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Value Now, Not Just Cost............... 39

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CO V E R S T O R Y

Twilight for Fee for Service?  
Long criticized for fostering volume over value, fee for service may be nearing extinction, but vestiges are likely to remain for many years. After all, birds are dinosaurs.

Q&A With Health Care Economist David Cutler  
The current slowdown in cost increases need not be an anomaly, says the Harvard professor and presidential campaign adviser.

FOCUS ON BIOLOGICS

Health Reform Steers Discussion Toward Value  
The ACA is changing payers’ business models.

PIPELINE: Immunomodulatory Research Advances  
Rheumatoid Arthritis Care Turns a Corner  
Biomarkers will improve management of this disease.

Minimal Disruption for Maximum Results  
If physicians and clinician executives at plans sometimes feel overwhelmed by medicine's complexity, think of how patients must feel.

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Communicate. Connect. Rule your world.
Fee for Service Is Going Down, Slowly and Maybe Not Entirely

By John Marcille

We die from the moment of birth, and even the ground we walk upon has a beginning and — the physicists (or is it cosmologists?) tell us — an end that we won’t witness. The fee-for-service (FFS) payment system spins on the circle of life, as well.

It has been dying for an awfully long time, as our cover story on page 21 notes. Will we ever see the end of FFS? It won’t happen this year, or maybe even this decade, but little engines of change rev throughout the health care system.

The accountable care organizations and patient-centered medical homes that the Affordable Care Act promotes try to push FFS to the side. Can they? Contributing Editor Joseph Burns notes FFS’s stubborn refusal to go. It is entangled with the Current Procedural Terminology system, for one thing. And most health plans lack the information systems needed to sustain whatever might replace FFS. Contracts with thousands of provider groups would need to be rewritten.

The Catalyst for Payment Reform, an organization headed by Suzanne F. Delbanco, PhD, says that only 11% of payment to providers is not FFS. It “might be at 13% in the next year or two,” says Jim Evans, a McKesson consultant.

Still, are there not some health care operations where FFS makes sense? What if an asteroid hadn’t ended the age of dinosaurs? What if they just decided to not show up for work one day? The Centers for Medicare & Medicaid Services reports that nearly 10,000 physicians opted out of Medicare, which is mostly FFS, in 2012, more than twice the number of doctors who had made that same decision in 2009.

Physicians have long bristled at CMS’s now-you-don’t-see-it, now-you-do pay raises. This time looms the threat that Medicare payments might be slashed by about 25% next year. Congress might step in again, but doctors tire of the game.
Specialty pharmacy got its name, in part, because unique medications were approved for use in special situations — for rare diseases or for use only after failure of traditional therapy.

In some ways, health plans have created an impression that specialty biologics and high-cost medications are out of reach by limiting access to them through formulary design and utilization management policies. Unfortunately, such policies designed to ensure appropriate use and control costs may have damaged the image of health plans in the eyes of patients and physicians.

Effect of scientific discovery

The special status and limited role of specialty medications is changing. They are being used much earlier in the course of treatment for certain diseases. Drugs that were approved as second-line therapy are now receiving approval for new indications as first-line agents, and some drugs are receiving FDA approval for multiple conditions. Variations in the prescribing patterns and therapy regimens of individual physicians also add to the expanded use of specialty products.

For health plans, the implication is that they need to remain or become more diligent in managing these products. Some health plans, such as UnitedHealthcare, are stepping up efforts to keep pace with the expanded use of specialty drugs.

“I am seeing expanding use of biologics in certain disease states,” says Atheer Kaddis, PharmD, senior vice president at Diplomat Specialty Pharmacy. “In cancer, which is difficult to treat and where therapy varies greatly, we are seeing that drugs originally used as second-line therapy are being used much sooner. For example, this is happening with Afinitor and Tarceva, which were originally recommended as second-line therapies. We now see them used as first-line therapies.”

In some cases, like the cancer drug Tarceva, the movement from second- to first-line therapy is the result of scientific and technologic advances. Tarceva is a tyrosine kinase inhibitor approved in 2004 for second-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of at least one chemotherapy regimen.

In it original 2004 trials, epidermal growth factor receptor (EGFR) mutations correlated with response to Tarceva, but the exact details of this association were not known. Tarceva lengthened survival in the EGFR-positive subgroup and the subgroup whose EGFR status was unmeasured, but it did not appear to affect survival in the EGFR-negative subgroup.

The results and confidence levels for the various groups were wide and overlapped so that a survival benefit in the negative subgroup could not be excluded. Therefore, the drug was approved without any restriction for EGFR status.

Between 2005 and 2010, Tarceva received additional approvals for pancreatic cancer and second-line maintenance treatment for NSCLC that had not progressed after first-line chemotherapy.

Last May, Tarceva was approved for first-line treatment of patients with metastatic NSCLC with one of two EGFR mutations. This approval erased the second-line requirement in the 2004 approval. In the two covered mutations, Tarceva showed progression-free survival of 10.4 months compared with 5.4 months for patients who received chemotherapy.

Tarceva’s latest approval was made possible by advances in molecular diagnostics and the FDA’s process for the timely development and approval of companion diagnostic tests. The FDA’s first-line designation requires the use of a genetic test that was approved by the FDA.
specifically to identify the two mutations. Often in oncology, says Kaddis, “The advances in specialty agents cause them to be used first-line. In many cases, they have demonstrated benefits over the previous first-line therapies.”

Zytiga is another example of a specialty medication that trumped earlier drugs. It is an oral oncolytic approved in 2011 for treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) after failure on the first-line agent, docetaxel.

Last December, following the release of results from a second clinical trial, Zytiga received approval as first-line therapy for mCRPC. In this study, Zytiga significantly extended overall survival and progression-free survival.

“This approval demonstrates the benefit of further evaluating a drug in an earlier disease setting and provides patients and health care providers the option of using Zytiga earlier in the course of treatment,” said Richard Pazdur, MD, in the FDA’s announcement.

**Early use**

Specialty products are being used more for other diseases as well. “In the case of inflammatory diseases and TNF inhibitors, there is increasing use as first-line therapy for Crohn’s disease, psoriasis, and ulcerative colitis,” says Kaddis. “The idea of stepping through successive traditional agents and corticosteroids has gone by the wayside. Some individuals diagnosed with mild Crohn’s now receive biologic therapy earlier.”

The trend in inflammatory diseases is to achieve remission as soon as possible. That requires rapid assessment of the effect of initial therapy and escalation of therapy if progress is not made. In Crohn’s disease, guidelines say that corticosteroids are first-line treatment and may be followed by biologics such as Humira and Cimzia if progress is not evident.

The treatment of hepatitis C has been turned on its head by two new specialty products. “Prior to mid-2011 the recommended treatment was a combination of a pegylated interferon and ribavirin, then came the protease inhibitors, and they immediately changed the recommended therapy,” says Kaddis. “Now a patient with hepatitis infection is put on triple therapy including pegylated interferon, ribavirin, and a protease inhibitor, either Victrelis or Incivek.”

Therapy guidelines for hepatitis C recommended triple therapy almost immediately after the release of the protease inhibitors. The Express Scripts 2013 Drug Trend Report says that in 2012, the utilization of specialty medications for hepatitis C increased by 29% — driven almost entirely by Victrelis and Incivek.

**Keeping pace**

Health plans face a challenge in keeping up with early use of specialty drugs that may be becoming the standard of care.

“One might think that health plans have the advantage of monitoring claims so that they can see changing treatment patterns in the use of specialty drugs, such as early treatment, but that is not necessarily the case,” says Brian Solow, MD, chief medical officer at OptumRx, UnitedHealthcare’s in-house PBM.

While health plans and PBMs are working to capture complete, accurate, and timely claims information, there are many holes in the process that are beyond the control of health plans, starting with pharmacies submitting claims.

“One of the biggest challenges that managed care organizations have is understanding the course of treatment at the level of the individual patient,” says Kaddis.

“In many cases, it’s difficult to coordinate and track use of conventional drugs under the pharmacy benefit and biologics under the medical benefit. That means it’s difficult to track evolving patterns in the course of therapy for diseases with specialty drugs.”

The data-analysis approach may not be the answer. “I don’t think tracking claims is the way to go,” says Brian Solow, MD, CMO of OptumRx. He doesn’t want to merely respond after the fact.

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An option to help protect your members from relapse

Once-monthly Abilify Maintena has demonstrated it can significantly delay the time to relapse vs placebo for up to 1 year* ($P<0.0001$).

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

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

INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena™ (aripiprazole) for extended-release injectable suspension

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

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

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

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

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

Continued on next page.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on the following pages.
**FOR THE TREATMENT OF SCHIZOPHRENIA**

An option to help protect your members from relapse

Once-monthly Abilify Maintena has demonstrated it can significantly delay the time to relapse vs placebo for up to 1 year* \((P<0.0001)\).

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

**IMPORTANT SAFETY INFORMATION**

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

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

Continued on next page.

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

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

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

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

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

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

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

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

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

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to the increase in central nervous system (CNS) temperature regulatory activity. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

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

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

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

Most commonly observed adverse reaction: The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. Changes in appetite and weight were not observed with oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections; the incidence of adverse reactions was similar between the two treatment groups. The average reaction grade 5% incidence and at least twice the rate of placebo for oral aripiprazole and the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole was: weight gain (14.7% vs. 25.0%). Body weight for extended-release injectable suspension for intramuscular use.

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

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

Injection Site Reactions: In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena and 2.1% for aripiprazole.

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

Pregnancy/Nursing: Based on animal data, may cause fetal harm. Ciprofloxacin should be used during pregnancy only if clearly needed. Data from clinical trials do not establish a risk of fetal harm for extended-release injectable suspension.
IMPORTANT SAFETY INFORMATION for Abilify Maintena™ (aripiprazole) for the treatment of schizophrenia (continued)

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

1. Hyperglycemia/Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoadiposis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes mellitus should be monitored for worsening of glucose control those with risk factors for diabetes and those who develop under baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continued treatment of the hyperglycemia.

2. Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between the aripiprazole- and placebo-treated patients in the proportion of patients with normal triglyceride levels, fasting LDL cholesterol, or HDL cholesterol. These changes may become apparent early in the course of aripiprazole treatment, and they may persist for several weeks after dosage reductions are not advised for patients with diabetes mellitus.

3. Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored daily during the first few days of treatment and at least weekly thereafter. If a patient develops signs of infection (e.g., fever, sore throat, malaise, or localized infection), their complete blood count should be evaluated. Any granulocyte count below 1000/mm3 should prompt immediate consultation with a hematologist. Patients with abnormal WBC counts should discontinue treatment with aripiprazole.

Seizures/Convulsions: Aripiprazole may be used in patients with a history of seizures or with conditions that lower the seizure threshold.

Pregnancy/Nursing: Based on animal studies, adverse effects on the fetus may occur due to antipsychotic drugs administered to pregnant women. If aripiprazole use is necessary, aripiprazole must be administered with great care in women of childbearing potential.

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

Briefer Summary of Prescribing Information

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION, including Boxed WARNING, on adjacent pages.
and for which the incidence in patients treated with aripiprazole was greater than the incidence in therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those (aripiprazole 8%; placebo 4%).

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day, increased maternal body weight gain, prolonged gestation, and an increase in days to weaning were observed. In a separate study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day, decreased fetal body weight and increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which was associated with maternal toxicity. Consequently, Aripiprazole is not recommended for use in pregnant women during the first trimester of pregnancy unless the potential benefit justifies the potential risk to the fetus.

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during organogenesis, decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

In pregnant rats treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day during organogenesis, fetal abnormalities and decreased fetal body weight were observed. In a separate study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day, skeletal abnormalities, i.e., cleft palate, were observed at the highest dose, which was associated with maternal toxicity. Consequently, Aripiprazole is not recommended for use in pregnant women during the first trimester of pregnancy unless the potential benefit justifies the potential risk to the fetus.

In pregnant women receiving aripiprazole, the drug is distributed to the breast milk. In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day during pregnancy, the highest dose also caused some maternal toxicity. Consequently, Aripiprazole is not recommended for use in pregnant women during the first trimester of pregnancy unless the potential benefit justifies the potential risk to the fetus.

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patients treated with placebo in the combined dataset. Adverse reactions that occurred in 2% or more of patients treated with oral aripiprazole (doses ≥2 mg/day) are shown in Table 4. The pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute trials was akathisia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia.

Commonly Observed Adverse Reactions of Oral Aripiprazole:

- Sedation
- Tremor
- Gynecomastia

Possible risk factors for gynecomastia/priapism include pre-existing low blood cell count, chronic kidney disease, and concomitant use of steroids or selective serotonin reuptake inhibitors (SSRIs). In the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients, the exposure of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight ossification were seen at the highest dose, which also caused some maternal toxicity.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole: Aripiprazole is highly protein bound in plasma and has a large apparent volume of distribution (2400-3000L). The drug is predominantly metabolized in the liver by cytochrome P450 (CYP) enzymes, mainly CYP 2D6 and CYP 3A4. In rats and rabbits at doses 1-10 times the oral maximum recommended human dose (MRHD) of 30 mg/day based on mg/m 2 body surface area. ABILIFY MAINTENA should be used only in patients for whom oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of infection. In patients with severe neutropenia (absolute neutrophil count <1000) and those with a history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant decrease in WBC of 2.0-4.9 x 10^9/L, ABILIFY MAINTENA should be used only if the benefit outweighs the risk. ABILIFY MAINTENA is contraindicated in patients with a history of leukopenia or neutropenia.
Knee osteoarthritis (OA) is a degenerative disease with primary and secondary types and is one of the five leading causes of disability among noninstitutionalized adults. OA is believed to affect the cartilage, and pathophysiologic changes also occur in the synovial fluid, the joint capsule, and underlying bone over time. Treatments focus on relieving symptoms and improving mobility. When conservative treatments (e.g., nonsteroidal anti-inflammatory drugs, physical and/or occupational therapy, weight loss for overweight or obese patients) fail to provide sufficient relief, any of several minimally invasive treatments are typically offered (autologous [i.e., self-derived] mesenchymal stem cell [MSC] injections, arthroscopic debridement, microfracture, osteochondral autograft, chondrocyte or platelet-rich plasma injections, or polymer spacers/synthetic scaffolds). This report focuses on autologous MSC injections.

Methods of obtaining and preparing autologous MSCs vary widely. The amount of manipulation and whether other agents are added to the mix determine how the FDA classifies them and whether they are subject to regulatory approval processes. Clinicians collect MSCs from the patient’s anterior superior iliac crest or stromal vascular fraction (i.e., adipose tissue) and process the cells in one of three manners: 1) isolating and expanding MSCs in a laboratory before reimplantation to the patient’s knee a few weeks later; 2) adding growth factors, antibiotics, or proprietary supplements to MSCs before reimplantation; 3) collecting and isolating MSCs by gradient centrifugation, and then reinjecting the concentrated MSCs into the patient during the same visit (i.e., no expansion or culturing and not subject to FDA regulation).

Several problems can arise when MSCs are cultured outside the body, including having a suitable culture medium for MSC growth and differentiation. Reported processes have involved use of fetal bovine serum, human serum, and/or other growth factors; however, animal-derived products can trigger severe immunologic responses (i.e., anaphylaxis) when the cultured MSCs are reimplanted into the patient. Among other risks is the potential for viral or bacterial transmission through contaminated cell media supplements. Some MSC culturing processes may add antibiotics to prevent infection, which could also trigger anaphylaxis. Other risks include unanticipated transformation of MSCs, potentially leading to cancer or differentiation into an undesired type of cell, such as osteocytes (bone) or cartilage upon reinjection into the patient. The mechanism by which MSCs lead to bone or cartilage formation is unclear at this time.

Regulation

FDA categorizes therapeutic stem-cell-based products as human cells, tissues, and cellular and tissue-based products, including those intended for implantation, transplantation, infusion, or transfer into humans. Whether autologous MSCs are subject to FDA regulatory approval processes depends on the amount of cell manipulation. Some centers offering the procedure collect, concentrate, and reinject MSCs into the patient the same day without adding other agents. FDA considers processes that include culturing, expanding, and adding growth factors or antibiotics to be significant manipulations that require regulation. Some companies and clinicians have countered that the activity reflects the "practice of medicine"
and not development of a new drug or biologic because processing of a patient’s MSCs is individualized for that patient. However, in July 2012, the U.S. District Court for the District of Columbia ruled in a case brought by FDA against Regenerative Sciences, Inc. (Colorado, USA) that \textit{ex vivo} expansion and manipulation of autologous MSCs exceeded minimal processing and was subject to FDA regulation. The court granted FDA a permanent injunction preventing the company from making its product unless it completes the required regulatory approval processes. According to a later report in the Wall Street Journal, the company moved some of its clinical operations to the Cayman Islands to enable continued patient access to the therapy. Another company, CellTex Therapeutics Corp., received an FDA warning about its autologous MSC product and has indicated it will conduct clinical trials to seek regulatory approval. No U.S. companies have yet received FDA approval for any autologous MSC therapy.

The International Society for Stem Cell Research (ISSCR) published \textit{Guidelines for the Clinical Translation of Stem Cells} (which includes MSCs) in 2008 and emphasizes that “processing and manufacture of any cell product should be conducted under expert, independent review and oversight, to ensure as much as possible the quality and safety of the cells.” ISSCR recommends that diffusion of these products not occur outside the context of well-designed and -conducted clinical trials. Seven ongoing studies — one of which is a U.S. study — continue to assess the feasibility and safety of autologous MSCs for OA.

**Key questions and findings**

1. \textbf{How does autologous MSC implantation compare with other OA treatments (i.e., for reducing time to next intervention or to partial- or full-knee replacement, reducing pain, improving range of motion, improving function, increasing articular cartilage volume, and quality of life [QOL])?}

Five low-quality nonrandomized retrospective and prospective controlled studies reported on 266 patients (Koh et al. 2012; Lee et al. 2012; Nejadnik et al. 2010; Varma et al. 2010; Wakitani et al. 2002). Each study compared MSCs with a different minimally invasive treatment. Study design weaknesses (e.g., lack of control for important patient variables in the study groups, lack of statistical analyses, incomplete reporting) and the absence of data for many outcomes prevent effective comparison of the efficacy of MSC with that of other minimally invasive treatments for relief of pain, and improving range of motion, knee function, QOL, and other outcomes.

2. \textbf{What adverse events (AEs) are reported in studies of autologous MSCs, and how do AEs reported with autologous MSC implantation compare with AEs reported for other surgical treatments for OA?}

Three of the five studies (Koh et al. 2012; Nejadnik et al. 2010; Wakitani et al. 2002) provided AE data on 146 patients; no comparative data were provided. Reported AEs were minor pain, swelling, and a second intervention in one case.

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Breakthrough Drug Category Demands More Communication
The FDA wants to significantly shorten the development time for new medications by cutting years out of the R&D process

By John Carroll

The FDA has several regulatory avenues mapped out for the most promising new drugs in the pipeline. A favored therapy can be put on the agency’s fast track, offered an abbreviated priority review, and occasionally provided an accelerated approval. But it’s the agency’s new “breakthrough drug” (BTD) designation that’s all the rage these days in drug development circles.

Congress included the breakthrough drug designation in the 2012 Food and Drug Administration Safety and Innovation Act, an olive branch for an industry that was required under the Affordable Care Act to offer discounts for drugs used by Medicare and was charged hundreds of millions of dollars in added fees.

The rule of thumb in biopharma, spelled out in studies undertaken by the Tufts Center for the Study of Drug Development, is that it takes 10 years and a billion dollars to get a new therapy through all stages of drug development.

That’s a controversial bottom line — debated endlessly among industry critics and supporters. But an uncontested drought of new drug approvals between 2000 and 2010 prompted lawmakers to demand that the FDA commit itself to an open-door policy for the leading experimental drugs that offer a pioneering approach that could transform the treatment of serious diseases.

Breakthrough drug programs will require a “different communication structure,” FDA oncology chief Richard Pazdur promised a large group of cancer researchers recently, “with much more of a continuous dialogue with sponsors.”

While it’s still early in the game, the FDA’s initial moves have clearly signaled that the rules have changed for these drugs. The intention is to significantly shorten the development time line for some drugs, with a goal of cutting years out of the R&D process and restructuring marketing time lines for pharma managers at health insurers who will now need to red-flag fast moving therapies in the clinic.

Carving out Phase III

Under the new regulations, agency officials are vowing to provide monthly internal reviews to help guide companies, offering pointers on adapting clinical trial designs, perhaps, to hammer out a more efficient path to endpoint data. Developers should also find ready help qualifying a drug’s manufacturing process or even coming up with an acceptable commercial name.

But the single biggest opportunity for drug developers is getting a green light to potentially land a new drug approval at the FDA ahead of the big, long Phase III study that has dominated drug development efforts for decades. Under this new scenario, a drug could gather enough data in a relatively small study using surrogate endpoints — perhaps a biomarker that can be substituted for a traditional clinical endpoint like overall survival rates — for an approval, with the long-term Phase III conducted after the therapy arrives on the market.

In a matter of months, the FDA has handed out 17 publicly discussed breakthrough designations, almost all within the 60-day period the law allows for a decision. It’s still the early days in the process. As of the end of July, no BTD had won marketing approval, but the first wave of these drugs says a lot about which treatments are likely to get green-lighted for the regulatory short cut.

All but one of these first-year drugs are either entirely owned by a big pharma company or a large biotech organization. Small developers flying solo have largely been excluded from this first round, though the agency says there is no bias based on company size. And the biggest
initial effect is likely to be felt in the oncology market, while diseases like diabetes, where the FDA has insisted on very high safety standards and huge Phase III studies, are not covered.

**Impressive survival data**

Almost half of these breakthrough drugs are for cancer. One of them, ibrutinib from Pharmacyclics and Johnson & Johnson, has won a record three BTD designations. The drug is designed to inhibit the enzyme Bruton tyrosine kinase, and has produced some impressive survival data for patients with B-cell malignancies. In early July it was submitted to the FDA for chronic lymphocytic leukemia/small lymphocytic lymphoma as well as previously treated mantle cell lymphoma.

The breakthrough drug designation “allowed us to focus and optimize the use of Phase II data for registration,” says Urte Gayko, PhD, Pharmacyclics’ senior vice president for regulation and a 16-year veteran in the field. That has helped shorten the new drug application process by seven to nine months.

The scientific understanding of how many of these new targeted cancer drugs work — both through improved safety profiles as well as enhanced survival times — has clearly benefited a whole wave of cancer therapeutics which stand to benefit from the new classification.

Carving a few months — or a few years — out of the development timeline is a big deal in the industry. Ibrutinib helps illustrate just how big a deal it is.

After it bought Celera, Quest Diagnostics wound up with a mid- to high-single-digit royalty interest in the drug. It just sold that royalty stream for $485 million, more than it paid for Celera, leaving some analysts to speculate the deal was based on expected peak sales of $6 billion to $7 billion a year. At the high end, a single extra month’s revenue would be worth about $600 million.

“He need to try to expedite,” says Jenkins, “see if there are places where we can be more open to approve something other than commercial manufacturing. That can come later,” provided that the FDA “thinks that process can assure the integrity and quality” of the therapy. But he emphasizes that this aspect of the breakthrough process is still being hammered out.

Jenkins says the agency is disease-agnostic when it comes to handing out these designations, but adds that the FDA already has plenty of experience at speeding up approvals for oncology therapies, where single-arm (without a control group) trials may be more welcome than in disease fields that require large numbers of patients for testing.

**How good are the data?**

The FDA’s primary concern is how good the data are, he adds, not the size of the company. And these drugs promise to quickly dominate the disease niche they’re targeted at — even without some of the advanced pharmaco-economic studies that payers are demanding more and more often.

“Not all of these breakthrough drug designations are at the same stage,” says John Jenkins, director of the FDA’s Office of New Drugs. “Some are pretty much done,” leaving the agency only limited opportunities to find a shortcut to an approval.

Others, such as Merck’s early-stage cancer immunotherapy lambrolizumab, are still in Phase I and Phase II, and there the agency promises to make a real impact.

Not only can the FDA provide developers some clear ideas about smaller trials or surrogate endpoints that could pave the way to a fast approval, but there’s also the prospect of a shortcut on the manufacturing path.

Typically, the FDA requires drug developers to prove that they have a full-fledged manufacturing process in place ahead of marketing approval, with approved facilities ready to produce commercial quantities. A breakthrough drug, though, could find ways to an inside track that would rely on a developer’s proven ability to produce clinical trial drug quantities, with the more burdensome hurdle held in abeyance.

How good are the data?
EHR Adoption Advances, But With Too Many Kinks

At least 40% of office-based physicians have a basic electronic health record (EHR) system, but they are unable to do some of the functions necessary for meeting stage 1 of the federal meaningful use objectives, according to a report by the Robert Wood Johnson Foundation (http://tinyurl.com/RWJ-report).

There are 15 core objectives in stage 1 that must be met in order for the government to underwrite up to $44,000 in new technology costs per physician (http://tinyurl.com/use-report).

The authors surveyed 172 hospitals and physician groups between August and November 2012.

About half of the physicians say that they find it very difficult, somewhat difficult, or basically impossible to “generate lists of patients by lab results or need for overdue care, track referrals, or [generate] reports on quality of care.”

However, physicians who did meet the standards “were more likely to report that panel management functionalities were easy to use compared to physicians who did not meet the objectives.”

The three stages for implementing meaningful use standards are:

- 2011–2013: collect and share data
- 2014–2015: implement advanced clinical processes
- 2016 and after: improve patient outcomes

“In 2012, 40% of office-based physicians had adopted at least a basic EHR,” the survey says. “These physicians were most likely to be primary care physicians in a practice of 11 or more physicians owned by a hospital, academic medical center, health maintenance organization, or other health care organization in rural places.”

Wellness Benefits Not in the Mind

Wellness is as wellness does, to coin a phrase that probably can’t stand on its own but means in this instance that workers get out of a program what they put into it.

So much for the obvious. What’s new in a study in the American Journal of Health Promotion is that the positive effects of wellness programs on mental health are negligible at best.

That study, “Is Usage of a Wellness Center Associated With Improved Quality of Life?”, says that “a wellness center can improve physical health and has limited or no effect on maintaining mental health.”

Researchers at the Mayo Clinic measured quality of life (QOL) for about 1,100 members of a wellness center from September 2008 through December 2009.

Even for those who used the centers the most and got the most physical benefit as a result, the mental health benefits were practically nonexistent, and they actually declined for those who used the centers the least, from 51.4% to 34.5%.

The authors have some suggestions.

“The benefits of physical activity are well established, but perhaps to fully affect mental QOL, wellness centers need to offer a wide range of strategies for spirituality, stress reduction, sleep, social support, relationships, career advancement, and financial planning.”

Pediatric Care Hurt By Language Gap

Insurers should help pediatricians bridge the language gap with patients who have little or no proficiency in English, say researchers measuring the use and effectiveness of translators.

“Reimbursement for language services by private insurance companies is not currently mandated, except in California, and few private insurance companies provide reimbursement,” say the authors of “Changes in Language Services Use by U.S. Pediatricians,” published in the journal Pediatrics.

The study compares data from 2004 and 2010 for 700 pediatricians and finds that there has been just a slight increase in the proportion of doctors using formal interpreters, from 50% to 56%.

Most pediatricians rely on what the authors call “suboptimal communication methods,” meaning, for the most part, patients’ family members.

While use of that method fell from 70% to 57%, that’s still too much, say the authors.

“Despite continued growth of the U.S. population with limited English proficiency, there has been only modest improvement over time in pediatricians’ use of language services,” the study states.

The use of telephone interpreters increased significantly between 2004 and 2010 in states with high growth of the Latino population.

“Telephone interpretation may be a practical necessity when the supply of in-person interpreters is low or when [limited-English-proficiency] patients or specific language groups are uncommon.”

Respondents said that the most common languages in which interpreters are needed are Spanish (92%),
Chinese (13%), and Vietnamese (6%).

“A key policy implication of our work is that reimbursement for language services may be an important mechanism for enhancing access,” says the study.

**Briefly noted**

*UnitedHealthcare* seems to be jumping onto the accountable care bandwagon in a big way. The insurer says it plans to increase payment to providers through contracts linked to quality and cost-efficiency to $50 billion by 2017. “Our unparalleled experience with accountable care models — and there are many — demonstrates that they can work better for everyone in health care, from patients to payers to care providers,” says Austin Pittman, the president of UnitedHealthcare Networks....

Meanwhile, *WellPoint* **must** pay a fine of $1.7 million for exposing the personal information of over 600,000 beneficiaries because an online application database could be hacked. WellPoint informed those who may have been affected and beefed up online security. The hacked data includes names, birthdates, addresses, and Social Security numbers....

You can **knock yourself silly** exercising but that doesn’t necessarily mean you’ll lose weight, according to researchers at the University of Washington. Even though Americans are exercising more, the obesity epidemic continues to grow. We still consume more calories than we burn off, says the study’s senior author Ali Mokdad, PhD, at the university’s Institute for Health Metrics and Evaluation....

**Americans are living longer** but not necessarily more happy lives compared to other countries. A study of health statistics in 34 countries published recently in the *Journal of the American Medical Association* shows that rates of substance abuse, psychiatric disorders, and muscle and joint pain all increased in the United States in the last 20 years. Life expectancy in the U.S. increased from 75.2 in 1990 to 78.2 in 2010.

— Frank Diamond

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**Childhood asthma rates rise**

About 14% of children in the United States were diagnosed with asthma in 2011, according to the National Center for Health Statistics. That continues a trend of growing childhood asthma rates, though there is a caveat. “Between 1980 and 1995, childhood asthma more than doubled, to 8%. Methods for measurement of childhood asthma changed in 1997, so earlier data cannot be compared to data from 1997–2011.”

The statistics were published in the report “America’s Children: Key National Indicators of Well-Being, 2013” (http://tinyurl.com/CDC-children).

The main thrust of the report is that nearly a quarter of children in the United States live in poverty, affecting their safety, education, and health. Exacerbating the situation is the fact that many children with asthma lack health insurance.

The report also says that about 10% of children in 2011 had asthma and that 5% of all children had one or more asthma attacks in the previous year.

**Percentage of children up to age 17 with asthma, 1997–2011**

<table>
<thead>
<tr>
<th>Year</th>
<th>Ever diagnosed with asthma</th>
<th>Currently have asthma</th>
<th>Having at least one asthma attack in past year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>9.5%</td>
<td>5.5%</td>
<td>2%</td>
</tr>
<tr>
<td>1999</td>
<td>12%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>2001</td>
<td>14%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>2003</td>
<td>15%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>2005</td>
<td>16%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>2007</td>
<td>16%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>2009</td>
<td>16%</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>2011</td>
<td>14.0%</td>
<td>9.5%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*NOTE: From 1997 to 2011, children are identified as ever diagnosed with asthma by asking parents “Has a doctor or other health professional EVER told you that your child has asthma?” If the parent answered YES to this question, they were then asked (1) “Does your child still have asthma?” and (2) “During the past 12 months, has your child had an episode of asthma or an asthma attack?” The question “Does your child still have asthma?” was introduced in 2001 and identifies children who currently have asthma.*

*SOURCE: National Center for Health Statistics, National Health Interview Survey.*
Twilight for Fee for Service?

Although Medicare and most health plans are reworking how they pay for health care, it will take years to eliminate the old way

By Joseph Burns
Contributing Editor

n the 1958 movie The Blob, a gelatinous alien creature grows out of control, consuming everything and everyone in its path. The police force and townspeople are unable to stop it.

In some ways, the fee-for-service payment system in health care is like the blob: ubiquitous, feared, and seemingly unstoppable.

Flawed system

Just this year, four organizations called for an end to fee-for-service payment, saying it’s a flawed system that needlessly drives up costs.

FFS provides an incentive for health care professionals to increase the volume of services they deliver, because the only way a provider gets paid is by doing things that are billable.

As the health care system shifts from volume to value, FFS payment is at the heart of what’s wrong, according to the “Report of the National Commission on Physician Payment Reform” from the Society of General Internal Medicine (SGIM). The commission’s work is funded in part by the Robert Wood Johnson Foundation and the California HealthCare Foundation. SGIM called for adopting new payment methods over the next five years and eliminating FFS within 10 years.

In recent months, reports from the Bipartisan Policy Center (“A Bipartisan Rx for Patient-Centered Care and System-Wide Cost Containment”), the Engelberg Center at the Brookings Institution (“Bending the Curve: Person-Centered Health Care Reform”), and the Partnership for Sustainable Health Care (“Strengthening Affordability and Quality in America’s Health Care System”) had similar recommendations.

For health plan medical directors, the search for alternative ways to pay for care is not new. Perhaps better than most, they recognize how financial incentives drive up costs, and so they have tinkered with FFS for years with varying degrees of success.

As yet, however, they have not eliminated fee for service and recognize that they may not be able to do so entirely, in part because FFS is inextricably linked to the nation’s Current Procedural Terminology (CPT) system, says François de Brantes, executive director of the Health Care Incentives Improvement Institute (HCI3). For more than 20 years, de Brantes has been developing replacements for FFS, such as HCI3’s Prometheus Payment model. Under this form of bundled payment, providers are paid for all services required for certain acute or chronic episodes of care, and would be at risk for any costs above a set price and for any potentially avoidable complications.

Bundled payment and other forms of payment not based on FFS make up only about 11% of all forms of pay to providers, according to the “National Scorecard on Payment Reform,” a report issued last March by Catalyst for Payment Reform (CPR). “Almost 90% of payments remain in traditional fee for service, paying providers for every test and procedure they perform regardless of necessity or outcome,” CPR said.

Baseline

CPR’s scorecard provides a baseline against which health plans and employers can measure future progress toward payment reform, CPR said. In 2010, for example, only about 3% of payments reflected provider performance and not value, CPR reported. At the time, CPR said 20% of commercial payment would be related to value by 2020.

The report by SGIM goes further, saying that
Programs that focus on cost reduction are often accused of limiting care to keep costs down, says Doug Chaet, senior vice president for contracting and provider networks at Independence Blue Cross.

By recognizing the flaws in FFS payment, health plans are already redesigning care delivery to reward quality and lower costs, says Jeff Rideout, MD, chief medical officer for Covered California, the public health insurance exchange. These plans are not simply making modest changes to payment systems while continuing to use FFS, he says. “It’s easy to be cynical and say that what health plans are doing is just putting another label on FFS,” says Rideout. “But if you dig under the covers in almost every market, you will see that health plans are changing how they pay for care by using some good definitions of quality and some fairly strict criteria that go beyond simple limits on utilization.”

The most visible ways health plans are fostering an increase in value is by rewarding quality in two recently developed delivery models: patient-centered medical homes (PCMHs) and accountable care organizations (ACOs), Rideout says.

Why replacing fee for service is such a challenge

Fee for service is likely to remain the dominant payment model for years to come because most health plans lack the information systems needed to make any other payment system viable, says Jim Evans, vice president for financial and network management at McKesson Health Solutions. Even health plans with the most sophisticated health information technology would need at least three years to introduce a FFS replacement, he comments.

Clinical management and payment systems today are built around current procedural terminology codes. The CPT coding system is designed to represent everything that happens between a provider and patient. “Because the CPT codes have served as a reasonably useful proxy for so long, to get the marketplace off this system would be extremely difficult unless you went through a radical overhaul,” Evans explains.

Instead of sending claims listing all the CPT codes used for each encounter, a physician, hospital, or other provider could simply submit a bill based on data in the patient’s electronic medical record, Evans suggests. “You would issue a bill and append the EMR as justification. But that’s never going to happen because we have a clinical infrastructure built on these reasonable proxies for clinical events,” he says. Having invested so much in developing a system that revolves around CPT codes, such a radical overhaul is unlikely, he adds.

“Half of the compensation for primary care physicians [PCPs] is FFS and the other half is split reimbursement model, you would need an advanced pricing system, an advanced bundled payment engine that works across all the different kinds of provider systems, and an advanced data management system, because you need to align all these enhanced systems for all the different providers you have under contract,” he says. “Then you would need a new contract with each provider group.”

Modifying the current payment systems even minimally would still require going from one provider group to the next and changing everything, including contract terms, information systems, and the payment infrastructure, Evans explains. “When you talk to some health plans about paying in some way that’s different from FFS, they think you’re out of your mind.”
between delivering value-based care and reducing medical costs,” he says. Physicians can earn increased payment by meeting HEDIS goals and by achieving any of three levels of PCMH status from NCQA.

**Rewarding primary care**

Historically, PCPs were rewarded for controlling the total costs of care, except for inpatient costs, but a total-cost-of-care element (including inpatient care) has recently been added to Independence’s PCP incentive program, Chaet says. It’s significant that specialist physicians are not eligible to participate because CPR reported that 75% of total outpatient payments go to specialists. “One figure to watch as health care delivery and payment reforms aim to emphasize more primary care will be the portion of payments that go to specialists versus primary care physicians,” CPR said.

“We measure the 3,000 PCPs in our network based on how their cost performance compares with that of the rest of the network,” Chaet adds. All of Independence’s PCPs are in the plan’s HMO, where they get a capitated rate, and in its PPO, where they are paid FFS. In either the HMO or PPO, the primary care physicians can double their income if they hit all quality and cost targets, he says.

“Theyir income would go up but the total cost of services would go down because they would be effectively managing pharmacy costs, ancillary services, ambulatory surgery, and other sorts of outpatient procedures such as surgical and imaging,” Chaet comments. Any program that focuses on cost reduction is liable to be criticized for limiting care to keep costs down. To avoid this problem, Chaet says, PCPs must hit the quality targets.

“The providers have to perform at a minimally acceptable level on the quality side before they become eligible for the medical cost reduction incentives. That’s the safeguard we built in. You could blow the doors off the medical costs but if you’re underperforming on the quality side, you are no longer eligible for bonuses. We want to ensure that no one is rationing care,” he explains.

**Beyond pay for performance**

For 10 years, the Independence initiative was basically a pay-for-performance program because physicians who reached the quality goals were because many services have been migrating from physicians’ offices to the usually higher-paid outpatient department setting as hospital employment of physicians has grown,” Medpac wrote. “This shift toward [outpatient departments] has resulted in higher program spending and beneficiary cost sharing without significant changes in patient care.”
eligible for a 25% bonus. But two years ago, Independence added the cost-control measures and increased the bonus potential, essentially doubling what a physician could earn.

Chaet declines to release data on how much the program has affected overall costs. “The results are positive because even though the cost of PCP services has increased, the overall cost of care has come down. To get the bonus, physicians had to bring down the total cost of care,” he says.

A second Independence program, for ACOs, is similar in that providers can share any savings by focusing on quality improvement and cost control, Chaet says. This program is offered to integrated provider networks, including physician practices, health systems, or hospitals with employed physicians. Providers are responsible for the total cost of care including, inpatient costs. If providers achieve all the quality targets, such as keeping readmissions low and reducing the rate of hospital-acquired infections, they can share as much as 50% of the savings.

In negotiations with provider organizations, Independence has cut the annual rate of increase in an effort to get them to focus on achieving quality and cost-control targets, Chaet explains. This program is two years old and has helped to control the overall cost of care, he adds.

Making fundamental changes

WellPoint has a similar effort to shift from volume-based FFS to value-based payment through an aggressive expansion of its patient-centered accountable care programs. Growing fast, these initiatives now cover more than 1.75 million health plan members in 14 states, says Jill Hummel, WellPoint’s vice president for payment innovation.

Like Independence, WellPoint shares the savings with physicians when medical costs are lower than

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SGIM report makes 12 recommendations for improving payment

In its “Report of the National Commission on Physician Payment Reform,” the Society of General Internal Medicine made 12 recommendations for improving physician payment:

1. Payers should largely eliminate stand-alone fee-for-service payment to medical practices because of its inherent inefficiencies and problematic financial incentives.

2. The transition to an approach based on quality and value should start with the testing of new models of care over five years, incorporating them into increasing numbers of practices with the goal of broad adoption by the end of the decade.

3. Because fee for service will remain an important mode of payment in the future, even as the nation shifts toward fixed-payment models such as capitation, it will be necessary to continue recalibrating fee-for-service payments to encourage behavior that improves quality and cost-effectiveness and to penalize behavior that misuses or overuses care.

4. For both Medicare and private insurers, annual updates should be increased for evaluation and management codes, which are currently undervalued. Updates for procedural diagnosis codes should be frozen for three years, except for those that are demonstrated to be currently undervalued.

5. Higher payment for facility-based services that can be performed in a lower-cost setting should be eliminated.

6. Fee-for-service contracts should always incorporate quality metrics into the negotiated rates.

7. Fee-for-service payment should encourage practices having fewer than five providers to form virtual relationships with external providers and thereby share resources to achieve higher quality care.

8. Fixed payments, such as capitation, should initially focus on areas where significant potential exists for cost savings and higher quality, such as care for people with multiple chronic conditions and in-hospital procedures and their follow-up.

9. Measures that safeguard access to high-quality care, assess the adequacy of risk-adjustment indicators, and promote strong physician commitment to patients should be put into place for fixed-payment models.

10. The Sustainable Growth Rate (SGR), should be eliminated. The SGR is the formula based on domestic economic growth that the Centers for Medicare & Medicaid Services uses to set physician payment rates.

11. Repeal of the SGR should be paid for with savings from the Medicare program as a whole, including cuts in payments to physicians and reductions in inappropriate utilization of Medicare services.

12. The Relative Value Scale Update Committee (RUC) should make decisions in a more open fashion and should diversify its membership so that it is more representative of the medical profession as a whole. Critics have charged that the RUC tends to favor specialists at the expense of primary care. At the same time, CMS should develop alternative open, evidence-based, and expert processes to validate the data and methods it uses to establish and update relative values.

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continued on page 34
Introducing a **NEW** approach in type 2 diabetes treatment...
Introducing INVOKANA®—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition.

A1C Reductions as Monotherapy

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

A1C Reductions vs Sitagliptin

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

- Difference from sitagliptin†: –0.37%.

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
- 100 mg: 3.6%.
- 300 mg: 3.0%.
- Placebo: 2.6%.

With metformin and a sulfonylurea over 52 weeks:
- INVOKANA® 300 mg: 43.2%.
- Sitagliptin 100 mg: 40.7%.

Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue.

Convenient Once-Daily Dosing

Recommended starting dose: INVOKANA™ 100 mg.

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

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.

References:

Learn more at INVOKANAHcp.com/journal.

**ENVISION NEW POSSIBILITIES**

In adults with type 2 diabetes, now available INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

**WARNINGS and PRECAUTIONS**
- Hypoglycemia; INVOKANA™ causes intravascular volume contraction. Symptoms include hypoglycemia; INVOKANA™ causes intravascular volume contraction. Significant hypoglycemia can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR ≤30 mL/min/1.73 m²), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™, patients who are more than one of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

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**Effect on Weight**

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

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

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

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

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

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

A1C Changes From Baseline With INVOKANA™ Monotherapy

<table>
<thead>
<tr>
<th>Dose</th>
<th>A1C Change From Baseline (mean)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>–0.91</td>
<td>–1.09, –0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>300 mg</td>
<td>–1.16</td>
<td>–1.34, –0.99</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
**Introducing INVOKANA™—** the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition.

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Learn more at INVOKANAhcp.com/journal

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IMPORTANT SAFETY INFORMATION (continued from first page)

WADINGS and PRECAUTIONS (Cont'd)

**Hypoglycemia**: Patients with hypoglycemia may be more susceptible to these changes. Hyperglycemia in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

**OVERDOSE**

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

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**ADVERSE REACTIONS**

The most common (≥30%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥10% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation. Please see Brief Summary of full Prescribing Information on the following pages.

**Drug Interactions**

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

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IMPORTANT SAFETY INFORMATION (continued from first page)

DRUG INTERACTIONS

- UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonspecific inducer of several UGT enzymes, including UGT1A1 and UGT1A9, decreased canagliflozin area under the curve (AUC) by 15%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 300 mg once daily, have an AUC > 2000 mg/mL/72 h, and require additional glycemic control. Consider either a hypoglycemic agent in patients with an AUC of 40 to less than 2000 mg/mL/72 h receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- Ocrelizumab: There was an increase in the area AUC and mean peak drug concentration (Cmax) of digoxin 20% and 36%, respectively) when co-administered with INVOKANA™ (canagliflozin), peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ (canagliflozin), and require additional glycemic control. Consider either a hypoglycemic agent in patients with an AUC of 40 to less than 2000 mg/mL/72 h receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

Adverse Reactions

- Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from in vitro studies, canagliflozin may affect fetal development. A study in pregnant rats showed transient glycemic changes. Therefore, a lower dose of insulin or insulin secretagogue may be required to maintain the risk of hypoglycemia when used in combination with INVOKANA™.

- Central Nervous System: Canagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncompromised males were more likely to develop genitourinary infections. Monitor and treat appropriately.

- Hyperglycemia: The following adverse events were more common in patients taking INVOKANA™ relative to placebo: increased urination (9% vs. 4%), genital mycotic infections, vulvovaginal candidiasis, urinary tract infections, and decreased-weight (5% vs. 2%). Adverse reactions in patients taking INVOKANA™ with concomitant digoxin may be managed appropriately.

- Fluid Retention: In clinical studies of INVOKANA™, there were no reports of fluid retention and there were no increases in serum creatinine or blood pressure. There was an increase in the area AUC and mean peak drug concentration (Cmax) of digoxin 20% and 36%, respectively) when co-administered with INVOKANA™ (canagliflozin), and require additional glycemic control. Consider either a hypoglycemic agent in patients with an AUC of 40 to less than 2000 mg/mL/72 h receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

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

- Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues: In clinical studies of INVOKANA™ in patients with type 2 diabetes, treatment with INVOKANA™ did not result in a decrease in the frequency or severity of hypoglycemic events when used in combination with insulin or insulin secretagogues. A decrease in hypoglycemia has been observed when INVOKANA™ is co-administered with insulin or insulin secretagogues.

USE IN SPECIFIC POPULATIONS

- Pregnancy: There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from in vitro studies, canagliflozin may affect fetal development. A study in pregnant rats showed transient glycemic changes. Therefore, a lower dose of insulin or insulin secretagogue may be required to maintain fasting glycemia when used in combination with INVOKANA™.

- Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in two clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse events related to reduced intravascular volume with INVOKANA™ (such as hypotension, peripheral edema, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients. More prominent increases in the incidence were seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (≥75 years of age) patients (-0.13% with INVOKANA™ 100 mg and -0.19% with INVOKANA™ 300 mg relative to placebo), compared to younger patients (-0.32% with INVOKANA™ 100 mg and -0.36% with INVOKANA™ 300 mg relative to placebo).

- Renal Impairment: The efficacy and safety of INVOKANA™ were assessed in all clinical studies, with patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m²). These patients had less overall glycemic efficacy compared to placebo (−0.74% in INVOKANA™ relative to placebo).

- Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment.

OVERDOSAGE

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

ADVERSE REACTIONS

- The most common (≥15%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥10% of patients were: genitourinary pruritus, thoracic pain, and rash.

See Please Brief Summary of full Prescribing Information on the following pages.

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April 2013
K02CAN13149
INVOKE™ (canagliflozin) tablets

CONTRAINDICATIONS

Contraindicated in patients with type 1 diabetes mellitus (or for the treatment of diabetic ketoacidosis). Limitation of Use: INVOKE™ (canagliflozin) is not recommended in patients with type 1 diabetes mellitus (see Contraindications and Adverse Reactions).

INDICATIONS AND USAGE

INVOKE™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in conjunction with metformin, sulfonylurea, or metformin and pioglitazone.

ADVERSE REACTIONS

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

Dose-related increases in cholesterol levels occur with INVOKE. The occurrence of adverse reactions in pool, placebo- and active-controlled trials.

Micturition Urgency:

Potential for micturition urgency, polyuria, polydipsia, and nocturia is observed in clinical trials with INVOKE.

ADVERSE REACTIONS

The most commonly reported adverse reactions are described below and elsewhere in the labeling.

Polyuria

Potential for polyuria, polydipsia, and nocturia is observed in clinical trials with INVOKE.

ADVERSE DRUG REACTIONS

The listing of adverse drug reactions is descriptive and not exhaustive.

Fluid, Electrolyte, and Sodium Abnormalities

Potential for dehydration is observed in clinical trials with INVOKE.

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In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 60 mL/min/1.73 m² (mean baseline eGFR 48 mL/min/1.73 m²), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

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

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 6.9% with INVOKANA 100 mg, and 8.9% with INVOKANA 300 mg. Discontinuations due to renal-related adverse reactions were 0.3% with placebo, 0.8% with INVOKANA 100 mg, 1.1% with INVOKANA 300 mg, and 1.8% with INVOKANA 300 mg (see Warnings and Precautions).

Glucose-Related Adverse Reactions: Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event (canagliflozin) tablets

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>5 (2.6)</td>
<td>7 (3.6)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>3 (1.6)</td>
<td>16 (4.3)</td>
<td>17 (4.6)</td>
</tr>
</tbody>
</table>

Hypokalemia: INvOKANA was associated with the development of hypokalemia more commonly in patients treated with oral or topical antifungal agents and antimicrobial agents (see Warnings and Precautions).

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>22 (12)</td>
<td>30 (16)</td>
<td>34 (18)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>2 (1)</td>
<td>6 (3)</td>
<td>8 (4)</td>
</tr>
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Photosensitivity-related adverse reactions (including photosensitivity reactions, photodynamic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 1.6% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Females who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and antifungal agents (see Warnings and Precautions).

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>3 (0.3)</td>
<td>7 (0.7)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

In a study of four placebo-controlled clinical trials, male genital mycotic infections (e.g., balanitis, balanoposthitis) occurred in 0.6%, 0.3%, and 1.1% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in patients with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and antimicrobial agents (see Warnings and Precautions).

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>4 (0.3)</td>
<td>7 (0.6)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>
Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was observed).

### Laboratory Tests:

Increased in Serum Potassium: Dose-related increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 2 weeks) in a trial of patients with moderate renal impairment [see Clinical Studies (14.2) in full Prescribing Information]; in this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 11%, 14%, and 21% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively. More severe elevations (i.e., greater than or equal to 6.5 mEq/L) occurred in 1%, 2%, and 2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively, compared to 0% with placebo. In a trial of patients with moderate renal impairment (see Clinical Study 31 [14.3] in full Prescribing Information), serum magnesium levels increased by 3%, 3%, and 4% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively, compared to -0.8% with placebo.

In increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (2034 patients 65 years and older) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium level was 0.24 mEq/L (95% CI -0.04, 0.52) in the pool of four placebo-controlled trials, compared to -0.8% with placebo. In a trial of patients with moderate renal impairment (see Clinical Study 52 [14.2] in full Prescribing Information), serum magnesium levels increased by 2%, 3%, and 7% with placebo, INVOKANA 100 mg, and INVOKANA 200 mg, respectively.

In Zeros Sulfonylurea-Related Hyperglycemia: Patients with severe hyperglycemia were defined as those with a glucose level greater than or equal to 180 mg/dL (10 mmol/L) more than 30 minutes. In a trial of patients with moderate renal impairment (see Clinical Study 11 [14.2] in full Prescribing Information), the mean change in serum glucose level was 4.0 mg/dL (0.56 mmol/L) with placebo, 1.7 mg/dL (0.22 mmol/L) with INVOKANA 100 mg, and 3.2 mg/dL (0.42 mmol/L) with INVOKANA 200 mg, respectively. In patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), with ESRD, increased kidney growth and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when fetal exposures may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (see Full Prescribing Information).

### Pediatric Use:

Pediatric use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established. This drug is not recommended for use in pediatric patients.

### Geriatric Use:

Two thousand thirty-four (2034) patients 65 years and older, and 246 patients 75 years and older, were exposed to INVOKANA in nonclinical studies of INVOKANA (see Clinical Studies (14.2) in full Prescribing Information). Patients 85 years and older had a higher incidence of adverse reactions related to reduced intravascular volume (which may lead to hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients. The majority of deaths in these trials were in patients with severe hepatic impairment and is therefore not recommended for use in patients with severe hepatic impairment, and is therefore not recommended (see Clinical Pharmacology (12.3) in full Prescribing Information).

### Hepatic Impairment:

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment, and is therefore not recommended (see Clinical Pharmacology (12.3) in full Prescribing Information).

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Severe [N (%)]</th>
<th>Overall [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13 (3.4)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Placebo + Pioglitazone</td>
<td>15 (4.0)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Placebo + Sulfonylurea</td>
<td>14 (2.5)</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Placebo + INVOKANA 100 mg</td>
<td>10 (1.8)</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td>Placebo + INVOKANA 300 mg</td>
<td>16 (2.7)</td>
<td>16 (2.7)</td>
</tr>
</tbody>
</table>

* Number of patients experiencing at least one episode of hypoglycemia based on either biochemical documentation or severe hypoglycemic events in the trial population.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
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Titusville, NJ 08560

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projected and physicians meet or exceed quality targets. Physicians must hit the quality targets, and the better their performance against the quality measures, the more they can earn.

Almost 23,000 physicians, including nearly 15,000 primary care physicians, participate in this type of program. Even as it expands its shared-savings initiatives, WellPoint continues to partner with physicians and hospitals in its more traditional pay-for-performance program, where adjustments to fee schedules are based on performance against quality metrics.

To date, more than 75,000 physicians, including more than 50% of all primary care physicians in WellPoint’s network, participate in one of WellPoint’s value-based payment programs. In addition, payments to more than 700 hospitals — covering over 70% of WellPoint’s inpatient admissions — are tied to quality performance.

But Hummel admits that while WellPoint is shifting from volume- to value-based payment, a complete shift away from FFS to a global capitation model is not around the corner for many reasons. Aside from provider readiness to accept and manage that kind of risk, a number of states or markets consider that type of payment to be the business of insurance. As such, those states would require the provider organization to be licensed as an insurer to the extent that payments are being made by, or on behalf of, an entity that does not have an insurance license.

Many of the employers that companies like WellPoint serve are self-funded, which means that they are at risk for the medical costs of their enrolled population. These employers are not licensed insurers and in some states a licensed insurer cannot make global capitation payments on their behalf unless the provider organization is a licensed insurer.

The practical impact is that this would prevent WellPoint from including self-funded employers, who make up a large percentage of WellPoint’s commercial business, in many global capitation arrangements today.

“It would be very difficult to have one payment model for our fully insured commercial business and a different payment model for our self-funded commercial business,” says Hummel. “Operationally, it would be challenging and it would be confusing to providers. A shared-savings model, where claims continue to be paid on a fee-for-service basis but providers earn bonuses based on quality and costs, is a good interim step.”

**Tinkering at the margins**

Essentially, most health plans are tinkering with FFS but not truly eliminating it, says Jim Evans, vice president for financial and network management at McKesson Health Solutions.

“There’s a lot of thinking about moving away from fee for service, but not many actual modifications of standard fee-for-service models,” he says. Instead, health plans are tweaking FFS.

- One change involves contracting with physicians or group practices in either a PCMH or an ACO that have some form of shared risk. In these arrangements, the plan pays a care coordination fee so that the physicians or groups can hire a nurse or other provider to assist in managing care, particularly for patients with chronic conditions.
- The second change involves the use of capitated budgets; this is done most often in Medicare Advantage plans. “Plans in California have been doing this for a while, but now it’s moving into other areas of the country,” Evans says. In these first two models, FFS is the basic form of payment but a year-end adjustment accounts for savings beyond what has been budgeted or for excess expenditures, he says.
- “The third area involves real innovation — bundled payment. Episodic payment models mostly are being tested in medical homes or ACOs in which the providers already have some level of alignment with the health plan, making the introduction of bundled payment relatively easy,” Evans explains.

“But none of these efforts represents an overwhelming wave of payment reform,” he adds. “All of these changes are moving slowly and will be done in bits and pieces. If, as CPR says, only 11% of payment is made in anything other than FFS, then we might be at 13% in the next year or two.”

Perhaps what’s needed is to call in the U.S. Air Force, as the townspeople did when confronting the Blob. But who knows if even the Air Force would have much luck against FFS payment?
When David M. Cutler, PhD, predicted this spring in Health Affairs that a slowdown in health care cost increases could mean $770 billion in reduced spending over 10 years, he recognized that the long-term reality could go either way. “We chose the wording in the article very carefully,” he says.

“This is a hard issue and there’s no right or wrong.” Still, he believes the road to continued cost savings is now clear — through payment reform, increased efficiencies, greater investment in technology, and a gradual reduction in the growth of the health care workforce — and that the government and the private sector need to keep heading in the right direction, only faster.

Cutler is the Otto Eckstein Professor of Applied Economics at Harvard, where he previously served as associate dean of the faculty of Arts and Sciences for Social Sciences. He participates in a wide range of public policy work. He is a research associate at the National Bureau of Economic Research, a member of the Institute of Medicine, and a fellow of the Employee Benefit Research Institute.

He served on the Council of Economic Advisers and the National Economic Council during the Clinton administration and has advised the presidential campaigns of Bill Bradley, John Kerry, and Barack Obama. Cutler is the author of Your Money or Your Life: Strong Medicine for America’s Health Care System, published by Oxford University Press in 2005 and a forthcoming book, The Quality Cure, due out this fall. His bachelor’s degree is from Harvard and his PhD in economics is from the Massachusetts Institute of Technology. He spoke recently with Managed Care editor John Marcille.

MANAGED CARE: You predict that if the current slowdown in health care cost increases continues, we will spend $770 billion less over 10 years. What will that mean for the economy and for health care?

DAVID M. CUTLER, PHD: It is going to mean quite a lot, probably more for health care than for the economy. For health care, it’s obviously going to mean less revenue for health care providers. For the economy, it will probably matter less. When health care is growing rapidly, there are lots of new jobs created. When health care grows slowly, jobs are created elsewhere as people spend their money elsewhere.
MC: Is that bad for health care?
CUTLER: At the end of the day, what we really want to do is spend money on health care if we are getting good value and not spend money if we are not getting good value. It is like asking, Should we build another bridge to cross the river? Well, if a lot of people are going to use it and it’s going to significantly shorten delays, then yes. But if you are just building a bridge to hire people — and if we are not in a recession, when you want to hire people — then let them do something more productive.

MC: We have been pushing for cost savings in health care for quite a while.
CUTLER: As this happens over time, we need to ask, Are we getting rid of things we want to get rid of, in which case it’s great, or are we getting rid of things that we would like to have? Here’s an example: Suppose that we reduce our readmission rates because hospitals get better at discharge planning and insurance companies get better at helping coordinate care among providers. Readmissions are pretty common, so if readmissions go down, overall use of hospitals will go down, and that means we will need fewer nurses, fewer orderlies, and fewer people in billing offices. Is it good or bad to get rid of those readmissions and not employ those people? The answer is that it is very good because you don’t want to waste your money as a society supporting a bunch of services that you just don’t need.

MC: But many sectors in the industry seem to thrive on high costs.
CUTLER: A lot of this is going to depend on the payment system. We have seen that with readmissions. Hospitals are eliminating readmissions because the government is penalizing them and because there are promises of even bigger changes in terms of episodic, bundled payments. If you make something financially undesirable, you get less of it. If you make it financially desirable, you get more of it.

MC: You say that one-time occurrences such as the recession played a role in the slowdown of health care cost increases. Where else is the slowdown coming from? Are payment reforms having an effect already?
CUTLER: Yes, and we are seeing more efficiency improvement. Hospital readmissions are down, hospital rates of infection are down, and a variety of indicators of poor care are doing better than they were. There has also been a slowdown in new technology, which I am sure health plan medical directors have seen. There is nothing on the horizon like massive sellers such as Lipitor or Prozac. That’s neither good nor bad by itself, it has just meant less spending. Another explanation is that people’s cost sharing is very high. The typical individual has a deductible of $1,000, and that is higher for families. That’s more money than most people have in the bank, which is discouraging a lot of utilization.

MC: Will that mean higher future utilization?
CUTLER: We will have to wait and see. When you raise cost sharing, people cut back across the board. They cut back on services they don’t need, and they cut back on services they do need. People are not that good at figuring it out. On one hand, they get fewer images in situations where images aren’t that valuable, and on the other hand, they get fewer cancer screenings.

MC: What are you hearing from other health economists about your prediction?
CUTLER: I went to a conference with economists, health policy folks, and others, and I gave them a survey. It’s not scientific in any way, but I asked whether they thought: A, it’s temporary and we will go back to where we were or costs will be higher because people will catch up on utilization they have postponed; B, we’ll go back up some, but maybe not to where we were; or C, we’ll stay where we are or may even fall lower because we’re just getting a handle on how to address efficiencies and payment reform. The vast bulk of people said B. My personal view is that C is probably more accurate.

MC: The popular press has been addressing the opaqueness of the system recently; it’s getting more attention.
CUTLER: The Steven Brill article in Time and the articles on colonoscopies and pregnancies that ran in the New York Times are examples of stories that are highlighting how frustrating it is not to know how much something is going to cost. It strikes a chord for a lot of people. Even insured people can have very, very high cost sharing. Most insurers are

T he Affordable Care Act takes a big step forward on the public side, but we need to do more.... The same is true for private insurers.
under pressure to give people better information, particularly since they have been out selling these high-deductible policies. Their enrollees have skin in the game, but it doesn’t do any good to do that if they can’t figure out how to spend the money wisely.

MC: But what percentage of high-cost care is discretionary?

CUTLER: Quite a lot. In almost any disease setting you can think of, there is some discretion about how much care to provide. I was talking to an oncologist about how his group did things. And it was, “Well, there are 12 protocols and we always follow those.” I asked whether there were ever situations in which the protocols were unclear. And the answer was, “Absolutely.” It turns out that the protocols are about what drug to give when a person has a certain type of cancer, but they are less clear about how frequently a physician should monitor a patient afterwards. Should they come in monthly? Should they get an MRI monthly? What should happen to them? And as a result of that uncertainty, you can spend enormously different amounts of money. Even if people have blown through the deductible, they may still have pretty high cost sharing and be at risk for a lot of the cost of an MRI.

MC: Providers come up with their own practice standards, then.

CUTLER: Yes, and those norms are very much influenced by the money flow. So when providers are paid on a fee-for-service basis, the norm is to do an MRI every month. When they are paid on a global basis, the norm might be to do an MRI every three months or every six months. They are still going to provide the very expensive frontline drug because that’s what the literature says, but around the edges there is a lot of care for which the clinical evidence is not definitive.

MC: Are all of the incentives economic?

CUTLER: There are several different incentives. There’s the economic one; There’s “do I feel at risk for being sued?”; There’s “what have I experienced in my own practice?”; And there’s “what summary of the literature struck me as most accurate?” All of which are malleable. We know that you can change doctors’ behaviors through money. We also know you can change doctors’ behaviors by having all of the oncologists sit down in a conference room and talk. Fortunately doctors want to do the right thing, and if you can show them that the right thing involves less of something or more of something, they will often really want to do it.

MC: We may save $770 billion from the slowdown in health care cost increases, but you’ve also said that we waste a very similar amount every year.

CUTLER: That’s the best guess by the Institute of Medicine and others, that a third of medical spending is waste. That’s about that same order of magnitude, $700 billion or $800 billion a year.

MC: That is wasted from a societal perspective, but obviously the billing companies, the software makers, and others who have a stake in the overhead part of the business may disagree.

CUTLER: One person’s waste is someone else’s income. The way I think about waste, though, is that if you decide you want to spend $800 billion less this year, you would have to unemploy a lot of people in health care. If you decide that 10 years from now, you want to spend $800 billion less than you otherwise would have spent, you won’t have to unemploy anyone. You just won’t add so many people in as many areas of medicine. For example, most hospitals are adding orthopedic surgeons pretty rapidly because there is more and more need for the surgeries that they are doing. If we got to a point where we agree that we don’t need to do as much surgery on backs and if we kept people healthier when they had arthritis, we wouldn’t need to replace as many knees and hospitals wouldn’t have to hire as many orthopedists.

MC: That is not jarring because it’s a slow process?

CUTLER: It’s slow and nobody’s being fired. You’re just not having new people come in. That is happening in cardiac surgery today. Open-heart surgery is way down. Things can be done with minimally invasive surgery or with stents. So if you were coming out of medical school, you would have to be very careful before you decided to go into that. And that’s what will happen in other aspects of medicine, too.

MC: Is a robust primary care system something that we are going to see, or are the economics still not conducive?

CUTLER: I hope we will, particularly when we really penalize going into a hospital. But primary care will probably look different. It won’t be all physicians. There is such a high demand for primary care that the key is figuring out how to find more of it. We need to think creatively about how to stretch resources.
MC: You often talk about health care being a service industry that doesn’t act like one. We can’t e-mail our physicians; clinics close at 5 p.m. Where are the opportunities?

CUTLER: I have asked audiences, Which is more enjoyable, interacting with the health care system or buying a used car? Would you care to guess what they answered?

MC: They are both horrible.

CUTLER: They far prefer buying a used car. This is totally unscientific, but the level of frustration with the inability to access medical care is immense. And we are entering an era when baby boomers are going to need a lot of medical care, and they have never stood for anything they didn’t like, so I would expect the pressure for better service quality to grow. One way or the other, the system will have to adapt to the demand for better service, or people are just going to explode at it.

MC: Have we seen evidence of improvements?

CUTLER: We have seen lots of people hiring concierge physicians. We see people even with relatively low incomes going to MinuteClinics, paying $40 or $50 for the convenience of it. We see ratings services about physicians. It looks like people are starting to shop around, but nobody has quite hit on how to bring it to the masses. In the right payment environment, you can actually improve profit by providing better service quality in cheaper settings.

MC: Reducing administrative burdens on physicians could have a big effect, too. You cite studies that have found that doctors and nurses spend a good part of their time documenting care rather than providing it.

CUTLER: Yes, the administrative burden is immense. And it’s a big source of waste. A lot of the new hiring in health care is going into administrative costs rather than into care processes. It’s not so much administrative costs at insurance companies, although there is certainly some of that. It’s administrative costs in providers’ offices as they have to deal with the many insurance plans that they have to respond to. That’s something that we need to really automate so that we get those costs down.

MC: Do you think that is an argument for a single-payer system?

CUTLER: We could do that, but not enough people really want to do that. In most industries, we have reduced those costs not through a single-payer system but through technology.

MC: What are the best investments we could make in our health care system?

CUTLER: The Affordable Care Act takes a big step forward on the public side, but we need to do more. Everything we have done so far has been half measures, and we need to do full measures. The same is true for private insurers. They recognize they need new computer systems, for instance, but are they really doing it on the scale that they need to as fast as they need to?

MC: Has the federal government done its part by setting the tone, or are there still things that need to be changed?

CUTLER: Administratively, they need to keep pushing things as fast as they can. They also probably need some legislation because certain payment policies are set by Congress, and Congress has to change them. And private insurers have to be in the lead, not just be following.

MC: Which private insurers are in the lead now?

CUTLER: Probably the most famous example is the one here in Massachusetts — the Alternative Quality Contract with Blue Cross Blue Shield of Massachusetts. It has gotten much more attention than anything else, partly because it has been studied, not because it is necessarily that far ahead of where other folks are.

MC: So a program like that should be replicated?

CUTLER: Yes, and we should pay close attention to understanding exactly what impact it has.

MC: You are known for your early studies on evaluating technologies in health care to determine whether the investment has been worth it. How has your thinking evolved in this area, and what should medical directors and P&T committees be thinking about most right now?

CUTLER: Technology is interesting because on the one hand, it does enormous amounts of good. On the other hand, we frequently overuse things. It is a real problem in the system if you develop something that is expensive but good only if done in the right people, because we waste a lot of money doing it on people for whom other treatments are actually better and cheaper.

MC: Like MRIs?

CUTLER: Yes, like MRIs. We could significantly increase the value of technology by making sure it is used on the people who need it and not used on the people who don’t need it.

MC: Thank you.
Value is in the eye of the beholder, they say. One man’s definition of value is just one man’s definition. Whatever you bring to the table will be judged by someone else’s idea of its worth.

This is true of biologics and other specialty drugs. In the decade-plus since biologics began to get payers’ attention, the “value proposition” conversation hasn’t changed much. Driven by data gathered for marketing approval, pharma proffered its science. Payers wanted real-world outcomes. The difficulty in bridging the two made innovative benefit design hard to achieve. All the while, specialty drugs matured from a $17 billion market in 2001 into a $160 billion enterprise today.

Clinical dynamic

It took health care reform to jump-start change in the value conversation, from one based on dollars, cents, and Kaplan-Meier curves to something more holistic. “Health care reform has brought out the economics of the clinical dynamic,” says Randy Vogenberg, PhD, RPh, principal at the Institute for Integrated Healthcare. “You can’t just focus on ‘I can improve survival by a few weeks’ in oncology, or ‘I can walk 10 more steps to the bathroom if I take this drug for MS.’ It’s not about quality of life; it’s about looking at the economics. Does it make sense to pay for 10 more steps to go to the bathroom, at a cost of, say, $100,000? That’s where we are: How do we match the economics with the clinical?”

How that will play out is unclear. But for now, the Affordable Care Act is changing payers’ business models, forging new stakeholder alliances, and generating new research — all of which are altering the value conversation.

Three underlying phenomena are influencing change.

Perhaps the least apparent of these is how the ACA is splintering the market for health insurance. With the advent of the exchanges, says Vogenberg, administrative services-only plans that partner with self-insured employers become a more distinct product line. Small-group, individual, and Medicaid form a separate product line through the exchanges. Medicare makes up another. The realignment clearly defines each customer — empowering each with a stronger voice for defining value.

“Then, you may be in bed with a provider group, like an accountable care organization, so throw into the mix shared risk contracts with provider organizations,” says Vogenberg. “The whole dynamic begins to shift. It raises the question: ‘Who is making the decision about what drugs are used?’”

A more obvious trend is the move toward evidence-based payment. With the notable exception of Cigna’s 2011 contract with EMD Serono for interferon beta-1a (Rebif) that based rebates on clinical outcomes and adherence, outcomes-based contracting hasn’t caught on in the United States as it has in Europe. But accountable care organizations, pathways, and the Centers for Medicare & Medicaid Services’ coverage with evidence development policies are all proxies for it by pushing risk away from the payer. Each challenges the pharmaceutical industry to deliver real-world outcomes.

Total costs

Finally, biologics nullify the educational model pharma has used with MCOs for less-costly, traditional drugs: that its products prevent downstream medical costs. Prime Therapeutics, the Blues-owned pharmacy benefit manager, looked at total costs over three years among one plan’s members...
with rheumatoid arthritis and multiple sclerosis. For both diagnoses, specialty drugs accounted for more than half of total costs. What’s more, patients’ average annual medical costs didn’t differ much — regardless of whether they used specialty or nonspecialty drugs.

“The cost of specialty drugs overwhelms any opportunity to get a return on investment on the medical side,” says Pat Gleason, PharmD, director of clinical outcomes at Prime. “That’s not to say that there’s not value, it’s just an understanding of what comes with drug therapy and what you can expect with outcomes on the medical-benefit side. The ability to obtain medical cost avoidance that offsets the investment of the drug is not there.”

Who’s driving change?

PBMs are doing much of the heavy lifting here, marrying medical and pharmacy claims data to help customers reframe the value discussion. When a positive return on investment can’t be shown, as with the RA and MS data above, says Gleason, “We can move away from having to prove to me that these drugs are going to save me money on the medical benefit, and start talking about other ways to manage the specialty drug. At least, we can ensure that the right people are getting them for the right reasons and the right duration.”

The “right people, right reasons” logic is driving pharma’s interest in biomarker research and diagnostics. Oncology is the most fertile area here; in patients with lung cancer, for instance, presence of an EGFR mutation or an ALK gene rearrangement corresponds strongly with response to certain treatments. “Everyone we speak with — physicians, payers, and regulators — believes that this is the path forward,” says Marie Cassese, managing director of the Life Sciences Practice at Navigant Consulting.

Though the industry knows that biomarkers offer an important avenue for value demonstration, it is a long way from large-scale replication of its successes in oncology. “It is much easier to identify biomarkers that predict a response to therapy, than it is much harder to design, validate, and commercialize companion diagnostics,” says Cassese. Questions her pharma clients pose in this area “center on the debate about the importance of bringing diagnostics capabilities in-house.”

When pharmacoeconomic or diagnostic tools are lacking, some health plans are getting creative in assessing value. WellPoint uses a form of comparative effectiveness research to create an

### Total cost of care for patients with RA and MS

Prime Therapeutics evaluated total cost of care for members with rheumatoid arthritis and multiple sclerosis over a three-year period (data are only for 2010, the final year for which expenditures were analyzed). Within each diagnosis, medical costs were not substantially different, regardless of whether a member used a specialty or nonspecialty drug. In the specialty drug-only populations, specialty drugs accounted for more than half of the total cost of care.

| Pharmacy and medical benefit cost comparisons | | | | | |
| --- | --- | --- | --- | --- |
| Diagnosis and treatment regimen | Pharmacy specialty drug ($) | Medical specialty drug ($) | Medical, all other ($) | Pharmacy, all other ($) | Total cost ($) |
| **Rheumatoid arthritis** | | | | | |
| Treated with or without a specialty drug* (n=4,398) | 4,533 | 1,870 | 14,576 | 2,149 | 23,128 |
| Treated with a specialty drug (n=1,556) | 12,812 | 5,286 | 13,710 | 2,356 | 34,164 |
| 53% of total expenses | | | | | |
| **Multiple sclerosis** | | | | | |
| Treated with or without a specialty drug* (n=1,685) | 19,130 | 1,070 | 14,118 | 2,583 | 36,091 |
| Treated with a specialty drug (n=1,209) | 26,661 | 1,491 | 11,080 | 2,528 | 41,760 |
| 67% of total expenses | | | | | |

*Individual patients may have received no specialty drugs, or a specialty drug may have been added to the treatment regimen during the study period. Study sample was derived from integrated pharmacy and medical claims data from 1.2 million commercially insured members in a single health plan.

Source: Prime Therapeutics, Eagan, Minn.
For more information, ask your Synagis Account Manager about Cradle with Care today.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

**INDICATION**

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

**SELECT SAFETY INFORMATION**

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

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

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

Synagis® is a registered trademark of MedImmune, LLC.
Brief Summary of Prescribing Information
SYNAGIS® (PALIVIZUMAB)
For Intramuscular Administration
Rx only

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

The following point should be considered when prescribing Synagis:
• The safety and efficacy of Synagis have not been established for treatment of RSV disease.

DOSEAGE AND ADMINISTRATION
Dosing Information
The recommended dose of Synagis is 15 mg per kg of body weight given monthly by intramuscular injection. The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season. Children who develop an RSV infection should continue to receive monthly doses throughout the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass. Children undergoing cardio-pulmonary bypass should receive an additional dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

The efficacy of Synagis at doses less than 15 mg per kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.

CONTRAINDICATIONS
Synagis is contraindicated in children who have had a previous significant hypersensitivity reaction to Synagis.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Other acute hypersensitivity reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Synagis should not be administered to individuals with a history of a severe acute hypersensitivity reaction to Synagis or a component of Synagis.

If a re-administration decision is made, the patient should be monitored closely for any evidence of anaphylaxis or other adverse reactions, which may be severe, have also been reported on initial exposure or re-exposure to Synagis. Synagis should not be administered to individuals with a history of a severe acute hypersensitivity reaction to Synagis. Synagis should be immediately discontinued and appropriate medications (e.g., epinephrine) and provide supportive care as required. If a mild hypersensitivity reaction occurs, clinical judgment should be used regarding cautious readministration of Synagis.

Coagulation Disorders
Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any coagulation disorders.

RSV Diagnostic Test Interference
Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture, and therefore may also interfere with viral culture assays. Palivizumab does not interfere with reverse transcriptase-polymerase chain reaction based assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained, should be used in conjunction with clinical findings to guide medical decisions.

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

Proper Administration
The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

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

Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) and the liquid formulation of Synagis. Three hundred seventy-nine children contributed to the 4 to 6 months post-final dose analysis. The rate of anti-palivizumab antibodies at this time point was low in both formulation groups (anti-palivizumab antibodies were not detected in any subject in the liquid formulation group and were detected in one subject in the lyophilized group (0.5%), with an overall rate of 0.3% for both treatment groups combined).

These data reflect the percentage of children whose test results were considered positive for antibodies to palivizumab in an enzyme-linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay. The ELISA has substantial limitations in detecting anti-palivizumab antibodies in the presence of palivizumab. Immunogenicity samples tested with the ELISA assay likely contained palivizumab at levels that may interfere with the detection of anti-palivizumab antibodies.

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

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

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

General Disorders and Administration Site Conditions: injection site reactions

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

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

USE IN SPECIFIC POPULATIONS

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

Animal Data
Animal reproduction studies have not been conducted.

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

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

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

Synagis® is a registered trademark of MedImmune, LLC.

Manufactured by: MedImmune, LLC Garfieldsburg, MD 20878 U.S. License No. 1799 1-877-633-4411
Revision Date: April 2013 RAL-SYNV16 Component No.: 10423A
outcomes-based formulary. Once efficacy and safety are established, WellPoint uses observational studies to align formulary classes with real-world outcomes.

**Greater treatment benefit**

WellPoint made news when it applied this approach to asthma. In clinical trial literature, inhaled corticosteroids are superior to oral medications. But when WellPoint found that real-world compliance with inhaled controllers was only 3% — and that ER visits and hospitalization rates were higher in members using inhaled products — it concluded that members using oral medications were probably enjoying a greater treatment benefit. WellPoint then lifted the prior authorization requirement for the most commonly used oral drug on its formulary.

You might call that a patient-focused approach to defining value. The Patient-Centered Outcomes Research Institute is also mindful of the patient experience when funding comparative effectiveness research. Two PCORI grants, awarded in May, illustrate how.

**The two-edged sword of health economics and outcomes research**

Efficacy and safety profiles have their place, but payers and purchasers have long wanted more. Employers, in particular, are keen on data on how treatments improve productivity. Most of that research, though, has been small-scale and difficult to extrapolate because the economic assumptions in each are unique. The PROWD study of adalimumab (Humira) by Paul Emery, MD, presented at the European League Against Rheumatism in 2007, was the first double-blinded, placebo-controlled trial to use work loss as a primary endpoint. Few have replicated his model.

New methods of health economics and outcomes research (HEOR) could, in time, plug gaps in stakeholders’ view of value. In an article in *Rheumatology* two years ago, for instance, Nicki Welton, PhD, used a *value of information* (VOI) analysis to quantify the effect of uncertainties in a cost-effectiveness analysis (CEA). Applying her analysis to biologics that treat RA, Welton suggested that VOI could help researchers to determine whether a head-to-head trial was needed to close the holes in the CEA or less costly research would be close enough for payers.

If that sounds like a lot to get your head around, it is, says Tommy Bramley, RPh, PhD, an HEOR veteran and senior vice president for scientific consulting at Xcenda. HEOR, he says, is growing in its sophistication, “which is good and bad.” Concepts like VOI, indirect comparisons, and network meta-analysis “are getting very statistically driven, which is good. But it can also make the data less accessible to payers.”

The problem, he says, is that complicated analyses are difficult to understand. “The adage ‘There are lies, damn lies, and statistics’ starts to apply. That’s my concern. I think it’s very valuable, and it adds rigor to the science. But I think you can argue: Are you compounding some of the error in some of your analyses? Is it usable?”

“Good data and good science drive good decisions. But it’s important to make sure that decision makers understand and can be able to judge that.”

In one PCORI-funded study, University of Nebraska researchers will evaluate treatment preferences of patients with advanced lung cancer. Most treatments have similar effectiveness, but side effects can limit their value. Another study at the University of Pennsylvania factors patient preferences into a comparison of corticosteroids and anti-TNF agents used to treat inflammatory bowel disease. Researchers aim to distill a relative net benefit for each — filling a crucial gap in the literature.

If you’re keeping score, that’s PBMs, the pharma industry, health plans, patients, and PCORI all changing how value is assessed. But there’s one more group, long characterized as being unconcerned with the economics of clinical practice. With the ACO growth and the re-emergence of risk-bearing physician groups, now doctors are thinking differently about value, too.

**Looking at everything**

“Providers are looking carefully at everything they do — especially things that are complex, such as IV therapies that are more expensive, either
for the patient or for the provider and the plan,” says Edmund Pezalla, MD, MPH, national medical director for pharmacy policy and strategy at Aetna. “Those things are getting their attention, and they’re asking, ‘Is this the right patient for this therapy? Has this patient tried therapies that have fewer side effects or are less costly and possibly will work very well?’

“The difference is that the providers are asking these questions, too.”

**Relationships with physicians**

The takeaway from Pezalla’s observation is that the advent of new voices in the value discussion is changing the health plan’s role and its relationships with others.

“It’s getting us out of this business of telling physicians that you must do this or cannot do that,” says Pezalla. “It changes it from an adversarial approach to a more collaborative approach.”

Collaboration starts with recognizing one other’s strengths. As the one closest to any given patient, the physician may know the most clinically effective way to reach a specific outcome. Health plans can share their expertise in claims data analysis, helping the physician arrive at an equally efficient way to strive for that outcome.

“There’s a richness in clinical data that we don’t see,” says Pezalla. “On the other hand, there are patterns in claims data that, up to this point, physicians haven’t seen very much of. There’s a lot of power in bringing those together at the point of care.”

That thrusts the health plan squarely into the role of information provider. Beyond helping physicians to interpret claims data, a health plan might teach an ACO to use traditional utilization management tools.

**Help needed**

“They can learn from us about step edits and prior authorization, but they can also apply it in a different way,” says Pezalla. “An ACO might say, I’m not going to do PA, but I want everyone who gets this medication to have been seen by a specialist. I want to be sure they have the right diagnosis and have had other appropriate treatments first, and the best way to do that is to make sure they have seen an ear, nose, and throat person, or an ophthalmologist, or whomever.”

No doubt, physicians will need help getting the hang of payer thinking. “The challenge with specialty medications is that regimens are complicated, there is a lot of information for physicians to sift through, and the treatment landscape is constantly evolving,” says Mary Dorholt, president and clinical practice lead for specialty pharmacy at Accredo, Express Scripts’ specialty pharmacy. Express Scripts recently launched a decision-support module for oncologists, loaded with more than 1,700 evidence-based treatment regimens.

Following these guidelines, Dorholt says, can “decrease unwarranted deviations from evidence-based medicine from 35% to less than 10%,” ultimately reducing an ACO’s waste and costs.

Health plans’ relationships with pharma companies are also evolving. It’s becoming common, says Pezalla, for health plans to share de-identified claim data with manufacturers interested in learning from them.

Aetna doesn’t sell data to pharmaceutical companies, he points out, but it may share analyses that can help a pharma company react to its requests for information. “Or, for example, we may develop economic models to [help a manufacturer] understand the impact that a particular medicine may have on pharmaceutical costs.”

**Observational studies**

In response to payer questions about value, biopharmas are engaging in their own forms of CER. United BioSource (UBC), an Express Scripts subsidiary that provides support services to pharmaceutical companies, conducts retrospective and prospective observational studies in several therapeutic areas.

“Prospective observational studies, compared with retrospective studies, can offer more insights into clinical detail, allowing us to better define subcohorts that may respond differently to the therapy,” says Chris Pashos, PhD, vice president at UBC.

“Prospective studies also have the advantage of being able to include patient-centered outcomes and data collected from patients and their caregivers. This increases the amount of data available to assess benefit versus risk.”

An exciting aspect of this work, says Tommy Bramley, RPh, PhD, senior vice president for scientific consulting at Xcenda, is in the use of de-identified data from electronic medical records.
The EMR provides more clinical richness than can be extracted from claims. “Within data from administrative claims, you may know that a hemoglobin HbA1c test was done, but you don’t know the results,” says Bramley. “With the electronic medical record, you see the results of that test and what was done with therapies based on that test.”

**Pharma still struggling**

Bramley has used EMR-based research to help pharma clients respond to payer needs. In one case involving a therapy that had been getting payer pushback, EMR research helped to identify a range of patients who benefitted most from the therapy, based on dosage-to-weight proportions. A patient’s weight isn’t to be found in a claim, but its presence in the EMR helped researchers to uncover why patients in a certain weight range experienced more serious side effects.

“It became clear that if you’re not able to dial in the dose of that specific area, you’re at risk for significant side effects that may cost the payer money or may lead to discontinuation of the therapy.”

Efforts like these are steps in the right direction, but pharma still seems to be struggling to produce consistent, real-world value assessments meaningful to payers. Cassese, at Navigant, co-wrote an article in *In Vivo* last year that documented these difficulties.

“We completed a systematic review of health technology assessment reports and the clinical trial evidence for 24 new pharma products approved by the FDA and EMEA between 2008 and 2010. Our aim was to evaluate the level of payer uncertainty about the clinical value of new therapies. For nearly three-quarters of the products reviewed, payers raised doubts about the clinical meaningfulness of the endpoints,” she says. “For nearly half of the products, payers expressed a need for longer-term data to show the durability of the benefit, and for about one quarter, they raised issues that the study group was not representative of the population that would be routinely treated.”

**Very little R&D**

Part of the problem, says Vogenberg, at IIH, lies in the fact that big pharma has, by and large, become “a sales and marketing organization with very little R&D.” Much of the R&D work is being done by smaller biotechs that develop new products, but most don’t have the wherewithal to collaborate with payers on clinical trial design.

The smaller companies seem to understand the importance of doing this, but “it hasn’t trickled down in a way that’s changing behaviors,” says Glen Giovannetti, global biotechnology leader at Ernst & Young. In *Beyond Borders*, released in January, Giovannetti noted that while 93% of smaller biotechs considered demonstrating the value of their wares to payers was important, only 13% had added this expertise to their clinical development teams.

“We made the point that they can’t afford to ignore the phenomenon in the market,” says Giovannetti. “To get all the way to the end, spend all this money and be somewhat successful, and then find out that you can’t get the product paid for, then what was it all about?”

As a route to demonstrating value, Giovannetti advises biopharmas to think about “value leakages,” such as where care isn’t optimized or properly coordinated. “If you think of those as leakages, that’s where the money is,” he says. “If you can address that, it’s going to be easier to demonstrate [value], as opposed to ‘Our medicines allow patients to get back on their feet faster’ or something that has a longer-term payoff.”

**What is value, anyway?**

The difficulty in defining value over time raises the question: Is value always measurable? Bramley laughs. “Oh, boy. That’s a tough one. That’s probably a big philosophical debate.”

“Sometimes, there are moral judgments involved in value. You see that in terms of cultural values for particular therapies, and what Americans view and value may be very different from what Europeans or the Latin American market values. I think some aspects of value are not measurable, at least with our current tools.”

Giovannetti sums up the one thing about which everyone seems to agree. “There is a value discussion that extends beyond just the medicine to ‘What really improves patient outcomes?’”

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**Michael D. Dalzell is a former managing editor of Managed Care.**

**Feedback Please!** Send your letters and comments to editors@managedcaremag.com
Noncancer Research Quietly Advances This Summer

While much of the news about clinical breakthroughs this summer came out of the American Society of Clinical Oncology annual meeting (below), biotechs focused on immunomodulatory and rare diseases were busy moving their discoveries closer to market.

In the immunomodulatory area, some players are tossing out only enough information to pacify investors. Novartis says secukinumab, an interleukin 17A inhibitor, bested etanercept (Enbrel) in a head-to-head trial in patients with psoriasis. Endpoints included PASI-75. Celgene says apremilast achieved its primary endpoint of ACR-20 at Week 16 in treatment-naïve patients with psoriatic arthritis. Both manufacturers promise to tell the full stories at medical congresses later this year.

On the rare disease front, Sanofi, too, is tight-lipped about outcomes from its pivotal study of SAR302503, a JAK-2 inhibitor for myelofibrosis, a rare blood cancer. The primary endpoint was a reduction in spleen volume, which Sanofi says it achieved. Data will be released later this year. In California, a tiny biotech, Alvine, reports success with a phase 2 study of AVL003 in patients with celiac disease. The drug breaks down gluten to prevent inflammation. AbbVie promptly bought the rights to the drug, which is moving on to a phase 2b trial of 500 patients.

Not so hot

After two once-promising treatments for blood cancers didn’t meet their trial endpoints, one hit the dustbin. Eli Lilly ended development of enzastaurin after the kinase inhibitor failed to show a significant improvement in disease-free survival in patients with diffuse large B-cell lymphoma. Pfizer says inotuzumab missed its endpoints in a study of patients with CD22+ non-Hodgkin’s lymphoma, but the drugmaker will sift subpopulation data for clues to other potential uses. Inotuzumab is an antibody-drug conjugate.

At Baxter, investigators are also analyzing subgroup data for signs of hope after Gammagard was no better than placebo in a late-stage study of Alzheimer’s patients. Gammagard is an immune-boosting agent.

Did you hear?

Ketamine — known as Special K among those who abuse the animal sedative for a quick high — is under study as a possible antidepressant. Johnson & Johnson used a reformulation of the drug in research involving 72 hard-to-treat patients. Response rates after 1 day were 64% in the ketamine group versus 28% in a sham group, and after a week, ketamine response remained at 46% versus 28%. The drug is a long way from market, but J&J views it as a legitimate prospect.... European regulators have approved two biosimilar versions of infliximab (Remicade).

‘In 5 years, this meeting will be about immunotherapy’

It’s taken decades to learn how to prod the immune system to fight cancer. This year, the promise of immunotherapies was on full display at the American Society of Clinical Oncology annual meeting in Chicago.

Some caution is warranted: Many of the results presented were from small early-stage studies. Projecting the ability of these therapies to reproduce their successes in larger, noncontrolled environments is like predicting whether a double-A pitcher will throw his curveball for outs against major league hitters. But there was no doubting the enthusiasm over the feeling that cancer researchers are closing in on a new era in treatment — one that will make chemotherapy look downright barbaric. “If you look five years out, most of this meeting will be about immunotherapy,” Mario Sznol, MD, professor of medical oncology at Yale, told the New York Times.

Bristol-Myers Squibb turned heads with nivolumab, which shrunk tumors in 41% of patients with metastatic melanoma when used in combination with ipilimumab (Yervoy). Nivolumab is in a new class called PD-1 therapies, which help the body overcome tumor-induced suppression of the immune system. Lambrolizumab, Merck’s PD-1 for advanced melanoma, also got attention with a 38% overall response rate (ORR) in a 135-patient trial.

Early research suggests that immunotherapy may be a viable approach for many kinds of cancers. For now, most of the data reported are on metastatic melanoma, which until recently was more or less untreatable. In a phase 3 trial, Amgen’s talimogene laherparepvec, or T-Vec, registered a 26% ORR in patients with advanced melanoma, compared with 6% for a control arm, T-Vec, a re-engineered herpes simplex virus, invades tumors and allows the immune system to kill them. In time, Amgen may combine T-Vec with A PD-1.

It’s all very impressive, but as Heidi Ledford reported in Nature from ASCO, few know what the cost of all of this will be. As immunotherapy transforms cancer into a chronic disease, society may have some hard choices to make.
Infliximab is the biggest biologic to gain biosimilar competition in Europe. It has patent protection there until 2015 and in the United States until 2018.

—Michael D. Dalzell

All clinical trials described in this column are phase 3, randomized, controlled studies unless otherwise specified.
Biomarkers are unquestionably the most compelling topic in rheumatoid arthritis right now. Just this past June, at the annual meeting of the European League Against Rheumatism (EULAR) in Madrid, they were the focus of an unprecedented number of studies, whether directly, in the case of putative or proposed biomarkers in various stages of validation, or indirectly, as the proposed solution to problems ranging from adherence to switching to redefining early and established disease.

For some time now experts have agreed on the need for early and aggressive treatment of RA, an approach that increases the likelihood of achieving remission, reduces disability related to RA, lowers the risk for cardiovascular and other complications, and improves long-term outcomes. But while this approach has indeed begun to improve treatment, it is rapidly becoming old news. Physicians and researchers are already looking ahead, hoping that biomarkers might bring greater objectivity and precision to the treatment of RA, and in turn, more opportunities to improve overall management of the disease.

Among the most coveted biomarkers are those that would enable diagnosis of RA at earlier (and eventually presymptomatic) stages of the disease, and dynamic biomarkers that would lead to improvements over current disease assessment tools. Research in each of these areas has already yielded two commercially available tests: 14-3-3eta, a proprietary protein biomarker (Quest Diagnostics) used to improve early diagnosis of the disease, and Vectra DA (Crescendo Bioscience), a multibiomarker panel that enables more objective assessment of disease activity. Yet clinicians are still eagerly awaiting the availability of additional tests.

“Of course we would like to have biomarkers that would tell us who is most likely to respond to the different treatments available,” says Joan Bathon, MD, director of the division of rheumatology at New York–Presbyterian Hospital and Columbia University Medical Center and editor-in-chief of Arthritis and Rheumatism. “And it also would be very desirable to identify patients who are likely to have more aggressive disease. If, for example, a biomarker could tell us that a particular patient’s disease is likely to be mild, we might not want to take some of the risks associated with aggressive therapy.”

What biomarkers do

Biomarkers, which have been defined as characteristics that can be objectively measured as indicators of normal or pathologic biological processes, or responsiveness to therapy, already have been used for years to assist in making a clinical diagnosis of symptomatic RA. Testing for the presence of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) is currently the primary means by which RA is diagnosed. However the sensitivity and specificity of these markers is limited. The next generation of biomarkers will be not only actionable but also what William H. Robinson, MD, PhD, associate professor of rheumatology and immunology at Stanford University, describes as “mechanistic,” or more firmly rooted in disease pathogenesis.

“In rheumatoid arthritis,” says Robinson, “there is a tide of inflammation, meaning that many different cells and pathways and molecules become activated and elevated. In many cases those that are activated are just along for the ride, but not actually causing the disease.” From among the select number that do cause disease, researchers hope to identify mechanistic biomarkers from which they can extract valuable information that can guide

Will Biomarkers Be Next Leap Forward in RA?
Along with greater precision, they could bring opportunities to coordinate the efforts of health plans and PBMs
clinical decision making. But regardless of new discoveries, RF and ACPA tests will continue to have value.

“It’s important to recognize,” says Robinson, “that single biomarkers may be informative on a population level, but not necessarily on the level of an individual patient.” Multiple biomarkers “are likely to give more complete information about the state of the immune system and the autoimmune process.”

A validated biomarker used in conjunction with RF and ACPA, then, might help to improve the sensitivity and specificity of diagnostic testing, and that is exactly the idea behind 14–3-3-eta, the protein biomarker that Quest Diagnostics made commercially available in 2013, under a licensing agreement with Augurex. The 14–3-3-eta protein can be considered a mechanistic biomarker as defined by Robinson at Stanford, since its functions include the regulation of intracellular communication networks that are involved in inflammatory processes relevant to RA.

Health plans hope RA biomarkers will improve outcomes

Most health plans and PBMs are well aware that new biomarkers for RA may be on the horizon and are already hoping that they will help bring welcome changes in clinical practice. For example, three of the most widely used RA biologics — Humira, Enbrel, and Remicade — together rank among the top expenditures in specialty pharmacy, and there is still a lack of data to support the use of one of these over the others. New biomarkers could help guide the selection of treatment and improve many other facets of RA management.

“Biomarkers are very important,” says Ed Pezalla, MD, MPH, national medical director for Aetna’s pharmacy policy and strategy, “because for some diseases you just don’t want to wait for disease progression to find out whether a patient is responding to treatment. With high blood pressure, for example, it’s easy to obtain a measurement and to know right away — sometimes within a week — whether a medication is working. But with a disease like rheumatoid arthritis, assessment can be much more difficult.

“A patient’s symptoms might start to improve, there may be less stiffness, but other things can take a lot longer to figure out. Is the inflammation in the patient’s joints leading to more joint damage? You have to do tests to answer certain questions and the old tests are just not specific enough.”

Pezalla says that new biomarkers may have the potential to improve the coordination of medical and pharmacy efforts by eliminating duplication and the unnecessary use of certain medications. They may even reduce the need for prior authorization and other controls.

“If biomarkers could provide us with information up front about how a particular patient should be treated, that would be extremely helpful. We know that there are different courses of the disease and that patients should not be treated the same.

“If someone has mild disease that won’t progress very much, then you want to be sure that you aren’t exposing that patient to more side effects than necessary. With regard to the selection of treatment, in some cases valuable information from biomarkers could preclude the need for PA and other sorts of controls, but these are unlikely to be eliminated entirely. While certain specialists are very good about following appropriate guidelines during treatment, there are instances where we find that appropriate testing is not being done. So we’ll continue to use prior authorization not only to control costs, but also to ensure that everyone prescribing treatment is following appropriate guidelines.”

Biomarker developers in all therapeutic areas have suggested that by eliminating some of the waste associated with current treatment protocols, biomarkers might ultimately pay for themselves. Pezalla says that while payers would welcome cost-effectiveness analyses, ultimately outcomes are most important.

“Biomarkers show a lot of promise when it comes to reducing costs, but it’s difficult to make a broad statement about whether they will pay for themselves. It depends on the relative cost of the different therapies and the costs of the tests. Certainly the primary goal in health care is to improve overall outcomes. So when we look at covering a test we aren’t just looking at the cost.

“We want to know whether the test does what it is supposed to do, and if it’s an FDA approved test, we know that it does. And most importantly, we want to know whether a test leads to better outcomes for a patient or better clinical decision making.

“If those things can be demonstrated,” says Pezalla, “Then we are going to cover the test.”
There’s no slacking off once you become a patient. Appointments bombard the calendar. There are phone calls to make and pills to take — and lots of them as the health problems multiply. So now there are trips to the pharmacy. Maybe there are lab tests or therapy sessions. “All the work accumulates,” says Victor Montori, MD, an endocrinologist and shared decision-making expert at the Mayo Clinic. “It has to be implemented and it competes with the other things the patient needs to do.”

And let’s not forget that the people doing this work are dealing with an illness, so they are probably also dealing with a draining combination of fatigue, pain, gastrointestinal distress, and assorted other woes. It’s a lot to ask. So Montori and others have proposed a new way of approaching health care that they’ve dubbed minimally disruptive medicine. Great idea …

The concept, first proposed in a 2009 BMJ opinion piece, is for providers to work at striking a balance between the increasingly complex burden of treatment people assume when they are ill, and the capacity they have for handling treatment-related tasks and demands.

In some cases, minimally disruptive medicine might mean cutting back or simplifying treatments. In others, it might mean “capacity building” so people are better able to shoulder their treatment burden. Those capacity-building efforts could range from treating depression to arranging transportation to appointments to updating a prescription for corrective lenses so a patient could see better.

Montori says overwhelmed patients stumble into noncompliance: “They are not choosing to be noncompliant; they just don’t have the capacity to comply.” So, by his reasoning, minimally disruptive medicine would improve compliance, which presumably cascades nicely into better outcomes, lower hospitalization rates, and reduced costs.

The target population for the approach is people with several chronic diseases, but anyone with a complicated health situation would stand to benefit, Montori figures.

Carl May, a prominent British medical sociologist, wrote the BMJ article with Montori and Frances Mair, a British expert on primary care. May is known for his normalization process theories that offer explanations for how and why new technology gets adopted. Minimally invasive medicine reflects the flip side, in medical context: how and why people do not adopt new treatments.

You can also see traces of motivational interviewing in Montori’s formulation because of the emphasis on patient preference and tapping into intrinsic motivations. And, naturally, there’s a hefty dose of shared decision making, given his background, although shared decision making has tended to focus on major medical events such as surgeries rather than on sifting through the day-in, day-out tasks of keeping a chronic disease in check.

Maureen Bisognano, president of the Institute for Healthcare Improvement (IHI) in Cambridge, Mass., — the organization that gave us the “triple aim” — is enthusiastic.

“I think it is the next horizon in health care,” she says. “It is this wonderful way to say ‘I am the professional. I will take on the burden of redesigning health care so you can focus on your health.’ That is what I love about minimally disruptive medicine.”

… but hard to make happen

Sounds pretty good. But are there any takers? Montori concedes that adoption of minimally disruptive medicine “has been an extremely frustrating ride.”

continued on page 56
Indications

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

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

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

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

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

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

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

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

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

Safety Considerations

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

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

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

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

SERIOUS INFECTIONS

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

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

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

- Do not start HUMIRA in patients with an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- Consider the risks and benefits of treatment in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection. Patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.
- Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.
- Drug interactions with biologic products: A higher rate of serious infections and other potential pharmacological interactions.

MALIGNANCY

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

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.
- Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.
- Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NUMEROUS REACTIONS

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

HEMATOLOGIC REACTIONS

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

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

CONGESTIVE HEART FAILURE

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

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

AUTOIMMUNITY

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

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

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

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


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

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Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to severe chronic plaque psoriasis who are candidates for systemic immunosuppression and azathioprine or 6-mercaptopurine and their malignancies that are not usually observed in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn’s disease (CD), ulcerative colitis (UC), and psoriasis. Over 34,000 patient-years of HUMIRA, the observed rate of lymphomas in clinical trials of HUMIRA cannot be compared to rates of lymphomas observed in a broader patient population. Patients with RA or psoriasis have a higher incidence of lymphomas compared to the general population. HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of treatment of 4 months for HUMIRA-treated patients and a median duration of treatment of 4 months for control-treated patients. In the context of clinical trials of all the TNF-blockers, the most frequent serious infections observed among TNF-blocker-treated patients have been cutaneous abscesses, parotiditis, osteomyelitis, pericarditis, pneumonia, and sepsis.

HUMIRA can cause serious side effects.
- Infection and Infusion Reactions
- Anaphylactic and anaphylactoid reactions
- Serious infections involving various organ systems and sites that may lead to severe chronic plaque psoriasis who are candidates for systemic immunosuppression and azathioprine or 6-mercaptopurine and their malignancies that are not usually observed in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn’s disease (CD), ulcerative colitis (UC), and psoriasis. Over 34,000 patient-years of HUMIRA, the observed rate of lymphomas in clinical trials of HUMIRA cannot be compared to rates of lymphomas observed in a broader patient population. Patients with RA or psoriasis have a higher incidence of lymphomas compared to the general population. HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of treatment of 4 months for HUMIRA-treated patients and a median duration of treatment of 4 months for control-treated patients. In the context of clinical trials of all the TNF-blockers, the most frequent serious infections observed among TNF-blocker-treated patients have been cutaneous abscesses, parotiditis, osteomyelitis, pericarditis, pneumonia, and sepsis.

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points for antibodies to adalimumab during the 6- to 12-month period.

Immunogenicity

- HUMIRA: 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week. 
- Patients on HUMIRA may receive concurrent medications, except for two specific medications. 

- It is recommended that, if possible, be brought up to date with vaccination against influenza and pneumococcal vaccine. 

- The vaccination guidelines to be followed are given in the “Immunocompromised Patients” section of the label. 

- The combination of HUMIRA with TNF blockers increases the risk of developing adverse events, including infections.

- There have been reports of severe hepatic reactions including acute hepatic failure.

- Treatment with HUMIRA can lead to a higher rate of autoimmune disease development compared to placebo.

- These trials included reports of serious infections.

- The rate of positive PPD test in patients with active TB was 0.07 per 100 patient-years and the rate of positive PPD test in patients with active infection by live vaccines in patients receiving HUMIRA. 

- HUMIRA may not be given to patients with a history of severe infusion reactions. 

- The safety profile for patients with UC treated with HUMIRA was similar to that previously observed in patients with CD treated with HUMIRA.

- The safety profile for patients with PsA and AS treated with HUMIRA was similar to that previously observed in patients with RA treated with HUMIRA.

- Approximately 1% of patients treated with HUMIRA developed characteristically smooth, shiny papules that may resolve with continued treatment or may persist or become hyperpigmented. 

- The following adverse reactions have been identified during post-marketing surveillance of HUMIRA.

- The frequency and type of adverse reactions occurring during treatment with HUMIRA are similar to those observed in placebo-controlled and open-label extension studies. The safety profile in patients with RA, HUMIRA Studies RA-I through IV.

- The safety profile for patients with PsA and AS treated with HUMIRA was similar to that previously observed in patients with RA treated with HUMIRA.

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Live Vaccines
Avoid the use of live vaccines with HUMIRA (see Warnings and Precautions).

Cytokine/Adalimumab Substrates
The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA or other adalimumab therapy, adalimumab concentrations may be increased or decreased, respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nonclinical studies have not been conducted in animals to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the mouse micronucleus test or the in vivo clastogenicity test. However, a clastogenic or mutagenic effect of HUMIRA was observed with the in vivo mouse micronucleus test or the Salmonella/E. coli (Ames) assay, respectively.

The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administration of live-attenuated vaccines.

Human Data
In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood (e.g., as in cord (n=10) and infant blood (n=6) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16–19.7 μg/mL in cord blood, 4.39–17.1 μg/mL in infant blood, and 0.06–1.6 μg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab activity across the placenta. In addition, one infant had levels at each of the following levels: 16 weeks (1.94 μg/mL), 6 weeks (1.31 μg/mL), 8 weeks (0.933 μg/mL), and 11 weeks (0.532 μg/mL). In animal studies, adalimumab is detectable in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data
An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg. Doses up to 10 mg/kg have been administered to pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood (e.g., as in cord (n=10) and infant blood (n=6) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16–19.7 μg/mL in cord blood, 4.39–17.1 μg/mL in infant blood, and 0.06–1.6 μg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab activity across the placenta. In addition, one infant had levels at each of the following levels: 16 weeks (1.94 μg/mL), 6 weeks (1.31 μg/mL), 8 weeks (0.933 μg/mL), and 11 weeks (0.532 μg/mL). Suggesting adalimumab can be detected in utero, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA or other adalimumab therapy, adalimumab concentrations may be increased or decreased, respectively.

The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administration of live-attenuated vaccines.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nonclinical studies have not been conducted in animals to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the mouse micronucleus test or the Salmonella/E. coli (Ames) assay, respectively.

What the future may hold
The ability to diagnose RA at a pre-symptomatic stage could become a reality soon. Researchers have identified a combination of serum autoantibodies and cytokines that already have been used to identify asymptomatic individuals who will go on to develop RA up to two years after testing. While the prospect of such a test might be exciting, it would have limited utility in clinical practice, since screening the general population for RA is not feasible.

However, because first-degree relatives of patients with RA have a greater chance of developing the disease, there is a scenario in which this type of early diagnosis could offer value in the clinical setting.

“I might consider using such a test,” says Bathon, “if, for example, I had a patient with RA in her 60s and she expressed concern about whether her children might develop RA.”

Like many biomarkers currently in the pipeline, this diagnostic panel must undergo more testing. Progress with regard to the validation of biomarkers has been slow because of a number of hurdles, many of which can be traced to an incomplete understanding of immunology. Although there is cause for optimism, RA is unlikely to experience the kind of rapid success with biomarkers that oncology has seen, in part because so far genetic tests do not appear to be useful. While genetic traits may have some utility in RA, Robinson says the magnitude of their value isn’t sufficient to base predictive tests on them.

“In cancer,” says Robinson, “a single genetic biomarker can completely guide treatment because that single gene is causing the disease. In contrast, RA appears to be polygenic — we believe that 10 or 20 or more genes may work together to cause susceptibility to the disease.”

Susan Worley is a free-lance writer who specializes in science and medicine.
Roadblocks loom for even minor adjustments that would reduce treatment burden just by making health care more convenient, he has found. For example, at Mayo, the system for scheduling appointments can’t synchronize the appointments of two people. As a result, if a couple wanted to save time and money by having their appointments on the same day at the clinic, it would be difficult to arrange. Another example: timing medication refills so that they occur on the same day, which would save multiple trips to the pharmacy. Pharmacy and payer rules and procedures stand in the way of that commonsensical bit of rescheduling.

The current zeal for performance measurement is another problem, says Montori. “When the patient is overwhelmed and you want to pull back a bit and let things play out, you don’t have a lot of flexibility in that environment,” he says. “You don’t want to look to your colleagues like you are a bad provider because your patients’ blood sugar or blood pressure levels are high because you are focused on the burden of treatment.”

So in the near term, he says, building up patient capacity is the more feasible strategy for putting minimally disruptive medicine into action. What that would mean would vary, but Montori mentions some now-familiar approaches — health coaches, for example — as well as some that aren’t so usual, such as mindful meditation. But isn’t this adding more treatment to treatment-besieged patients? As Montori points out, investing time and effort into solving one or two health problems can often make the rest of them easier to handle.

A quiet cultural change

Montori has been busy drumming up support for his ideas. In addition to articles in peer-reviewed medical journals such as *BMJ*, he gives talks and has a Web site, www.minimallydisruptivemedicine.org. In medicine, if it can’t be measured, it doesn’t exist, so he has also been working with colleagues on ways to measure the burden of illness.

But shared decision making has been around a lot longer than minimally disruptive medicine, and getting shared decision making incorporated into medical practice has been slow going, says Jack Fowler, senior scientific adviser at the Informed Medical Decisions Foundation in Boston, a major promoter of shared decision making. “The rate at which it is practiced in routine medical care is not high — and that is what we are trying to change.”

Despite Montori’s misgivings about slavish attention to performance measures, the right kind might provide the leverage needed to bring about the kind of change he is looking for. Increasingly, provider compensation is being tied to patient survey results, and today’s surveys are digging much deeper than the bland patient satisfaction surveys of yore.

Bisognano sees fertile soil for Montori’s ideas in today’s renewed efforts to manage health care costs and quality with value-based contracts and payment schemes like shared savings and episode-based payment. She notes that as many as half of all prescriptions go unfilled. Shift to a minimally disruptive medicine mindset and adherence would improve, she believes, because providers would be focused on removing the obstacles that people face in getting and taking those medications. Cost savings will follow if the medical management of chronic health conditions is improved.

Bisognano also sees an opening for Montori’s ideas because being more sensitive to patient preferences and values should bear cost-savings fruit: “When patients describe what matters to them, in most cases, what they want is less, not more, and that is where the savings come in.” Payment that rewards providers for time spent engaging patients, not just prescribing to them, will also help, she says.

Ultimately, though, Montori says that American medicine needs an overhaul, a culture change. The goal should be to view health care as a means to an end. “We need to recognize people are living, not to be good patients, but to be good parents, good siblings, good spouses, good teachers, good coaches,” says Montori. “We need to get as much health back into their lives as possible. And then we need to get out of their way.”

Peter Wehrwein is a frequent contributor to Managed Care.
How oncologic medications are covered in state health exchanges “might lead to new definitions and standards for medical necessity,” according to a study (“Analyzing the Affordable Care Act: Essential Health Benefits and Implications for Oncology,” http://tinyurl.com/ACA-oncology) by the American Society of Clinical Oncology. The authors review state-required oncologic drug classes in place now with respect to range — meaning, for instance, that Health Plan X might be allowed to cover no drugs in a certain class in a certain state while Health Plan Y decides to cover eight drugs in that same state. It also looks at the average for each class and how the drugs in the classes are most commonly covered in the states. “Given the rapid technology innovation in the oncology drug category overall, the challenge for state exchanges will be to control care cost,” says F. Randy Vogenberg, RPh, PhD, principal of the Institute for Integrated Healthcare and a member of Managed Care’s Editorial Advisory Board. Underwriting and actuarial equivalence requirements will most likely create unintended consequences state by state regarding coverage of any specific drug, especially newer generation brand drugs, he predicts. Medical device and diagnostic advances may provide better diagnosis under medical coverage sections of the exchange, but could face the same fate as drugs. “Off-patent generic oncologic agents will become a bulwark for most state exchange formularies in order to create some level of consistency in coverage while containing cost and creating more predictability in coverage exposure,” says Vogenberg. “Medicaid and insurance carriers participating in Medicaid will be challenged to provide essential health coverage while not bankrupting state budgets. How essential benefits get defined more clearly and operationalized will be an important step to determining whether state exchange coverage of cancer drugs fulfills the intended promise of health care reform expansion.”

### How anti-neoplastics are covered in states now

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples of drugs</th>
<th>Range</th>
<th>Average</th>
<th>Most common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Altrenine, chlorambucil, melphalan, lomustine, cyclophosphamide</td>
<td>0–8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Anti-angiogenic agents</td>
<td>Lenalidomide, thalidomide</td>
<td>0–2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Anti-estrogens/modifiers</td>
<td>Estramistine, tamoxifen</td>
<td>0–3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Anti-metabolites</td>
<td>Mercaptopurine</td>
<td>0–2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anti-neoplastics</td>
<td>Not listed</td>
<td>0–52</td>
<td>30</td>
<td>52</td>
</tr>
<tr>
<td>Anti-neoplastics, other</td>
<td>Fludarabine, leucovorin, mitoxantrone</td>
<td>0–6</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Aromatase inhibitors, third generation</td>
<td>Anastrozole, letrozole</td>
<td>0–3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Enzyme inhibitors</td>
<td>Etoposide, topotecan</td>
<td>0–3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Molecular target inhibitors</td>
<td>Erlotinib, gefitinib, everolimus, dastatinib, imatinib, nilotinib, lapatinib, pazopanib, sorafenib, sunitinib</td>
<td>0–11</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Monoclonal antibodies</td>
<td>Rituximab</td>
<td>0–3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Retinoids</td>
<td>Alitretinoin</td>
<td>0–3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Notes: Columns 3–5 show the number of drugs covered. The report aggregates supplemental information regarding state EHB benchmark selection, provided from CCIIO regarding the EHB proposed rule. Abbreviations: CCIIO, Center for Consumer Information and Insurance Oversight; EHB, essential health benefit. Source: “Analyzing the Affordable Care Act: Essential Health Benefits and Implications for Oncology,” American Society of Clinical Oncology.
New Sentinel Lymph Node Mapping Tool Spots Cancer With Futuristic Effectiveness

In two studies, Lymphoseek outperformed previous agents in identifying nodes containing metastatic malignancies

Thomas Morrow, MD

With this summer’s release of a new Star Trek movie, a new generation of viewers was exposed to visions of the future — something Star Trek first provided more than 47 years ago. Although most of us will never get our wish for access to a “beam me up, Scotty” device, we have been rewarded with some pretty significant technology in part inspired by this series, such as the cell phone.

In addition to consumer devices, Star Trek has fascinated audiences with visions of medicine in the future. One of the most interesting devices has been the tricorder, a hand-held device that had the ability to diagnose problems deep within the body. Who would have thought it possible in 1966, the year Star Trek was first released, that we would eventually see three-dimensionally within the body with the technology of CAT, PET and MRI scans or the impressive ultrasound devices we now have?

Uses of sentinel lymph node mapping

Now another example of Hollywood’s fiction has become a reality. With the approval of a new radiopharmaceutical “dye,” physicians can use a hand-held gamma counter, a device slightly larger than the tricorder, to find hidden lymph nodes in patients diagnosed with breast cancer or melanoma.

Surgeons have long used sentinel lymph node (SLN) mapping to find nodes that drain the area of a newly diagnosed malignancy to determine if they are free of disease or have microscopic pockets of the malignancy. This surgical endeavor is a key part of staging these two deadly cancers and is used to determine future treatment options. The gold standard process for this procedure is to inject a compound, vital blue dye (VBD — literally a blue ink-like substance) into the site of the tumor and follow it downstream to the associated lymph nodes. VBD has been used since most of today’s adults were in diapers.

In conjunction with this, more recently, some physicians used a home-brewed colloidal radiotracer with mixed results, but the VBD is still the gold standard. The overall efficiency of the SLN identification is highly dependent on the specificity and retention of the agents used in the mapping injection.

The ideal radiopharmaceutical agent should be:

- Standardized, with minimal need for preparation
- Nontoxic and relatively painless, to avoid the need for a local anesthetic that might interfere with the rate of lymphatic uptake
- Promptly taken up by lymphatic vessels
- Quickly transported to the first-echelon lymph nodes in high quantities
- Characterized by minimal pass-through to the second-echelon lymph nodes
- Able to co-localize in nodes that were stained by the VBD

Is Lymphoseek what we seek? Obviously the ultimate goal is to identify nodes containing tumor regardless of whether they are stained blue with traditional VBD injections. As mentioned earlier, worldwide there are numerous colloidal preparations that have been used with varying success. Until recently, none were universally accepted, specifically targeted, or FDA-approved.

This has all changed with FDA approval of a new marker named Lymphoseek (technetium Tc-99m tilmanocept) (Navidea Biopharmaceuticals), a targeted radioactive

Thomas Morrow, MD, is the immediate past president of the National Association of Managed Care Physicians. He has 24 years of managed care experience at the payer or health plan level. Contact him at TMorrow@ManagedCareMag.com.
Lymphoseek contains a mannose-based ligand that attaches to the CD206 receptor on the macrophages and dendritic cells within the lymphatic tissue. A ligand and receptor is analogous to the two pieces of velcro or a lock and key that must match in order to attach to each other. Tilmanocept contains numerous mannose moieties that allow for easy binding to these receptors.

Thus, the radio-tagged injection accumulates in lymphatic tissue and can be detected by the hand-held probe allowing surgeons to easily find the tissue for biopsy. After an injection of Lymphoseek, the nodes can be detected within 10 minutes as the radioactive agent is actually taken within the cells, where it remains for many hours. There is minimal leakage into distant nodes.

Two almost identical open-label, multicenter, single-arm, phase 3 studies were performed to obtain FDA approval of Lymphoseek. Each enrolled patients with either melanoma or breast cancer. A total of 332 patients were enrolled over a three-year period, roughly half with breast cancer and half with melanoma. After mapping was done with both VBD and Lymphoseek, 685 nodes were removed as part of the combined studies.

Inclusion criteria included:

- No presurgical evidence of lymph node metastases
- Histologically confirmed presence of unilateral breast cancer or confirmed presence of cutaneous melanoma
- Candidacy for surgical intervention
- Planned lymph node mapping
- Age ≥18 at time of consent
- Negative pregnancy test, postmenopausal status or status after sterilization procedure

The radiopharmaceutical agent and the VBD were administered in one of two routes. For melanoma patients both were injected intradermally; for breast cancer patients the injections were given into the subareolar or periareolar region. The patients were injected with both the Lymphoseek and the VBD shortly prior to exploratory lymph-node surgery, and intraoperative lymphatic mapping was performed visually, manually and using a hand-held gamma detector probe. Masses found were surgically excised by any of the above methods. All material was sent to the laboratory for histopathology.

A comparison of the number and percentage of resected nodes that contained Lymphoseek and/or the blue dye was made. Lymphoseek was present in 94%–100% of resected nodes as compared with 59%–70% found by blue dye in breast cancer and melanoma patients. Thus, Lymphoseek found more associated nodes.

Lymphoseek found a much greater percentage of metastatic cancer-containing nodes than did VBD. In fact, of malignant nodes found, Lymphoseek alone (and not VBD) was present in 241 removed nodes (29%–41% of nodes) in the combined data. Conversely, VBD alone (with no radioactive agent) was present in only eight nodes in the entire study, none of which contained malignancy.

Of even more interest is that 4 of the 34 metastatic nodes in the melanoma patients were detected by Lymphoseek alone. In the breast cancer patients, metastatic disease was picked up by Lymphoseek in 31 of the 33 positive patients and only 25 of the 33 were found in the VBD group. (Note, some nodes were discovered by palpation or visually with no dye during the open surgery.) In both types of cancer no patient had a malignancy that was found only by VBD.

Managed care implications

Proper diagnosis and staging are crucial in the treatment of cancer. The clinical trials associated with FDA approval of Lymphoseek clearly demonstrated the superiority of Lymphoseek over the “blue” standard. This new radiopharmaceutical combined with a gamma probe now offers a more precise staging tool, which has the potential to improve outcomes, a concept that Trekkies will welcome in their continued search for Tomorrow’s Medicine.

The author is a director in the value-based health department at Genentech. He has had no other industry affiliations in the past three years. The views expressed in Tomorrow’s Medicine are the author’s alone.
Physician-Owned Hospitals Forced To Plead Their Case

The Affordable Care Act stunts the growth of these institutions, but will quality of care and competition suffer as a result?

By Frank Diamond

The Affordable Care Act prohibits construction of new doctor-owned hospitals if those institutions want to accept Medicare or Medicaid patients, because government officials worry that the doctors’ financial interests in such institutions encourages more tests and procedures.

In the meantime, though, physician-owned hospitals, which, for the most part, specialize in heart and orthopedic surgeries, are winners in health reform provisions that reward hospitals for quality. Nine of the ten hospitals getting the largest bonuses are owned by physicians.

Typical scenario

Jaan Sidorov, MD, a consultant and member of Managed Care’s editorial advisory board, says that for the most part clinician executives at health plans don’t like doctor-owned hospitals. “The typical scenario is that Acme Managed Care Insurance has, say, two hospitals in a region and along comes a third, a specialty hospital devoted to high-volume and high-margin cases that can really hurt a medical loss ratio,” says Sidorov. “Even though the third hospital typically promises to do the same cases for a lower DRG — competition is theoretically good — versus the two other competitors, what they lose in payment is made up by internal efficiencies and more patient throughput. Plus they create their own preference-sensitive demand. The latter is the problem.”

As might be expected, R. Blake Curd, MD, the vice president of Physician Hospitals of America, doesn’t agree, saying that doctor-owned hospitals increase competition, and that competition is good. “We certainly throw another variable into the mix,” says Curd. “If you have one hospital in town and that’s the only place people can get care, it’s pretty easy for that institution to drive the purchase price. That’s basic economics. If you have only one provider, what choice do you have? In every study that I have seen, physician-owned hospitals in their marketplace are either the number one hospital in that market, or certainly within the top three.”

Insurers should not be overly concerned that doctor-owned hospitals might charge higher rates based on performance, says Curd. “In general, the payers sets the rates and then in most instances you either accept them or you don’t get access to their patient population.”

But Richard G. Stefanacci, DO, MBA, associate professor of health policy at the University of the Sciences in Philadelphia and member of Managed Care’s editorial advisory board, says that “the concern for managed care and Medicare is the ability for self-referrals and increased costs associated with that behavior.”

Nevertheless, Curd views the ACA’s restrictions on doctor-owned hospitals as undermining competition. “In many markets the health care system doesn’t change because it’s monopolized by these monolithic health care institutions that have been around for a long time. The not-for-profits frequently don’t change the way they do business until they’re forced to by some kind of competition.”

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Physicians and hospitals will become more integrated* in the next three years, according to a survey by the Deloitte Center for Health Solutions (http://tinyurl.com/Deloitte-doc-survey). This, of course, continues a trend whose ramifications for health insurers we've explored (http://tinyurl.com/provider-power). Primary care physicians (PCPs) and surgeons are most likely to think that this will happen, but there is clear agreement among all providers.

The Deloitte survey says, “Physicians consolidated in the past one to two years to gain or retain income security (29% of all physicians who had consolidated) or leverage negotiation power with payers (21% of all physicians who had consolidated).”

Most physicians are pessimistic about the future of medicine, with 57% saying that the practice of medicine is in jeopardy and 72% that the best and brightest might not consider a career in medicine. Physicians believe that they face a trade-off between clinical autonomy and bargaining power. “Larger work settings offer better conditions for contracting with third-party payers (89% of all physicians feel this way) whereas clinical autonomy was a valued feature of and more likely to be a feature of solo practices (81% of all physicians).”

Most satisfying element about practicing medicine

* Harry Greenspun, MD, senior adviser for health care transformation and technology at the Deloitte Center for Health Solutions, says, ”While the term [integrated] was not specifically defined for respondents, physicians commonly interpret it to encompass a broad spectrum from loose affiliation to outright employment by a hospital.”

Source: Deloitte 2013 Survey of U.S. Physicians