations.

CCyR, complete cytogenetic response; CHR, complete hematologic response; DAS, dasatinib; HSCT, hematopoietic stem cell transplant; IM, imatinib; IS, International Scale; mCyR, minor cytogenetic response; NIL, nilotinib; PCyR, partial cytogenetic response

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at 12 months and improved PFS and OS at 3 years (Hehlmann 2012). Another study showed that achievement of MMR at any time correlated significantly with an improved rate of 5-year EFS, and that achievement of both CCyR and MMR at 18 and 24 months correlated significantly with higher rates of 5-year and 7-year EFS (Furukawa 2011). Several studies have found that achievement of specific BRC-ABL1 levels, generally ≤10% (IS), after 3 months of imatinib therapy was a highly significant predictor of long-term outcomes, such as the 12-month probability of MMR and CMR (Naqvi 2011), the 12-month probability of CCyR, the 24-month probability of MMR and PFS, and the progression to AP or BC at any time (Hochhaus 2011); 5-year OS and PFS (Hanfstein 2012); 8-year OS, PFS, and EFS; and the probability of CCyR, MMR, and

<p>| TABLE 3 | European LeukemiaNet (ELN) definitions of response milestones for treatment with first-line imatinib (white rows) and provisional definitions of response with second-line nilotinib or dasatinib (gray rows) (Baccarani 2009) |</p>
<table>
<thead>
<tr>
<th>Optimal response</th>
<th>Suboptimal response</th>
<th>Failure</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
<td></td>
<td>• High-risk Sokal or Hasford score</td>
</tr>
<tr>
<td>Nilotinib or dasatinib</td>
<td></td>
<td></td>
<td>• Clonal chromosomal abnormalities in Ph+ cells</td>
</tr>
<tr>
<td><strong>3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>CHR and ≥mCyR</td>
<td>mCyR</td>
<td>No CyR</td>
</tr>
<tr>
<td>Nilotinib or dasatinib</td>
<td>≥PCyR</td>
<td>mCyR</td>
<td>No CyR</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>≥PCyR</td>
<td>&lt;PCyR</td>
<td>No CyR</td>
</tr>
<tr>
<td>Nilotinib or dasatinib</td>
<td>CCyR</td>
<td>PCyR</td>
<td>mCyR</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilotinib or dasatinib</td>
<td>MMR</td>
<td>&lt;MMR</td>
<td>&lt;PCyR</td>
</tr>
<tr>
<td><strong>18 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>MMR</td>
<td>&lt;MMR</td>
<td>&lt;CCyR</td>
</tr>
<tr>
<td>Any time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR</td>
<td>Stable or improving MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imatinib-sensitive mutations</td>
<td>Imatinib-sensitive mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of CHR</td>
<td>Loss of CCyR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imatinib-resistant mutations</td>
<td>Imatinib-resistant mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonal chromosomal abnormalities in Ph+ cells</td>
<td>Clonal chromosomal abnormalities in Ph+ cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rise in BCR-ABL1 transcript levels</td>
<td>Rise in BCR-ABL1 transcript levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clonal chromosomal abnormalities in Ph− cells</td>
<td>Clonal chromosomal abnormalities in Ph− cells</td>
</tr>
</tbody>
</table>

CCyR, complete cytogenetic response; CHR, complete hematologic response; CML-CP, chronic myeloid leukemia in chronic phase; minCyR, minimal cytogenetic response; mCyR, minor cytogenetic response; PCyR, partial cytogenetic response; MMR, major molecular response; Ph+, Philadelphia chromosome–positive; Ph−, Philadelphia chromosome–negative; TKI, tyrosine kinase inhibitor

CMR (Marin 2012). Based on the strength of these clinical data, the NCCN recently updated the criteria for the 3-month treatment response milestone to include a BRC-ABL1 level of ≤10% (IS) (Table 3).

At present, only preliminary data are available regarding early responses to the newer TKIs, but these data indicate a significant correlation between a favorable response to nilotinib, dasatinib, and bosutinib at 3 months and improved long-term outcomes (Brümmendorf 2012; Hochhaus 2012; Hochhaus 2011; Jabbour 2011; Marin 2012; Nicolini 2011).

Overall, these clinical findings highlight the importance of accurate molecular monitoring as a means of measuring treatment responses. The NCCN and ELN guidelines provide management recommendations for patients who fail to meet specific treatment-response milestones, including the evaluation of patients for adherence or intolerability, BRC-ABL1 mutational analysis, dose escalation, or a change in drug therapy (Table 2) (Baccarani 2009; National Comprehensive Cancer Network 2012). Because the guidelines’ recommended treatment modifications are based on the patient’s response to treatment, consistent implementation of accurate and reproducible response measurements is crucial and must be an integral part of patient management. Despite the importance of molecular monitoring to assess treatment response, nearly half of clinicians surveyed do not follow practice guidelines in this respect (Chen 2012; Fogarty 2008; Quintas-Cardama 2011), indicating an important gap in their knowledge of CML that may have negative implications for patient outcome.

Important issues to consider in the molecular assessment of treatment response

Frequency of monitoring and implications of increases in BCR-ABL1 levels

Both the NCCN and the ELN guidelines recommend regular molecular monitoring of BRC-ABL1 transcript levels by qRT-PCR during TKI treatment (Tables 4 and 5). The NCCN recommends testing at baseline, every 3 months for 3 years, and every 3 to 6 months thereafter if CCyR has been achieved and maintained (National Comprehensive Cancer Network 2012). Similarly, the ELN recommends testing every 3 months until MMR is achieved and maintained, and at least every 6 months thereafter (Baccarani 2009). This testing frequency allows clinicians to monitor 1) the achievement and maintenance of optimal treatment response, and 2) increases in BRC-ABL1 levels (a sign of potential relapse or emerging resistance). Early detection of events, such as a loss of response or possible signs of disease progression, may signal to the clinician that patients are having problems with their medication and allow the clinician to intervene in a timely manner to minimize the potential impact that these issues may have on long-term outcomes.

There is evidence that the loss of response during treatment, as determined by an increase in the BRC-ABL1 level, precedes and predicts the emergence of clinical symptoms of disease relapse. In one study, a third of patients with CCyR and MMR who subsequently lost MMR (i.e., they had an increase in BRC-ABL1 levels) experienced disease relapse a median of 14 months later (Press 2007). In another study, 10% of patients with stable CCyR who had lost MMR and/or had a >1-log increase in BRC-ABL1 level subsequently experienced disease progression (Kantarjian 2009).

These findings underscore the importance of regular molecular monitoring of BRC-ABL1 levels, as outlined in practice guidelines, as a means to identify patients at risk of disease progression, who may benefit most from closer follow-up and a reassessment of their treatment strategy.

The loss of a treatment response or failure to achieve a response may indicate that patients are having difficulty with medication adherence. Studies have found that patients on long-term imatinib therapy with lower adherence rates had a higher risk of losing CCyR (Ibrahim 2011) and a lower probability of achieving MMR and CMR (Marin 2010) compared with patients with better adherence. In addition, lower rates of adherence to TKI therapy for CML have been found to correlate with higher health care and medical costs, excluding the cost of the drug (Darkow 2007), and higher health care utilization, including inpatient hospitalizations and emergency room visits (Wu 2010). According to one study, a major reason for nonadherence in patients with CML receiving imatinib therapy is the presence of side effects (Eliasson 2011). Therefore, detection of a lost response may help clinicians to identify tolerability and/or adherence issues that may require additional patient support, such as education or ancillary medications.

In my clinical experience, poor adherence to TKI therapy can be a manifestation of broader psychosocial issues. In an outcomes study currently ongoing in our practice, we have found that patients with insufficient or no health insurance often face an array of psychosocial challenges, such as financial troubles and transportation issues, that can negatively affect clinical outcomes. These patients often miss clinic appointments, make unauthorized reductions in the medication dose, or discontinue treatment without the
clinician’s consent or knowledge. Such “intentional nonadherence” — defined as a patient’s decision to alter or discontinue treatment (Eliasson 2011) — is not uncommon among patients with CML. More important, patients without adequate health insurance have worse cancer survival rates than patients with adequate coverage (American Cancer Society 2008). It is important for payers to understand that regular monitoring of **BRC-ABL1** levels tracks TKI treatment response and provides opportunities for clinicians to connect regularly with patients to assess any problems — such as unsatisfactory treatment adherence or the inability to cover medication copayments — that might be improved by educational reinforcement or by enrollment in a drug-company–sponsored patient assistance program. An increase in the **BRC-ABL1** level detected on molecular monitoring may also signal the emergence of new **BRC-ABL1** mutations that can confer resistance to TKI therapy. It should be noted, however, that **BRC-ABL1** mutations may account for about half the cases of acquired resistance (as few as 19% and as many as 91%), depending on the detection method, patient population, and stage of disease (Branford 2003; Gorre 2001; Hochhaus 2002; Shah 2002). Other **BRC-ABL1**–dependent (e.g., **BRC-ABL1** gene amplification) and **BRC-ABL1**–independent (e.g., clonal evolution, drug efflux) mechanisms may also confer TKI resistance. Both the NCCN and the ELN recognize the link between **BRC-ABL1** mutations and TKI resistance, and their guidelines recommend performing mutational analysis in cases of inadequate response, loss of response (including loss of MMR with ≥1-log increase in **BRC-ABL1** level), or disease progression to AP or BC (National Comprehensive Cancer Network 2012), or in cases of suboptimal response or treatment failure (Baccarani 2009).

The detection of a new mutation warrants a reassessment of the treatment strategy (Soverini 2011). The choice of subsequent therapy may be influenced in part by the specific mutation detected (Table 6) because the most commonly detected mutations vary in their in vitro sensitivities to nilotinib and dasatinib (Soverini 2011). Clinicians should keep in mind, however, that treatment selection should also take into account clinical and pathological factors of

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**TABLE 4**


<table>
<thead>
<tr>
<th>Disease / treatment course</th>
<th>Disease monitoring</th>
<th>Frequency of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td>• Bone marrow cytogenetics</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>• Peripheral blood FISH (if bone marrow collection is not feasible)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>• <strong>BRC-ABL1</strong> transcript levels by qRT-PCR</td>
<td>—</td>
</tr>
<tr>
<td>After treatment initiation</td>
<td>• Bone marrow cytogenetics</td>
<td>• At 3 months, if qRT-PCR (IS) is not available to assess response to TKI therapy</td>
</tr>
<tr>
<td></td>
<td>• <strong>BRC-ABL1</strong> transcript levels by qRT-PCR</td>
<td>• At 12 months, if neither CCyR nor MMR is achieved</td>
</tr>
<tr>
<td></td>
<td>• At 18 months, if not in MMR and no CCyR at 12 months</td>
<td>—</td>
</tr>
<tr>
<td>After achievement of CCyR</td>
<td>• Bone marrow cytogenetics</td>
<td>• No recommendation</td>
</tr>
<tr>
<td></td>
<td>• <strong>BRC-ABL1</strong> transcript levels by qRT-PCR</td>
<td>• Every 3 months if responding to treatment</td>
</tr>
<tr>
<td>Increase (≥1 log) in <strong>BRC-ABL1</strong> transcript levelsb</td>
<td>• Bone marrow cytogenetics</td>
<td>• If no MMR</td>
</tr>
<tr>
<td></td>
<td>• <strong>BRC-ABL1</strong> transcript levels by qRT-PCR</td>
<td>• If MMR, repeat in 1-3 months</td>
</tr>
</tbody>
</table>

*Please refer to NCCN Guidelines for more detailed description of disease monitoring recommendations. Adherence evaluation and mutational analysis are also recommended. CCyR, complete cytogenetic response; FISH, fluorescence in situ hybridization; MMR, major molecular response; qRT-PCR, quantitative reverse-transcription polymerase chain reaction.

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the patient and disease (Soverini 2011). Mutational analyses conducted for the ENESTnd and DASISION studies found that treatment with nilotinib and dasatinib, respectively, did not increase the frequency of new mutations in BRC-ABL1 compared with imatinib therapy (Kantarjian 2011; Kantarjian 2012).

**Choice of control genes**

The use of control genes in qRT-PCR testing is essential for the generation of reliable and reproducible results, and compensates for factors that can cause sample variation, such as the amount of total sample RNA, sample degradation, and the efficiency of the reverse transcription reaction (Hughes 2006). The three most studied control genes suitable for BRC-ABL1 qRT-PCR testing (Hughes 2006) are BCR, which was used in the IRIS study (Hughes 2003), and ABL1 and the β-glucuronidase (GUSB) gene, which were used by a consortium of labs in Europe (Gabert 2003). These control genes are suitable for BRC-ABL1 testing because their expression levels are broadly similar to that of BRC-ABL1 at diagnosis of CML; their transcript stability is similar to that of BRC-ABL1; and primers for these control genes do not inadvertently amplify other sequences in genomic DNA (Hughes 2006). The use of other genes as controls is problematic because they may not satisfy one or more of the above criteria, thus rendering the qRT-PCR results obtained with these genes potentially unreliable and unsuitable for comparison with other data.

**The International Scale (IS)**

The IS was established in the IRIS study as a means to standardize the results of BRC-ABL1 qRT-PCR testing and to make data obtained in multiple laboratories suitable for comparison (Hughes 2006; Hughes 2003). In addition, because the IS is anchored to two defined values — the standardized baseline, representing 100%, and MMR, representing 0.1% (i.e., a 3-log reduction from the standardized baseline) — qRT-PCR results reported on the IS are absolute values and therefore do not depend on an individual patient’s baseline BRC-ABL1 level (Hughes 2006).

A reference laboratory that uses the IS has determined a laboratory-specific conversion factor based on the BRC-ABL1:control gene ratio used in that laboratory that is equivalent to the MMR established in the IRIS study, which allows the laboratory to convert its BRC-ABL1 results to the IS (Hughes 2006). In practical terms, working with reference laboratories that use the IS can simplify certain aspects of patient management, such as allowing clinicians to use a common set of clinical decision

### TABLE 5

**Summary of ELN Guidelines on disease monitoring in patients receiving imatinib therapy** (Baccarani 2009)

<table>
<thead>
<tr>
<th>Type of monitoring</th>
<th>Disease / treatment course</th>
<th>Frequency of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>At diagnosis</td>
<td>—</td>
</tr>
</tbody>
</table>
|                    | During treatment            | • Every 15 days until CHR is achieved and confirmed  
|                    |                             | • At least every 3 months thereafter, or as required |
| Cytogenetic*       | At diagnosis                | —                       |
|                    | During treatment            | • At 3 and 6 months  
|                    |                             | • Every 6 months until CCyR is achieved and confirmed  
|                    |                             | • Every 12 months, if regular molecular monitoring cannot be assured  
|                    |                             | • Always for occurrences of treatment failure and unexplained anemia, leukopenia, or thrombocytopenia |
| Molecular by qRT-PCR| During treatment            | • Every 3 months until MMR is achieved and confirmed  
|                    |                             | • At least every 6 months thereafter |
| Mutational analysis (molecular) | During treatment | • For occurrences of suboptimal response or failure  
|                    |                             | • Always before switching to other TKIs or other therapies |

*Note: Cytogenetics should be performed by chromosome banding analysis of marrow-cell metaphases until CCyR has been achieved and confirmed. Interphase fluorescent in situ hybridization cannot be used to assess a less-than-complete response, but it can substitute for chromosome banding analysis to monitor the completeness of a CCyR, provided that BCR-ABL1 extrasignal, dual color, dual fusion, or in situ hybridization probes are used and that at least 200 nuclei are scored.

The control gene, sample handling, include differences in the choice of the control gene, sample handling, and the qRT-PCR technique. Although not yet available for routine clinical use, automated testing of BRC-ABL1 transcript levels can potentially increase access to reproducible BRC-ABL1 monitoring by qRT-PCR and may improve the accuracy and efficiency of monitoring. In a cost-feasibility study, the use of an automated system that executes RNA extraction and qRT-PCR was found to yield highly reproducible results and to be a cost-effective option for laboratories that perform fewer than 300 BRC-ABL1 tests annually (Cayuela 2011). In a separate analysis, a comparative cost model of automated versus laboratory-developed testing to monitor BRC-ABL1 levels showed a 3.2% improvement in overall accuracy with automated testing over 5 years. In addition, automated testing provided a 19% cost reduction for every 100 patients monitored per laboratory according to NCCN guidelines (Ratcliffe 2011). Although self-contained automated assays are under review by the U.S. Food and Drug Administration for marketing approval, they are not currently approved (Giles 2011) and therefore are not widely available.

### Use of a single reference laboratory

The use of a single reference laboratory, particularly one that uses the IS, can further simplify the process of molecular monitoring. The likelihood of interlaboratory differences is eliminated (Hughes 2006), and intralaboratory variations are reduced, since variables such as the choice of the control gene, sample handling, the qRT-PCR technique, and the reporting of results should be consistent. In practical terms, working with a single reference laboratory could yield potential time and cost efficiencies. It is often the case, however, that the choice of a laboratory may vary as insurance contracts are changed, which can make it difficult to work with only one reference laboratory (Radich 2009).

### Automation of qRT-PCR testing

Interlaboratory variability can include differences in the choice of the control gene, sample handling, and the qRT-PCR technique. Although not yet available for routine clinical use, automated testing of BRC-ABL1 transcript levels can potentially increase access to reproducible BRC-ABL1 monitoring by qRT-PCR and may improve the accuracy and efficiency of monitoring. In a cost-feasibility study, the use of an automated system that executes RNA extraction and qRT-PCR was found to yield highly reproducible results and to be a cost-effective option for laboratories that perform fewer than 300 BRC-ABL1 tests annually (Cayuela 2011). In a separate analysis, a comparative cost model of automated versus laboratory-developed testing to monitor BRC-ABL1 levels showed a 3.2% improvement in overall accuracy with automated testing over 5 years. In addition, automated testing provided a 19% cost reduction for every 100 patients monitored per laboratory according to NCCN guidelines (Ratcliffe 2011). Although self-contained automated assays are under review by the U.S. Food and Drug Administration for marketing approval, they are not currently approved (Giles 2011) and therefore are not widely available.

### Remaining questions about molecular monitoring

**Definition of CMR**

CMR is variously defined in practice guidelines as “no detectable BRC-ABL1 mRNA by qRT-PCR (IS) using an assay with a sensitivity of ≥4.5 logs below the standardized baseline” (National Comprehensive Cancer Network 2012) or as “undetectable BRC-ABL1 mRNA transcripts by real-time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity >101)” (Baccarani 2009). In the European Treatment Outcome Study (EUTOS), the extent of a molecular response was defined either by a threshold level of detection (e.g., MR1 = detectable disease ≤0.01% BRC-ABL1) or as a function of the control gene’s transcript level (e.g., MR4 = undetectable disease in cDNA with ≥10,000 ABL1 transcripts) (Cross 2012). Because the definition of CMR is variable and depends on the assay’s level of sensitivity and on the reliability of the results, establishing a universally accepted definition of CMR remains an important goal of standardization.

The ability to accurately determine and to monitor stable CMR has implications for potential treatment dis-
continuation in patients with CML. Numerous case reports (Ali 2005; Breccia 2006; Cortes 2004; Guastafierro 2009; Mauro 2004; Merante 2005; Okabe 2007; Verma 2008) and clinical studies (Goh 2011; Goh 2009; Mahon 2010; Mahon 2011; Matsuki 2011; Rousselot 2007; Takahashi 2012; Yhim 2012) describe patients who have discontinued imatinib therapy after achieving and maintaining stable CMR before discontinuation. After discontinuing imatinib, about half of the patients in clinical studies who discontinued — as few as 13% (Goh 2009) and as many as 90% (Goh 2011) — were found to have remained in remission for extended periods (Goh 2011; Goh 2009; Mahon 2010; Mahon 2011; Matsuki 2011; Rousselot 2007; Takahashi 2012; Yhim 2012). Clinical studies of dasatinib and nilotinib discontinuation are also underway (Rea 2011).

The factors associated with successful imatinib discontinuation have not been definitively identified, but factors such as a shorter period to BRC-ABL1 negativity (Rousselot 2007), male gender (Mahon 2010), a low Sokal risk score (Mahon 2010), longer duration of imatinib therapy (Mahon 2010; Takahashi 2012), prior IFN-α therapy (Takahashi 2012), greater imatinib dose intensity (Takahashi 2012), and longer duration of CMR before discontinuation (Takahashi 2012) may be important. At this time, treatment discontinuation for CML patients remains an important issue worthy of continued investigation and should not be attempted outside of a clinical study.

The prospect of treatment discontinuation, whether temporary or permanent, could have important implications for patients (Mattison 2009; Smith 2011), clinicians, and payers. For patients, the possibility of treatment discontinuation could bring relief to those dealing with persistent side effects (Cortes 2004; Ghanima 2004); allow patients to start families (Ali 2005; Cortes 2004; Kobayashi 2009), cope with a concomitant illness (Breccia 2006), or be free from continuous medication. It is likely, however, that patients who are able to discontinue treatment may need more frequent disease monitoring and follow-up.

For clinicians, treatment discontinuation may affect the frequency of disease monitoring and patient follow-up.

For payers, treatment discontinuation could affect both medical costs (e.g., drug costs) and health care costs (e.g., potentially necessitating a different schedule for follow-up clinic visits and molecular monitoring, as well as future management and treatment of patients who relapse). At present, however, no published studies have described health care utilization in patients who have discontinued TKI treatment, although this type of study would be valuable.

**Use and understanding of molecular monitoring in routine clinical practice**

Currently, many health care providers do not appear to appreciate fully the need for regular, consistent monitoring of BRC-ABL1 levels (Kantarjian 2007; Radich 2009). They do not understand why monitoring is needed after CCyR has been achieved (Radich 2009); how often molecular monitoring should be performed (Kantarjian 2007; Radich 2009); or how to interpret and act on test results that show rising BRC-ABL1 levels (Radich 2009). It should be impressed upon treating clinicians that molecular monitoring of BRC-ABL1 can be used to rapidly assess treatment response, to predict outcomes, and to plan for contingencies, particularly when the test results suggest that therapeutic modifications may be expected. As I have witnessed in clinical practice, being proactive rather than reactive in the management of patients can be life-saving. The sooner potential problems with treatment and the patient’s response are identified, the greater the opportunity clinicians have to intervene before disease progression.

**Conclusion**

The advent of BCR-ABL TKIs for CML has made possible the achievement of deep molecular responses in a high proportion of patients. Because evidence shows that CML patients who remain in remission have a greater likelihood of favorable long-term outcomes, practice guidelines recommend regular and consistent molecular monitoring of BRC-ABL1 transcript levels as a method to regularly assess the patient’s response to treatment and disease progression. Clinicians’ adherence to guidelines ensures the early detection of any changes in response or disease progression, which allows reassessment of and modifications to treatment plans to meet the patient’s changing disease status.

**Acknowledgments**

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**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.

» Dystonia: 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.

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 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.

©2013 Otsuka America Pharmaceutical, Inc., Rockville, MD  March 2013  0913A-7028
**ABILIFY MAINTENA** (aripiprazole) for extended-release injectable suspension, for intramuscular or subcutaneous administration in adults with schizophrenia and depressive symptoms associated with schizophrenia.

**BRIEF SUMMARY OF PRESCRIBING INFORMATION** (For complete details, please see Full Prescribing Information and Medication Guide.)

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

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 exposure in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

**INDICATIONS AND USAGE: ABILIFY MAINTENA** is contraindicated in patients with known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole.

**CONTRAINDICATIONS:** ABILIFY MAINTENA is contraindicated in patients with a history of a seizure disorder, a seizure disorder that is currently under treatment, or a history of drug abuse.

**WARNINGS AND PRECAUTIONS:** Increased mortality in elderly patients with dementia-related psychosis. 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 exposure in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

**TARDIVE DYSENESIA:** 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 (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

**CEREBELLAR ADVERSE REACTIONS:** Including Stroke in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., transient ischemic attacks and including fatalities, in all aripiprazole- and placebo-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole. 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 (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

**TABLE 3:** Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain:

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Weight from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>No change to Normal (&lt;19%)</td>
<td>Aripiprazole</td>
<td>14/52 (27.1)</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>(-19% to ≤5%)</td>
<td>Placebo</td>
<td>2/28 (7.1)</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>(&lt;5% to ≥15%)</td>
<td>Aripiprazole</td>
<td>2/332 (0.6)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>≥15%</td>
<td>Placebo</td>
<td>25/432 (5.8)</td>
<td>5.8</td>
</tr>
</tbody>
</table>

**Table 2:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** Changes in Fasting Glucose From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Change from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>≤100 mg/dL</td>
<td>Aripiprazole</td>
<td>31/822 (3.8)</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>(&lt;100 mg/dL to ≤126 mg/dL)</td>
<td>Placebo</td>
<td>32/822 (3.9)</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>&gt;126 mg/dL</td>
<td>Aripiprazole</td>
<td>31/176 (17.6)</td>
<td>17.6</td>
</tr>
</tbody>
</table>

**Table 3:** Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain ≥2% of Body Weight

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment Arm</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Aripiprazole</td>
<td>852</td>
<td>88 (10)</td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Aripiprazole</td>
<td>456</td>
<td>10 (2.2)</td>
</tr>
</tbody>
</table>

**Table 4:** Changes in Excretion of Fasting Glucose From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Change from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>≤100 mg/dL</td>
<td>Aripiprazole</td>
<td>31/822 (3.8)</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>(&lt;100 mg/dL to ≤126 mg/dL)</td>
<td>Placebo</td>
<td>32/822 (3.9)</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>&gt;126 mg/dL</td>
<td>Aripiprazole</td>
<td>31/176 (17.6)</td>
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</tr>
</tbody>
</table>

**Table 5:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
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<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 9:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 10:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</td>
<td>Aripiprazole</td>
<td>4/222 (1.8)</td>
<td>1.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 11:** Changes in Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

<table>
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</tr>
<tr>
<td>Placebo</td>
<td>4/202 (2.0)</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>
Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its effect on serotonin receptor. Orthostatic hypotension occurred in 14/567 (2.5%) 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 changing from standing to supine) was 0.2% (1/575).

Leukopenia, Neutropenia, and Agranulocytosis: Class Effect: In clinical trials and post-marketing experience, leucopenia and neutropenia have been reported temporally 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 leucopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leucopenia/neutropenia perform a complete blood count (CBC) for the first 6 to 8 weeks of therapy. In such patients, consider discontinuation 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.

Postural Hypotension and, More Rarely, Orthostatic Impairment, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA will not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anti-cholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS: The following adverse reactions are described in more detail in other sections of the labeling in the Full Prescribing Information:

• Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]

• Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.2)]

• Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.3)]

• Tardive Dyskinesia [see Warnings and Precautions (5.4)]

• Metabolic Changes [see Warnings and Precautions (5.5)]

• Orthostatic Hypotension [see Warnings and Precautions (5.6)]

• Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.7)]

• Seizures [see Warnings and Precautions (5.8)]

• Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.9)]

• Body Temperature Regulation [see Warnings and Precautions (5.10)]

• Gynecomastia [see Warnings and Precautions (5.15)]

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of the same drug or to the rates observed in practice. Safety and Efficacy of ABILIFY MAINTENA and Oral Aripiprazole: Aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and in 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment 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 patient-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 oral aripiprazole. Data from the safety data presented below 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 injections 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 Associated with Antipsychotic Medications: Commonly Observed Adverse Reactions in Adults Treated with Oral Aripiprazole:

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>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td>Vision</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>Pharyngolaryngeal Pain</td>
<td>3 2</td>
<td>2 2</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients Treated with Oral Aripiprazole

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction profiles in response to the difference in the basis of age, gender, or race.

Dose-Related Adverse 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 doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 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/day, was somnolence (including sedation); incidences were placebo, 7.1%, 10.5%, 8.3%, 15%, 8.3%, 7.5%, 5.0%, 2.6%.

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 injection site-related adverse reaction was 5% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0-100 mm pain) to 100-unebearably painful was minimal and improved in subjects receiving ABILIFY MAINTENA from the open-label, stabilization phase (0-1 to 4.9).

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 in 97% of patients. Adverse reactions of ABILIFY MAINTENA were 9% of subjects following the first injection and 77-96% 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.

Objective 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 (for dyskinesias). 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, 0.68 placebo, -0.93).

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 dyskinesias) 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. While these 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: In the aripiprazole-treated group 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% [12/153] for oral aripiprazole vs. 2% [3/153] for placebo). In this study, the majority of cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred earlier in therapy (8/12 <49 days), and were of limited duration (7/12 <10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole.

In another, a long-term, active-controlled study, the incidence of tremor was 5% (4/83) for oral aripiprazole.
In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy may experience an increased risk of neurological or other complications. Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. In the rat, aripiprazole produced developmental toxicity, including a high incidence of placental defects, increased resorption, reduced post-implantation loss, and decreased fetal body weight. The pattern of adverse effects observed in neonates exposed to oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included within the adverse reaction tabulation. In addition, medically unexplained events that were not already listed in the tabulated results from placebo-controlled trials appear in this listing; those occurring in ≥1/100 to <1/10 patients; and those occurring in ≤1/100 patients.

Blood and Lymphatic System Disorders:
- ≥1/100 patients - thrombocytopenia
- <1/100 patients - platelets, coagulation disorders, lymphopenia

Cardiac Disorders:
- ≥1/100 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardiac arrest, atrioventricular block, extrasystoles, angina pectoris
- <1/100 patients - supraventricular arrhythmia, pericarditis, prinzmetal's angina, ventriculo-tachycardia
- Eye Disorders:
- ≥1/100 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia
- Gastrointestinal Disorders:
- ≥1/100 patients and <1/100 patients - nausea, vomiting, abdominal pain, steatorrhea, pancreatitis
- General Disorders and Administration Site Conditions:
- ≥1/100 patients - asthenia, peripheral edema, chest pain
- <1/100 patients and <1/100 patients - face edema, angiodema
- <1/100 patients - hypothermia, Rebound Hypotension: <1/100 patients - hypotension, jaundice
- Immune System Disorders:
- ≥1/100 patients and <1/100 patients - hypersensitivity, Injury, Poisoning, and Procedural Complications:
- ≥1/100 patients - fall, <1/100 patients - heat stroke
- Investigations:
- ≥1/100 patients and <1/100 patients - blood prolactin increased, blood increased, blood creatinine increased, blood bilirubin increased; <1/100 patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased; Metabolism and Nutrition Disorders:
- ≥1/100 patients and <1/100 patients - hyperglycemia, hypoglycemia, hyperlipidemia, hypertriglyceridemia, hyperuricemia, polycystic ovary syndrome; <1/100 patients - diabetic ketoacidosis; Musculoskeletal and Connective Tissue Disorders:
- ≥1/100 patients and <1/100 patients - muscle rigidity, muscle weakness, muscle tone decreased; ≥1/100 patients and <1/100 patients - myopathy; Nervous System Disorders:
- ≥1/100 patients - coordination abnormal; ≥1/100 patients and <1/100 patients - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; ≥1/100 patients - ataxia; ≥1/100 patients - orthostatic hypotension; ≥1/100 patients and <1/100 patients - loss of libido, suicide attempt, hostility, libido increased, anger, agitation, delirium, intentional self harm, obsessive-compulsive disorder, schizophrenia, thought disorder, suicidal ideation; ≥1/100 patients and <1/100 patients - hypothermia

Postmarketing Experience:
The following adverse reactions have been identified during post-marketing use of oral aripiprazole. Because these reactions are reported voluntarily from a population of patients treated with oral aripiprazole, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm).

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Due to the prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

The largest known case of acute ingestion with a known oral aripiprazole overdose (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdose (alone or with other substances) include acidosis, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, deep tendon reflexes decreased, dizziness, drowsiness, decreased sensorium, dysphoria, extrapyramidal disorder, hypothermia, hyperglycemia, hypokalemia, hypotension, lethargy, loss of consciousness, OR complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

OVERDOSE: Human Experience:
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Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdose (alone or with other substances) include acidosis, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, deep tendon reflexes decreased, dizziness, drowsiness, decreased sensorium, dysphoria, extrapyramidal disorder, hypothermia, hyperglycemia, hypokalemia, hypotension, lethargy, loss of consciousness, OR complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdose: In case of overdose, call the Poison Control Center immediately at 1-800-222-1222.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ABILIFY MAINTENA.

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Medicare Part D and the Department of Veterans Affairs (VA) are two major government payers of health benefits that use different approaches to managing prescription drug benefits, and a study that looked at managing brand-name prescription drugs shows a vast difference in efficiency.

Walid F. Gellad, MD, MPH, and colleagues reviewed brand-name diabetes medication use by Medicare beneficiaries and by a corresponding group of veterans ages 65+, all with diabetes.

"Use of brand-name drugs for Part D beneficiaries for these medications was two to three times higher than VA patients," says Gellad, a physician and researcher at the VA Pittsburgh Healthcare System and the University of Pittsburgh.

Part D beneficiaries were more likely to use brand-name rather than generic oral hypoglycemic agents (35% vs. 13%), statins (51% vs. 18%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) (43% vs. 21%), and insulin analogues (75% vs. 27%) than their VA counterparts.

"We can look at the rates of generic use in the VA and use that as a benchmark. We should be able to take care of patients with diabetes using fewer brand-name agents and still maintain high quality care. I think most clinical executives know that, but here’s a concrete example of a system in which we can take good care of these patients with many fewer brand-name drugs — there’s incredible cost savings associated with that," says Gellad. The researchers found that if Medicare were to use the same percentage of generic antidiabetes drugs as the VA, it would save $1 billion in a year.

That billion-dollar savings is within Medicare’s reach, too. “What’s most amazing is that we don’t have to talk about whether Medicare has to negotiate drug prices — we don’t have to talk about prices of brand-name drugs at all,” says Gellad. He concedes that obtaining the savings might be easier said than done, “but it doesn’t require changing any law; it simply requires that patients be prescribed fewer brand-name drugs.”

The results show that providers can push generic rates a lot higher and maintain high-quality care. “There’s a lot to learn from the VA in how to manage a prescription drug system, which can be applied to the private sector,” says Gellad. “We all have limited resources, and we can maintain high quality care with fewer brand-name drugs.”

### Part D’s underuse of generics wastes $1B per year

**Prescription spending and projected spending if use of brand-name drugs should change in 4 drug groups. Patients had diabetes, were age 65+, and were in Medicare Part D in 2008.**

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Actual spending (millions)</th>
<th>Spending using VA prescribing patterns (millions)</th>
<th>Total (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hypoglycemics</td>
<td>1,215</td>
<td>626</td>
<td>1,841</td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td>693</td>
<td>504</td>
<td>1,197</td>
</tr>
<tr>
<td>Statins</td>
<td>869</td>
<td>464</td>
<td>1,333</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>711</td>
<td>528</td>
<td>1,239</td>
</tr>
<tr>
<td>Total</td>
<td>3,488</td>
<td>2,122</td>
<td>5,610</td>
</tr>
</tbody>
</table>

Horizon Rolls Out Exchange For Mid-Sized Companies

The insurer hopes to give businesses of between 50 and 400 employees more flexibility under defined contribution

By Frank Diamond

Officials at Horizon Blue Cross Blue Shield of New Jersey think that they might have found a niche customer base. The public health insurance exchanges opening in October will include the Small Business Health Options Program (SHOP) through which companies with 50 or fewer employees can obtain coverage from participating health insurers. New Jersey’s exchange will be run by the federal government.

While Horizon will participate in SHOP, it has also developed a private exchange for mid-sized businesses that want to offer an online menu of defined contribution coverage.

The product, Horizon Select, is being rolled out this summer, tailored for companies with 51 to about 400 employees, says Christopher M. Lepre, senior vice president for market business units. “The private exchange is a response to employers who have told us that they’re looking for alternatives to the standard health insurance model.”

Horizon spokesman Thomas Vincz says, “It’s a private online marketplace, in the sense that public exchanges are also online marketplaces. The difference is that it is private and between the employer and employee and Horizon.”

Under the traditional model, employers charge their employees a set amount, usually 20% to 30% of the total premium, says Vincz. “It’s a defined benefit model,” he says. “Fundamental to the private exchange is a defined contribution approach to benefits.”

Defined amount

Theoretically, employers contribute a defined amount to each employee’s benefits and the workers can then use that money to choose their coverage in the private marketplace created under Horizon Select.

“A private exchange allows more customization of benefits, so employees often find more choices than what they would have under a traditional benefit plan,” says Vincz.

Horizon hopes to have 15 to 25 employers sign up for Horizon Select in the initial year, then to expand it. The gradual approach, says Lepre, should help ensure a smooth transition at a time when the market will be adjusting to the many changes in the Affordable Care Act.

“This is new and different; we want to make sure we execute fully for our customers.”

Wellness will be a big part of making Horizon Select work, says Vincz. “There’s a growing appetite among businesses for health and wellness products, and our own clinician executives are focused heavily on health and wellness — both for our own employees and our 3.6 million members. Hence, the products that will be offered through the private exchange will give more tools and options that help members manage their individual health and wellness needs.”

Wholesale to retail

Lepre points out that the exchanges reflect a shift in the insurance marketplace from wholesale, in which employees receive coverage through their employer, to retail, in which consumers buy directly from, and interact with, insurance carriers.
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Few people spend their days thinking about their lysosomes. These amazing intracellular structures are miniature digestive organs that contain enzymes that constantly break down waste material as well as viruses and bacteria. They rely on a complex system of enzymes to degrade the material into some basic building blocks and then to transport the components to other areas of the cell. About 50 different diseases have been discovered that are the result of defects in these specialized proteins. The resulting disorders read like a who’s who of the most expensive diseases, including Gaucher’s disease, Hunter’s disease, Hurler’s disease, and Pompe disease.

Another lysosomal storage disease, nephritic cystinosis, is caused by accumulation of the amino acid cystine. Eventually leading to kidney failure, blindness, weak bones, muscle weakness, pulmonary dysfunction, and eventually death, nephrotic cystinosis is slightly more common in males (ratio 1.4 to one) and disproportionately affects blond, blue-eyed children of European descent who carry the autosomal recessive genetic mutation to the cystinosin, a protein encoded by the lysosomal cystine transporter gene (CTNS) on chromosome 17 p13. The gene is over 26,000 base pairs long. Over 80 mutations of this gene, leading to decreased activity or total inactivity of the CTNS gene, have been identified. Without the transport protein, cystine levels build up 50 to 100 times the normal level and form crystals that in turn slowly kill individual cells in most major organs. As with most genetic diseases, the level of dysfunction varies depending on the site of the mutation on the gene. The most common is a deletion of a large part of the gene; it accounts for about 50% of those affected by cystinosis, and results in complete loss of cystinosin.

Untreated, the accumulation of crystals causes renal tubular destruction (nephritic cystinosis) and in its worst form presents in patients between ages 6 and 9 months as poor growth and rickets along with polyuria, polydipsia (excessive thirst), and dehydration. The crystals, readily observed by age 16 months, accumulate in the cornea and can be seen on slit lamp exam. Death occurs by age 10 if the patient is not treated.

Scientists created a way to use cysteine bitartrate, in the chemical class called aminothiol, to force a metabolic transformation of cystine into cysteine and cysteine-cysteamine mixed disulfide compounds. This reaction occurs within the lysosomes. Both cysteine and cysteine-cysteamine mixed disulfide can exit the lysosome in patients with cystinosis. Thus, cystine is slowly transported away and levels can remain low as long as the substrate, cysteamine bitartrate, is available.

Procysbi

Cystagon (cysteamine bitartrate), an oral immediate-release therapy, was approved in 1994 by the FDA. If it used as directed, most late complications of cystinosis can be delayed or perhaps avoided. One reference suggested that those affected can live to at least 50 years. But Cystagon must be taken every six hours and can cause a repulsive body odor, can cause nausea and vomiting, and increases gastric acid production.

Recently the FDA approved a new drug with the same active ingredient, cysteamine bitartrate, but in an enteric coated delayed-release formulation.

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.
formulation named Procysbi. Indicated for management of nephritic cystinosis in persons ages 6 years and older, Procysbi is available as a capsule in 25-mg and 75-mg strengths that can be administered 12 hours apart instead of every six hours. The advantage is obvious — patients maintain a normal sleep interval and avoid the need for a mid-day dose.

Procysbi was studied in 6 clinical trials. Three studied only healthy volunteers. The other three were performed on 72 patients with proven nephropathic cystinosis. Because there was a similar drug available, the trial design leading to FDA approval involved a head-to-head study against the immediate-release drug. The pivotal trial comparing Procysbi with immediate-release cysteamine was Trial 3.

Trial 3 was randomized and “demonstrated that at steady state, Procysbi administered every 12 hours was non-inferior to immediate-release cysteamine bitartrate administered every six hours.” The primary endpoint for this study was “depletion of WBC [white blood cell] cystine levels,” a common and clinically meaningful measurement for patients suffering from this disease.

Remember that cystinosis is rare, so the pool of patients available for clinical trials is small. Because of this, the FDA label for this drug includes a review of previous trials involving the immediate-release form of cysteamine bitartrate as well as the new trials involving the delayed-release form.

Healthy volunteers reported diarrhea, nausea, abdominal pain/discomfort, headache, vomiting, and abnormal urine odor. The most commonly reported adverse reactions in patients with nephritic cystinosis were vomiting, abdominal pain/discomfort, headaches, nausea, diarrhea, anorexia/decreased appetite, breath odor, fatigue, dizziness, skin odor, and rash.

There were no unexpected serious adverse events, but “a higher incidence of adverse reactions was reported in patients during the Procysbi treatment period compared with the immediate-release cysteamine treatment period.”

Trial 4 includes patients continuing treatment from Trial 3 and consisted of 40 patients treated longer than one year. Similar adverse reactions occurred during the extension period.

The conclusion from Trial 3 is that at “steady-state, Procysbi administered Q12 H was non-inferior to immediate-release cysteamine bitartrate administered Q6H with respect to the depletion of WBC cystine levels.”

Thus, tomorrow's medicine marches on with an improvement for patients born with this genetic disease allowing them to sleep through the night. It also allows these children and adults to have a drug that can be given half as many times per day with clinical trial proof that the delayed release is not inferior to the existing legacy form of this chemical.

But that improvement comes at a very high additional cost. The New York Times reported that the cost of the enteric-coated formulation will be about $250,000 annually on average. This compares to an annual cost of $8,000 for the existing immediate-release formulation.

Managed care implications

Procysbi comes at an astronomical increase in price over the existing drug with no proven improvement. There were no data in the FDA label that demonstrated any other advantages over the immediate-release form. The question can be reasonably raised: why should the cost increase over 3,000%? Will the decreased frequency of administration lead to improved adherence and eventually improved clinical response? Should society, through insurance and government programs, pay nearly a quarter of a million dollars in additional costs each year, per patient, to avoid having to awaken once during sleep and to avoid a mid-day dose? And perhaps what also needs to be asked is why it costs so much to obtain FDA approval for what basically is just a coating on an existing drug.

Certainly, the company that developed the delayed form of cysteamine bitartrate, Raptor Pharmaceuticals, feels the need to recoup its reported $37.4 million in development costs directly attributed to this drug and an additional $70 million in total corporate expenses during the development period. But without demonstrated improvement, payers will be hard pressed to cover this drug.

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.
Stroke-related costs to double by 2030

The cost of treating stroke victims will soar in the next two decades, according to a study by the American Heart Association and the American Stroke Association that was published in the journal Stroke. Real total direct annual stroke-related medical costs are expected to increase from $72 billion to $183 billion (2010 dollars) between 2012 and 2030.

That’s not the entire story.

“Overall total annual costs of stroke are projected to increase to $240.67 billion by 2030, an increase of 129 percent,” the study states. Indirect costs include lost productivity from morbidity and premature mortality.

The main reason is that “the aging of the United States population in coming decades has the potential to increase stroke cost substantially, because the risk of stroke is higher for older ages.”

Bruce Ovbiagele, MD, the main author of the study, says, “Strokes will absolutely strain the health care system. Only 10 percent recover completely after a stroke.”

Policy changes can help address the problem. The authors cite a study in the New England Journal of Medicine (“Full Coverage for Preventive Medications After Myocardial Infarction,” Dec. 1, 2011 — http://tinyurl.com/preventive-meds) reporting that “eliminating copayments for relatively inexpensive, commonly used medications for prevention of cardiovascular events resulted in improved medication adherence and reduced the rate of vascular events, while significantly reducing costs for patients … without increasing the insurer’s health care cost.” (This looks like value-based plan design, something we’ve covered for years, including this cover story from 2009 — http://tinyurl.com/value-based.)

“Getting patients specialized acute stroke care as soon as possible is critical,” says Ovbiagele, who is a professor and chairman of the department of neurology at the Medical University of South Carolina in Charleston.

“During every minute of delayed treatment, brain cells are dying. EMS systems nationwide should take patients directly to a designated stroke center equipped to quickly diagnose and administer drugs to restore blood flow to the brain.”

The study asserts that health reform might alleviate some of the problem. The Affordable Care Act “provides an unprecedented emphasis on the provisions of evidence-based clinical preventive services and calls for a substantial investment in community-based prevention strategies that may help to reduce the growing future burden of stroke.”

Larger aged population means many more strokes

Projected total (direct and indirect) costs of all stroke by age, 2012 to 2030 (in billions of 2010 dollars).