Dry eye disease (DED) is a growing public health concern. Twenty-nine million adults in the US have reported symptoms associated with DED.1-2 In the US we are diagnosed with DED, and the number is expected to increase.3 DED is often chronic, can be progressive, and is a very common complaint presenting to eye care professionals today.4-6 This multifactorial disease can result in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the surface of the eye.7 In addition to traditional risk factors such as age, female sex, and hormone changes, modern risk factors such as prolonged screen time, contact lenses, and LASIK can increase the risk of DED in both commercial and Medicare members.4-8,10

Our changing understanding of DED

Once considered to be the result of reduced tear volume, we now know DED is most often the result of abnormal tear composition.8 It is estimated that ~10% of DED is purely due to a deficit in tear production.9 Increased tear evaporation, decreased tear production, and/or decreased blink rate can alter tear composition, promoting inflammation on the surface of the eye.10 This inflammation is now recognized as both a cause and consequence of DED, playing a prominent role in the self-perpetuating cycle of the disease (Figure).4,12,13

The Gene Genie Is Out of the Bottle

By Peter Wehrwein

It has been 63 years since Watson and Crick described the double helix, 33 years since the first gene was mapped, and 13 years since the human genome was completely sequenced. But we seem to have arrived at a time when all this beautiful science of genes and genomics is getting its hands dirty in the everyday business of American health care.

In this issue of Managed Care, Michael Dalzell, a senior contributing editor of the magazine, writes about the effects that predictive biomarkers are having on drug development and discovery (p. 10). Many of those markers reflect changes happening at a genetic level. The story he tells is, by and large, a heartening one of medical treatment becoming more effective because drug developers and physicians have biomarkers to guide their choices. It’s as if medicine is now navigating with GPS instead of with a sextant and the stars. Abandoned or problematic drugs have gotten a new lease on life. But as Mike reports, all this added precision may feed an expensive spiral of ever-smaller markets for drugs—and higher prices to make up for fewer patients.

The story by Contributing Editor Joseph Burns on health plans trying to gain some control over genetic and molecular testing (p. 20) serves as a useful counterpoint to Mike’s story. Rather than bringing lucidity, the flood of tests is muddying the waters for insurers. Some tests for genetic variants are done simply because today’s sequencers make it easy and relatively cheap to do so. The result is a common one in these information-drenched times: a scarcity of meaning amid an abundance of data. Health plans have responded with familiar tactics, prior authorization and utilization management, but they are jobbing them out because of the expertise that’s required.

It seems like the genie is finally out of the bottle as far as genetics and genomics is concerned. Good will come of it, but it’s going to be messy.
COVER STORY

Magic Markers: Precision May Be Pricey
Predictive biomarkers are revamping drug development and breathing new life into old and failed drugs. Questions about cost and accessibility arise.

Genetic Testing Tests Management Techniques
Labs are pushing panels that include assays for scores of genetic variants. The result: Information overload and health plans trying to manage the costs.

Plans May See More Drug Risk-Sharing Offers
Drug makers are courting health plans with risk-sharing deals that link outcomes to rebates and discounts in exchange for a spot on the formulary.

Caps on Drug Costs Like Whack-a-Mole
Crushing drug prices are creating a move toward monthly limits on out-of-pocket medication expenses. The caps may shift costs to premiums.

Q&A: Entering the Lists of Drug Value and Price
Steven Pearson, MD, head of the Institute for Clinical and Economic Review, is leading his comparative effectiveness shop into the drug value fray.

ORIGINAL RESEARCH

Why the Surge in Prescription Drug Prices?
Competition among manufacturers, industry consolidation, and capitalization on me-too drugs are cranking up generic and branded drug prices.

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Socially Motivated Intervention Slows Inappropriate Antibiotic Prescribing

Peer pressure doesn’t end in high school, or even med school, for that matter. Researchers at the University of Southern California found that the natural inclination of doctors (and other clinicians who work in primary care practices) to be the best can be channeled to attack one of medicine’s more intransigent problems: inappropriate prescribing of antibiotics.

Researchers tried a number of approaches to limit inappropriate antibiotic prescribing for 248 clinicians from 47 primary care practices. The behavioral interventions included suggesting alternatives to antibiotics; giving physicians the opportunity to justify their prescribing decisions (accountable justification); and sending emails comparing the physicians’ prescribing patterns with top-performing doctors in their region who do not prescribe inappropriately (peer comparison). In other words, they wanted to see how socially motivated interventions worked.

The study, published Feb. 9 in JAMA, concluded that “the use of accountable justification and peer comparison as behavioral interventions resulted in lower rates of inappropriate antibiotic prescribing for acute respiratory tract infections.”

The study compared antibiotic prescribing rates for respiratory tract infections 18 months preintervention (14,753 visits) and 18 months post-intervention (16,959 visits). Interventions occurred between Nov. 1, 2011, and Oct. 1, 2012. Average antibiotic prescribing rates went from 23.2% to 5.2% for accountable justification and from 19.9% to 3.7% for peer comparison—or “statistically significant reductions in inappropriate antibiotic prescribing while suggested alternatives, which lacked a social component, had no statistically significant effect.”

Mean antibiotic prescribing rates decreased from 22.1% to 6.1% for suggested alternatives. (“The figures for suggested alternatives were not statistically significant because there was too much variation,” the study’s corresponding author, Jason N. Doctor told Managed Care. “Some prescribers were affected by it and others were not. The average did go down a lot, but not all responded.”)

The study included three health systems in two geographic locations: Massachusetts, where the patients were predominately white and had a wide range of incomes; and California, where the patients were predominately Hispanic and many of them poor.

Behavioral modification seemed ripe for study. “Changing clinician decision making has been challenging in acute respiratory visits and other care domains,” the study states. “For example, pay-for-performance has yielded mixed results, and traditional alerts and reminders, which can contribute to information overload, are often disruptive and ignored.”

Clinicians who did not overprescribe were told in emails that they were the top performers. Those who did overprescribe were told via email that they were not top performers.

The peer-comparison intervention, depending on electronic health records and an email “nudge,” as the researchers called it, reflects a certain simple beauty. However, the study authors noted that such comparisons depend on valid performance measures.

Health plans have been providing audits and feedback to doctors for years, Doctor commented, but not much of it has tapped into social motivations. To improve the performance of physicians, health plans can provide socially motivated feedback, he said.

Observation Units Not Used as Dodge

Hospitals are fined when Medicare patients are readmitted to the hospital within 30 days for certain conditions, such as acute myocardial infarction, heart failure, and pneumonia. Readmission rates for those conditions fell to 17.8% in 2015 from 21.5% in 2007, according to a study published in the New England Journal of Medicine.

Good news, but what researchers were really after was whether hospitals avoided the penalties by putting returning patients into observation units rather than formally readmitting them to the hospital.

A Wall Street Journal investigation in December 2015 found that observation-stay rates increased 48% for about 3,500 short-term acute-care hospitals from 2010 to 2013, even as readmission rates dropped 9%.

Observation stays might help hospitals avoid penalties, but they make patients face cost sharing that they might not have to deal with for regular inpatient stays. Also, patients referred to a nursing home are often stuck with the bill because Medicare doesn’t pick up the tab for such a transfer after an observation stay.

The NEJM study rebuts the Wall Street Journal report by not finding “evidence that changes in observation-
unit stays accounted for the decrease in readmissions."

Data were analyzed for Medicare beneficiaries at 3,387 hospitals from October 2007 through May 2015. Researchers looked at more than 7 million hospital stays for targeted conditions and more than 45 million stays for nontargeted conditions. Targeted conditions also include total hip or knee replacement and COPD, although they were not included in this study because they were added to CMS’s Readmissions Reduction Program only last year. Nontargeted conditions are everything that’s not targeted that can lead to a readmission.

Hospitals are penalized if their readmission rates are higher than expected compared with previous years. For example, 2015 penalties are based on readmissions from 2010 through 2013, the study states.

Readmission rates for both targeted and nontargeted conditions began to fall after the passage of the ACA, which tied readmissions to penalties, although targeted readmission rates declined at a steeper rate.

Researchers pointed out that there had been growing concern about readmission rates well before the ACA, and efforts to reduce those rates came from various quarters, including CMS’s Partnership for Patients.

"Within hospitals, there was no significant association between changes in observation-service use and changes in readmission rates after implementation of the ACA," the study concludes. "For this reason, our analysis does not support the hypothesis that increases in observation stays can account in any important way for the reduction in readmissions."

PCP Involvement Boosts Prevention

Prevention works if orchestrated by primary care physicians (PCPs) who can perform 60- to 90-minute annual physicals, as opposed to the 15-minute examination that’s the norm, says a study in Population Health Management. Researchers with Optum, UnitedHealthcare’s data management and IT arm, argued that the “personalized preventive health care” that fosters a close doctor–patient relationship cuts hospital and urgent care facility costs and manages chronic diseases better.

Who pays? In this instance, the patient. The study compared about 10,000 UnitedHealthcare enrollees in a network called MD-Value in Prevention (MDVIP) with about 10,000 United non-MDVIP members. The MDVIP members paid a fee of about $150 a month, similar to the fee that concierge medical practices charge.

Did the program work? Yes, with some caveats. Average medical and pharmacy costs for years 1, 2, and 3 exceeded those of non-MDVIP patients, thanks to increased pharmaceutical costs and more stringent management of chronic disease. On the other hand, there were significantly lower rates of ED visits and urgent care facility use by MDVIP members. (Data were collected from 2009 to 2014.)

The idea was to at least cover the $150 fee. “In years 1 and 2, 24% to 26% achieved savings at this level,” the study states. “By year 3, 63% (most between $150 and $299 per month savings) had achieved positive savings at or above their monthly membership fees, making a shift over time to increased proportions of the population achieving savings.”

The annual 60- to 90-minute examination included health screenings (for depression, anxiety, sleep problems, nutrition, sexual function, vision, hearing), diagnostic testing (for diabetes, bone disease, cardiovascular disease), and wellness consultations, which included personalized coaching and online instruction for exercise and weight control.

The wellness piece is crucial. Lifestyle counseling is not offered consistently by PCPs, the study notes.

"Obstacles to effective lifestyle counseling by PCPs have been identified, including lack of time, reimbursement, and training, as well as physician skepticism regarding patient adherence," the study states.

Savings from care for older patients were achieved earlier as chronic conditions came under control; it was achieved later for younger patients as prevention took root, according to the study. The study included people aged 35 to 84.

The MDVIP approach seems counterintuitive, in a sense, when
Top-ranked hospitals getting pickier about ACA plan networks

Almost all of the top-performing regional hospitals in the country are available to consumers purchasing health coverage on the ACA exchanges, according to a report by the Robert Wood Johnson Foundation. The foundation looked at the 156 regional hospitals that made the U.S. News and World Report list of best regional hospitals last year and found that 96% were in the network of at least one of the 2016 plans sold on the exchanges.

That finding may allay some of the concern that people who buy plans sold on the exchanges are stuck with narrow networks with inferior hospitals.

But there are plenty of caveats—so many, in fact, that a rosy appraisal really isn’t warranted. For one thing, the foundation’s report doesn’t distinguish between gold, silver, and bronze plans. Plans with the top-ranked hospitals may be more expensive.

Consider also that the proportion of hospitals in the network of only one plan sold on the exchanges increased from just 7% in 2015 to 20% in 2016. For example, the University of North Carolina Hospital was in four ACA plan networks in 2015 and is in only one this year. Moreover, more than half of these well-regarded hospitals reduced the number of networks they belonged to, and some important hospitals are not in any ACA plan networks in 2016—including New York University Langone Medical Center, the Mayo Clinic’s hospital in Phoenix, and University of Texas Southwestern University Hospital in Dallas.

Marketplace plan network participation by regionally ranked hospitals

Wait Time for Biosimilar Regs Drags On

It seems like Godot may arrive sooner. Seven years after the biosimilar law was enacted, stakeholders are losing patience with the FDA.

By Richard Mark Kirkner

Last year, when the FDA approved filgrastim-sndz (Zarxio) as a biosimilar to filgrastim (Neupogen), a biologic that stimulates the production of white blood cells, many in the biopharma industry thought maybe, just maybe, that the regulatory spigot was finally opening for biosimilars.

A drop does not a flow make. Since then the agency has not approved a single biosimilar, not a one, although in fairness an FDA panel did recommended approval of a biosimilar form of infliximab (Remicade) in February.

The FDA's foot-dragging on drafting regulations on biosimilars, as spelled out in the Biologics Price Competition and Innovation Act (BPCIA) of 2009, has frustrated and confounded not only the biopharma industry, but also the public, health plans, and pharmacy benefit managers because potential lower-cost competitors to expensive biological agents are stalled in the regulatory pipeline. Key senators are in that mix, too. Last year a Senate committee grilled Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, on why, six years on, the agency hasn't been able to come up with the regulations for biosimilars.

Similar, not identical

In the market, the biologics are supposed to serve the same function as generics for small-molecule medications: Drive down prices by creating an unbranded alternative. But whereas the active agent in generics are identical to the patented agent, biosimilars are, well, similar, as Kay Holcombe, senior vice president for science policy at the Biotechnology Innovation Organization (BIO), explains it. "Biosimilars are not worse than their reference product, they are not better than their reference product, but they are not identical either; they are similar," she says. Hence the BPCIA set up a regulatory pathway separate from that for small molecule drugs.

Biosimilars are in the limelight because expensive biological agents have put such a strain on the health care system. A 2014 Rand Corp. report predicted that biosimilars could reduce U.S. spending on biologics by $44.2 billion over the next eight years—about 4% of total spending on biologic therapies. A Milliman white paper detailed the potential savings of biosimilars. "Savings are difficult to project given the many uncertainties that still exist regarding market penetration and price; however, we project savings of 0.3% to 0.8% of total health care expenditures by 2019 for a typical commercial employer," says Milliman actuary Katie Holcomb.

What's in a name?

The naming of biosimilar agents has kicked up plenty of controversy. The core question is whether they should have the same molecule name as the branded reference product.

The FDA actually did make some headway on drafting regulations on biosimilars, as spelled out in the Biologics Price Competition and Innovation Act (BPCIA) of 2009, has frustrated and confounded not only the biopharma industry, but also the public, health plans, and pharmacy benefit managers because potential lower-cost competitors to expensive biological agents are stalled in the regulatory pipeline. Key senators are in that mix, too. Last year a Senate committee grilled Janet Woodcock, director of the FDAs Center for Drug Evaluation and Research, on why, six years on, the agency hasn't been able to come up with the regulations for biosimilars.

According to the guidance, a biosimilar should have a distinguishable name that includes the same active drug name as the reference biologic but would have a suffix that would allow doctors, pharmacists, and patients to know what variation of the biologic agent they're getting. The rationale is that this would allow the FDA to trace adverse events after the product gets approved.

That's the position the likes of BIO and the Pharmaceutical Research and Manufacturers of America have staked out and prefer. "We believe that all biological products should have distinguishable names, so that the provider in particular, as well as the dispenser of the product, will understand clearly what's being provided to the patient," says BIO's Holcombe.
Unnecessary confusion

“Each side is looking to protect its own interest,” counters Jeffrey Casberg, a registered pharmacist and director of clinical pharmacy for IPD Analytics, a research firm in suburban Miami. A naming convention that does not align with the original chemical name or adds a prefix or suffix that has no meaning would create unnecessary confusion, he says.

Casberg and others favor following the World Health Organization’s International Nonproprietary Name (INN) convention for naming medications with no FDA-designated suffix. The biosimilar and the branded product’s generic name would be the same. So, for example, it would be filgrastim and filgrastim, not filgrastim and filgrastim-sndz.

That position—an INN name with no “FDA-designated suffix”—is the one backed by AHIP and, no surprise, the Generic Pharmaceutical Association’s (GPhA) Biosimilars Council. The FDA draft guidance, however, makes no mention of the INN. In the United States, another group, the United States Adopted Names Council, acts as a naming gatekeeper, although it works closely with the WHO program.

Biosimilar companies and others say the FDA doesn’t need a name difference to keep track of biosimilars and any untoward effects that they might have. When the FDA unveiled its naming guidance last year, Bertrand Liang, chair of GPhA’s Biosimilars Council and CEO of Pfenex Inc., a biosimilar development company in San Diego, countered that the agency can monitor postmarket adverse events using the national drug code, lot number, and company name. He also noted other countries are already allowing biosimilars and their reference products to share an INN name without any patient safety issues.

“Adding a random collection of letters to the product’s nonproprietary name confers no additional safety benefit, and in fact would require the health care professional to be armed at all times with a code-breaking reference,” Liang argues.

What does “interchangeability” mean?

Most people consider interchangeability akin to substitution. In many states, for example, the pharmacist can switch a prescription from a brand-name drug to a generic medication as long as the prescriber leaves the “no substitution” box on the prescription unchecked. With biosimilars, it’s not that straightforward—again, because of their similarity versus being deemed identical. FDA guidance on interchangeability is a big missing piece of the regulatory puzzle. The biopharma industry is expecting it to be filled this year.

The BPCIA created two biosimilar pathways: 351(k)(2)(A) for non-interchangeable biologics, the provision under which Zarxio got approval; and 351(k)(2)(B) for interchangeable ones. But for interchangeability, it’s really a two-step process, as BIO’s Holcombe explains: “So the FDA makes one decision—yes, the product is biosimilar to the reference drug; and then a separate decision—yes, the product is interchangeable,” she says.

Interchangeability is tricky business. For one thing, a drug might be deemed a biosimilar but interchangeable for only one of the indications of the reference biologic.

FDA regulatory guidance might help clear up some of the knotty issues involved in interchangeability. “When you have two products that are similar but not identical, the question is, what are the key things the FDA is going to look at to make that second decision” about interchangeability? says Holcombe.

For companies that make biosimilars, the stakes are high. If a product has been on the market, Casberg asks, will the company hesitate to apply for interchangeability for fear of public fallout if the application gets turned down? What additional studies will the FDA require to prove interchangeability?

States decide substitution rules

While the FDA designates whether a biosimilar is interchangeable with its reference agent, it’s up to states to regulate whether a pharmacist can substitute an interchangeable biosimilar for a reference biologic agent.

Eighteen states have such laws and 11 more are pending. The state laws vary, but many include provisions that would give the prescriber the power to prevent substitution by stating “dispense as written” or “brand medically necessary” and that the prescriber must be notified of any allowable substitution made at a pharmacy.

But until the FDA provides a policy and a biosimilar receives an interchangeability rating, those laws could be collecting a lot of dust.
As outrage over the potent, but pricey hepatitis C treatments escalates, payers are feeling the heat. Concerned that patients face harmful coverage restrictions, a fresh crop of lawsuits was recently filed by consumers against both insurers and the Medicaid program in the state of Washington. At the same time, the New York Attorney General accelerated an investigation of several carriers over the issue.

All of this activity followed warnings last fall from the Obama administration that state Medicaid programs may be violating federal law by restricting access to hepatitis C medicines. By then, consumers had also filed nearly a dozen lawsuits against insurers in California for denying coverage, as did inmates against the Massachusetts prison system.

These moves, of course, reflect the cost of the medications. The treatments may promise cure rates exceeding 90%, but the price tags on the first batch of the antivirals—Sovaldi and Viekira Pak—have ranged anywhere from $63,000 to $94,500, depending upon dosage and regimen. Although costs may drop now that Merck entered the market with Zepatier, priced at $54,600, the hepatitis C medications continue to strain budgets, especially as more people are tested.

But coverage restrictions—notably treating the sickest patients while denying medication to others who also are infected—are prompting a growing backlash that is predicted to continue unless payers alter their guidelines. “This has become a crucial issue for payers,” says Roger Longman, who heads Real Endpoints, a research firm that tracks pharmaceutical reimbursement topics. “We’re going to see more pressure applied on them.”

Indeed, more litigation is being considered, according to Kevin Costello, a senior associate director at the Center for Health Law and Policy Innovation at Harvard Law School, which is working with the attorneys who filed a class-action lawsuit against the Washington State Health Care Authority. The lawsuit alleges the program rations treatments for only the sickest patients to meet financial goals.

Last year, the American Association for the Study of Liver Diseases revised its guidelines to emphasize that, while the sickest patients should be treated first, any patient with hepatitis C whose doctor recommends treatment should not be denied. In its update, the organization chastised payers for denying treatment when a doctor has prescribed one of the medicines.

Changing coverage policies
Meanwhile, the pressure seems to be producing results. Earlier this year, Anthem Blue Cross in California eased its coverage restrictions so that all patients with hepatitis C qualify for treatment. Recently, the Washington State Insurance Commissioner surveyed insurers and found they are gradually updating coverage criteria, although specifics were lacking.

Similarly, a spokeswoman for the New York Health Plan Association also maintains that plans are revising coverage, noting that the state’s Drug Utilization Board, which oversees coverage for the state Medicaid program, plans to review access to hepatitis C treatments at an upcoming meeting. She adds, however, that plans have been following clinical guidelines and says there is no evidence that coverage has been withheld.

An investigation by New York Attorney General Eric Schneiderman may offer a window into the future beyond just hepatitis C medications, according to one Wall Street analyst. Schneiderman is, effectively, arguing that there may be “deceptive advertising in terms of what is being covered,” Sanford Bernstein analyst Ronny Gal wrote in a recent investor note.

What if, for instance, Schneiderman files a lawsuit against one or more insurers and wins? Presumably, this would help drug makers, because such an outcome would limit what health plans could do with their formularies.

Another expert, however, believes it may not come to that. Payers are simply pushing back as hard as they can to remain solvent, says Randy Vogenberg, a partner at Access Market Intelligence, a consulting firm that specializes in managed care, and a member of Managed Care’s Editorial Advisory Board. “Any spotlight could be troublesome for insurers, especially during selling season as well as merger reviews,” he says. “But I think these [lawsuits and probes] will get resolved.”

Ed Silverman founded the Pharmalot blog and has covered the pharmaceutical industry for 20 years.
Within our lifetimes, we may look back at chemotherapy and group it with insulin shock therapy, electric baths, bloodletting, and other barbaric medical practices discredited long ago. Today, advances in identifying biomarkers that may predict who will or won't respond to a treatment offer vast potential for reducing the use of ineffective or even harmful therapies. These biomarkers, typically genetic (prognostic) or genomic (predictive), are propelling the evolution of precision medicine from pipe dream to work-in-progress to clinical reality.

Biomarker science is, perhaps, having its most pronounced effect on the development of new drugs, and that has gotten most of the attention. In some cases, biomarkers have resurrected drugs that were pulled off the market. Biomarkers that predict treatment success change how a disease is viewed, subdividing it into smaller and smaller therapeutic categories.

All of this is forcing the pharmaceutical industry to rethink drug lifecycles in concert with academics, repurposers, and diagnostics companies. None of this is happening in a vacuum; the power of predictive biomarkers

Right biomarker, right definition

Not so long ago, biomarker meant vital signs: body temperature, pulse, and blood pressure. Today, the term refers to a host of things that are objective and measurable. The FDA's 2014 guidance on qualification of drug-development tools defines several types of biomarkers:

- **Diagnostic** biomarkers are characteristics that suggest disease, such as the presence of the ZnT8 antibody in people with Type 1 diabetes.
- **Pharmacodynamic** biomarkers measure a patient's biological response to a medication, such as changes in HbA1c levels in people with diabetes.
- **Prognostic** biomarkers indicate a patient’s risk of disease occurrence or progression. The presence of a BRAF gene mutation, for instance, is a strong prognostic factor for recurrence of colorectal cancer.
- **Predictive** biomarkers categorize patients by their likelihood of responding to a treatment. Predictive biomarkers are established through the ability to measure gene expression, such as protein production and cell replication.

In clinical trials, showing the presence of a predictive biomarker can be a strategy for identifying groups of people who are most likely to respond to a treatment or regimen.
to alter the treatment of subpopulations has handed the FDA and payers complex considerations about how to approach drug approval, coverage, and payment.

Biomarkers can be a boon for patients, says Edmund Pezalla, MD, Aetna’s national medical director for pharmacy policy and strategy. But he offers two cautions. First, all the talk of precision notwithstanding, today’s generation of biomarkers are not perfect. Immuno-oncology drugs, for instance, work by blocking cellular pathways, like PD-1, that inhibit the immune system from attacking cancer cells, yet some patients may have an immune response that defeats the drug. “That would have nothing to do with the marker but rather some other genetic component of the patient we don’t understand,” Pezalla says.

Second, biomarkers that limit a drug’s patient population shouldn’t be expected to generate big savings to the health care system. In fact, just the opposite could happen. “Personalized medicine is more efficient, but I don’t think it will necessarily lower costs,” says Pezalla. If a company produces a cancer drug that is effective in only 10% of patients that a biomarker has identified, then the manufacturer may price the drug much higher than another drug that is effective in a broader group of patients, he notes.

That is what happened with gefitinib (Iressa), introduced in 2003 for metastatic non–small-cell lung cancer (NSCLC). At the time, its annual cost was $20,000. Today, gefitinib is limited to patients with a specific biomarker who fared much better in clinical studies than did a broader population (see “3 off the scrap heap,” page 13). Its annual cost today: $80,000.

With the advent of biomarkers, can the American health care system absorb the costs of drugs that are effective in smaller and smaller groups of patients? “It’s one of the questions we have to ask,” says Pezalla.

Still, these are early days. Just 18 of the 113 drugs approved from 2013 to 2015 had a prognostic or predictive biomarker in their indication. Of the 18 approved during the last three years, 17 require use of an FDA-approved test to detect the biomarker.

**Biomarker tests increasingly prevalent in new FDA approvals**

At the end of 2015, 44 drugs on the market had a predictive biomarker in their indication statement. Eighteen (40%) of those received FDA approval between 2013 and 2015, suggesting how quickly biomarkers are changing drug development. Of the 18 approved during the last three years, 17 require use of an FDA-approved test to detect the biomarker.

**Total FDA-approved drugs with biomarker in indication statement**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs requiring an FDA-approved test to detect the biomarker</th>
<th>Drugs without a test requirement for detecting the biomarker</th>
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<td>2015</td>
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*Test requirement was added to the indication of 1 previously approved drug in 2013. 
Source: MANAGED CARE magazine analysis of FDA approvals

“Personalized medicine is more efficient, but I don’t think it will necessarily lower costs,” says Edmund Pezalla, MD, Aetna’s national medical director for pharmacy policy and strategy.
"liquid biopsies" that circumvent traditional diagnostic challenges by capturing rare cells of interest in a test tube of blood, says Peggy Robinson of the diagnostics company Angle.

The relevant biomarker, however, may be a moving target. In metastatic breast cancer, for example, a woman’s HER2 status may change and with it, the most effective therapy, notes Peggy Robinson, a U.S.-based vice president for Angle, a British diagnostics company. The German SUCCESS study group, she says, is looking at HER2 expression and FISH gene copy expression on circulating tumor cells (CTCs) in women whose breast cancer metastasized.

Typically, the presence of a biomarker would be confirmed through a biopsy and molecular characterization of the cancerous cells, which shows which genes are expressed. As a means for tracking disease, however, frequent biopsies are impractical, and biopsies can be difficult to perform when cancer metastasizes. Diagnostics companies recognize the practical and cost challenges associated with biomarker detection and confirmation, however, and are racing to develop simpler techniques that may reveal clues through metabolites and blood.

Angle is one of a number of companies working on “liquid biopsies” that circumvent traditional diagnostic challenges by capturing rare cells of interest, such as CTCs, in a test tube of blood. When coupled with a gene-expression profile, a CTC harvest can help with the selection of therapy, says Robinson. “Drawing the tube of blood and doing the appropriate characterization can be much more cost effective” than a biopsy, she adds. Angle plans to seek FDA 510(k) clearance for this technology, called Parsortix, later this year.

Angle’s business plan is to work with pharmaceutical companies during preclinical development to detect relevant biomarkers. “If the pharma company knows that a cellular pathway causes cell proliferation, it may target something in one of those pathways to stop cancer cells from reproducing,” says Robinson. “So, by looking at CTCs, we can see the impact of that target on those circulating tumor cells.”

Parsortix, she says, may help drug developers understand therapeutic response better by stratifying the patient population. “It comes down to what is the biomarker that they are using, and how does that relate back to the rare cell?”

The niche-population conundrum
Biomarkers have splintered diseases we once thought of as single entities into several distinct conditions. Once biomarkers have disaggregated a disease, different treatment may be needed for the various subsets.

Cystic fibrosis (CF)—an inherited, genetically determined condition—is an interesting illustration. When it was initially approved in 2012, ivacaftor (Kalydeco) was indicated only for CF patients with a particular mutation in the CFTR gene. That’s just the kind of precision that biomarkers are supposed to bring to the table. The manufacturer, Vertex, has since been successful in getting the FDA to add indications for patients with other CFTR mutations.

Finding and treating those slivers of patients was at the heart of one of several recommendations in 2012 by the President’s Council of Advisors on Science and Technology. The council endorsed creation of a drug-approval pathway called Special Medical Use (SMU), which would grant an agent provisional approval for use in narrow populations on the basis of small and rapid trials. Approval would be contingent on risk–benefit data from larger subsequent studies. FDA Center for Drug Evaluation and Research Director Janet Woodcock later testified to Congress in favor of the SMU pathway, and authority for this sort of microapproval is written into the 21st Century Cures legislation circulating in Congress.

Pezalla, an invited expert who contributed to the development of the council’s report, is generally supportive of regulatory pathways that validate the promise of biomarkers. But he’s concerned about
3 off the scrap heap

Iressa: We didn’t know what we didn’t know
Gefitinib (Iressa) received FDA approval in 2003 as third-line treatment for metastatic non–small-cell lung cancer (mNSCLC). In phase 3 trials, the tyrosine kinase inhibitor shrank tumors in only 11% of the efficacy population, but the change in that 11% was dramatic enough to warrant approval. When postmarketing studies showed no meaningful increase in response in a broader population, however, AstraZeneca voluntarily pulled gefitinib off the market. In 2012, the FDA withdrew its approval.

When gefitinib was approved, nobody knew why those 11% did so well. But in 2009, physicians at Massachusetts General Hospital and Harvard Medical School sequenced the EGFR genes in trial participants. Nearly all patients whose tumors had responded to gefitinib had mutations in the tyrosine kinase domain of the EGFR gene. No such mutations existed in nonresponders. This gave rise to the hypothesis that responders could be predicted if selected carefully.

AstraZeneca readied new clinical trials in patients with the relevant biomarkers. This time, response rates reached as high as 70%, and the duration of response exceeded that of the original studies. In July 2015, the FDA granted first-line approval to gefitinib in mNSCLC patients whose EGFR gene shows deletions on exon 19 or mutations on exon 21. The drug’s indication statement requires that these mutations be detected by an FDA-approved test.

Lynparza: Back from the depths—twice
On the heels of a disappointing phase 2 trial, AstraZeneca decided to end development of olaparib (Lynparza) as maintenance therapy for women with ovarian cancer. The placebo-controlled study of 265 patients whose cancer had relapsed produced a modest 3.6-month progression-free survival (PFS) advantage in the olaparib arm. AstraZeneca’s announcement in 2012 that it would terminate the program came even before investigators published their work in the New England Journal of Medicine.

But the investigators sensed that the outcomes weren’t telling the whole story. A subgroup of study participants with known BRCA gene mutations had shown a more promising response. Noting that their study was not designed to address differences among patients on the basis of BRCA status, the NEJM authors wrote that “there is a need to identify biomarkers to select patients for this therapy.”

Two years later, AstraZeneca retrospectively identified BRCA status for 97% of the women in the study. In 137 participants with BRCA mutations, the progression-free survival benefit was seven months, prompting AstraZeneca to request accelerated approval. Concerned about the sample size, however, an FDA advisory committee voted 11–2 against approval.

But in December 2014, the FDA recognized the underlying mechanism of disease and overruled the committee. It approved olaparib for women with germline BRCA mutations detected by an FDA-approved test. Continued approval may be contingent on the clinical benefit reported in ongoing phase 3 trials.

Payers are likely to watch these outcomes closely. At a cost of about $7,000 per month, olaparib exceeds conventional standards of cost-effectiveness, even when restricted to patients with BRCA mutations, according to a study presented at last year’s Society of Gynecologic Oncology annual meeting.

Iclusig: Dot all the (T315)i’s
Ten months after the FDA approved ponatinib (Iclusig) as second-line treatment for some leukemias, the agency ordered Ariad Pharmaceuticals to stop sales and marketing. Real-world incidence of blood clots hit 27%, far higher than what the labeling showed, and fatal and serious events occurred in some patients just two weeks after starting therapy. “FDA cannot identify a dose level or exposure duration that is safe,” the agency warned in October 2013.

In the phase 2 trial that led to ponatinib’s approval, 54% of patients given the BCR-ABL inhibitor had achieved major cytogenic response (MCyR). But in a subset of patients—those with a BCR-ABL kinase domain mutation called T315i—MCyR reached 70%. This subgroup was no less at risk for vascular occlusion, but given its high response rate and the fact that the T315i mutation causes resistance to other kinase inhibitors (nilotinib [Tasigna], imatinib [Gleevec], and dasatinib [Sprycel]), the FDA knew that ponatinib addressed an unmet need.

Ultimately, the agency limited ponatinib’s indication to patients with a T315i mutation and approved a Risk Evaluation and Mitigation Strategy before sales resumed. Though the biomarker requirement cut ponatinib’s market to about 1,300 eligible patients in the United States, it may have saved the product and assured its availability to a handful of patients with few other options.

In returning to a market that has shriveled to a fraction of its original size, however, Ariad was forced to recoup R&D costs from a smaller group of patients. When ponatinib was first approved, its wholesale acquisition cost (WAC) was $9,580 for a 1-month supply. When it reintroduced the drug, Ariad increased the WAC price of ponatinib to $10,350, an 8% hike.
Drugs goes by a lot of names—some less flattering than others—but put simply, repurposing involves applying a drug’s mechanism of action to an indication far from its original intended use. The best-known example may be sildenafil (Viagra), which failed in early trials as a hypertension agent but became a household word after men in those studies enjoyed, well, a certain side effect.

With the cost to bring a drug to market north of $1 billion, finding a use for a once-promising compound collecting dust on a shelf but has nonetheless cleared preclinical and early safety studies may make strategic sense. Numbers on the size of the repurposing industry are hard to come by, but the existence of several repurposing conferences—when just a few years ago none were held—is a testament to its growth.

Some repurposing involves a bit of serendipity, albeit high-tech serendipity. Using complex computational methods, researchers pair the medicinal effects of a drug with molecular features of disease, such as cellular pathways, to predict usefulness for a given purpose. This approach led researchers at Johns Hopkins and the University of Texas to the discovery that itraconazole, the common antifungal agent, inhibits the Hedgehog signaling pathway. In a subsequent phase 2 study published in the Journal of Clinical Oncology, the researchers reported that itraconazole reduced Hedgehog pathway activity and cell growth in patients with basal cell carcinoma. In January, Japanese researchers published evidence of itraconazole’s effectiveness against endometrial cancer cell proliferation.

Other efforts take a personalized medicine approach. For example, Almac, a Northern Ireland company with U.S. operations, works with pharmaceutical clients to examine databases to identify subgroups that might signal the presence of a predictive biomarker.

NIH gets into the game

The National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health, puts a new twist on repurposing. In its Discovering New Therapeutic Uses for Existing Molecules program, NCATS uses the power of crowdsourcing to match pharmaceutical company-donated assets with scientists who envision new conditions for which they may be effective. The program funds repurposing projects for drugs with an established safety profile and that once advanced to clinical studies, but are no longer under commercial development. Christine Colvis, director of drug development partnership programs at NCATS, says the primary focus is improving the efficiency of addressing unmet needs, not the commercial viability of a molecule.

“The program demonstrates that public posting of industry assets to solicit new therapeutic use ideas from the academic community via crowdsourcing is an effective way to launch new collaborations,” says Colvis. She points to one project in which a team at Yale found that saracatinib—originally developed as a cancer therapy—could be used to treat Alzheimer’s disease.

“By repurposing an existing drug, investigators were able to begin testing it in humans within three months of receiving their award. Typically, it would take more than a decade from the discovery of a promising compound to its readiness for clinical trials.”

The project is one of the early successes of the New Therapeutic Uses program. Shortly before AstraZeneca made saracatinib—a Fyn kinase inhibitor—available for study, the Yale team had discovered that activation of the Fyn kinase protein triggers a process that leads to synapse loss, a characteristic of Alzheimer’s. The team, led by Stephen Strittmatter, MD, hypothesized that blocking Fyn activity may modify the course of Alzheimer’s. After four weeks, saracatinib reversed synapse and memory loss in mice. Strittmatter’s team went on to complete a successful phase 1b trial and has advanced to a multisite phase 2a study of saracatinib.

NCATS has funded 13 projects, with another round of funding likely next year. “Some of our projects will use a personalized medicine approach to identify patients that are most likely to respond to therapy,” says Colvis. Those studies are ongoing now, so details are not yet publicly available.

For a drug already on the market, a successful repurposing may or may not boost its cost. A 2014 analysis in the Journal of Market Access and Health Policy found that potential for cost increases is greatest when the treatment setting shifts from outpatient to hospital, route of administration changes, an unmet need is addressed, or if the drug is classified as orphan.
off-label use of drugs with narrow indications, saying “it’s incumbent on the provider to use the drug appropriately.” His concern is founded; a 2015 study, for instance, found that 60% of oncologists do not make NSCLC treatment decisions based on EGFR mutation subtype. EGFR mutations are believed to exist in as many as 30% of NSCLC patients, and they are an important prognostic factor for guiding treatment choice. As with breast cancer patients who are tested for hormone receptor of HER status before initiation of treatment, guidelines recommend EGFR mutation testing when a patient is diagnosed with NSCLC.

Yet both the president’s council and 21st Century Cures legislation explicitly forbid prohibition of off-label use of drugs that are approved under a new accelerated pathway. The council called for strong limitations, perhaps through insurers, in the SMU pathway. For indications provisionally approved for small populations on the basis of a biomarker, Aetna would like to see confirmatory evidence supporting a link between surrogate endpoints and meaningful improvements, according to Pezalla. “In the cancer trials, it might be progression-free survival, overall survival, or improvements in patient quality of life,” he says. In relatively short trials, “some of those data are lacking or not statistically significant because of the small number of patients.”

A biomarker that shows with reasonable certainty why a drug will or won’t work in populations, says Pezalla, “is really going to help patients and help doctors talk about therapy, and it may also help therapies that have been reserved for the more advanced cancers to be used earlier in the disease, perhaps with better outcomes.” But because not every biomarker is promising, he adds, “it’s great if the FDA looks at these as part of their approval pathway, because it helps us understand just how well a biomarker works.”

New life for old molecules

One of the side benefits of biomarker discovery is the reintroduction of a handful of currently approved drugs that were either once taken off the market or shelved halfway through development. Gefitinib, the lung cancer drug, is the prime example. Tested on more than 1,500 people with metastatic NSCLC, the kinase inhibitor was approved in 2003 because of its dramatic performance in a small subpopulation. But when postmarketing studies failed to confirm the drug’s benefit in a broader population, gefitinib was pulled from the market.

What researchers didn’t know then was that gefitinib wasn’t originally tested on enough of the right people. Six years after gefitinib’s approval, researchers identified genetic abnormalities in those original responders. In 2015, the drug made it back to market after being studied in 106 patients whose EGFR gene expressed the same abnormalities. Today, it is indicated specifically for that population.

Gefitinib’s rebirth is a cold, hard lesson in missed opportunity, lost time, and wasted resources. “If you have success in a broad population but it’s all due to a subgroup, you’re exposing that whole population to determine that subgroup until you have the right biomarker,” says Pezalla. “That’s not only expensive, but for some people, their cancers may progress and it may be difficult to regain that ground.”

That realization has led the FDA to scale back the indications for a handful of other targeted drugs, such as cetuximab (Erbitux) and panitumumab (Vectibix), that reached the market before science fleshed out our understanding of their biomarkers. Panitumumab was approved by the FDA in 2006 for metastatic colorectal cancer but was rejected in 2007 by the European Medicines Agency (EMA), the European analog to the FDA, for lack of efficacy. Amgen subsequently showed EMA that the drug doubled progression-free survival in a subset of patients without a KRAS mutation. As a result, the FDA changed panitumumab’s indication in 2009 to warn that the drug was “not recommended” in patients with KRAS mutations, changed it again in 2012 to say it was specifically “not indicated” for this group, and again in 2014 to require use of an FDA-approved test to confirm that a patient does not have a KRAS gene mutation.

As biomarkers transform cancer and turn other diseases into niche conditions, some treatment decisions are becoming more clear cut. But they are something of a lesson in systems theory—introducing complexities that will fuel dialogue about cost and access for years to come. MD

Michael D. Dalzell is a N.J.-based freelance journalist and a former managing editor of Managed Care.
Human behavior is a mystery. Sometimes we don’t even know ourselves why we do things. But IBM’s Watson Health thinks it can put its big-brain cognitive thinking cap on and figure us out, as revealed in the data fingerprints we leave behind when we enter the health care labyrinth.

IBM Watson Health has been growing fast, as parent IBM patches new health care analytics companies into the entity it created about a year ago. The company’s $2.6 billion purchase of Truven Analytics is a recent example. The result: a company with ginormous data sets (health information on 300 million Americans) and sophisticated algorithms. CVS Health, venturing far beyond its just-a-pharmacy roots, has partnered with IBM Watson Health (named for IBM’s founder, not Bell’s assistant) to tackle adherence woes and improve the sharing of information between its pharmacists and physicians.

The problems with adherence start right after a patient walks out of the doctor’s office. Prescription in hand, he shoves it into his pocket, where it may never be seen again. One in five prescriptions don’t get filled to begin with, says William Shrank, MD, chief scientific officer for CVS Health. Even when the bottle is sitting on a counter at home, many more people don’t open it. Shrank talks about a recent study of Aetna members who had just had a heart attack and were offered their medications for free. They still took their medications only half the time.

People don’t take their medications for any number of reasons. Maybe they’re expensive, have annoying side effects, come in a bottle with a label that the person can’t read, or are prescribed for a reason that was never explained. Or some people may feel fine and just don’t believe they really need the medication. Such an array of rationalizations and excuses requires a personalized response. “We need to create a wide menu of interventions and target them to the right person,” Shrank told an audience at the annual meeting of the Health Information and Management Systems Society (HIMSS) in March.

Some of that targeting involves getting into the heads of individuals and finding the best way to reach them. Other times it’s really not that complicated. For instance, CVS has already gained better medication adherence by understanding the common problem of too many medicine bottles. Expecting older or frail patients to keep track of multiple doses of multiple drugs each day is a formula for nonadherence and medication mistakes. CVS started packaging all of a patient’s drugs together, so all of the morning doses are in one container, as are those for the rest of the day.

The IBM–CVS partnership is using cognitive computing to turbocharge and refine population health. They’re using the data and Watson’s ability to learn, not just compute, so that it may be foreseen when, for instance, a person with cognitive impairment and heart failure is heading downhill and needs an intervention. “We’re already making great progress in our ability to anticipate who is going to have a decline [in health],” said Shrank at the HIMSS meeting. “If you can start identifying those folks with reasonable precision you can intervene early and in a cost-effective way.”

Understanding human behavior

CVS also envisions a future that goes beyond sending a terse text to a patient who doesn’t show up for his checkup. Instead, this future uses data and Watson’s off-the-charts artificial intelligence IQ to understand why he didn’t show up and tailor the message accordingly. The ambition is also to share those insights with old-fashioned human beings—the physicians, nurses, family caregivers, and pharmacists whom, in an ideal world, would form a cohesive care team.

That sounds a little like what doctors used to aspire to before they were swamped with information, tending to EHRs, and speeding through 15-minute appointment blocks. “There’s really no time to try to better understand what’s going on with your patient between visits,” Shrank said.

Watson, he believes, can be there to help.

Jan Greene is a veteran health care journalist based in northern California. Her work has appeared in the Los Angeles Times, Health magazine, Hospital & Health Networks, and many other publications.
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They say there are no stupid questions. But what about the questions that surprise us because they were asked?

For several years, Michael Laposata, MD, chairman of the Department of Pathology at the University of Texas Medical Branch in Galveston, has told the story about a doctor who ordered a common pharmacogenomic test to assess a patient’s ability to metabolize clopidogrel (Plavix), a platelet inhibitor. The test identifies the variants of the CYP2C19 gene. A patient who metabolizes clopidogrel abnormally is said to have an allele labeled as *2, shown on the test report as CYP2C19*2. No one in the doctor’s office—including the doctor himself—knew the significance of the asterisk. “The doctor called me and said, ‘I got this interesting value. It was CYP2C19 squared,’” Laposata says. “And I said, ‘What do you mean, squared?’ The doctor thought it was a superscript and *2 meant it was squared. I said, ‘My God, when you have a genetic test, that’s an allele.’ And when I said that, I got this—a question I get quite often—‘What’s an allele?’”

Learning a new language

The conversation about the confusion happened several years ago, but Laposata says misunderstandings about genetic and molecular tests are still common. It shows, he says, how today’s torrent of information about genetic and molecular markers for disease have outstripped the ability of physicians, health plans, and patients to know what it all means. As the New York Times reported recently, “The genetic data is there, but in many cases, doctors do not know what to do with it.”

One reason the science is ahead of our ability to know what it means is that clinical labs introduce some 8 to 10 new genetic testing products every week, according to NextGx Dx, a Nashville health IT company that tracks and curates data for genetic tests.

Imagine what that number means for UnitedHealthcare, which said in March that it would require all physicians ordering genetic tests to get prior authorization for these tests starting in the third quarter of this year. The nation’s largest health insurer made the announcement in its Network Bulletin newsletter. UnitedHealthcare spokesman Richard P. Daryl explains that the company had already required prior authorization for some tests, such as those for the BRCA genes linked to breast and ovarian cancer, and asks members to get counseling before testing with an independent genetic counselor.

Still, UnitedHealthcare has been slower than other large health plans to adopt prior authori-
zation for genetic tests, according to Paul von Ebers, a health plan consultant and former president of the Blues plans in North Dakota. Aetna, Cigna, and most Blues plans have used prior authorization for genetic tests for several years, he says.

Managing the explosion
While some health plans are using prior approval, others seem to have a wide variety of approaches, says Linda D. Liston, director of clinical lab contracting for McKesson Business Performance Services. Whatever the method, cost control is the reason, given that molecular and genetic tests can cost anywhere from $250 to more than $6,000.

Hiring utilization management vendors is another way that health plans are seeking to control the ballooning cost of genetic and molecular testing. The complexity of such tests involves much more than a yes-or-no answer, says Lon Castle, MD, chief of molecular genetics and personalized medicine at eviCore healthcare, a medical benefits management company in Bluffton, S.C., outside of Savannah.

Genetic and molecular testing is the fastest growing segment of the lab market, and Castle says the best estimates are that it will generate $11 billion in sales this year for lab companies “and that’s just molecular and genetic tests.”

“Every time we meet with a plan, we hear that genetic testing is a pain point for them because of the explosion and because they don’t have the resources to keep up with it,” says Bill Kerr, CEO of Avalon HealthCare Solutions, a Tampa, Fla., lab services management company.

While the volume is high, spending on genetic tests remains relatively low at only about 10% of health insurers’ total lab costs, making health plans reluctant to invest much money in managing it just yet, Kerr says. “While the majority of cost savings are in routine testing, genetic test costs are trending upward at 15% to 20% annually,” Kerr says. That rate of increase worries health plan executives enough to make them start looking for ways to manage testing so that they get an early return on any investment now and are prepared before spending gets out of control, adds Kerr, who previously worked in cancer research and as chief medical officer for Florida Blue.

There are between 7,000 and 8,000 different tests today that can identify genetic variants, says Castle. But there are about 60,000 different testing products on the market for those variants because so many different labs have developed tests for the same variants, he says. Thousands of clinical labs in this country are introducing 8 to 10 tests every week, he figures. “If you’re a health plan, that’s a lot to keep up with,” says Castle. And that’s why insurers are outsourcing utilization management of genetic testing to companies like his, he says. Von Ebers agrees: “In general, insurers will pay when a genetic test is clearly indicated for a certain patient due to his or her ethnic background, disease state, or other factors,” says consultant Paul von Ebers.
Health plans reviewing genetic test requests are evaluating a variety of management techniques

Trying to find out what works and what doesn’t, health insurers are adopting a wide array of approaches to genetic and molecular testing.

Among the first to announce a program to manage these expensive lab tests was Cigna, which said in 2013 it would require genetic counseling with an independent board-certified genetic counselor or clinical geneticist for breast and ovarian cancer, colorectal cancer syndromes, and long QT syndrome. Cigna also has a precertification requirement and medical necessity review for most common genetic tests.

Since then, other health insurers have partnered with companies specializing in developing genetic testing regimens. Independence Blue Cross (IBX) in Philadelphia announced earlier this year that it would cover next-generation whole genome sequencing for a variety of cancers. In a partnership with NantHealth, IBX will cover whole genome sequencing for members with specific rare cancers, tumors in children, metastatic cancer of unknown primary origin, primary brain cancer, triple negative breast cancer, and certain metastatic cancers. The coverage for this testing began in March among members in IBX’s commercial plans. NantHealth is one of the companies involved in President Obama’s Cancer Moonshot program to eliminate cancer.

Geisinger Health Plan in Danville, Pa., does its own utilization management for genetic and molecular tests and recently announced that it would cover whole exome sequencing for children with certain developmental delays, says Phil Krebs, Geisinger’s director of medical policy and appeals.

In January, Horizon Blue Cross Blue Shield of New Jersey and Foundation Medicine, a genetic testing company, announced a precision medicine initiative in which the two companies would collaborate with Clinical Outcomes Tracking and Analysis (COTA), a data analytics company. The three companies will seek to improve the treatment of patients with metastatic non–small cell lung cancer using Foundation’s comprehensive genomic profiling test, called FoundationOne.

Some health plans use prior approval when it comes to managing genetic testing, says Linda D. Liston of McKesson Business Performance Services. Others try different approaches. As a result, eviCore uses a two-step process to evaluate the evidence behind each test to determine if the test does what the lab says it will do, Castle explains. First, eviCore uses a technique the CDC’s Office of Public Health Genomics developed more than 10 years ago called the ACCE Model Process. ACCE stands for analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications. The process involves 44 questions that, among other things, ask about the test’s sensitivity, specificity, whether there is a remedy available for the disorder that might be identified, and whether there is access to that remedy.

After determining clinical utility, eviCore evaluates whether the test is appropriate for that particular patient. The company wants to know if the test result will, in fact, inform or possibly change a physician’s treatment decision. “We want to ensure that for any test once you get the result back, you will make a treatment decision that is either yes or no or left or right depending on the patient and the patient’s condition,” Castle explains. If the test legitimately informs a treatment decision, eviCore approves the test: “We’re looking to manage inappropriate testing and not waste anyone’s time getting clinical information and slowing the process for physicians or patients.”

Panels get closer look

Currently, health insurers are having the most trouble with coverage decisions about panels of tests that may include assays for 25 to 50 genetic variants or more.

With any panel of tests, eviCore seeks to ensure that it meets the standards established by the American College of Molecular Genetics (ACMG). The ACMG has issued policy statements on genetic tests for Alzheimer’s disease, breast cancer, cystic fibrosis, prenatal/preconception carrier screening, and Down syndrome, among others.

Different tests get different levels of scrutiny. The
test for cystic fibrosis can cost $300 or more, notes Castle, but experience has shown that it's rarely ordered inappropriately so the review is usually routine. But the large panels for other conditions, such as general screening for cardiac conditions that involve 20 to 30 genes, tend to get examined more closely. “Sometimes there are genes in these panels that just don't have the clinical utility we're looking for,” Castle says. But once a lab has a panel of 25 to 50 tests, it's difficult to separate the few tests a patient needs from the ones the pathologists developing the tests believe belong in the panel, notes Phil Krebs, director of medical policy and appeals for Geisinger Health Plan.

'Big part of the conversation'
"I was on a conference call with other health plan administrators recently, and the whole issue of how to analyze and pay for large panels of tests was a big part of the conversation,” Krebs explains. “There's just no way to break up panels efficiently once they're put together.” Geisinger Health Plan does its own utilization management for molecular and genetic tests and gets advice from the Genomic Medicine Institute, a division of the Geisinger Health System.

Geisinger Health Plan wants to cover whole exome sequencing for children with certain developmental delays, says Phil Krebs, the plan's director of medical policy and appeals.

Liss, at Independence Blue Cross, worries about results from panels that lead to unnecessary concern among patients or physicians. “One of the risks of panels is getting a test result that shows a genetic variant of uncertain significance,” he says. “A patient asks, 'What does this mean?' But the physician has no idea. There is an abnormality, but nobody knows whether it's a big deal or just background noise. That's a huge challenge because it causes a lot of anxiety.”

Clinical labs have an interest in adding genes to panels because they can charge more for larger panels than they can for an individual test, Liss comments. “But we want to pay for the services that are reasonable and appropriate and are going to aid in diagnosis and treatment planning and don't want to pay for those tests that haven't shown a proven benefit,” he says. “Some tests that labs include in large panels are a bit of a solution in search of a problem.”

One reason it's difficult to break up large panels is that having many genes on one panel helps to keep overall testing costs low because all of the assays in the panel can run on one analyzer. Usually those analyzers are next-generation sequencing (NGS) machines, which are helping to bring down genetic and molecular testing costs. The cost of NGS testing for a large panel of 25 to 30 tests averages about $1,200 to $1,500 but the price can go up to several thousand dollars depending on the disease and the scope of the panel, says Krebs.

Discussion about large panels of 25 or more tests can get testy, Castle says. "Now, you're getting to where the science and the business side of lab testing clash a bit," he adds. That's because it's less expensive for labs to run a multitude of tests in one panel than to run separate tests for each gene variant.

Labs developing large panels want to provide clinical answers for physicians treating patients while also collecting data on the incidence of gene variants in a population, Castle explains. They put together large panels for their own internal research to learn more about genetic variants. Understandably, health plans balk at paying for testing that benefits the lab and could have benefits for patients down the road but have little, if any, clinical utility at the moment.

Clinical labs tend to push the boundaries of what's allowed because genetic and molecular testing has so much appeal, says von Ebers. It is done under the banner of precision medicine and scientific advancement—and who can be against that? President Obama threw his weight behind it with his $215 million Precision Medicine Initiative. "Precision medicine is a wonderful idea and will probably help the medical system focus its treatments to what works at the individual patient level—eventually," says von Ebers.

The problem is that genetic and molecular testing labs package multiple tests into a single panel, citing the potential savings from precision medicine. But so far, the emphasis is on potential savings. "Until labs can prove that these tests with great potential actually affect treatment, insurers will say no,' von Ebers adds.

Appropriate management
Kerr, at Avalon, views genetic testing the way radiology benefits were managed 10 to 15 years ago. In the earliest days of testing with CT, MRI, or PET scans, it was difficult to know which was best, he comments.

“If I were looking for which test to order and didn't consult a radiologist in advance, I'd order a CT scan, for example. Then when I got the result back, the radiologist might write a note saying, 'You probably should have ordered an MRI for this patient,'” he says. The point is that health plans today are trying to get ahead of the development of the technology and eventually will be successful in managing genetic testing appropriately, Kerr concludes.
Drug Companies Ask Plans To Just Say ‘Yes’ to Risk

Manufacturers are starting to offer significant rebates in exchange for preferred status on an insurer’s formulary.

By Thomas Reinke

A new era may be dawning for drug manufacturers—one in which they transition from a world of jeopardy to one with double jeopardy.

Pharmaceutical companies have always faced the reality of losing billions on drugs that fail in late-stage clinical trials. Now there are new challenges: guaranteeing the performance of medications that have found a market and demonstrating value in emerging payment-reform models.

So far, drug companies have largely managed to stay out of the line of fire as health care payment shifts to value-based systems. They have not been subject to a gauntlet of quality measures, financial benchmarks, and downside risk featured in CMS’s Comprehensive Care Joint Replacement initiative and the various ACO programs.

But some drug companies are waking up to the fact that their time will come, if it hasn’t already, as the variety and volume of criticism about high drug prices crescendos. They are entering into risk-sharing agreements that may blunt some of that criticism. Early adopters may gain some marketing edge over their less adventurous rivals.

Risk contracts have the potential to make a drug unprofitable because of Medicaid best-price policies, says Robert Dubois, MD, of the National Pharmaceutical Council.

Risk-sharing agreements have been used in this country but on a limited basis. A global study of risk agreements by University of Washington pharmacy experts, published September 2015 in the American Journal of Managed Care, identified 148 such arrangements, but only 18 of them were or are in this country and only seven involved private payers.

An article on risk-sharing arrangements published in Health Affairs in 2011 called enthusiasm for them premature. If they are to catch on, the authors predicted, the drug will have to be expensive, uncertainty about its effectiveness will have to be high, and payers will need to be concerned about inappropriate use. Their four-year-old analysis of the factors needed for risk-sharing arrangements to succeed still rings true.

Earlier this year, Aetna and Cigna signed deals with Novartis that link payments for its new heart failure medication, a valsartan–sacubitril combination (Entresto), to the hospitalization rates of people on the medication. Entresto’s list price is $4,500 per year, and it is up against inexpensive medications for heart failure with long track records.

There are a number of criteria that can be considered for outcomes-based pharma contracts that align pricing with value, according to Christopher Bradbury, senior vice president of integrated clinical and specialty drug solutions for Cigna Pharmacy Management.

“Criteria to look at can include: significant spend in the drug class; expensive drugs; the existence of therapeutic alternatives—as these agreements can create additional competition beyond getting an excellent unit price; and an agreed upon outcome metric that can be measured and is valued,” Bradbury says.

Robert Dubois, MD, executive vice president of the National Pharmaceutical Council, a research organization funded by the pharmaceutical manufacturers, says that, “One reason manufacturers were historically interested in risk agreements was to differentiate their product from others in drug classes where there are similar agents in terms of mechanism of action and clinical results. An emerging reason to consider risk-sharing agreements is to address the growing concern about the price, expenditures, and value of pharmaceuticals in new payment models.”

Crowded categories

It’s fair to say that drug companies, not health plans, are the ones pushing for risk-sharing agreements.

The proposed contracts generally involve new high-cost medications whose makers hope to carve out market share in a crowded drug category. The manufacturer will offer significant rebates in exchange for preferred status on the health plan’s formulary. In addition, the manufacturer will provide guarantees in the form of additional rebates if agreed upon clinical outcomes are not achieved.
The advantage for the drug company is the market share it gains through its preferred or exclusive status.

**Health plan** pharmacy directors are always looking for assurances that their expenditures are justified, says Brian Smolich, the pharmacy director at Health Alliance health plan.

In exchange, the health plan receives a significant discount and some peace of mind related to the guarantee of clinical outcomes.

Health Alliance, an Urbana, Ill., health plan owned by the Carle Foundation, the not-for-profit owner of a 393-bed regional hospital and a 400-member physician group, was an early adopter of risk agreements with a contract for risedronate sodium (Actonel), an osteoporosis medication. Warner Chilcott, the drug’s manufacturer, guaranteed that the drug would lower fractures in patients who met adherence criteria or increase its rebates if it didn’t. Brian Smolich, Health Alliance’s pharmacy director, says agreement on the adherence measure as a qualifier was key to the deal, and that the osteoporosis drug did, in fact, reduce fractures.

Obstacles to risk-sharing agreements include the administrative burdens they create compared with simpler discount and rebate arrangements, according to the University of Washington study. The added workload comes from tracking and reporting clinical results for patients taking the medications. For example, health plans have to document that patients are adherent and must track the specific outcome measure. In addition, if there are poor outcomes, the health plan may have to provide other data to prove that the medication, and not other factors, was the cause.

Despite some success with its risk arrangements for Actonel and interferon beta-1b (Betaseron), a multiple sclerosis drug, Smolich says Health Alliance is phasing them out this year and transitioning all rebates to its PBM, in part because of the administrative costs associated with managing the rebates.

But other regional health plans are jumping into the risk-sharing agreements with drug manufacturers. Harvard Pilgrim Health Care signed a risk-sharing contract with Amgen for its PCSK9 inhibitor, evolocumab (Repatha), in November 2015. Michael Sherman, MD, the chief medical officer, notes that risk

**Amgen, Harvard Pilgrim enter risk arrangement for PCSK9 inhibitor**

While drug companies are showing an increased and expanded interest in risk agreements, they also are a tool for health plans. Harvard Pilgrim Health Care, a 1.3 million-member health plan in eastern Massachusetts, and Amgen have established a risk arrangement for evolocumab (Repatha) that is a good example of how manufacturers are using these arrangements to establish market share of a new medicine in a competitive situation.

Amgen’s evolocumab and Regeneron’s alirocumab (Praluent) are in a race to establish PCSK9-inhibitor market share. That competition is especially fierce because the two drugs have the same mechanism of action, very similar efficacy and safety profiles, and almost identical prices.

Health plans and PBMs approached both manufacturers long before FDA approvals to begin twisting their arms on price, rebates, and positions in their formularies. Health plans were deeply concerned about expenditures for these medications because of their price (about $14,000 a year) and potential for widespread use among patients whose LDL couldn’t be controlled with statins or other drugs. They were also concerned about the safety and LDL-lowering ability of the medicines outside of the highly controlled circumstances of a clinical trial.

“With new high-cost medicines, health plan pharmacy directors are always looking for some protection or other assurances that their expenditures will be justified,” says Brian Smolich, pharmacy director at Health Alliance health plan in Urbana, Ill.

Michael Sherman, MD, Harvard Pilgrim’s chief medical officer, says the health plan’s agreement with Amgen requires evolocumab to lower LDL levels consistent with results observed in the drug’s clinical trials, which have found, for the most part, that the injectable medication reduces LDL by about 50%. Sherman says the contract does not include cardiac events because the causes are hard to isolate. Harvard Pilgrim is limiting access to evolocumab to its approved indications and then only after the statins and ezetimibe (Zetia) have not brought LDL levels down.

Evolocumab is the only PCSK9 agent on Harvard Pilgrim’s standard formulary. In exchange for exclusivity, the health plan gets the drug at a reduced price. For Amgen, exclusivity keeps alirocumab at bay and helps it build market share. It has the added benefit of making revenue more predictable than in a competitive situation. Sherman says Harvard Pilgrim will receive additional rebates from Amgen if the LDL levels in adherent patients are higher than agreed-upon levels. The health plan will also receive additional rebates if prescriptions for the drug exceed an anticipated number.
Risk-sharing agreements that rely upon clinical outcome measures may be feasible for health plans but not for PBMs. It is difficult for PBMs to obtain and track patient-specific clinical outcomes unless they perform prior authorizations and also receive claims data from the health plan. It would also be a logistical nightmare for them to administer specific contract terms for multiple health plans unless the rebates and performance terms were identical across plans.

In contrast to Harvard Pilgrim’s evolocumab contract, Express Scripts has both PCSK9 medications—evolocumab and Regeneron’s alirocumab (Praluent)—on its preferred national formulary. While the specific terms of its arrangements with Amgen and Regeneron are not known, drug manufacturers usually insist on higher prices when they are not the exclusive agent on a formulary. The different approaches of the two companies indicate the flexibility that payers have in determining which medications or categories are candidates for risk arrangement, depending on the specifics of their member bases and priorities.

Dubois points out that drug companies face a unique regulatory obstacle to broadly entering into risk arrangement. The discounting and rebate terms in a risk contract may cause a problem for them with Medicaid best-price regulations, he says. The financial terms could drop the price of a medication below the price the manufacturer has with Medicaid. Any time that happens, the manufacturer is required to give that price to all Medicaid programs. So, for drug manufacturers, instead of being a creative new approach to contracting with payers, or a way to experiment with new arrangements with payers, risk contracts have the potential to make a drug unprofitable.

**Risk arrangements** are simple if they target short-term and easily measurable clinical outcomes such as LDL levels, says Michael Sherman, MD, CMO at Harvard Pilgrim Health Care.

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**Parties to a contract**

Some drug companies are looking past these immediate obstacles to the future potential of risk arrangements. “In talking with our members, just about every one of them is very interested in these contracts. I think many more will bubble to the surface and become evident,” says Dubois. “An interesting question is whether they will continue to be with payers; there’s a lot of talk about working directly with providers.”

There has been a lot of talk about managing pharmacy within ACOs but little action. So far, there have been no publicly announced risk-sharing contracts with ACOs.

Risk arrangements directly with providers may be feasible in the more sophisticated Next Generation ACOs, for which capitation is an option. A risk arrangement in a capitated ACO could include a subcapitation for pharmacy—a fixed price based on the projected utilization for the capitated lives.

The ideal arrangement in a risk arrangement with an ACO or health plan, Dubois says, is for drug companies to have upside and downside risk, as opposed to the downside-only risk they now face. In theory, upside risk could be built into contracts with ACOs.

The bottom line in risk-sharing contracts is that drug companies and health plans, or potentially providers, are seeking two things: quality outcomes for patients taking medications and maximizing value. The parties are aligned on the first goal, and while there is growing interest by manufacturers and payers, the ideal model for widespread risk contracting has yet to be developed. PMC

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**Key success factors for risk-sharing agreements**

**Manufacturers**
- Ability to measure outcomes in short time frame, with clear indicator (biomarker)
- Undeveloped evidence base, opportunity to gather real-world evidence
- Product with clinical advantage over lower-cost competitors
- Few comorbid conditions, limited size of target patient population
- Availability of multiyear clinical data (midlife cycle rather than newly launched products)
- IT infrastructure to track and audit data and manage patient registries

**Payers**
- IT infrastructure to track outcomes and switched patients, simple audit systems
- Clear payment or reimbursement mechanism (free initial therapy preferable to later rebates if outcomes are not reached)
- Unequivocal outcome measure (for example, valid biomarker)
- Clear outcome-reporting flow from physicians

Source: Newman P.J. et al., *Health Affairs*, December 2011
Even though physicians make the correct diagnoses and prescribe the right treatments, it doesn’t mean patients will fill their prescriptions and take every pill. There are several points along the patient journey where people get sidetracked and stop taking their medications. Making matters worse, as managed care plans increase the out-of-pocket expenses for patients in efforts to reduce their pharmaceutical expenditures, optimum treatment outcomes are increasingly being lost.

In the short run, shifting costs to patients may result in lower pharmaceutical costs for a health plan, but it may actually mean higher overall medical expenditures. Direct costs related to people not taking their medication as prescribed have been estimated at over $100 billion dollars annually. Lack of adherence is associated with a 30% to 50% increase in treatment failures. Here are some common factors that can affect treatment adherence:

**Understanding the importance of treatment.** Physicians often don’t get a chance to fully explain the importance of taking medications as prescribed because of the limited time they have with patients. A patient’s perception of the value of a drug and her beliefs about whether it can improve her health make up a major factor affecting adherence. Some basic motivational interviewing skills and tools can help clinicians engage patients in their treatment, which has been shown to have a strong influence on adherence.

**Ability to pay.** The cost of prescription drugs represents a significant barrier to adherence. Unfortunately, out-of-pocket (OOP) costs have been increasing for some time, growing by nearly 40% from 1996 to 2005, and data show that they continued to climb after that. The ACA slowed the trend, but it is expected to pick up again in the next decade.

Medicare Part D protects low-income enrollees from high OOP costs. But for the other beneficiaries in traditional Medicare with Part D coverage, it’s a different story. For them, the OOP costs are 100% of the cost of medications until they meet their deductible, 25% during the initial benefit, 45% in the “donut hole” coverage gap, and then 5% when their spending reaches the catastrophic phase of their coverage.

**Helping people take their meds.** Of course, there’s still an enormous gap between having medications and actually taking them and even a wider gap between taking them as directed. This is fertile territory for innovation and for integration of digital technology into the health care system. A number of smartphone-based apps prompt people to take their pills. Some work wirelessly with specially designed pill bottles. A company called AiCure has developed a facial recognition app that works by people taking pictures of themselves as they take their medication. Automated medication dispensing machines used in hospitals have been adapted for home use. In some cases, adherence technologies go beyond simple reminders, reinforcing messages about the value of the medication or addressing psychological adherence barriers.

**Juggling act**

If managed care plans want to get the most value out of prescribed medications, they must be nimble and work on several fronts. One way is to work with providers so they stress to patients the critical importance of taking medications as prescribed. Another way is to remind patients to take their medications—and get savvy about using digital technology to deliver reminders. Finally, they need to move away from policies with high OOP costs. There are enough barriers to taking medications without throwing financial roadblocks in people’s way; instead of barriers, managed care plans would be better served by providing assistance to promote adherence. By addressing these key issues, optimum treatment outcomes can be achieved.

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Scott Guerin, PhD, leads the Government Policy Systems team for the Access Group.
Cap on, Premiums up

California and other states have put monthly caps on out-of-pocket medication expenses. But the caps might shift some costs over to premiums.

By Joseph Burns
Contributing editor

During the beginning part of year, people with high-deductible health plans who have large medical bills can end up shelling out thousands of dollars (up to $6,850 for individuals, $13,700 for families) before their coverage kicks in. This hit to the pocketbook comes after the holiday season when many bank accounts are in recovery mode.

No retailer or financial services firm would recommend asking customers to pay so much at once. Why not spread out the payments?

But health plans may be stuck in the Dark Ages when it comes to out-of-pocket payments, which were—and still are—meant to deter members from overusing their benefits. Cost-sharing also helps to keep premiums down. The problem now is that not only do high deductibles deter members from overusing care, for many people they have become an insurmountable barrier to getting care at all.

Last fall, Drew Altman, president of the Kaiser Family Foundation, told the Baltimore Sun that since 2006 the average deductible more than tripled, from $303 then to $1,077 today—a rate that was 7 times faster than wages in the same period. The Sun quoted Altman as saying, “when deductibles are rising 7 times faster than wages ... it means that people can’t pay their rent.... They can’t buy their gas. They can’t eat.”

It’s possible that they cannot afford medical care, either. When the Commonwealth Fund surveyed 2,762 Americans aged 19 to 64 last summer, 2 of every 5 people who had high deductibles (defined as 5% or more of income) reported not getting needed care because of their deductible, including not going to the doctor when they were sick, or delaying or not getting a follow-up test recommended by a physician. One of five adults surveyed and whose deductibles were deemed affordable said they delayed needed care because of their deductible, the Commonwealth Fund survey found.

California cap

It’s hard to imagine deductibles and other out-of-pocket payments going away entirely. But making them more manageable is certainly doable. Perhaps taking a lesson from retailers, California’s insurance exchange, called Covered California, has put a monthly cap on what consumers pay for medications. The cap is designed to ensure that members in marketplace plans have access to the medications they need, including those high-cost drugs for patients with HIV, AIDS, diabetes, and hepatitis C, Covered California says.

“There is reason to believe that standardization of plans and perhaps caps on out-of-pocket costs will be helpful for consumers,” says Justin Giovannelli of Georgetown.

The limit of a $250 payment per script per month eases the pain by spreading it out over 12 months. The Democratic-controlled California legislature thought so much of Covered California’s plan that it adopted a similar measure that requires all health plans in the state—not just those sold on the exchange—to have a $200 monthly cap on medications starting next year.

In a report last fall, the Center on Health Insurance Reforms at Georgetown University said six other states...
have some caps on drug costs. California, Delaware, Louisiana, and Maryland limit the amount insured persons pay for a month’s supply of drugs. California’s cap applies to all covered drugs, but in other states, the cap applies only to specialty drugs. Maine and Vermont have annual caps on out-of-pocket costs for drugs. New York has prohibited specialty tiers, which can result in people facing higher out-of-pocket costs for certain medications. Meanwhile, Hillary Clinton has made caps on out-of-pocket drug expenses one of the chief talking points in her health care proposal, so we may be hearing more about them from the campaign trial.

“It’s too early to tell much about how well these limits are working,” says Justin Giovannelli, a project director at the Georgetown center. “But there is reason to believe that standardization of plans and perhaps caps on out-of-pocket costs will be helpful to consumers.”

Helping consumers afford their medications is the goal, says John Bertko, Covered California’s chief actuary and director of research. By capping payments monthly, patients with costly medications can pay over time.

**Expect costs to pile up** as more cancer drugs are approved, says John Bertko of Covered California. Prices are set by the pharmaceutical companies.

Let’s say your doctor gives you an expensive prescription in February, says Bertko. Under most health plans, that would mean you’d have to cough up the full deductible right then. Now let’s say that same health plan member got that expensive prescription from his or her doctor in September instead of February. Depending on how much is left in the deductible, that member would have to pay a large chunk of it that month and then the full deductible when the plan year restarts in January if a refill is needed early in the year, says Bertko: “That's two big hits in succession.” In contrast, Covered California is smoothing out the payment with its $250-a-month cap.

**Premium increases**

But for every time someone squeezes costs in one place, costs rise elsewhere. And so Bertko has had calculations done showing that capping copayments means premiums will, indeed, go up for everyone. In other words, Covered California is spreading the risk from those members who have high-cost medications to all members in the form of a premium increase that will total roughly 1% this year. Put this in the category of “the money has to come from somewhere.” Milliman actuaries have estimated the ceiling on out-of-pocket expenses could be responsible for a 3% increase in premiums over the next three years—and that’s before any other costs that might put upward pressure on premiums.

How does Milliman know this? Well, specialty drugs in the pipeline are expected to drive up medication costs for health plan members who have cancer, for example. “In particular, the oncology drugs that are in development look extremely promising and in addition to that promise, the price is set by the pharmaceutical companies,” says Bertko. He expects “the costs to pile up” as more cancer drugs get approved.

Spreading the financial risk to all members certainly appears to be actuarially sound, but opponents counter that premium increases are not without consequence. Each increase in premiums causes health policy observers to cringe as people elect not to buy insurance, even if ACA tax subsidies reduce the net expense.

Celynda Tadlock, Aetna’s vice president of pharmacy development, is one such observer. She worries that when states introduce their own requirements, as Covered California is doing, those rules cause costs to rise and make management of health plans more complex. “We’re not in favor of managed increases in premiums because every new piece of legislation adds on costs. Over time, if more states add new rules, absolutely there would be a concern that premiums would need to rise,” she says.

But like Covered California, her company is concerned that high copayments will result in people not taking medications. Aetna tries to strike a balance, she says, between setting copayments low enough so they don’t discourage adherence while keeping them in line with what competitors are charging. Copayments that are too low can lead to adverse selection and an actuarially untenable situation of attracting too many high-cost members.

Tadlock says entering into value-based agreements with pharmaceutical companies is a better approach to controlling rising drug costs. As an example, she cites the value-based contract that Aetna has with Novartis for its new congestive heart drug, a sacubitril–valsartan combination that Novartis is marketing as Entresto. The FDA approved Entresto last July. At that time, Novartis said it would cost about $12.50 a day, or $4,500 annually. Under Aetna’s agreement with Novartis, the health insurer will look to find whether the outcomes for Entresto in clinical trials can be matched by those when the drug is prescribed in real-world clinical practice. Novartis has a similar pay-for-performance contract for Entresto with Cigna.

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TOMORROW’S MEDICINE

Muscular Dystrophy Drug Could Pave Way for RNA Medications

Sarepta’s eteplirsen functions like an RNA patch so functioning dystrophin gets made. Other drugs like it may be used to treat Ebola and other viral infections.

Thomas Morrow, MD

There are more than 30 different forms of genetic diseases characterized by progressive weakness and degeneration of skeletal muscles that make up the various muscular dystrophies. The most common form of muscular dystrophy is Duchenne muscular dystrophy (DMD), a recessive, X chromosome-linked defect that leads to an absence or near absence of functional dystrophin. Dystrophin is a component of a protein complex that connects the cytoskeletal actin of muscle fiber to the extracellular matrix. By acting as a kind of shock absorber, dystrophin prevents damage to the actin.

When someone has muscular dystrophy and the dystrophin isn’t working right, the constant contraction and relaxation of the muscle proteins leads to damage, inflammation, and eventually, scarring.

Although biochemical and molecular evidence of DMD can be found shortly after birth, DMD does not become clinically evident until between the age of 2 and 3 because normal growth and development obscure the ongoing muscle damage.

DMD is an X-linked disease that mainly affects boys. They are typically diagnosed starting at about age 4 or 5 when they demonstrate waddling gait, toe walking, falls, and delayed speech. These children actually demonstrate improved functional ability until about age 7 when the degeneration and loss of muscle outpaces maturational development and physical growth.

After this, DMD patients enter into a relentless and worsening decline in physical function. By their 8th birthday, most DMD patients lose their ability to rise from the floor and climb stairs. They often fall while walking. Between ages 10 and 14, most become dependent on a wheelchair for mobility and by their mid- to late teens they have difficulty breathing. Some people with DMD are living into their 40s and 50s these days but most die in their 20s or 30s from respiratory or heart failure.

Worldwide, the incidence of DMD is between 1 in 3,500 and 1 in 5,000 newborn males with DMD. Links to race, place of birth, and other factors have not been found. According to the best estimates, between 9,000 and 12,000 Americans are living with DMD, or just 0.003% of the population, so it’s a rare condition that is nevertheless relatively well known because Jerry Lewis’s Labor Day telethon raised money for the Muscular Dystrophy Association for decades.

Broken zipper

Currently there are no approved therapies for DMD in this country. Standard medical therapy consists of glucocorticosteroids, which has been demonstrated to slightly delay the loss of ambulation. Nutritional support, a variety of physical and occupational therapies, and psychosocial care, as well as palliative care, are offered to these patients, but they do not generally change the course of the illness.

The most common causes of DMD involve a mutation to one or more of the DMD exons. (An exon is a string of DNA. Different exons have different functions but for the sake of clarity, let’s consider only those exons that code for protein synthesis.) Exons can be identified with advanced genetic testing. A string of exons is transcribed into RNA, which, in turn, is “read” by the ribosomes as a blueprint to assemble proteins by stringing together amino acids.

Thomas Morrow, MD, is the chief medical officer of Next IT. He has been the founding medical director of five HMOs and a disease management company, a medical director at Genentech, and president of the National Association of Managed Care Physicians. You can contact him at TMorrow@ManagedCareMag.com.
Several mutations to the dystrophin gene that result in missing exons have been linked to DMD. Deletion of exon 51 is the most common and causes about 13% of all cases of DMD. Deletions of exons 53 and 45 cause about 8% of cases.

When an exon has gone missing, the remaining exons are thrown “out of frame” and protein synthesis stops when the ribosomes get to its location. Think of a zipper that has a missing tooth. When the slider gets to that section, the zipper ceases to close.

Scientists have developed a way to “skip” the missing exon. This involves the creation of an RNA bridge that in turn allows the remaining exons to be realigned, making them “in frame.” By restoring the reading frame, protein synthesis can continue, albeit with a functional but slightly shortened form of dystrophin.

The concept of patching RNA as a way to treat DMD came to light because there is a naturally occurring milder form of muscular dystrophy called Becker muscular dystrophy. It is caused by exon deletion from the dystrophin gene, but the result is a compromised but still functional dystrophin. Becker muscular dystrophy was good evidence that the presence of some dystrophin, albeit shorter, might result in disease amelioration.

**Distinct class**

Sarepta Therapeutics, a Cambridge, Mass., biotech company developed eteplirsen, a drug designed to fool ribosomes into skipping over the missing exon 51 and assemble the dystrophin protein “in-frame.” As in Becker muscular dystrophy, the dystrophin is shorter by a few amino acids but both ends are normal.

Eteplirsen belongs to a distinct class of synthetic antisense RNA compounds known as phosphorodiamidate morpholino oligomers, which are, thankfully, usually referred to by their initials, PMO. PMOs can be assembled in precise sequences that correspond to a section of RNA. Eteplirsen is a sequence of 30 bases that is complementary to the bases in the missing exon 5. However, the compound is structurally distinct from RNA and other RNA analogues as well as other classes of antisense compounds that researchers are studying in hopes that they might be used as medications.

To prove that it was an effective treatment for DMD caused by the missing 51 exon, eteplirsen was studied in two different studies, 201 and 202, although 202 was just the open-label extension of study 201.

Study 201 was a double-blind, placebo-controlled study of eteplirsen in 12 ambulatory boys with DMD. Patients were determined eligible if their DNA demonstrated deletion of exon 51. The 12 patients were randomized into three groups of four. Group 1 received weekly intravenous infusions of 30mg/kg of eteplirsen, group 2 received 50mg/kg of the drug, and group 3 received a placebo infusion. After 24 weeks, the four placebo recipients were rolled (two each) into the two different doses of eteplirsen for an open-label study, the aforementioned study 202.

The primary endpoints were a 6-minute walk test (6MWT) and the percentage of dystrophin-positive fibers in a muscle biopsy. The study also measured the North Star Ambulatory Assessment (NSAA), pulmonary function tests, loss of ambulation, and other functional abilities. Clinical data have been collected through Week 168 for patients enrolled in the pair of studies.

The results are encouraging at many levels. Functional dystrophin has been found in all of the patients treated with eteplirsen. That alone is exciting proof that agents that target RNA defects and the assemblage of proteins hold promise.

The studies also demonstrated increased levels of dystrophin in the actual muscle fibers relative to levels prior to treatment. This dystrophin production was sustained through week 180 as measured by three different tests that were developed in consultation with the FDA.

The FDA required external comparable control groups to augment the short duration of
the placebo portion of study 201. It is important to note that the manufacturer stated “there was a high degree of homogeneity and comparability between the eteplirsen and the untreated external control patients for baseline characteristics including age, 6MWT, and representation of DMD genetic subtypes.”

Eteplirsen treated patients demonstrated a durable and “large magnitude” improved outcome of 151 meters in the 6MWT over the course of three years when compared with the untreated external control group. The study included a series of sensitivity analyses of the 6MWT that demonstrated statistical significance.

**Uphill battle**

As we went to press, an FDA advisory panel was scheduled to discuss eteplirsen on April 25. The same panel was scheduled to hold that discussion in January, but heavy snowfall forced a postponement. It may be an uphill battle for the drug. Before the postponed meeting, the FDA staff gave eteplirsen a largely negative review. At about the same time, the FDA rejected Kyndrisa, a rival DMD drug developed by BioMarin, a California biotech company.

Yet eteplirsen has been shown to improve the production of a functional form of dystrophin, according to documents on file with the FDA, and improve outcomes relative to a comparative group of patients. If the FDA does ultimately decide to allow the drug on the market, it will be the first drug that treats muscular dystrophy at its source, instead of ameliorating symptoms, although no one is saying that it is a cure.

Approval of eteplirsen might throw open the doors to other uses of PMO technology. First up might be treatments of muscular dystrophy caused by less common exon deletions.

But PMOs might also be a new way to treat some viral diseases. When a virus infects a cell, it inserts its genetic code into the cell’s DNA and RNA and commandeers that cell’s machinery into replicating more virus. By interfering with RNA, PMOs could be used to gum up the works that leads to viral replication. Sarepta is currently working on applying its PMO technology to some of the world’s deadliest viral diseases, including influenza, dengue, Marburg, and Ebola.

Moreover, PMO-based drug development has the potential to address countless diseases not amenable to traditional small molecule or biologic drugs. The human genome contains about 22,000 genes that account for more than 250,000 RNA transcripts and about 150,000 proteins, so there is no shortage of targets for PMO-based therapies. Of course targets are one thing, hitting them in a way that produces an effective treatment is another.
The Institute for Clinical and Economic Review (ICER), a comparative effectiveness research organization in Boston, received a $5.2 million grant last year from the Laura and John Arnold Foundation to conduct reviews of newly approved drugs. Steven Pearson, MD, is the president and founder of the organization.

How do the drug reviews differ from the other sorts of reviews you’ve done of devices and procedures? Really, not at all, because our basic approach is pretty much the same. You’re going to have different kinds of evidence, depending on what kinds of interventions you look for. For instance, it’s not very common to have randomized trials of diagnostic interventions available to look at, and for some procedures. Usually for drugs, we expect to see randomized controlled trials as part of the FDA approval process.

How many new people have you acquired to take on drug review? We are basically going to double in staff. The goal is to hire 10 to 12 new staff.

You do these reviews with New England CEPAC* and the California Technology Assessment Forum. Now there is a third group, Midwest CEPAC. We feel it’s very important for our reports to serve as a vehicle for public discussion of these issues, so everything is in a public domain. But we also think it’s important to have them vetted in public meetings. We recruit and convene an independent panel of clinicians, methodology experts, and public representatives to basically debate the merits of the evidence and of our review, and to take votes.

So you’ve modeled this like the FDA—a staff report, a public meeting, and an advisory panel–type vote. Yeah, elements are like that. It’s also like MedPAC.

And you are planning on doing 15 to 20 reports a year, and you published a list of drugs that you’re going to review this year, right? Right. It’s a tentative list because we’re somewhat at the mercy of what happens in the late stages of review. If we anticipate doing a drug in an area and suddenly the evidence doesn’t look so good, sometimes we have to kind of punt.

Your reports have proved to be pretty controversial. Let’s talk about hepatitis C drugs. You came out with a report about the hep C drugs and revised it a couple months later. The very first report we did on the hep C drugs was on Sovaldi. Well, it was technically on Sovaldi and Olysio, a drug that has kind of fallen by the wayside. At that point, the panel voted that Sovaldi was low value. It was clinically superior but low value, and we just had one kind of vote on value. And we recognized that buried in that judgment of low value by our independent panel were really two things. One was the long-term cost-effectiveness, which was actually quite good, and the second was potential short-term budget impact, which was really intense. It was really going to strain a lot of budgets.

So, that’s kind of what our reports do now. Whatever the list price is, we use our calculations to suggest a price at which it’s aligned with the long-term value to patients. And we provide kind of a price at which it would or wouldn’t ring an alarm bell as far as short-term budget impact.

What sets off the alarm bell? There are several states that have laws that say that the health care costs cannot go up higher than state GDP, or things start happening. Alarm bells start ringing. And the ACA had a provision that said that Medicare needed to do something when its costs were going up faster than GDP plus 1%. So, we decided to adopt the GDP plus 1%, and then the rest is just math. You have to figure out how many drugs are likely to come into approval over the next year. And you come up with a kind of average budget impact for each new drug if you want to stay within the GDP plus 1% rate.
I think you have angered some drug companies by using health system value. I think the word value bugs them. It does. And that’s part of almost a cultural divide. If you talk to payers, they will say, “How can you talk about value without thinking about the short-term impact on budgets?”

We developed our model with input from manufacturers, payers, patient groups, and others. Not everybody wants budget impact to be part of the conversation about value. But it is a very important concern for employers, for payers. To us, it didn’t make sense to leave it out.

Adoption rates are not factored into your calculations of budget impact, and the budget impact might look quite different depending on your assumptions about adoption rates. This is tough because we don’t view it as our role to try to prejudge how tightly health plans will try to manage utilization of a new drug. That’s up for them to decide, and to work out kind of going forward from the time that we try to assess the evidence. At the same time, we know that a new drug is not going to be taken by 100% of the eligible patients. So we model what we call a potential budget impact based on unmanaged adoption assumption.

The PCSK9 inhibitors. Your assumption was that everybody eligible for it would get it? No, 20%. After five full years of being out there, we said if the health plans don’t manage it tightly, and they just basically let doctors and patients do what they want to do, we said maybe 20% of eligible patients would be using it.

How did you arrive at 20%? We basically looked at the history of other adoptions and the issues around the fact that it’s injectable. We look at some of the companies’ own statements. In our reports, we actually have this graph that we developed so that you can say, “I think it’s only going to be 10%;” and you can easily see what the budget impact is going to be. Or you can say, “I think it’s going to be 50%” and see what it will be.

Are you guys the answer to our high drug costs? Is this sort of research a sword in the hand of St. George slaying the health care cost dragon? We want to foster the kinds of dialogue and give people the tools to have the dialogue. We don’t have all the answers. We help ask the questions. So, if you don’t think that our approach to value and pricing is the right one or the best one, let’s talk about what a better one could be.

I understand the focus on drugs, and right now, they are a sector of the health care economy that seems to be growing faster than others. But it’s all connected. So, I think it’s important for people to recognize that drugs do often bring good value to the health care system. But we have to think a little bit harder because the policy structure gives so much power to manufacturers to set their prices. I think it’s created a need for information like what ICER provides.

Do you think Medicare ought to negotiate prices? I think they should only consider doing that if they know what the endgame is. The question is, how are they going to know what to negotiate to? What’s a fair price? I think it’s reasonable to try it in the private market before we try it out at a federal level. So, I’m not against it full stop, but I think we have a lot to learn before we decide to have Medicare negotiate prices.

Why do we need ICER to do this? Some professional organizations, like ASCO, are coming up with value-based systems. For the public, it’s going to be confusing that one group, with strange initials, comes out with a value assessment, and another group comes out with a different one. Welcome to America, where we chose not to have a single federal agency do this. When PCORI was set up, there was the thought that it might do cost-effectiveness research. But they interpreted their own statute as meaning that they could not even fund cost-effectiveness research. AHRQ—it helps provide the evidence on clinical effectiveness and that is always the anchor on any kind of cost-effectiveness research. Medicare is not allowed to negotiate drug prices, so it doesn’t look at cost as part of their decisions about coverage for Medicare. There is a gap, and people struggle to understand value and to generate information around it.

If you look at what ASCO has done, they’re designing a framework for use by the individual patient and doctor. That’s different than a framework that’s supposed to be used by payers and others. We’re not going to have a monolithic approach to value because we don’t have a monolithic system.

Isn’t there some criticism that what you guys are doing puts a damper on innovation? You’re kind of the wet blankets of the biotech industry. Well, some people would say that Martin Shkreli needed a few more wet blankets on top of him at some point.

We’re kind of holding a mirror up to the system and saying, look, if you want to talk about value, the benefits brought to patients over the long term, and you want to also keep your eye on the short-term budget impact, this is what it looks like. Should that mean we do something? Again, we’re not trying to provide all the answers; we’re trying to provide the material with which to have the right conversation.
**Biosimilar Research Proceeds in Cancer, RA, and Hep B**

Sorrento Therapeutics/MabTech have completed late-stage trials in China for STI-001, a cetuximab (Erbitux) biosimilar for the treatment of EGFR-expressing metastatic colorectal cancer, and STI-002, an infliximab (Remicade) biosimilar to treat rheumatoid arthritis. Compared with irinotecan alone, STI-001 plus irinotecan significantly improved overall response (32.9% vs. 12.8%) and progression-free survival (5.6 vs. 3.2 months) in one double-blind, randomized trial in 501 patients with colorectal cancer. The combination therapy had an overall survival advantage of 0.7 months. In the controlled study of 330 patients with rheumatoid arthritis, STI-002 administered with methotrexate demonstrated efficacy similar to infliximab, with less immunogenicity and antidrug antibody formation rates lower than those of infliximab.

Data from two Gilead Sciences-sponsored trials evaluating the use of once-daily tenofovir alafenamide (TAF) in treatment-naïve and experienced adults with hepatitis B showed that TAF was noninferior to tenofovir (Viread). TAF also showed improved renal and laboratory safety parameters compared with the reference drug, which also is made by Gilead.

CHS-0214, Coherus BioSciences’ biosimilar of etanercept (Enbrel), demonstrated equivalence in a confirmatory head-to-head study in patients with moderate to severe rheumatoid arthritis. The primary efficacy endpoint was the proportion of subjects achieving ACR20 at Week 24. There were no clinically meaningful differences in the safety and immunogenicity profiles of the two products.

**Hope for people with rare surgical complication**

Defibrotide improved survival rates in adult and pediatric patients with hepatic veno-occlusive disease (VOD) with multiorgan failure (MOF) following hematopoietic stem-cell transplantation (HSCT). Statistically significant improvement was seen in Day 100 survival, the primary endpoint, and in rates of complete response by Day 100 compared with historical controls. The estimated difference between groups in Day 100 survival was 23%.

VOD, also known as sinusoidal obstruction syndrome, is a potentially fatal form of hepatic injury. VOD with MOF is a rare complication of HSCT, and no therapy is specifically indicated for it. Writing in the journal Blood, study investigators said the historical-control methodology offers a new approach for phase 3 evaluation of orphan diseases associated with high mortality in which a placebo control would be unethical.

**OA injectable meets endpoint**

FX006 (Zilretta), an investigational nonopioid/non-NSAID injectable, beat placebo in reducing moderate to severe osteoarthritis of the knee. Over 12 weeks of treatment, FX006 patients experienced pain reduction averaging 50 percent from baseline. FX006, which combines triamcinolone acetonide (TCA) with a polymer intended to provide persistent concentrations of the drug and to amplify the magnitude of pain relief, is designed to avoid serious side effects common to oral therapies, says its maker, Flexion Therapeutics. FX006 also achieved significant improvements in stiffness and function against placebo and immediate-release TCA, but missed a secondary goal of significantly improving scores on a daily pain rating scale compared with TCA. The drug has received fast-track designation by the FDA.

**Osteoporosis fracture risk lower with “romo”**

Women taking Amgen/UCB’s romosozumab for osteoporosis experienced a 73% reduction in risk for spine fractures and a 36% reduction in risk for all clinical fractures compared with placebo last year. But romosozumab is injected once a month and may not need a black box warning for osteosarcoma, whereas abaloparatide is a daily injectable. Teriparatide (Forteo), another daily injectable, carries a black box warning, and analysts believe the same may be true for abaloparatide once approved.

A head-to-head trial comparing romosozumab to alendronate (Fosamax) is underway, with data due next year.

**Setback for kidney transplant agent**

Chimerix ended two late-stage studies of its oral antiviral brincido-
**BIOLOGICS IN DEVELOPMENT**

**Selected FDA approvals of biologics and other specialty drugs, Jan. 1, 2016–Feb. 29, 2016**

**New marketing approvals**

<table>
<thead>
<tr>
<th>Date (type)</th>
<th>Manufacturer</th>
<th>Drug (trade) name; administration</th>
<th>Indication</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Jan. 28 (NDA)</td>
<td>Merck</td>
<td>elbasvir/ grazoprevir (Zepatier); oral tablet</td>
<td>For adults with chronic HCV genotypes 1 and 4</td>
<td>Efficacy and safety of this interferon-free regimen were evaluated in 6 clinical trials involving 1,373 participants with and without cirrhosis, HIV co-infection, or renal impairment. Across trials, SVR ranged from 94% to 97% in treatment groups. In about 1% of trial subjects, liver enzymes were &gt;5 times ULN at or after Week 8. $54,600 WAC may force Gilead to offer deep discounts for a similar medication, Harvoni, which goes for $94,500.</td>
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<tr>
<td>Jan. 15 (sBLA)</td>
<td>Novartis</td>
<td>ofatumumab (Arzerra); IV injection</td>
<td>Extended treatment of patients in partial or complete response after two or more lines of CLL therapy</td>
<td>New indication based on the phase 3 PROLONG trial, which showed that CLL patients on ofatumumab maintenance therapy had close to double PFS (29.4 months) vs. those on observation (15.2 months). Ofatumumab is already approved for previously untreated CLL patients for whom fludarabine-based therapy is inappropriate or who are refractory to fludarabine and alemtuzumab.</td>
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<tr>
<td>Jan. 28 (sBLA)</td>
<td>Eisai</td>
<td>eribulin mesylate (Halaven); IV injection</td>
<td>Unresectable or metastatic liposarcoma in patients who have received chemotherapy with an anthracycline</td>
<td>New orphan indication to treat a rare soft tissue sarcoma that occurs in fat cells. The first drug to show OS improvement in this population, eribulin bested dacarbazine by 7.2 months in patients with liposarcoma. In an open-label study of 446 patients with liposarcoma and leiomyosarcoma, OS gains were less impressive (2.4 months) for the entire study group, but approval was based on outcomes of the 143 patients with liposarcoma. Eribulin was originally approved in 2010 for metastatic breast cancer.</td>
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<tr>
<td>Feb. 5 (sNDA)</td>
<td>Bristol-Myers Squibb</td>
<td>daclatasvir (Daklinza); oral tablet</td>
<td>HCV genotypes 1 and 3</td>
<td>New labeling expands patient population to those with HIV-1 co-infection, advanced cirrhosis, or post-liver transplant recurrence of HCV.</td>
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<tr>
<td>Feb. 12 (sNDA)</td>
<td>Gilead</td>
<td>ledipasvir and sofosbuvir (Harvoni); oral tablet</td>
<td>HCV genotypes 1 and 4</td>
<td>New labeling expands genotype 1 patient population to include those with post-liver transplant recurrence or decompensated cirrhosis. Genotype 4 patient population expanded to include transplant recipients without cirrhosis or with compensated cirrhosis.</td>
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<tr>
<td>Feb. 19 (sNDA)</td>
<td>Pfizer</td>
<td>palbociclib (Ibrance); oral capsule</td>
<td>ER-positive and HER2-negative advanced or metastatic breast cancer</td>
<td>Patient population expanded to include women with disease progression after endocrine therapy, when taken with fulvestrant. Label revision based on PFS improvement in the PALOMA-3 trial; median PFS was 9.5 months for palbociclib + fulvestrant vs. 4.6 months for placebo + fulvestrant.</td>
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<tr>
<td>Feb. 26 (sBLA)</td>
<td>Genentech</td>
<td>obinutuzumab; (Gazyva); IV injection</td>
<td>Follicular lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen</td>
<td>New approval based on the phase 3 GADOLIN study. Patients given obinutuzumab plus bendamustine followed by obinutuzumab alone had a 52% reduced risk of disease worsening or death than patients who were treated with bendamustine alone.</td>
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**New indications of previously approved treatments**

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CLL=chronic lymphocytic leukemia, ER=estrogen receptor, HCV=hepatitis C virus, IV=intravenous, NDA=new drug application, OS=overall survival, PFS=progression-free survival, SVR=sustained virologic response, sBLA=supplemental biologics license application, sNDA=supplemental new drug application.

Sources: American Society of Clinical Oncology, BioPharma Dive, FDA, Fierce Biotech, FixHepC.com, Lancet Oncology, Optum Rx, and manufacturer news releases and product labeling.
fovir after the drug failed to prevent cytomegalovirus (CMV) infection in patients undergoing hematopoietic cell transplantation. Investigators say the failure was caused by a rise in the rate of diarrhea, a symptom of graft-versus-host disease, in the drug arm, so corticosteroids were prescribed more frequently. Other problems included no evidence of a reduced rate of non-CMV DNA viruses, such as BK. But an antiviral effect was seen at Week 14, with patients who received brincidofovir experiencing fewer clinically significant CMV infections than those given placebo. Chimerix plans to continue testing brincidofovir for efficacy against serious adenovirus infections and smallpox.

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<th>Highlights from ASCO GI and GU cancer symposia</th>
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<td>Selected presentations from the American Society for Clinical Oncology’s January genitourinary and gastrointestinal cancer symposia:</td>
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<td>• The novel 177Lutetium-DOTATATE (Lutathera) demonstrated a 79% decreased risk of cancer progression or death compared with octreotide LAR for patients suffering from a rare form of cancer, advanced midgut neuroendocrine tumors, according to the phase 3 NETTER-1 trial. Lutathera is one in an emerging group of treatments called peptide-receptor radionuclide therapy, which target carcinoid tumors with radionabeled somatostatin analogue peptides.</td>
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<td>• Adding evofosfamide to gemcitabine in patients with metastatic pancreatic cancer did not provide an overall survival (OS) advantage, according to the phase 3 MAESTRO trial, nor did it show a significant OS improvement over gemcitabine alone (8.7 vs. 7.6 months).</td>
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<td>• Findings from the randomized phase 2/3 SCOPE 1 trial show that chemoradiotherapy with or without cetuximab (Erbitux) in patients with esophageal cancer yielded a 3-year OS rate of 47.2% in the chemoradiotherapy alone arm, which is comparable to data from surgical trials. Investigators called the result unprecedented.</td>
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<td>• Panitumumab (Vectibix) and best supportive care (BSC) may significantly improve OS in patients with chomérefractory wild-type KRAS metastatic colorectal cancer, compared with BSC alone. These phase 3 findings were the first to analyze panitumumab efficacy by wild-type KRAS (exon 2) and wild-type RAS tumor mutation status, providing information about OS in new subpopulations.</td>
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<tr>
<td>• New analysis of phase 3 CheckMate-025 data showed that nivolumab (Opdivo) as second-line therapy for patients with advanced renal cell carcinoma (RCC) produces consistent objective response and OS across subgroups. Versus everolimus (Afinitor), nivolumab performed better across baseline factors such as Karnofsky performance status, Heng risk criteria, or number of prior therapies regardless of prior treatment with sunitinib (Sutent) or pazopanib (Votrient).</td>
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<td>• Patients with advanced RCC treated with cabozantinib (Cometriq) had a median progression-free survival of 7.4 months compared with 3.9 months for patients treated with everolimus, according to an interim analysis of the phase 3 METEOR trial. Using the MSKCC risk-assessment criteria, 43% of patients had favorable-risk disease, 41% had intermediate-risk disease, and 15% had poor-risk disease.</td>
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Long-term studies in CML
Five-year results of the randomized ENEStnd trial show a positive risk-benefit profile for nilotinib (Tasigna) compared with imatinib (Gleevec) in patients with chronic myeloid leukemia (CML). Cardiovascular risk was slightly higher with nilotinib, but improvements in CML disease control could outweigh those risks. By the end of Year 5, 217 patients (77%) in the lower-dose (300 mg twice daily) and 217 patients (77%) in the higher-dose (400 mg twice daily) nilotinib groups achieved a major molecular response, versus 171 (60%) imatinib patients (400 mg once daily). Progression to accelerated or blast phase was more likely with imatinib.

Have you heard?
In an important application of drug repurposing—a topic covered elsewhere in this issue of Managed Care—results from the large STAMPEDE trial suggest that a bisphosphonate and a COX-2 pain reliever may prevent tumor regrowth in some patients with prostate cancer. In patients whose disease had metastasized, a combination of zoledronic acid and celecoxib had a median of 22 months of treatment–failure-free survival, compared with 19 months in a group that received standard of care. The 5-year failure-free survival rates were 29% and 26%, respectively. The results were statistically significant. The data suggest that inhibition of COX-2 with agents such as celecoxib could inhibit the growth and invasiveness of prostate cancer cells, and epidemiologic studies have suggested a protective effect against prostate cancer from nonsteroidal anti-inflammatory drugs.

— Katherine T. Adams

All clinical studies mentioned in this article are phase 3 unless otherwise stated.
Patients With Metastatic Bladder Cancer Have an Unmet Need

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

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

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

–Michael R. Harrison, MD, Duke Cancer Institute

Learn More About Immunotherapy Research

Visit [http://www.researchcancerimmunotherapy.com](http://www.researchcancerimmunotherapy.com)

**REFERENCES**

Cancer Groups Give Part B Plan an F

Organized oncology isn’t ready to give up on ASP+6 payment for Medicare Part B drugs. But experimentation with value-based pricing has some supporters.

By Peter Wehrwein

Change is hard and often unpopular. Change how people get paid, and they will get up in arms in a hurry.

The reaction from oncology groups was overwhelmingly negative last month when CMS proposed altering the way it will pay for Medicare Part B drugs administered in physician offices or hospital outpatient clinics. The Association of Community Cancer Centers lambasted the CMS plan for interfering with providers’ ability to “provide critical cancer care services in their communities.” The American Society of Clinical Oncology (ASCO) averred its support of payment reform but accused CMS for “using heavy-handed reimbursement techniques” to manipulate treatment choices.

Getting rid of the financial incentive

For more than 10 years, CMS has paid physician and hospital outpatient clinics for Part B-covered drugs at a price equal to the average sale price (ASP) of the drug plus an additional 6% of the ASP (ASP+6, for short). CMS has proposed replacing ASP+6 with a payment formula set at ASP plus just 2.5% of ASP and a flat fee of $16.80. Why? Because basing payment on 6% of ASP is believed (not everyone agrees) to create a financial incentive to prescribe more expensive drugs: 6% of a $1,000 drug means more money for the physician or the outpatient clinic than 6% of a $100 drug.

Other specialists would be affected by the move away from ASP+6. But oncologists would be among the most affected because of the buy-and-bill tradition in oncology and the high price of cancer drugs. In 2014, roughly $4 billion of the $20.4 billion in Part B payments based on the ASP+6 formula went to oncologists and hematologists, according to figures included in the CMS proposal. Switching to the new formula would, by CMS’s reckoning, reduce the Part B drug payments to oncologists by 0.6%, or by about $24 million—obviously not a huge percentage or sum but real money nonetheless.

One of the most interesting things about CMS’s proposal is the design. The agency wants to run it like a four-arm randomized clinical trial. CMS is proposing to randomize 7,048 Primary Care Service Areas (PCSAs)* to one of four groups (see box). Physicians and outpatient clinics will receive their Part B drug payments according to which group their PCSA has been randomized to. Critics have complained that this CMS proposal is an overreach because it is nationwide and doesn’t give practices any choice about participating. But many political and public health scientists want new programs tested in just this way because of the inherent selection bias when a program depends on volunteers.

One thing that has gotten a little lost in the we’re-against-it clamor is the second phase of the CMS proposal, which is scheduled to begin in 2017. During that part of the program, the agency wants to test a variety of value-based pricing schemes in the Part B program, including reference pricing (using a benchmark price to set the price for a group of drugs) and indication-based pricing (higher prices for indications for which a drug is more effective).

Michael Kolodziej, MD, Aetna’s national medical director for oncology, is no fan of the first phase of the CMS proposal, which he believes will be a flop. But experimenting with ways to tie payment to outcomes is “fascinating,” although difficult to pull off, he says.

“If we can promote a universe in which the better outcomes get rewarded better than the average or mediocre outcomes—what is not to like about that?” says Kolodziej. MC

*Primary Care Service Areas (PCSAs) are clusters of ZIP codes that reflect primary care delivery patterns. There are 7,144 PCSAs in the country, but Maryland is not included in this proposal because of its all-payer model.
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Commentary on Current Trends in Rising Drug Costs and Reimbursement Below Cost

Ana D. Vega, BS,1 Paul P. Meola, BS,1 Julio Ramon Barcelo Jr.,1 Heidi M. Perez Ruiz, BS,1 Stephanie A. Oh, PharmD,2 Taeho Oh, MS3

1Nova Southeastern University College of Pharmacy. 2Atlanta VA Medical Center. 3US Rx Care.

INTRODUCTION

Over the past 4 years, the United States health care system has seen dramatic increases in the prices of prescription drugs. Recently, high prices have caught the attention of Congress and prompted investigations of companies that have greatly increased the price of certain drugs. To investigate this issue, we examined national average drug acquisition costs (NADAC) data published by the Centers for Medicare & Medicaid Services (CMS). The NADAC registry is available to the public and, in some cases, is used by CMS to determine reimbursement rates for prescription and over-the-counter products filled in retail community pharmacies. This registry is created by surveying, on a monthly basis, the prices that retail community pharmacies pay to acquire medicines (CMS 2013). We analyzed NADAC files from December 2012, 2013, and 2014, and from July 2015 to identify generic and branded products with the largest price increases. Generic products with multiple NDCs and dosage strengths were excluded from the analysis. The top 50 generic drug price increases ranged from 474% to over 18,000% from December 2012 to July 2015. The top 50 branded drug price increases ranged from 63% to 391% during the same time period. The percentage price difference for the first-in-class drugs versus their me-too analogues ranged from –2.3% to 61,259%. The margin and margin percentage were calculated for claims adjudicated through four major payers.

ABSTRACT

Purpose: To quantify prescription drug price increases over a span of 3 years (2012–2015), as well as extrapolate current reimbursement rates expected by independent retail pharmacies. In addition, we investigate potential reasons for these increasing drug costs.

Design: Descriptive analysis.

Methodology: National average drug acquisition costs (NADAC) data published by the Centers for Medicare & Medicaid Services were examined. Specifically, December 2012, 2013, and 2014, and July 2015 NADAC files were analyzed to identify generic and branded products with the highest percentage price increases. Percentage price differences were also calculated for 17 first-in-class drugs and their “me-too” competitors. The margin and margin percentage were calculated for claims adjudicated through four major payers.

Results: The top 50 generic drug price increases ranged from 474% to over 18,000% from December 2012 to July 2015. The top 50 branded drug price increases ranged from 63% to 391% during the same time period. The percentage price difference for the first-in-class drugs versus their me-too analogues ranged from –2.3% to 61,259%. The margin for generic drug claims adjudicated ranged from –$237.11 to –$1,105.96. The margin for branded drug claims adjudicated ranged from $272.42 to $360.17.

Conclusion: Several potential reasons for the surge in prescription drug prices include manufacturer competition, industry consolidation, and capitalization on me-too drugs. This increase has compelled PBMs, health plan sponsors, and retail pharmacies to find novel ways to turn a profit, often at the expense of the consumer. Although there are no immediate solutions, legislation regulating PBM functions and the use of therapeutic interchange programs may offer health plans some assistance in managing drug costs.
In our analysis, if a medication was successfully adjudicated, the reimbursement payment for the medication was recorded. A medication is successfully adjudicated when a third-party payer approves coverage for a patient and reimbursement is made to the pharmacy filling the prescription. Drugs that required prior authorization were not analyzed. The gross margin (payer reimbursement minus drug cost) and the gross margin percentage (gross margin multiplied by 100) were recorded for each of the four payers. By looking at these values, it is possible to determine which drugs were profitable for an independent dispensing pharmacy in South Florida.

**Generic-drug adjudicated claims**

To conduct our analysis of four payers, we sampled one adjudication for each drug. Seventy of the 73 generic drugs included in our analysis were successfully adjudicated through Optum. The combined acquisition cost of the drugs adjudicated was $8,063.00 and the total amount that Optum reimbursed for the drugs was $6,957.05. The drugs that resulted in a positive margin yielded a total of $369.50 in profits. The drugs that resulted in a negative margin represented a loss of $1,105.95 and a margin percentage of −15.9% was recorded.

Sixty-three generic drugs were successfully adjudicated through CVS/Caremark. The total cost of the drugs adjudicated was $4,899.66 and the gross margin for CVS/Caremark was 7.9%. Overall, the pharmacy’s margin totaled −$1,105.95 and a margin percentage of −15.9% was recorded.

Sixty-seven generic drugs were successfully adjudicated through Medco. Their total cost was $7,912.89. Medco paid $7,675.78 for the adjudicated amount. Forty-five drugs produced a margin of $485.83. The drugs that resulted in a negative margin represented a loss of $922.94. Overall, the margin totaled −$237.11 and a margin percentage of −3.1% was recorded.

Sixty-seven generic drugs were successfully adjudicated through Humana with a total cost of $5,024.71. Humana paid $4,601.67 for the adjudicated amount. The drugs that resulted in a positive margin yielded a total of $405.63 in profits. The drugs that resulted in a negative margin represented a loss of $828.67. Overall, the margin was −$423.04 and the gross margin percentage was −9.2%.

**Branded-drug adjudicated claims**

We used the same process for analyzing branded drugs that we used for analyzing generic drugs, i.e., we sampled one adjudication for each drug. Twenty of the 34 branded drugs were successfully adjudicated through Optum. The cost of the adjudicated drugs was $4,153.78, and Optum paid $4,426.20 for them. The drugs that resulted in a positive margin yielded a total of $359.50 in profits. The drugs that resulted in a negative margin represented a loss of $922.94. Overall, the margin for Optum was $351.87 and the gross margin percentage was 5.6%.

Twenty drugs were successfully adjudicated through Humana with a total cost of $5,928.46. Humana paid a total of $6,280.33 for these drugs. The drugs that resulted in a positive margin yielded a total of $409.25 in profits. The drugs that resulted in a negative margin represented a loss of $57.38. Overall, the gross margin for Humana was $351.87 and the gross margin percentage was 5.6%.

One limitation of this analysis was that all payers required a prior authorization for a large percentage of the branded drugs. This reduced the amount of data that could be analyzed. Nonetheless, taking into account the gross margins for both generic and branded drugs combined, it is evident that reimbursements from the four payers resulted in a cumulative negative gross margin.

**Potential reasons for rising costs**

Drug manufacturers are not limited by price controls and can set prices on their products, depending on potential use and competition, to recover costs (Danzon 2014b). As the patent for a brand-name drug reaches expiration, the drug’s price increases progressively. Within 6 months of being introduced into the market, a generic drug is priced 20%–30% below brand (Morton 2012).

Once several manufacturers produce generic versions of brand-name drugs, two important things happen simultaneously. First, the price for generic drugs erodes dramatically, and second, there is a shift toward the use of these now less-expensive generic drugs, diminishing the use of branded drugs. However, over the past several
# TABLE 1
Price trend of generic drugs, December 2012–July 2015

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Price per unit ($)</th>
<th>Percentage (%) price increase 2012–2015</th>
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<tr>
<td>Tetracycline 500 mg capsule</td>
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</table>
Trends in Drug Costs and Reimbursement

Generic drugs must also demonstrate equivalency, in terms of pharmacokinetic and safety profiles, to their branded counterparts (FDA 2015). Many arguments have been made regarding the benefits, detriments, and worth of me-too drugs in the marketplace. There is some evidence to show that certain patients may respond differently to me-too drugs and, thus, having a surplus of parallel drug choices can aid therapeutic decisions (Eaglstein 2013). Conversely, me-too drugs are thought to lack innovation because they are very similar in structure and function to drugs already on the market (Gagne 2011). Many argue that research-and-development investments would be better served if allocated to disease states that have limited or no treatment options (Gagne 2011). Furthermore, the safety profiles of me-too drugs are often limited (DiMasi 2004). To gain market entry, these drugs must demonstrate “noninferiority” to the current standard of care.

Industry consolidation

The merger of two companies that produce generic drugs can eliminate competition among similar products on the market. This reduced competition can result in price manipulation. One high-profile announcement in the mergers and acquisitions of pharmaceutical companies was the $40.5 billion deal that Teva Pharmaceuticals reached to purchase Allergan (Logan 2015). There have been plenty of other high-profile takeovers in past years. For example, Pfizer reportedly spent more than $219 billion since 1994 in mergers with and acquisitions of rival pharmaceutical companies like Wyeth and Warner-Lambert (Lo 2015). This is one way by which pharmaceutical companies position themselves within the market to sell products for the highest possible margin (Miglierini 2014). An article in Forbes reported that in recent years, fewer and fewer applications have been made to the FDA to gain approval for generic drugs, with industry consolidation cited as a major factor (Why 2015). The resulting dampened competition has allowed prices of drugs to increase for both the payer and consumer (Why 2015).

“Me-too” drugs

The development of “me-too” or “follow-on” drugs has had a significant impact on payers and consumers in the United States. A me-too drug is defined as a drug whose chemical structure or mechanism of action is similar to that of a drug already on the market (Eaglstein 2013). Generic drugs are different from me-too drugs in that they are chemically identical to branded drugs (FDA 2015). Generic drugs must also demonstrate equivalency, in terms of pharmacokinetic and safety profiles, to their branded counterparts (FDA 2015). Many arguments have been made regarding the benefits, detriments, and worth of me-too drugs in the marketplace.

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### TABLE 1

**Price trend of generic drugs, December 2012–July 2015** (continued)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Price per unit ($)</th>
<th>Percentage (%) price increase 2012–2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluocinolone oil 0.01% ear drop</td>
<td>1.20</td>
<td>589</td>
</tr>
<tr>
<td>Erythromycin 2% gel</td>
<td>0.40</td>
<td>578</td>
</tr>
<tr>
<td>Cimetidine 400 mg tablet</td>
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<tr>
<td>Mesalamine 4 g/60 ml kit</td>
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<tr>
<td>Flurazepam 15 mg capsule</td>
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<tr>
<td>Haloperidol 5 mg tablet</td>
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<td>516</td>
</tr>
<tr>
<td>Ofloxacin 0.3% ear drops</td>
<td>0.90</td>
<td>503</td>
</tr>
<tr>
<td>B-complex 100 injection</td>
<td>1.00</td>
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<tr>
<td>Spironolactone/hydrochlorothiazide 25/25 tablet</td>
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<td>Isosorbide dinitrate 30 mg tablet</td>
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<td>Allopurinol 300 mg tablet</td>
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<tr>
<td>Terbutaline sulfate 2.5 mg tablet</td>
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</tr>
<tr>
<td>Clindamycin phosphate 1% solution</td>
<td>0.20</td>
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</table>

Information for this analysis was obtained July 10, 2015, from the National Average Drug Acquisition Costs (NADAC) data published by the Centers for Medicare & Medicaid Services. Nearly every drug listed showed a significant jump in price during the years analyzed. ER=extended release, HCl=hydrochloride.
### TABLE 2
**Price trend of branded drugs, December 2012–July 2015**

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<th>Drug name</th>
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<th>Percentage (%) price increase 2012–2015</th>
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</thead>
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<td></td>
<td>3.90</td>
<td>5.20</td>
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<td><strong>Eurax 10% cream</strong></td>
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<tr>
<td></td>
<td>1.40</td>
<td>1.50</td>
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<td><strong>Neupro 1 mg/24 hr patch</strong></td>
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<td></td>
<td>4.10</td>
<td>4.90</td>
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<td><strong>Exelderm 1% solution</strong></td>
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<td></td>
<td>2.70</td>
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<td><strong>Ulesfia 5% solution</strong></td>
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<td><strong>Ertaczo 2% cream</strong></td>
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<td><strong>Halog 0.1% cream</strong></td>
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<td>3.20</td>
<td>2.30</td>
</tr>
<tr>
<td><strong>Relistor 12 mg/0.6 ml syringe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47.70</td>
<td>95.90</td>
</tr>
<tr>
<td><strong>Horizant ER 600 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.40</td>
<td>4.80</td>
</tr>
<tr>
<td><strong>Leukeran 2 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.50</td>
<td>9.00</td>
</tr>
<tr>
<td><strong>Zyflo CR 600 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.10</td>
<td>17.50</td>
</tr>
<tr>
<td><strong>Apidra Solostar 100 units/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.40</td>
<td>17.40</td>
</tr>
<tr>
<td><strong>Vagifem 10 mcg vaginal tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>9.50</td>
</tr>
<tr>
<td><strong>Denavir 1% cream</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64.30</td>
<td>71.80</td>
</tr>
<tr>
<td><strong>Santyl ointment 250 units/gram</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.90</td>
<td>5.70</td>
</tr>
<tr>
<td><strong>Dipentum 250 mg capsule</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.30</td>
<td>5.60</td>
</tr>
<tr>
<td><strong>Urogesic Blue tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td><strong>Alinia 100 mg/5 ml suspension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.40</td>
<td>1.50</td>
</tr>
<tr>
<td><strong>Patanol 0.1% eye drops</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.00</td>
<td>26.00</td>
</tr>
<tr>
<td><strong>Welchol 3.75 g packet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.10</td>
<td>10.60</td>
</tr>
<tr>
<td><strong>Lantus 100 units/ml vial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.90</td>
<td>16.20</td>
</tr>
<tr>
<td><strong>Vusion ointment 0.25%/15% miconazole with zinc oxide</strong></td>
<td>5.00</td>
<td>5.60</td>
</tr>
<tr>
<td><strong>Cialis 5 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.70</td>
<td>4.40</td>
</tr>
<tr>
<td><strong>Edarbi 80 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.60</td>
<td>3.00</td>
</tr>
<tr>
<td><strong>Levemir 100 units/ml vial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.20</td>
<td>16.30</td>
</tr>
<tr>
<td><strong>Estrace 0.01% cream</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>3.20</td>
</tr>
<tr>
<td><strong>Frova 2.5 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.80</td>
<td>32.80</td>
</tr>
<tr>
<td><strong>Humalog mix 50/50 vial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.70</td>
<td>15.00</td>
</tr>
<tr>
<td><strong>Oxistat 1% cream</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.20</td>
<td>4.70</td>
</tr>
<tr>
<td><strong>Nucynta 100 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.40</td>
<td>3.60</td>
</tr>
<tr>
<td><strong>Azopt 1% eye drops</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.00</td>
<td>12.70</td>
</tr>
<tr>
<td><strong>Multaq 400 mg tablet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.30</td>
<td>5.60</td>
</tr>
<tr>
<td><strong>Lycra 100 mg capsule</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>3.60</td>
</tr>
<tr>
<td><strong>Humulin N 100 units/ml pen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.60</td>
<td>17.10</td>
</tr>
<tr>
<td><strong>Novolog mix 70/30 vial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.00</td>
<td>15.60</td>
</tr>
<tr>
<td><strong>Nasonex 50 mcg nasal spray</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.10</td>
<td>8.20</td>
</tr>
<tr>
<td><strong>Vexol 1% eye drops</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.40</td>
<td>9.10</td>
</tr>
</tbody>
</table>

*table continues*
Trends in Drug Costs and Reimbursement

High-risk drugs

Finally, we analyze the pricing impact of labeling drugs as “high-risk.” In 2012, CMS published a list of drugs that were identified, through evidence-based criteria, as carrying the potential to cause adverse effects in those age 65 or older (CMS 2012). This potential is due to either pharmacologic properties of the drug or inherent physiologic alterations in the elderly (AGS 2012). CMS has mandated restrictions on the use of high-risk drugs in the elderly. These restrictions are the basis for a performance measure, Use of High-Risk Medications in the Elderly, in the National Committee for Quality Assurance’s Healthcare Effectiveness Data and Information Set (HEDIS). This measure is currently being redrafted to reflect the 2015 American Geriatrics Society Beers Criteria and is defined as the percentage of patients older than 65 years of age who are prescribed one high-risk medication and who have received two fills of said high-risk medication (NCQA 2016).

As a result of these performance measures, high-risk drugs are less prescribed by providers, resulting in a decrease in the utilization of these drugs. This decline in utilization has created a downward spiral by reducing drug production (supply) and has driven an increase in the cost of these drugs. Because fewer manufacturers are producing various high-risk drugs, these manufacturers are capitalizing on the continued demand, creating an oligopoly, which has contributed to a rise in drug costs.

Amitriptyline provides an example of this pattern. Because of restrictions on prescribing, fewer companies are making amitriptyline, so the remaining suppliers have more market power and ability to control prices. Considered a high-risk drug in the elderly due to its anticholinergic side effects, amitriptyline increased in price by 2,442% from December 2012 to July 2015 (Table 1). Various approved indications for which this drug proves useful include depression, chronic pain, interstitial cystitis, and migraine prophylaxis. This creates an issue for patients who have been using this

---

TABLE 2
Price trend of branded drugs, December 2012–July 2015 (continued)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Price per unit ($)</th>
<th>Percentage (%) price increase 2012–2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onfi 10 mg tablet</td>
<td>6.00</td>
<td>7.10</td>
</tr>
<tr>
<td>Humulin R 500 units/ml vial</td>
<td>34.40</td>
<td>40.30</td>
</tr>
<tr>
<td>Adcirca 20 mg tablet</td>
<td>23.50</td>
<td>28.20</td>
</tr>
<tr>
<td>Edarbyclor 40/25 mg tablet</td>
<td>2.70</td>
<td>3.10</td>
</tr>
<tr>
<td>Forteo 600 mcg/2.4 ml pen injection</td>
<td>484.50</td>
<td>526.20</td>
</tr>
<tr>
<td>Viagra 25 mg tablet</td>
<td>21.80</td>
<td>25.70</td>
</tr>
<tr>
<td>Premarin vaginal cream-applicator</td>
<td>5.20</td>
<td>6.20</td>
</tr>
<tr>
<td>Premphase 0.625/5 mg tablet</td>
<td>2.80</td>
<td>3.40</td>
</tr>
<tr>
<td>Alocrll 2% eye drops</td>
<td>19.10</td>
<td>24.60</td>
</tr>
<tr>
<td>Nevanac 0.1% droptainer</td>
<td>43.60</td>
<td>46.70</td>
</tr>
<tr>
<td>Zetia 10 mg tablet</td>
<td>4.60</td>
<td>5.30</td>
</tr>
<tr>
<td>Latuda 20 mg tablet</td>
<td>15.10</td>
<td>19.90</td>
</tr>
</tbody>
</table>

Information for this analysis was obtained July 10, 2015, from the National Average Drug Acquisition Costs (NADAC) data published by the Centers for Medicare & Medicaid Services. Nearly every drug listed showed a significant jump in price during the years analyzed. CR=controlled release, ER=extended release.
Drug for several years without significant side effects, and who must now bear the burden of these increased costs. Similarly, digoxin, which has potential for increased toxicity in the elderly due to its narrow therapeutic index, has shown up to a 712% increase in cost over the past 2.5 years (Table 1, Priority 2016, Potentially harmful drugs 2012).

Potential reasons for decreased reimbursement rates

Pharmacy benefit managers (PBMs) serve as middlemen among plan sponsors, drug manufacturers, and retail pharmacies. PBMs’ functions include creating drug formularies, processing pharmacy claims, and negotiating rebates from drug manufacturers (Danzon 2014a). The contract between insurance plan sponsors and PBMs includes the amount the health plan sponsor will pay the PBM for a particular brand or generic drug. At the same time, PBMs negotiate prescription drug prices with retail pharmacies to set the reimbursement rates for each prescription (Florida Senate 2015). PBMs have stirred up a lot of controversy in the pharmaceutical industry because of their handling of manufacturer rebates and reimbursement rates. PBMs have been subject to litigation since 2004 under the Federal Trade Commission Act, which forbids “unfair or deceptive acts or practices in or affecting commerce” (Meador 2011). PBMs have been accused of withholding manufacturer rebates from health plan sponsors. Rebates are given to PBMs in exchange for the placement of certain drugs in a health plan’s formulary. Manufacturer rebates play an important role in determining PBMs’ profit streams, particularly if they are concealed from health plan sponsors. Without rebates being reflected in the final cost of a drug, PBMs can reimburse retail pharmacies at lower rates while charging higher prices to plan sponsors. This is known as spread pricing. The PBM spread is the difference between how much a PBM bills the employer for a drug’s cost and the amount it reimburses a

### TABLE 3
Price comparison between first-in-class and “me-too” drugs

<table>
<thead>
<tr>
<th>First-in-class</th>
<th>Quantity</th>
<th>WAC ($/dose)</th>
<th>Me-too</th>
<th>Quantity</th>
<th>WAC ($/dose)</th>
<th>% price difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil 5% cream</td>
<td>40 g</td>
<td>189.00</td>
<td>Carac 0.5%</td>
<td>30 g</td>
<td>22497.70</td>
<td>1,221</td>
</tr>
<tr>
<td>Zolpidem 10 mg</td>
<td>1000</td>
<td>90.00</td>
<td>Intermezzo</td>
<td>30</td>
<td>249.40</td>
<td>8.30</td>
</tr>
<tr>
<td>Zolpidem 10 mg</td>
<td>1000</td>
<td>90.00</td>
<td>Edluar</td>
<td>30</td>
<td>318.10</td>
<td>10.60</td>
</tr>
<tr>
<td>Risedronate 35 mg</td>
<td>4</td>
<td>198.30</td>
<td>Atelvia 35 mg</td>
<td>4</td>
<td>193.70</td>
<td>48.40</td>
</tr>
<tr>
<td>Bupropion ER 150 mg</td>
<td>250</td>
<td>112.50</td>
<td>Aplenzin 174 mg</td>
<td>30</td>
<td>666.80</td>
<td>22.20</td>
</tr>
<tr>
<td>Paroxetine 10 mg</td>
<td>500</td>
<td>114.20</td>
<td>Pexeva 10 mg</td>
<td>30</td>
<td>274.80</td>
<td>9.20</td>
</tr>
<tr>
<td>Metformin ER 500 mg</td>
<td>500</td>
<td>42.00</td>
<td>Glumetza 500 mg</td>
<td>100</td>
<td>5148.00</td>
<td>51.50</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>120</td>
<td>22.00</td>
<td>Veramyst 27.5 mcg</td>
<td>120</td>
<td>164.00</td>
<td>1.40</td>
</tr>
<tr>
<td>Brimonidine 0.2% 5 ml</td>
<td>5 ml</td>
<td>14.50</td>
<td>Alphagan P 0.1%</td>
<td>5 ml</td>
<td>110.90</td>
<td>22.20</td>
</tr>
<tr>
<td>Cyclobenzaprine 10 mg</td>
<td>500</td>
<td>12.79</td>
<td>Amrix 30 mg</td>
<td>60</td>
<td>1656.00</td>
<td>27.60</td>
</tr>
<tr>
<td>Gabapentin 300 mg</td>
<td>100</td>
<td>26.60</td>
<td>Gralise 300 mg</td>
<td>90</td>
<td>486.90</td>
<td>5.40</td>
</tr>
<tr>
<td>Suboxone SL 8/2 mg generic</td>
<td>30</td>
<td>168.78</td>
<td>Suboxone SL Film 8/2 mg</td>
<td>30</td>
<td>203.00</td>
<td>6.78</td>
</tr>
<tr>
<td>Omnaris</td>
<td>120</td>
<td>193.80</td>
<td>Zetonna 37 mcg</td>
<td>60</td>
<td>205.00</td>
<td>3.40</td>
</tr>
<tr>
<td>Simvastatin 20 mg &amp; niacin ER 500 mg</td>
<td>3.50</td>
<td>Simcor 20/500</td>
<td>90</td>
<td>407.00</td>
<td>4.50</td>
<td>28</td>
</tr>
<tr>
<td>Esomeprazole 20 mg &amp; naproxen 325 mg</td>
<td>7.30</td>
<td>Vimofo 20/375</td>
<td>60</td>
<td>1485.00</td>
<td>24.80</td>
<td>239</td>
</tr>
<tr>
<td>Sumatriptin 100 mg &amp; naproxen 500 mg</td>
<td>1.90</td>
<td>Treximet 85/500 mg</td>
<td>9</td>
<td>625.50</td>
<td>69.50</td>
<td>3,609</td>
</tr>
<tr>
<td>Ibuprofen 800 mg &amp; famotidine 20 mg</td>
<td>0.30</td>
<td>Duexis 800/26.6</td>
<td>90</td>
<td>1485.00</td>
<td>16.50</td>
<td>5,138</td>
</tr>
</tbody>
</table>

1 Wholesale acquisition cost (WAC) pricing and quantity taken from McKesson wholesaler on Sept. 19, 2015. The percentage price difference was reported to demonstrate the difference in price between first-in-class and me-too products. Drugs that do not have WAC and quantity reported are combination products. The price per unit of each combination product was calculated separately and the WAC per dose was reported, which was compared to the respective me-too drug. ER=extended release, SL=sublingual.
pharmacy for that same drug (Garis 2004).

**Markups by PBMs and hospitals**

While PBMs and hospitals actively manage their internal costs, they also look to maximize profits. Thus, their internal cost savings are not always reflected in prices for goods or services charged to payers. PBMs, for example, place a markup on drugs dispensed for their clients, often in the range of $10 to $20 per prescription above the amount paid to the dispensing pharmacies. Similarly, hospitals often mark up the drugs dispensed to their patients.

Hospitals and manufacturing companies often make purchasing contracts that can affect consumers in the long run. To illustrate, a hospital may be able to buy branded rosuvastatin (Crestor; currently, no generic is available) for a lower price than it would pay for atorvastatin, a commonly prescribed generic cholesterol-lowering drug in the same class as Crestor. Thus, these patients’ discharge instructions will include Crestor, which is more expensive when filled in the community than a generic alternative like atorvastatin.

**Florida legislation**

Until 2016, PBMs were not regulated in Florida. In January 2016, however, the new provisions of the Florida Pharmacy Act went into effect that allow monitoring and controlling of PBMs’ activities and contracts (Florida Legislature 2015). The statute sets parameters that PBMs must follow in their contracts with pharmacies. Reimbursement for generic drugs, determined by a fixed maximum allowable cost (MAC), is often incongruent with the real-market prices at which pharmacies acquire these drugs. One of the major contributing factors leading to retail pharmacies being reimbursed below the true cost of drug acquisition was that the frequency of updates to MAC figures had not been regulated. As drug prices increased dramatically, pharmacies continued to be reimbursed based on outdated MAC lists. A new provision in the Florida law requires the update of MAC lists at least once every week, maintaining consistency between time-sensitive pricing information and the lists.

**Managing drug costs**

Historically, pharmacists in different settings have used a variety of tools to control costs. Chain pharmacies have developed automated systems to identify the lowest-cost (highest profit) manufacturing sources, particularly for generic drugs. Independent pharmacies generally have no tools to manage their costs other than to join a purchasing group. Self-insured employers also typically have no internal capability to manage drug costs and are completely at the mercy of their third-party administrator and PBM. In the hospital environment, formularies, drug budgets, and group-purchasing contracts are used to garner high discounts on pricing. PBMs also use formularies as well as prior authorization requirements and manufacturer rebates to keep costs low.

Another way health plans and PBMs manage drug costs is through the use of therapeutic interchange programs (TIPs).

**CONCLUSION**

Within the past decade, the cost of prescription drugs has increased substantially. This increase has had a significant effect on reimbursements made by health plan sponsors, often resulting in retail pharmacies being reimbursed below the cost of medications. Potential reasons for this surge in prescription drug prices are manufacturer competition, industry consolidation, the identification of high-risk medications for the elderly by CMS, and industry capitalization on me-too drugs. This increase has compelled PBMs, health plan sponsors, and retail pharmacies to find novel ways to turn a profit, often at the expense of the consumer. Measures must be put in place to fix the dichotomy between escalating drug prices and payer reimbursement rates. These measures should create equitable reimbursements for medications as this will be beneficial for consumers in the long run and prevent more independent pharmacies from going out of business. Although there are no immediate solutions for rising prescription drug costs, legislation regulating PBM functions and the use of TIPs may offer some leeway in managing drug costs.

**REFERENCES**

Trends in Drug Costs and Reimbursement

Gagne JJ. How many “me-too” drugs is too many? *JAMA*. 2011;305(7):711–712.


Top pharmacists see rising prices, doubt fast takeoff for other trends

Drug prices will rise at least 5% annually from now until 2020, according to a survey of top pharmacists in the United States. In fact, 89% of the 134 pharmacists* who responded to the survey by the American Society of Health-System Pharmacists called this possibility "very likely," the highest percentage for that response to any of the 56 survey items.

The survey, which was conducted last summer, asked these pharmacists about the likelihood of 56 trends in health care and pharmacy reaching certain levels in their region by 2020.

For example, 76% thought it very likely that health systems will review at least one biosimilar for addition to their formulary sometime in the next four years, and 54% thought it very likely that three quarters of the health systems in their region will experience an increase of at least 25% in the use of antiviral therapy for hepatitis C.

The idea that the price of drugs should be tied to outcomes may be gaining some traction, but these health system pharmacists are skeptical about it catching on fast in chemotherapy. Only 15% thought it very likely that pricing of new chemotherapy agents will be pegged to the success rate in clinical trials, although an additional 52% gave that possibility the lukewarm “somewhat likely” rating. However, 41% thought 75% of the health systems in their area will have risk-sharing arrangements with payers by the end of the century’s second decade.

Despite the enthusiasm for biomarkers and genomic testing, only 10% of the surveyed pharmacists thought it very likely that health systems will make treatment recommendations based on pharmacogenomic information at the point of care. “Point of care” may be an important qualifier here, because past surveys have shown that pharmacists foresee pharmacogenomic testing being done by at least one academic medical center in their region.

How likely is it that the following will occur by the year 2020 in the geographic region where you work?

<table>
<thead>
<tr>
<th>Health system expenditures for all medications will increase by at least 5% annually.</th>
<th>At least 50% of health systems will partner with low-cost providers for some activities that traditionally have been conducted directly by the health system (e.g., chemotherapy infusion, diagnostic imaging, clinical laboratory).</th>
<th>Pharmacists in at least 50% of health systems will make treatment recommendations based on pharmacogenomics information at the point of care.</th>
<th>At least 90% of health systems will review at least one biosimilar product for formulary addition.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>89%</strong></td>
<td><strong>46%</strong></td>
<td><strong>76%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very likely</strong></td>
<td><strong>Very likely</strong></td>
<td><strong>Very likely</strong></td>
<td></td>
</tr>
<tr>
<td><strong>11%</strong></td>
<td><strong>18%</strong></td>
<td><strong>10%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Somewhat likely</strong></td>
<td><strong>Somewhat likely</strong></td>
<td><strong>Somewhat likely</strong></td>
<td></td>
</tr>
<tr>
<td><strong>0</strong></td>
<td><strong>2%</strong></td>
<td><strong>41%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very unlikely</strong></td>
<td><strong>Very unlikely</strong></td>
<td><strong>Very unlikely</strong></td>
<td></td>
</tr>
<tr>
<td><strong>0</strong></td>
<td><strong>14%</strong></td>
<td><strong>20%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very unlikely</strong></td>
<td><strong>Very unlikely</strong></td>
<td><strong>Very unlikely</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Leaders of the American Society of Health-Systems Pharmacists selected 159 pharmacists to be surveyed. They were picked because of their expertise in health system pharmacy practice, knowledge of trends, and ability to analyze the future of pharmacy practice. The response rate to the survey was 84%.

Source: American Society of Health-System Pharmacists, “Pharmacy Forecast,” December 2015
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