HIV
FRAGILE POPULATION ENTERS MANAGED CARE

Q&A: David J. Brailer, MD, PhD,
On IT’s Increasing Value.................. 26

The QALY Controversy:
What Is a Treatment Worth? ........... 32

Biologics
Next-Generation Sequencing .......... 38

www.managedcaremag.com
WE’RE SO EXCITED ABOUT OUR NEW OFFERING, WE CAN BARELY CONTAIN OURSELVES.
COMING SOON FROM THE GLOBAL LEADER IN RENAL THERAPY.

For more information please contact Fresenius Medical Care Medical Information & Communication at 855-616-2309.
Fresenius Medical Care and triangle logo are registered trademarks of Fresenius Medical Care Holdings, Inc. or its affiliated companies.
©2013 Fresenius Medical Care North America. All rights reserved. P/N 102168-03 Rev A 10/2013
Health Plans Must Stay Nimble As Daunting Challenges Mount

By John Marcille

For the thankful parents who are able to keep their young adult child on their health plan, as well as for the millions who are angry at having had their coverage terminated, there is no ignoring the Affordable Care Act. Opponents vow to repeal; supporters say, It’s the law, deal. Health insurers too have to deal with the ACA and the many challenges it presents. In our cover story on page 12, senior contributing editor Michael D. Dalzell does a wonderful job of explaining how the health system isn’t prepared to treat all of the HIV patients who are moving into Medicaid and commercial plans.

The article kicks off with an anecdote about a patient being moved into a Medicaid plan in which his assigned primary care physician seems to put most of his effort into selling a weight-loss product and whose paper handouts contain ads for a pizzeria.

ACA supporters can take heart that a rough launch does not necessarily mean a crash landing. David J. Brailer, MD, PhD, was the health technology “czar” under President George W. Bush. Brailer, the subject of our Q&A on page 26, was charged in 2004 with the daunting task putting every patient’s information into an electronic health record.

“No one then would have guessed how far we’ve come,” he recalls. “We have seen very little partisan bickering, and I think that in part is why it has moved forward so well.”

Our stories about quality-adjusted life-years (QALYs, page 32) and next-generation sequencing (page 38) point to further methodological and clinical advances. They are not just about the bottom line. They are about quality of care and of life. These are profound issues that touch everyone, and with which health plan clinicians must forge some sort of accommodation with patients and providers, not to mention the federal government.

Things are moving fast and we’ll be there to keep you up to date.
EDITORIAL ADVISORY BOARD

MANAGED CARE publishes original papers and feature articles dealing with diverse elements of the health care system. These include impartial peer-reviewed research and review articles examining clinical and financial aspects of managed care.

ALAN G. ADLER, MD
Senior Medical Director
Independence Blue Cross

PARTH S. ANBIL
Associate Partner, Strategy & Transformation
Healthcare & Life Sciences Industry
IBM Global Services

JAN BERGER, MD, MJ
President
Health Intelligence Partners
Chicago, Ill.

THOMAS BODENHEIMER, MD
Family and Community Medicine
University of California–San Francisco
San Francisco, Calif.

PETER BOLAND, PhD, ScD
President, Boland Healthcare
Berkeley, Calif.

J. LYLE BOOTMAN, PhD
Dean
College of Pharmacy
University of Arizona
Tucson, Ariz.

LARRY S. BORESS, MPA
President & CEO
Midwest Business Group on Health.
Chicago, Ill.

H. ERIC CANNON, PharmD
Chief of Pharmacy
SelectHealth/Intermountain Healthcare
Salt Lake City, Utah

GEORGANNE CHAPIN, MPH JD
President & CEO
Hudson Health Plan
Tarrytown, N.Y.

VIVIAN H. COATES, MBA
Vice President
Information Services and Health Technology Assessment
ECRI Institute
Plymouth Meeting, Pa.

HELEN DARLING
President
National Business Group on Health
Washington, D.C.

GARY SCOTT DAVIS, JD
Partner, Health Law Department
McDermott, Will & Emery LLP
Miami, Fla.

D.S. (PETE) FULLERTON, PhD, RPh
Strategic Pharmacy Innovations
Seattle, Wash.

ARCHELLE GEORGIOU, MD
Founder
Georgiou Consulting
Minneapolis, Minn.

JEFF GOLDSMITH, PhD
President, Health Futures Inc.
Charlottesville, Va.

ALICE G. GOSFIELD, Esq.
Principal, Gosfield & Associates, P.C.

MICHAEL T. HALPERN, MD, PhD
Senior Health Scientist
Health, Social, and Economics Research
Research Triangle Institute
Washington, D.C.

JAN HIRSCH, PhD
Associate Professor of Clinical Pharmacy
Scaggs School of Pharmacy
and Pharmaceutical Sciences
University of California–San Diego
San Diego, Calif.

GEORGE J. ISHAM, MD
Senior Advisor
HealthPartners
Minneapolis, Minn.

LUCY JOHNS, MPH
Independent Consultant
Health Care Planning and Policy
San Francisco, Calif.

ROBERT C. JOHNSON, MS
President, R.C. Johnson & Associates
Former President, American Pharmaceutical Association
Scottsdale, Ariz.

THOMAS KAYE, RPh, MBA
Pharmacy Consultant
Louisville, Ky.

RANDALL KRAKAUER, MD
National Medical Director, Medicare
Aetna
Princeton, N.J.

PETER KONGSTVEDT, MD, FACP
President
P.R. Kongstvedt Company
McLean, Va.

THOMAS H. LEE, MD, SM
Network President
Partners HealthCare System
Boston, Mass.

ATEEV MEHROTA, MD, MPH
Associate Professor
University of Pittsburgh
School of Medicine
Pittsburgh, Pa.

MICHAEL L. MILLENSON
Independent Consultant and Author
Highland Park, Ill.

THOMAS MORROW, MD
Director, Value-Based Health
Genentech Inc.
Alpharetta, Ga.

SAM NUSSBAUM, MD
Executive Vice President and Chief Medical Officer
WellPoint
Indianapolis, Ind.

MATT NYE, PharmD
Vice President
Pharmacy Care Support Services
Kaiser Permanente, California
Downey, Calif.

BURTON I. ORLAND, BS, RPh
President
BioCare Consultants
Westport, Conn.

STEVEN R. PESKIN, MD, MBA, FACP
Associate Clinical Professor of Medicine
University of Medicine and Dentistry of New Jersey —
Robert Wood Johnson Medical School.

UWE E. REINHARDT, PhD
James Madison Professor of Political Economy
Princeton University
Princeton, N.J.

EMAD RIZK, MD
President
Mckesson Health Solutions
Newton, Mass.

JOHN ROGLIERI, MD, MBA
Medical Director
New York Life Insurance Co.
New York, N.Y.

TIM SAWYERS, BPharm, MBA, PAHM
Director of Account Management
Magellan Managed Medicaid
Nashville, Tenn.

JAMES M. SCHIBANOFF, MD
Editor-in-Chief, Milliman Care Guidelines
Milliman USA
San Diego, Calif.

STEPHEN W. SCHONDELMEYER, PharmD, PhD
Professor & Director, PRIME Institute
University of Minnesota College of Pharmacy
Minneapolis, Minn.

JAAN SIDOBOV, MD, MHSA
Independent Consultant
Health and Technology Vector
Danville, Pa.

THOMAS D. SNOOK, FSA
Principal & Consulting Actuary
Milliman USA
Scottsdale, Ariz.

RICHARD G. STEFANACCI, DO, MGH, MBA, AGSF, CMD
Chief Medical Officer
The Access Group
Health Policy
University of the Sciences

F. RANDY VOGENBERG, PhD, RPh
Principal
Institute for Integrated Healthcare
Greenville, S.C.

JONATHAN P. WEINER, DrPH
Professor and Director
Center for Population Health
Johns Hopkins University
Bloomberg School of Public Health
Baltimore, Md.
Cover Story

Plans Confront an Influx of Patients with HIV

A lot can go wrong when care is disrupted for a fragile group of patients. Are commercial health plans and Medicaid prepared?

Q&A With David J. Brailer, MD, PhD

The former health technology “czar” on the state of IT today.

Measure Quality-Adjusted Life-Years?

One of several methods used to decide whether a treatment is worth the cost.

Focus on Biologics

Mixed Feelings About Next-Generation Sequencing

Many feel that it encourages use of costly unproven drugs.

Pipeline: Ponatinib Pulled Off Market

FDA questions safety but leaves door open for existing patients.

3 Ways Biomarkers Change Drug Development


Single-Pill Combinations for Hypertension

Patients given single-pill combination therapies have higher rates of compliance to better manage their blood pressure, this report says.

Departments

Editor’s Memo

Challenges just keep on coming.

News & Commentary

Peer pressure works on doctors.

Legislation & Regulation

What’s in a biosimilar name? Conflict.

Medication Management

Software tracks medication problems.

Evidence Review

GERD treatment raises questions.

Formulary Files

Clinical pathways now widespread.

Ad Index

Expect higher costs from heart disease.

Outlook

...
Peer Messengers Deliver On Doctor Improvement

The best way to help physicians improve is to let other physicians show them the way, according to a study in the Joint Commission Journal on Quality and Safety. “Peer messengers … appropriately supported with ongoing training, high-quality data, and evidence of positive outcomes, are willing to intervene with colleagues over an extended period of time,” the study states. “The physician peer messenger process reduces patient complaints....”

Those patient complaints are the foundation of the study “An Intervention Model That Promotes Accountability: Peer Messengers and Patient/Family Complaints.”

Complaints were used in this study to identify underperforming doctors. At a time when patients face more choice and greater financial burden, the researchers say, “Patients and their families are well positioned to partner with health care organizations to help identify unsafe and dissatisfying behaviors and performance.”

The complaints fell into six categories: communication, concern for the patient, care and treatment, access and availability, environment, and billing.

The study, conducted by researchers at Vanderbilt University Medical Center from 2005 to 2009, involved training 178 physician messengers on the best ways to discuss problems with 373 peers who were considered at high risk of dissatisfactory or unsafe performance.

The physicians worked for seven academic and nine other medical centers in the United States. About 25,000 were either employed or associated in some other manner with the institutions.

The messenger physicians received eight hours of training on how to conduct interventions, emphasizing that messengers “share data in a respectful, nonpunitive, nonjudgmental, and nondirective fashion.”

Most of the high-risk physicians (97%) accepted the feedback in a professional manner, and 64% were what the researchers called responders, that is, physicians who improved by at least 15%. The doctors whose scores worsened (17%) or remained unchanged were called “nonresponders.”

“Responders were more often physicians practicing in medicine and surgery than emergency medicine physicians, had longer organizational tenures, and engaged in lengthier first-time intervention meetings with messengers,” the study states. The overall mean and median percentage of reductions in patient complaints were 50% and 80% respectively. Not surprisingly, perhaps, one of the motivations for changing was fear of being sued.

Though highlighting the study’s success, the authors also note that the problem might in fact be much worse because “many persons fear lodging a complaint about their physician’s practice” and “unsolicited complaints surely represent the tip of an iceberg that may be 20 to 50 times the number of reports.”

Ruling Questions Dementia Screening

A lot can change in 10 years, but not a ruling by the U.S. Preventive Services Task Force (USPSTF) about screening tests and possible treatments for early cognitive impairment. In 2003 the USPSTF said that there was insufficient evidence for or against. The task force has reaffirmed that position.

The screenings are meant to be performed by primary care physicians, and while they might detect dementia, “there is no empirical evidence that screening improves decision making” because there’s the question of whether interventions will do more harm than good.

“Expert consensus guidelines state that early detection of cognitive decline may be beneficial because clinicians can optimize medical management, offer relief based on better understanding of symptoms, maximize decision-making autonomy and planning for the future, and offer appropriate access to services that will ultimately improve patient outcomes and reduce future costs,” the study states. “Although this is a logical argument, there is little or no empirical evidence to support it.”

The study “Screening for Cognitive Impairment in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force” is in Annals of Internal Medicine. It includes a meta-analysis of approved anti-dementia drugs that show only a slight benefit, say the authors.

“The average effects of changes in cognitive functioning observed in trials are small, and the clinical importance of population benefits is probably negligible when commonly accepted thresholds are used.”

Not everyone is convinced. David Knopman, MD, of the Mayo Clinic, worries that primary care physicians will totally abandon dementia screening. He tells MedPage Today that doctors should have a good reason to screen and should not do so just because a patient is old.

“On the other hand, if they detect that a person is making mistakes with medications, the person isn’t following their directions, the person is having...”
Iroko is a global specialty pharmaceutical company dedicated to scientific advancements in analgesia.

Using innovative technology, Iroko is developing new drug products based on existing NSAIDs (nonsteroidal anti-inflammatory drugs) with the potential to provide meaningful benefits to patients.

At Iroko, we are committed to responsible pain management.

VISIT IROKO.COM TO LEARN MORE
Register for FormKit.com today and be entered in a drawing to win 1 of 3 WiFi-enabled, 64 GB iPads

Deadline for all drawings: December 31, 2013
Second drawing: December 15, 2013
Third drawing: January 15, 2014

Winners will be notified directly. Announcements will be made in the December, January, and February issues of P&T.

Formkit.com provides around-the-clock free access to specific formulary kit information for the key decision-makers at hospitals, managed care organizations and federal facilities.

Formkit.com is part of PTCommunity.com. During your visit, take advantage of our P&T daily news headlines, weekly newsletters, and P&T TV. The complete contents of P&T can be searched and read online.

Formkit.com requires registration and verification of P&T committee status. Your name will be entered into the drawing once verification is complete.
more auto accidents than can be accounted for by chance..." — these are signs that should not be ignored.

Infections’ True Cost Difficult to Pin Down

When the total costs to society are considered, health care-associated infections (HAIs) acquired in acute-care hospitals are as big an expense as cancer, heart disease, or diabetes, according to a study in the Journal of Medical Economics. Such infections cost between $96 billion and $147 billion annually, says “Economic Burden of Healthcare-Associated Infection in U.S. Acute Care Hospitals: Societal Perspective.”

Researchers admit that assessing those costs is challenging. “Methodological issues abound,” they write. “Previous estimates have been derived in diverse ways from varied perspectives in different settings with dissimilar data. Results can be confusing. Full societal costs, which are more inclusive than commonly reported direct hospital costs, have never been fully measured or reported.”

The authors claim that they are the first to take on this daunting task. To do so they conducted Internet and literature searches for reports, clinical studies and component cost reports.

The data include:
• Epidemiologic information, including total annual hospitalizations and readmission rates
• Economic data, including use of clinical resources and lost work days and life years
• Legal data, including malpractice claims stemming from HAIs and the amounts of settlements

They suggest ways to improve outcomes that will have the added benefit of compiling better data for future studies. They argue for “improved surveillance systems, uniform clinical and economic measures for HAI cost accounting, standards for assessments, and precise reporting of results.”

Briefly Noted

Encouraging news about the future supply of doctors: For the first time the number enrolling in medical schools in the United States exceeded 20,000, says the Association for American Medical Colleges. The 2013–2014 school year sees enrollment of 20,055 students. Four new medical schools opened this year, and existing schools are expanding class sizes, researchers say.... Health literacy tests might benefit patients and doctors alike, according to a study in the journal Surgery. They could give patients a more positive outlook on their treatments while giving physicians a better idea of just what patients do and don’t understand. The tests need to be short and simple, though.

— Frank Diamond

A medical center improves its HEDIS scores

The leaders of Kaiser Permanente San Diego Medical Center didn’t think they were scoring high enough on nine HEDIS measures. Though the center was competitive nationally (above the 90th percentile on six of the measures and within three points of the 90th percentile on three others) it was among the lowest in Southern California.

“Clinical champions” (often specialty department heads) were asked to address the problem, and they set about showing doctors and support staff how to ensure that patients got the care they needed whenever they encountered the health care system. For example, a woman taken to the emergency department might be asked when she last had a mammography.

“In one instance, the clinical laboratory reported that every month, stool samples for colorectal cancer were often discarded because of illegible labeling by patients. A simple fix was to ensure that sample containers were labeled before distribution to patients.”

Performance on selected HEDIS measures improved by 1 to 8.6 percentage points.

HEDIS measure *

<table>
<thead>
<tr>
<th>May 2010</th>
<th>June 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer screening</td>
<td>95%</td>
</tr>
<tr>
<td>Breast cancer screening</td>
<td>90%</td>
</tr>
<tr>
<td>Cervical cancer screening</td>
<td>95%</td>
</tr>
<tr>
<td>Diabetes: Hba1c&lt;9</td>
<td>85%</td>
</tr>
<tr>
<td>Diabetes: Hba1c&lt;8</td>
<td>80%</td>
</tr>
<tr>
<td>Diabetes: LDL-C&lt;100</td>
<td>70%</td>
</tr>
<tr>
<td>Cardiovascular disease LDL-C&lt;100</td>
<td>60%</td>
</tr>
<tr>
<td>Blood pressure control in hypertension</td>
<td>70%</td>
</tr>
</tbody>
</table>

* Derived by dividing the number of people who received a service by all of those eligible for it.
Source: “Redesigning Chronic and Preventive Care to Provide a Regional Safety Net,” the Journal on Quality and Patient Safety, November 2013
Manufacturers Square Off Over Naming of Biosimilars

Argument about safety reflects biosimilars and brands jockeying for market share

By John Carroll

When a small-molecule drug goes generic — as that little purple blockbuster Nexium (esomeprazole magnesium) will next year — manufacturers use the same name for the active ingredient when they push out cheaper knockoffs. But with final FDA rules on biosimilar development still in the hands of regulators, and the World Health Organization looking to gain some global consensus on naming these “follow-on” biologics, there’s a lively regulatory dustup going on over whether the same rules should apply.

The two sides in this debate are easy to identify, as they are already at war over state laws that require pharmacists to notify physicians whenever they substitute a biosimilar for a branded product. And they are sparring over some familiar issues that date back to the original showdown over creating a regulatory pathway for their approval.

Big companies like Amgen and Genentech, which are pushing the state notification bills, have been backing lobbying organizations such as Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization (BIO), and the Alliance for Safe Biologic Medicines to demand different names for biosimilars.

The opposing side, including some of the big generic drug manufacturers such as Hospira, Novartis, and their lead trade group, the Generic Pharmaceuticals Association (GPhA), are insisting on being given the right to use what WHO refers to as the International Nonproprietary Name (INN).

Hanging in the balance is a set of naming rules that may well influence how much of an effort will be required of biosimilar manufacturers to gain widespread adoption of their discounted products. Depending on which side you listen to, the decision could influence drug safety as well as pharmaceutical benefit managers, who are responsible for steering patients to the right product for the right patient — at the best price.

Keeping track of adverse events

“Even identical twins get different names,” says Michael Reilly, executive director of the Alliance for Safe Biologic Medicines. Reilly was one of the industry figures to weigh in regarding the recent WHO meeting on biosimilar names in Geneva. “That meeting was really about whether or not unique names are needed for safety reasons,” says Reilly. From the alliance’s view, the argument is settled in favor of requiring different names.

“This is serious,” he says. “It’s important to know exactly what product [a doctor’s] patient is taking.” And when there are adverse events, which will be inevitable, the physician, regulators, and the industry need to understand precisely which drug was given, he adds.

Reilly and his allies argue that biosimilars are clearly not the same as the originals. Biologics are derived from living cells, and even a slight difference in the product could be a harbinger of a different therapeutic effect. To properly track side effects, a different name would be needed for each.

“Biosimilars are not generics,” adds Reilly. “The generic model doesn’t apply.” Therefore, he argues, neither should the same name be used.

A bipartisan group of six powerful senators, including John McCain (R-Ariz.) and Charles Schumer (D-N.Y.), went out of its way in late October to send exactly the opposite message to Margaret Hamburg, the head of the FDA.

“Biosimilars are not generics,” adds Reilly. “The generic model doesn’t apply.” Therefore, he argues, neither should the same name be used.

A bipartisan group of six powerful senators, including John McCain (R-Ariz.) and Charles Schumer (D-N.Y.), went out of its way in late October to send exactly the opposite message to Margaret Hamburg, the head of the FDA.

Congress, they wrote, considered requiring different names when lawmakers hammered out the Biologic Price Competition and Innovation Act. And Congress declined to do so. The reason, they say, is that legislators felt that different names would create unnecessary
confusion for doctors and patients, possibly triggering medical errors. Also, they add, any such federal regulation would needlessly interfere with state laws on generic substitution.

In the letter they also note that any rule that would require separate names could eliminate some major cost savings that a diverse group of payers has been advocating: “While not all biosimilars will be designated as interchangeable, it is essential that, once a biosimilar has such a designation, a unique name does not stand in the way of otherwise appropriate substitution. Mandatory generic substitution is a common cost saving tool for public and private benefit providers and payers that we cannot afford to lose.”

Express Scripts lobbyist Mary M. Rosado wrote her own letter to the FDA last year and came down squarely on the side of same-name rights, noting that a biosimilar by any other name creates an unnecessary barrier for anyone trying to spread the word on less expensive alternatives to a branded therapy. “To effectively market biosimilars,” she said, “products must share the same INN as the innovator’s product.”

Impeding less expensive biologics?

“People do not want a system to change that has been working quite well,” says Sumant Ramachandra, MD, the senior vice president and chief scientific officer of Hospira, which has been gaining approvals for biosimilars in Europe, where same-name privileges for the follow-ons are allowed.

“As a physician,” he adds, “it’s not my job to remember 10 different versions of a drug’s name. Three pharmacist organizations have said a unique name is not needed, so if anything, this is just one impediment to the adoption of more affordable medicines in the U.S.”

That’s a particularly critical issue, he adds, if you consider that over the next 5 to 10 years the GPhA asserts that biosimilars can start to deliver around $20 billion in annual savings — definitely the high end of the range of expected cost savings.

“The intent of the law was to establish that the biosimilar has been compared to a referenced product, using rigorous scientific principles” that prove that it meets the definition of a similar product, he adds. It’s true that just moving a biologic from one manufacturing site to another can trigger small changes in the therapy’s molecular structure, but the FDA doesn’t require the drugmaker to rename it, he says.

Pharmacy benefit managers in the managed care world would also prefer to keep things simple, says Ramachandra, with some less technologically sophisticated groups likely to experience some trouble classifying a multitude of newly-named biosimilars. “I’ve talked to several pharmacy benefit managers, and it depends on the sophistication of their IT system — their ability to classify different drugs in the same category. They say that keeping the same INN is the best way of keeping things simple and that brand names and National Drug Codes are sufficient for their systems.”

BIO’s position is that Congress should leave the decision to the FDA, allowing the agency to use its scientific know-how to come up with the right decision. The group is adamant that different names are necessary. “Minor differences between innovator and biosimilar products could lead to real differences for patients; therefore it would be inappropriate to permit use of the same nonproprietary name for biological products,” BIO said in a prepared statement.

Reilly notes that the same-name side doesn’t have an exclusive franchise on powerful supporters. Raffaella Balocco Mattavelli, PhD, the INN manager at WHO, has agreed that generic rules shouldn’t apply to biosimilars, he notes.

Reilly also doesn’t believe that the naming issue will play a big role when it comes to the pharmacy benefit administration business. “I don’t think so,” he replied when asked if the PBMs of the world would find it more difficult to steer patients to biosimilars if they had to use different names. “Most people think they’re going to figure out how to do it.”

Three pharmacist organizations have said a unique name is not needed, so if anything, this is just one impediment to the adoption of more affordable medicines in the U.S.”

— Sumant Ramachandra, MD, senior VP at Hospira

MC
Pharmacists Demonstrate Value Of a Problem-Focused Practice Model

Comprehensive medication management may improve outcomes in medical homes

By Thomas Reinke

When the Medicare Part D program was launched, pharmacists successfully promoted the idea that beneficiaries needed more than a way to pay for their medications. And so medication therapy management (MTM) gained a real foothold, sort of. Pharmacists thought they were on their way to realizing a high-priority goal, but Part D MTM services have fallen far short of the expectation that they would be able to move away from their benches into a direct patient care role.

Experts say pharmacists providing Part D MTM services are simply too far removed from the care that patients are receiving to deliver meaningful services. MTM is often provided remotely through call centers operated by the Part D pharmacy plans. Call center pharmacists and those in community pharmacies do not have the medical record information that is necessary for them to evaluate patients and make therapy management decisions.

The lack of patient information leads to inconsistency in the scope and quality of Part D MTM services. Pharmacists find themselves in the frustrating position of not being able to address important therapy problems such as undertreatment; they are left to go after low-hanging fruit such as nonadherence or switching to lower-cost formulary alternatives, things that can be done without access to the medical record.

The underlying issues are that the call center setting for Part D MTM services is wrong and that tools are not available for pharmacists to deliver optimal services. No wonder health plans have not bought into MTM for their commercial plans.

Medical homes are one logical setting for MTM services, Webb says. He adds that the inconsistency in providing MTM is in part due to lack of a clear definition of the service and lack of tools to conduct it. Resolving these problems will advance the role of pharmacists in ambulatory care.

Webb adds, "Physicians say, It makes sense that pharmacists have a role in patient care but I need to better understand your patient process and how it fits into patient-centered care."

Program for comprehensive MTM

A consistent approach to MTM services being designed at the University of North Carolina, UNC, Eshelman School of Pharmacy and implemented and studied in primary care medical practices is an attempt to clearly define MTM services with a focus on resolving medication-related problems and improving patient outcomes. It is for use in patient-centered medical homes and accountable care organizations.

The Individualized Medication Assessment and Planning (IMAP) practice model is a 10-step medication assessment and planning process that clearly lays out problem identification and resolution within MTM services. "The program is intended to be a road map which..."
has been missing in MTM services,” says Mary Roth, PharmD, associate professor at the university’s Eshelman School of Pharmacy. A test of the program was published in a recent issue of Pharmacotherapy.

The protocol or intervention used in the IMAP study leads the pharmacist through a process of preparing for the patient visit, conducting the comprehensive medication review, assessing and identifying medication-related problems, collaborating with the patient’s primary care provider to arrive at a plan for optimizing drug therapy, and working with the patient to implement the plan and ensure understanding. The process also allows for pharmacists to manage therapy according to collaborative practice agreements in place with physicians. This process of care is consistent with the process described by the Patient Centered Primary Care Collaborative in its publication “Integrating Comprehensive Medication Management to Optimize Patient Outcomes.”

IMAP is intended to meet the challenges facing medical homes and accountable care organizations. “IMAP is being developed with an eye on health reform issues,” says Roth. “We have to demonstrate an ROI and the improvements we are making in patient outcomes. Those are the outcomes that everyone is interested in.”

The ACCP’s Webb says, “If you’re going to be a high-performing medical home or ACO, you have to get the medications right. That’s where the value proposition is for earning bonuses or shared savings. Eighteen of the initial quality measures for ACOs have some implication for pharmacy services and therapy management.”

Solving problems

Two core elements in the IMAP model are a clear list of all medication-related problems (MRPs) and equally clear recommendations for resolving them. Roth says this helps deliver better outcomes.

There are six classes of problems: undertreatment, suboptimal dosing, medication monitoring needed, suboptimal drug, adverse drug event, and nonadherence. The problem categories are broken down into additional detail and the program includes specific recommendations for resolving each problem.

Payment difficulties are a major impediment to expansion of MTM services in all settings. “We’re still living in a fee-for-service world and these services are generally not recognized and billable to third-party payers,” says Roth.

The study

In a small pilot study involving 64 elderly patients with multiple chronic illnesses and multiple medications, the comprehensive MTM program led by a clinical pharmacist working in collaboration with a primary care team, reduced medication-related problems and acute health services utilization.

The cohort had many of the medication concerns that are common to the elderly. The mean number of prescription and nonprescription medications was 13.9, (range 5–31), with a mean of 8.6 (range 2–17) prescription medications. The mean number of chronic conditions was 8.5 (range 3–14).

During the six months, the pharmacists identified 419 MRPs — an average of 4.2 per patient. At baseline the most common problems were suboptimal drug use — the drug had no indication or a safer alternative was available; undertreatment — underuse of proven therapies, suboptimal dosing; and nonadherence. Thus, actual problems related to therapy were much more common than adherence problems, which receive much attention.

The program was used in three- and six-month follow-up visits to reassess problems and fine tune action plans developed through the initial assessment. Physicians accepted 94% of pharmacists’ therapy recommendations. At the end of the six-month study, most of the problems identified during that period were resolved. The mean number of outstanding MRPs/patient was 1.0 at the close of the study. The study also claims a 35% reduction in use of acute health services during the period.

The take-away for health plans is that pharmacists remain committed to demonstrating their value in direct patient care roles and are taking steps to establish themselves in more appropriate settings with a practice model that leads to improved outcomes.
Gastroesophageal reflux disease (GERD) occurs when the lower esophageal sphincter (LES) malfunctions and allows acidic stomach contents to enter the esophagus. This can cause persistent symptoms, including heartburn, regurgitation, dysphagia, and belching. Left untreated, acid from GERD can damage the esophageal lining, forming strictures, and in some cases can lead to Barrett’s esophagus, which increases esophageal cancer risk.

Clinical practice guidelines from the American College of Gastroenterology indicate that GERD treatment depends on symptom severity and includes lifestyle modification and control of gastric secretion through medication (typically use of proton pump inhibitors) or, in persistent cases, minimally invasive endoscopic or surgical treatments. The Linx Reflux Management System (Torax Medical, Shoreview, Minn.) is a relatively new minimally invasive laparoscopic surgery option for medically refractory GERD. It is a sphincter augmentation device consisting of a series of magnetic titanium beads connected on a stainless-steel cable. The device is intended to reduce the esophagus’s exposure to acid, improve symptoms, and reduce or eliminate the need for GERD medications. The beads are used to encircle the LES to reinforce the barrier, and magnetic attraction between the beads is intended to close the LES except when needed to allow swallowing of food and liquid. The beads are intended to separate during swallowing.

The evidence base for this technology consists of two prospective case series sponsored by the manufacturer and reporting on 144 patients (Ganz et al. 2013; Lipham et al. 2012). Interpretation of results is difficult because of deficiencies in the comparisons made, reporting of results, patient loss to follow-up, and post hoc analyses after one-year follow-up (for additional details, please download the full report). Outcomes were reported based only on the number of patients available at last follow-up (e.g., 116 of 144 enrolled patients at three-year follow-up, although patient numbers at follow-ups were sometimes unclear). The two available studies provided pre-post-treatment data on medical therapy versus Linx for some outcomes of interest.

The findings to 2 of our 4 key questions are as follows:

**Key question 1: How does the Linx Reflux Management System compare with medical therapy for treating medically refractory GERD regarding esophageal pH, GERD symptom frequency and severity, GERD-related quality of life (QOL), medication use, and patient satisfaction?**

Generally, because of the small evidence base and other quality factors (see above), the available evidence is insufficient to firmly conclude that device implantation resolves GERD symptoms, obviates the need for medication, or definitively improves QOL and patient satisfaction.

Ganz et al. (2013) reported data on an intent-to-treat basis for some outcomes of interest on 98 of 100 enrolled patients, as follows, at one year; 85 patients provided data at year 3.

**GERD-health-related quality of life (HRQL):** At year 3, some patients who received the Linx device reported improved HRQL scores, which rates symptoms on a scale of 0 (no symptoms) to 50 (incapacitated by GERD). Patients’ median baseline HRQL score of 11 had declined to a score of 2. The clinical significance of this change is not well defined.

**Esophageal pH:** No studies reported esophageal pH of patients while on PPI therapy at baseline compared with post-Linx esophageal
pH. Esophageal pH measures acid reflux decline and primarily uses 24-hour pH monitoring. Thus, the impact on esophageal pH of Linx relative to medication could not be determined.

Medication use: No data on medication use after Linx relative to other surgical or endoscopic procedures are available. PPI medication use before and after Linx are available. Ganz et al. (2013) reported that at one year, a 50% reduction in medication use was observed in 93% (93/100; 95% confidence interval 86 to 97) of patients. Thus, while medication use declined in many patients, many still required medication, so one cannot conclude from these data that Linx obviates the need for GERD medication.

Key question 2: What adverse events (AEs) are reported in studies of the Linx Reflux Management System?

Ganz et al. 2013 and Lipham et al. 2012 reported AEs. Dysphagia was the most commonly reported AE, occurring in 88 of the 144 patients enrolled, although some patients were lost to follow-up in these studies. In most patients reporting dysphagia, the condition resolved within a few months. However, study authors reported that “serious AEs” occurred in eight patients: four cases of persistent dysphagia required device removal; one case of persistent vomiting requiring device removal; two cases requiring hospitalization from nausea and vomiting, but no device removal; and one case in which the patient experienced pain requiring hospitalization. One Manufacturer and User Device Facility Experience (MAUDE) database report from FDA’s AE database indicated that a Linx bead had migrated to inside a patient’s esophagus.

The Linx device has been commercially available in Europe since November 2008 and was granted FDA marketing approval in March 2012. According to the manufacturer, more than 1,000 Linx implants had been performed as of mid-2013, approximately half of which occurred in the United States.

Four studies are ongoing that are expected to be completed between 2013 and 2016, but none are controlled trials that compare the device with other treatments for medically refractory GERD; thus, questions of the device’s efficacy relative to other surgical or endoscopic treatments will not be answerable from the data generated by these studies. **EM**

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

For inquiries about this report or membership in ECRI Institute’s Health Technology Assessment Information Service, e-mail htais@ecri.org.
HIV
A Fragile Population
Enters Managed Care

By the time the Illinois Medicaid expansion
takes effect January 1, new enrollees will have
been asked to pick a primary care physician.
Those who don’t will be assigned one.

Ann Hilton Fisher has a client whom she
describes as a “poster child for how things can go
wrong with this.”

Fisher’s client, whom we’ll call
Harold, has HIV infection, whose
complications have left him legally
blind. Harold’s longtime physicians
at Howard Brown Health Center in
Chicago weren’t in his new managed
Medicaid plan, so the plan assigned
him to a practice near his home.

“If you Google this doctor, mostly
what he does is sell Opti-Fast [weight-
loss] programs, and he’s certified in
bariatrics and internal medicine,” says
Fisher, executive director of AIDS Legal
Council of Chicago. “If you take the
flier he sent to my client and turn it
over, it’s an ad for a pizza restaurant.
The notion that someone thinks this
is an adequate primary care provider for a person
with HIV is horrifying.”

As the Affordable Care Act is about to funnel 15
million people into health insurance plans, Harold’s
story illustrates a bigger issue: Many of the newcom-
ers have complex conditions that require highly
specialized care. They were previously uninsurable
and are at risk of getting lost in systems never built
to address their needs. People with HIV embody all
of these concerns. “There are going to be plenty of
people who get stuck with some Opti-Fast doctor
who has not the first idea about what to do for some-
one with HIV,” says Fisher.

A provider network with adequate HIV experi-
ence is one key to preventing disruptions in care as
this population makes the transition from safety
net programs to commercial and Medicaid plans.
For payers, coordination with these programs,
along with intensive case management and links
to social services, is also essential — and the expe-
rience of health plans that have built strong HIV
programs around these elements can be instructive.

HIV experts warn that failure to integrate these
elements can quickly lead to poor health and poor
financial outcomes.

Ready for this?
Depending on how many states
expand Medicaid, up to 85,000 people
with HIV and AIDS who now get
services from safety net programs like
Ryan White clinics and AIDS Drug
Assistance Programs (ADAP) will
be eligible for Medicaid. As many as
78,000 will qualify for subsidies and
tax credits in the exchanges. People
with HIV generally have multiple
comorbidities, making them compli-
cated to manage — and expensive. A
Kaiser Family Foundation analysis
found that in Medicaid, per-capita
spending for enrollees with HIV neared $25,000
in 2007, nearly five times as high as the cost for
someone without an HIV diagnosis. Much of this
disparity is due to hospitalization.

The goal of HIV therapy is to achieve viral
suppression, making drugs important to keeping
HIV costs down. According to the pharmacy bene-
fit manager Catamaran, Truvada and Atripla, two
fixed-dose combination therapies for HIV, alone
accounted for $3.51 ($1.79 and $1.72, respectively)
in Medicare Part D per-member, per-month costs
last year. Expect those costs to climb: The recent
approvals of Stribild, a four-drug combination pill,
and Tivicay, an integrase strand transfer inhibitor, forged new standards of care at $33,700 and $14,100 a year, respectively.

More costs
HIV medications make up only a fraction of pharmacy costs for these patients. “Diseases like hepatitis are also highly prevalent in this population,” says Catamaran’s chief pharmacy officer, David Calabrese, RPh, MHP, noting that overall spending on antivirals increased 23% in 2012. “There is a great deal of work being done to develop new hepatitis C therapies that will replace injectable drugs like the interferons. More than likely, those drugs will further add to the cost of managing this population.”

At the population level, for health plans, the absence of claim histories and paper trails for some new members with HIV is a big problem.

“This is going to be key,” says Michael Horberg, MD, national director of HIV/AIDS at Kaiser Permanente. “It doesn’t apply uniquely to HIV, but we don’t know what health issues new members are going to have until they are here. That sounds obvious, but it’s going to require that we be proactive. For a lot of these people, it’s going to be the first time

An HIV checklist for plans

1. Designate your HIV specialists as PCPs to make referrals unnecessary. “People need to be able to go to their HIV provider as their primary care provider,” says Ann Hilton Fisher, executive director of AIDS Legal Council of Chicago. “HIV meds interact with so many other medications and cause so many conditions, it doesn’t make any sense for members to go somewhere else for high cholesterol when high cholesterol is a function of their HIV meds.”

2. Employ a multidisciplinary care philosophy that vests authority in everyone. “We have empowered almost every member of the team to make sure that what they do isn’t siloed,” says Michael Horberg, MD, national director of HIV/AIDS at Kaiser Permanente. “If someone calls our clinical pharmacist or clinic assistant, our person makes sure that patients are scheduled correctly or that labs are ordered. If the interruption of medications jeopardizes continuity, our person makes sure the medications get ordered so the doctor can sign off on them.”

3. Make care managers effective. Too often, Fisher sees care managers “who aren’t empowered to do anything” and point fingers at each other. “The Ryan White manager says, ‘I can no longer give you cab rides, because medical transportation is a Medicaid-covered service and you have to get that from your managed care plan.’ And the managed care guy says, ‘I can’t get you that because we need 48 hours’ notice.’ Care managers say, ‘I’m from managed care and I’m here to help you,’ but they tend to be pretty ineffective — perfectly nice people but not in a position to make things happen.”

4. Constantly measure and improve quality. “That is going to be essential with these new patients,” says Horberg. “We look at time to see their clinician. Making sure they are retained in care. Getting the labs they need, such as frequency of CD4 count measurement. Making sure they are on treatment, because we know that lowers transmission to others and achieves viral suppression.” Kaiser Permanente worked with the National Committee for Quality Assurance and other groups to develop 17 quality measures for HIV care and makes them available through an online initiative called the “HIV Challenge.”

“We offer many public clinics access to that, and if they want expert advice, we provide it,” says Horberg. “At national meetings, we spend a great deal of time talking with other health care systems about how we do it.”

5. Mine your data to identify people at risk of falling out of care. “We have programs that help us harness the power of technology to risk-stratify these patients based on the diseases they suffer, utilization patterns, and other factors that allow us to segment the population and position interventions,” says David Calabrese, RPh, MHP, chief pharmacy officer at Catamaran. “By having a sophisticated rules engine, we can extract data about patients who are falling out of appropriate care and communicating that either directly to the patient or to the provider or caregiver so that they are better engaged in their care.”

6. Build trust with your members to engage them. Amida Care President and CEO Doug Wirth says one complexity in a take-all-comers environment lies in how plans identify new members as having HIV and needing specialized services. “This really is an issue of how plans make it attractive for new members to share their health status.” Amida Care offers several services that Wirth says are responsive to what members say they need. “Our African dance classes, for instance, offer something for the mind, body, and spirit.”
they’ve had insurance.” That means they’re going to need help learning how to use their benefits to stay connected to care.

Staying in care is where the biggest leakage occurs in HIV (see “The HIV Treatment Cascade,” on page 16). Some of that has to do with lack of coverage, but a lot more is related to socioeconomic factors. “With HIV disease, you are dealing with mental health issues, addictions, substance use, unstable housing, and food insecurity,” all of which place members at risk of dropping out of care, says Doug Wirth, president and CEO of Amida Care, a 6,000-member special needs plan in New York City specifically designed for Medicaid beneficiaries with HIV.

**Care management**

Those socioeconomic factors “demand a different type of care management,” says Wirth. “It’s not like a high-risk pregnancy model, where you’re calling people two or three times, trying to get them at home, to ensure that they get prenatal care. It asks us to be more assertive and to develop a deeper level of trust with members.”

Amida Care’s manifesto calls for analyzing data from claims to identify people at risk of dropping out of care, then hitting the streets if that’s what it takes to bring them back.

ER use can signify difficulties members may be having in getting same-day or next-day appointments with their PCPs. only a fraction of the pharmacy costs for the new enrollees will be for HIV medications, points out David Calabrese, RPh, MHP, the chief pharmacy officer at Catamaran. Hepatitis is also very prevalent in this population.

The RICU comprises outreach workers who make initial contact with a member, health navigators who assess the member’s needs and arrange for services, and mobile engagement teams skilled in motivational interviewing to change member behavior. “Our teams go into the streets, bodegas, meal programs, neighborhood hangouts, and parks to find people and help them deal with issues so they can get back into lifesaving medical and mental health care,” says Wirth. “We can’t wait for clients who have dropped out of care or who are unconnected to come to us.”

Numbers validate Amida Care’s efforts. Last year, it re-engaged 80% of 934 members who had dropped out of care or were suboptimally managed. Amida Care reports that through aggressive data review and care management, it has reduced ER visits by 60%, admissions by 70%, and costs of long-term care and hospitalization by 30% since 2008.

Being proactive is essential because the HIV population isn’t necessarily more engaged in its care than are other populations. “Our concern is that they’re not [so engaged] because they have other basic needs,” says Horberg. “Other worries have kept them from attending to the intricacies of health care.” By helping members with HIV stay engaged in their care, Kaiser Permanente—which cares for 20,000 people with HIV, more than any other managed care organization—can boast numbers that far exceed national averages: 79% of members with HIV retained in care, 94% treatment adherence, and 69% virally controlled.

**Network adequacy**

In expansion, Medicaid faces a huge potential mismatch of supply and demand. Before the ACA matched Medicaid payments to Medicare levels for 2013 and 2014, Medicaid payments for primary care services averaged 66% of those for Medicare. In California, 57% of physicians accept new Medicaid patients while 90% take new commercially insured patients. With 8 million people joining Medicaid rolls in 2014, the provider shortage may be a ticking time bomb.

It’s unknown how many Medicaid providers
have expertise in HIV, but in the advocacy community the answer is “not enough.” Unless they are federally qualified, community health clinics can’t bill for Medicaid services. With so many HIV patients historically ineligible for Medicaid, neighborhood clinics and their HIV specialists largely stayed out of Medicaid. Now, with patients moving to Medicaid, the race is on to enroll as many HIV specialists in clinics as possible — lest those patients wind up with an Opti-Fast doctor or someone else who doesn’t know HIV.

“There are very clear data that if people with HIV are not cared for by a primary care provider who is experienced and meets HIV specialist criteria … their health outcomes are worse, their likelihood of being hospitalized is greater, and costs are higher,” says Wirth.

When helping clients understand their Medicaid options, AIDS Legal Council of Chicago advises, the most important thing to look for is a primary care physician who understands HIV. It’s not always easy to tell from provider directories who is an HIV expert, however, because there is no HIV board certification.

“One managed care plan listed all these infectious disease specialists,” says Fisher. “Many of them had no experience with HIV, but we had a cadre of internal medicine and family practice docs who, over the years, had become specialists in HIV.” The council is working with individual plans to make HIV expertise more apparent.

To broaden access to care for people with HIV who sign up with commercial insurers, the ACA initially obligated plans in the health care insurance exchanges to contract with essential community providers (ECPs), including Ryan White clinics. But the final regulations require only that plans make a good-faith effort.

**Threading a needle**

“There isn’t a lot of ‘stick’ in terms of enforcing the standard,” says Amy Killelea, senior manager of health care access at the National Alliance of State and Territorial AIDS Directors (NASTAD). “I get that [CMS] was threading a needle, trying to get plans to participate in the marketplaces. But at the same time, there is worry in the ECP community that there aren’t enough teeth to make sure that plans include community providers in their networks.”

**Drug coverage**

It’s critical that people with HIV adhere to medication regimens to avoid progressing to AIDS. As patients move out of safety net programs, their new drug coverage could be better, worse, or just different from what they had. In the exchanges, Killelea says, “The benchmark plans look good.” But in Medicaid, she says diplomatically, “There always have been and probably always will be variations from state to state.

“You have some states that are great. [Formularies] are incredibly comprehensive and there’s no worry. Then you’ve got states that have rolled back drug coverage, instituting four- or five-drug-per-month limitations. In many of those states, we have gotten HIV exceptions, but it’s always a fight.” ADAPs will step in and buy HIV drugs for members whose plans don’t cover their current drug regimens, Killelea notes; her bigger concern is limitations on medications that treat comorbidities.

That was a recurring issue when California implemented early Medicaid expansion in 2011. One situation involved a drug taken for a common HIV comorbidity. “The drug was on formulary but not at the dosing level needed, so providers spent a lot of time doing prior authorizations and getting really frustrated,” says Courtney Mulhern-Pearson, director of state and local affairs at the San Francisco AIDS Foundation (SFAF). “We met with the plan and explained the issue, and the formulary was adjusted. But flexibility for treating a new-to-insurance population is important.”

SFAF advises clients to get three-month refills through an ADAP before making the switch to Medicaid. “We saw a fair amount of treatment interruption” during California’s early expansion, says Mulhern-Pearson. Some people with HIV didn’t know they had been moved into new plans, “and once they found out, they couldn’t fill their prescriptions. Their new plan wouldn’t honor a...
prescription from their old provider.” Hoping to avoid a repeat when the calendar flips to 2014, SFAF is asking Medicaid and commercial plans to honor new members’ old prescriptions “for a set amount of time, maybe a couple for months.”

**Case study: California**

Just as care management, network adequacy, and drug coverage are aspects of continuity of care, so is coordination between payers and safety net agencies as people with HIV shift to mainstream coverage. During California’s early Medicaid expansion, lack of coordination left many people with HIV on the outside looking in.

The expansion provided coverage to several thousand uninsured people with HIV through new county-run Low-Income Health Programs (LIHPs). People who had received services under Ryan White programs were moved into LIHPs, sometimes involuntarily.

“They transitioned all over the place,” says Mulhern-Pearson. “They would be assigned to a clinic, but it might be a pediatric clinic or another with no HIV experience whatsoever. Even the clinic would say, ‘We don’t want these people. We don’t know how to treat them.’”

With no single agency overseeing the transition — and without any HIV expertise on the stakeholder advisory committee — the California Department of Health Care Services, which oversees Medi-Cal (California Medical Assistance Program, a Medicaid plan), didn’t plan for the specialized needs of people with HIV. “Its definition of network adequacy and our definition were very different,” says Mulhern-Pearson.

That was just the beginning. As a payer of last resort, the Ryan White Program is prohibited from paying for services covered by Medicaid programs such as LIHPs.

But the counties that administered LIHPs didn’t understand this and assumed Ryan White would pick up the tab. It didn’t take long for counties to scramble once they realized they were on the hook. Unprepared for the expense of treating people with HIV, some counties cut eligibility — in San Francisco’s case, from 200% to 25% of the federal poverty level.

The state had set up protections designed to allow people with HIV to opt out of the transition if it jeopardized their continuity of care. But when the transition began, Mulhern-Pearson says, “those protections failed. ”

“There was no rhyme or reason to it. Somebody would have a very basic request — ‘This person has HIV and therefore he can’t transition’ — and that would be approved. But if someone else had HIV and schizophrenia and kidney disease and was on all of these complicated treatment regimens and his care couldn’t be interrupted, that request would be denied.”

---

**The HIV treatment cascade**

The effectiveness of HIV care is often measured in terms of the “treatment cascade,” which assesses gaps in care. The drop-off from the share of patients who initiate care to those who stay in care is the biggest opportunity for improving treatment. Only one quarter of people with HIV achieve the goal of HIV therapy: viral suppression.

![HIV treatment cascade graph](chart.png)

*ART = Antiretroviral therapy.
Source: Centers for Disease Control and Prevention, Atlanta, 2012*

---

*continued on page 25*
**IMPORTANT SAFETY INFORMATION**

**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.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

---

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

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

---

**ENVISION NEW POSSIBILITIES**

**Invokana™ canagliflozin tablets**

---

**DATA ON FILE. Based on NBRx data sourced from WIS NPA Market Dynamics Database, weekly data through 9/20/13.**

---

**INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications.**

---

**Client:** J&J  
**Product:** Invokana  
**Job:** SCNT, CAUS, I0062  
**Job Name:** 10062_A3_Sita_Ad  
**Colors:** 4C  
**Sizes:**  
- Bleed: 8.75" w x 11.5" h  
- Lg. Trim: 8.5" w x 11" h  
- Sm Trim: 7.75" w x 10.5" h  
- Live: 6.75" w x 9.5" h  
**Publications:** ENVEISION NEW POSSIBILITIES
INVOKANA™ 300 mg demonstrated greater reductions in A1C vs sitagliptin 100 mg at 52 weeks:

**Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Sitagliptin 100 mg, Each In Combination With Metformin + a Sulfonylurea**

- INVOKANA™ 300 mg: 30.6%
- Sitagliptin 100 mg: 27.8%
- Difference from Sitagliptin: **–2.8%**

**Incidence of Hypoglycemia**

- With metformin + a sulfonylurea over 52 weeks:
  - INVOKANA™ (canagliflozin): 43.2%
  - Sitagliptin 100 mg: 40.3%

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

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS and PRECAUTIONS**

**Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue.

- More common with higher doses of insulin or insulin secretagogues.
- Avoid use of co-administration of insulin or insulin secretagogues unless closely monitored.

**Hypotension:** INVOKANA™ may cause intravascular volume contraction. Symptoms: dizziness, palpitations, syncope. Treatment: reduce dose, discontinue if symptoms persist.

**Hyperkalemia:** INVOKANA™ may 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.

**Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C regularly; consider monitoring more frequently than every 6 months if the LDL-C level exceeds the upper limit of the prespecified noninferiority margin of 0.3%**

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

**Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.**
INVOKANATM (canagliflozin) 300 mg:
With metformin + a sulfonylurea over 52 weeks:

WARNINGS and PRECAUTIONS

IMPORTANT SAFETY INFORMATION (cont’d)

Sitagliptin 100 mg:

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

Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:
Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANATM can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue.

Hypoglycemia: INVOKANATM compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea 52-week randomized trial. Diabetes Care. 2013;36(9):2508-2515.

Changes in Body Weight:

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (P<0.001)*

Change from sitagliptin:

SITAGLIPTIN 100 mg:

–2.8%

300 mg:

–0.37* (P<0.001)

Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m2 and ≥2.0 mmol/L (≥35 mg/dL) increase from the pre-treatment low of 0.15 mmol/L (0.9 mg/dL).‡

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

Learn more at INVOKANAhcp.com/journal
**DRUG INTERACTIONS**

**Drug Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A, UGT2B7, decreased canagliflozin area under the curve (AUC) by 31%. This decrease in exposure to canagliflozin may decrease efficacy if an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, nitrofurantoin) must be co-administered with INVOKANA™ (canagliflozin); consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other anti-obesity therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UC7 inducer and requiring additional glycemic control.

**Disopyramide:** 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™ compared with placebo. For patients receiving concurrent therapy with a UGT inducer and requiring additional glycemic control, consider other anti-obesity therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UC7 inducer and requiring additional glycemic control.

**Use in Specific Populations**

**Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results of rat studies, canagliflozin may affect the fetal kidney, impair renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at 20.1 times clinical exposure from a 300 mg dose. These outcomes occurred with drug exposure during the second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second- and third trimester. INVOKANA™ should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

**Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile animals directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvis and tubular dilatation) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure 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 or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.

**Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older, were exposed to INVOKANA™ in new clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg dose, compared to younger patients; more prominent incidence was seen in patients who were 75 years of age. Smaller reductions in systolic blood pressure with INVOKANA™ relative to placebo were seen in older patients (65 years and older, 0.6% with INVOKANA™ 100 mg and -0.76% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).

**Renal Impairment:** The efficacy and safety of INVOKANA™ have been evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m²). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m²). Patients treated with INVOKANA™ 300 mg were more likely to experience increases in plasma creatinine and serum potassium levels. The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR ≤30 mL/min/1.73 m²), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

**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.

**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 was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**ADVERSE REACTIONS**

The most common (≥10%) adverse reactions are described below and adverse reaction rates observed in the clinical development program of INVOKANA™. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

Please see brief summary of full Prescribing Information on the following pages.

**OVERDOSAGE**

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

**ADVERSE REACTIONS**

The most common (≥10%) adverse reactions are described below and adverse reaction rates observed in the clinical development program of INVOKANA™. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

Please see brief summary of full Prescribing Information on the following pages.

**OVERDOSAGE**

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

**ADVERSE REACTIONS**

The most common (≥10%) adverse reactions are described below and adverse reaction rates observed in the clinical development program of INVOKANA™. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**OVERDOSAGE**

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

**ADVERSE REACTIONS**

The most common (≥10%) adverse reactions are described below and adverse reaction rates observed in the clinical development program of INVOKANA™. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

**OVERDOSAGE**

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

Indications and Usage INOVOKA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (see Clinical Studies 16.1 for full prescribing information).

CONTRAINDICATIONS

• Hypersensitivity to the active substance, SGLT2 inhibitor or any of the excipients.

Warnings and Precautions

• Hyperkalemia: Although hyperkalemia is a known effect of SGLT2 inhibitors, severe hyperkalemia was not observed in clinical trials of INOVOKA. Hyperkalemia may occur with SGLT2 inhibitors or other antidiabetic drugs. Therefore, INOVOKA should be used with caution in patients at risk for hyperkalemia, including patients with impaired renal function and patients taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system. Patients taking INOVOKA should be monitored for hyperkalemia and treated if indicated.

• Hypoglycemia: Patients treated with INOVOKA are at increased risk of hypoglycemia. Therefore, patients should be advised to reduce their dose of insulin or insulin secretagogue in conjunction with the start of INOVOKA. INOVOKA should be used with caution in patients on an insulin regimen or with a higher risk for hypoglycemia.

• UGT Enzyme Inducers: Rifampin: Co-administration of INOVOKA with rifampin was associated with a decrease in canagliflozin area under the curve (AUC) and mean peak drug concentration (Cmax) of 20% and 36%, respectively when co-administered with INOVOKA 300 mg. Patients taking INOVOKA with concomitant rifampin should be monitored appropriately.

• Pregnancy: Pregnancy, consider appropriate alternative therapies, as data in pregnant women is limited. INOVOKA should not be used in women who are pregnant, or may become pregnant. INOVOKA should be used only if the potential benefit justifies the potential risk to the fetus. INOVOKA is not expected to be effective in pregnant women from the first trimester onward. Phenytoin, phenobarbital, and rifampin should be co-administered with INOVOKA.

• Nursing Mothers: Nursing Mothers: There is no adequate and well-controlled studies of INOVOKA in nursing women. The effects of INOVOKA on milk production are not known. A decision should be made whether to discontinue the drug or to discontinue nursing, taking into account the importance of the drug to the mother.

• Geriatric Use: Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INOVOKA in nine clinical studies of INOVOKA. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INOVOKA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydratation), particularly with the 300-mg daily dose, compared to younger patients; more prominent increases in the incidence was seen in patients who were 70 years of age. Smaller reductions in HbA1c with INOVOKA relative to placebo were seen in older (65 years and older) -0.8% with INOVOKA 100 mg and -0.76% with INOVOKA 300 mg relative to placebo compared to younger patients (-0.72% with INOVOKA 100 mg and -0.81% with INOVOKA 300 mg relative to placebo).

• Hyperkalemia: Hyperkalemia: Potassium levels should be assessed and corrected. Monitor for symptoms of hypokalemia and hyperkalemia after initiating INOVOKA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

• Renal and Hepatic Impairment: Patients with moderate to severe 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 INOVOKA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

• Insulin and Insulin Secretagogues: Patients on insulin or insulin secretagogues 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 INOVOKA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Clinical Studies Experience Clinical trials of INOVOKA were conducted under widely varying conditions; adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, to the incidence of adverse events in clinical practice, or to the overall incidence of adverse reactions in clinical practice. INOVOKA was evaluated in three clinical studies: Studies 1 to 3 and Study 4. In Study 1, INOVOKA was compared to placebo in 4,202 patients with type 2 diabetes mellitus who were randomized to treatment in the INOVOKA 0.5 mg monotherapy arm. In Study 2, INOVOKA was used as an add-on therapy in three trials: Studies 3 and 4 used as add-on therapy to metformin, and Study 5 used as add-on therapy to metformin plus sulfonylurea. In Study 6 using add-on therapy to metformin plus a thiazolidinedione. In study 7, INOVOKA was used as add-on therapy to metformin, sulfonylurea, or insulin. In study 8, INOVOKA was used as add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide. INOVOKA was used as an add-on therapy to metformin plus a sulfonylurea or exenatide.
In the pool of eight clinical trials with a longer mean duration of exposure to the comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) were common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, with the exception of dry mouth and polyuria.

The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA.

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in 2% or more of patients treated with either INVOKANA 100 mg, INVOKANA 300 mg, or placebo.

Table 1: Adverse Reactions During Clinical Studies Reports As % of Patients Treated With Placebo

<table>
<thead>
<tr>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Polyuria</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Itching</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Transient</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Infrequent</td>
<td>2.2%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

The four placebo-controlled trials included one randomization trial and three parallel-comparison trials with menin the treatment of type 2 diabetes. The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks and reflect exposure of 6177 patients to INVOKANA.
INVOKANA™ (canagliflozin) tablets

**PHARMACOLOGICAL CLASS:** Aldosterone (Type II) receptor antagonist

**USES:**
- Management of type 2 diabetes mellitus in patients using diet and exercise alone or in combination with metformin.
- In the presence of metformin, initiation of sulfonylurea or pioglitazone without dose adjustment.

**MECHANISM OF ACTION:**
- Inhibits glucosuria by inhibiting the sodium-glucose cotransporter 2 (SGLT2) in the renal tubular epithelium.
- Reduces glucose reabsorption leading to increased glycemic control.

**PHARMACOKINETICS:**
- Oral bioavailability: 80%.
- Peak plasma concentration: 2-4 hours.
- Elimination half-life: 10.8 hours.

**SIDE EFFECTS:**
- Hypoglycemia
- Hypovolemia
- Urinary tract infections
- Hypertension
- Orthostatic hypotension

**CONTRAINDICATIONS:**
- History of severe hypovolemia
- Moderate to severe renal impairment
- Hypokalemia

**WARNINGS AND PRECAUTIONS:**
- Use with caution in patients with history of hypovolemia or hypokalemia.
- Monitor for hypotension and orthostatic hypotension.
- Monitor for urinary tract infections.

**DRUG INTERACTIONS:**
- Avoid with other SGLT2 inhibitors.
- Monitor for hypoglycemia with insulin.

**DOSAGE AND ADMINISTRATION:**
- Oral once daily.

**CLINICAL STUDIES:**
- In a study involving patients with type 2 diabetes, treatment with INVOKANA (canagliflozin) resulted in a 1.4% decrease in hemoglobin A1C (HbA1C) compared to placebo.

**ADVERSE REACTIONS:**
- Urinary tract infections
- Hypertension
- Hypoglycemia

**ADDITIONAL INFORMATION:**
- INVOKANA is available as tablet strengths of 100 mg and 300 mg.

**FOR MORE INFORMATION:**
- Visit the INVOKANA website or contact your healthcare provider.

**PATIENT COUNSELING:**
- Inform patients about the risks and benefits of INVOKANA.
- Advise patients to report any adverse reactions promptly.

**REFERENCES:**
- Clinical Studies
- Safety and Tolerability
- Performance in Clinical Trials

---

**Table 1:** Adverse Reactions from Pos_startup (0-12 m) Placebo-Controlled Studies in Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.9%</td>
<td>7.6%</td>
<td>16.5%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.9%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>1.0%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0.9%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>0.9%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypotheresis</td>
<td>0.9%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>1.0%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>1.0%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>1.0%</td>
<td>2.9%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

**Table 2:** Population With At Least One Volume-Dilated Adverse Reactions (Post-Combination from 3 Trials)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Table 3:** Changes in Serum Creatinine and eGFR Associated with Treatment with INVOKANA in Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Table 4:** Incidence of Hypoglycemia in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Table 5:** Incidence of Hypoglycemia in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Table 6:** Incidence of Hypoglycemia in Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=1232)</th>
<th>INVOKANA 100 mg (N=1232)</th>
<th>INVOKANA 300 mg (N=1232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>
INVOKANA™ (canagliflozin) tablets

Hypoglycemia: In patients that experience hypoglycemia, consider the possibility of acute or chronic alcohol ingestion, exposure to stress (e.g., crush injury, other hypoglycemic medications), or concomitant illness (e.g., infections). If hypoglycemia occurs, stop INVOKANA and treat the patient accordingly. Avoid co-administration with strong inhibitors of CYP3A4 (e.g., clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, protease inhibitors, ritonavir, saquinavir, telithromycin, verapamil, voriconazole). If co-administration is necessary, consider dosage reduction of INVOKANA.

Drug Interactions:

1. Strong CYP3A4 Inhibitors: Concomitant use with strong inhibitors of CYP3A4 may increase plasma canagliflozin concentrations, resulting in increased risk of hypoglycemia and renal adverse events.

2. Strong CYP3A4 Inducers: Concomitant use with strong inducers of CYP3A4 may increase the risk of renal impairment and renal adverse events.

3. Strong CYP2C19 Inhibitors: Concomitant use with strong inhibitors of CYP2C19 may increase plasma canagliflozin concentrations, resulting in increased risk of hypoglycemia and renal adverse events.

4. Strong CYP2C19 Inducers: Concomitant use with strong inducers of CYP2C19 may increase the risk of renal impairment and renal adverse events.

5. Other Drug Interactions: Canagliflozin is metabolized by CYP2C19 and UGT1A9. Use caution when co-administering with drugs that are strong inhibitors of either CYP2C19 or UGT1A9. Avoid concomitant use with clarithromycin or azole antifungals as these agents can increase plasma canagliflozin concentrations.

6. Concurrent Use with Other Drugs: Consider the potential for interactions when using other concurrent medications.

7. Pregnancy: Instruct pregnant women to discontinue INVOKANA or nursing, taking into account the importance of the drug to the mother.

8. Nursing Mothers: Instruct nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of the drug to the mother.

9. Geriatric Use: Instruct patients to use caution and to titrate dosage as necessary.

10. Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions (e.g., angioedema, anaphylaxis) may occur, especially in patients with a history of allergy to canagliflozin.

11. Adverse Reactions:

   - Hyperglycemia: Monitor for increased risk of hyperglycemia in patients with moderate or severe renal impairment.
   - Hypoglycemia: Monitor for increased risk of hypoglycemia in patients with moderate or severe renal impairment.
   - Hemorrhage: Monitor for increased risk of hemorrhage in patients with severe renal impairment.
   - Hypokalemia: Monitor for increased risk of hypokalemia in patients with severe renal impairment.
   - Gastrointestinal: Monitor for increased risk of gastrointestinal adverse events in patients with severe renal impairment.
   - Urinary Tract Infections: Monitor for increased risk of urinary tract infections in patients with severe renal impairment.

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

13. Monitoring: Monitor patients with severe renal impairment for increased urine output, volume, and frequency.

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

15. Patient Counseling Information:

   - Inform patients to contact the Poison Control Center if they experience an overdose of INVOKANA (canagliflozin).
   - Inform patients to seek medical advice promptly if they experience symptoms of hypoglycemia or hyperglycemia.

16. Prescribing Information:

   - Inform patients to report any adverse reactions to their healthcare provider.

17. Contraindications:

   - Patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73 m²).
   - Patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²).
   - Patients with ESRD.
   - Patients treated with dialysis.

18. Warnings and Precautions:

   - Inform patients to report any adverse reactions to their healthcare provider.

19. Adverse Reactions:

   - Urinary Tract Infections: Inform patients of the potential for urinary tract infections in patients with severe renal impairment.
   - Gastrointestinal: Monitor for increased risk of gastrointestinal adverse events in patients with severe renal impairment.

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

21. Monitoring: Monitor patients with severe renal impairment for increased urine output, volume, and frequency.

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

23. Patient Counseling Information:

   - Inform patients to contact the Poison Control Center if they experience an overdose of INVOKANA (canagliflozin).
   - Inform patients to seek medical advice promptly if they experience symptoms of hypoglycemia or hyperglycemia.

24. Prescribing Information:

   - Inform patients to report any adverse reactions to their healthcare provider.

25. Contraindications:

   - Patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73 m²).
   - Patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²).
   - Patients with ESRD.
   - Patients treated with dialysis.

26. Warnings and Precautions:

   - Inform patients to report any adverse reactions to their healthcare provider.

27. Adverse Reactions:

   - Urinary Tract Infections: Inform patients of the potential for urinary tract infections in patients with severe renal impairment.
   - Gastrointestinal: Monitor for increased risk of gastrointestinal adverse events in patients with severe renal impairment.

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

29. Monitoring: Monitor patients with severe renal impairment for increased urine output, volume, and frequency.

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

31. Patient Counseling Information:

   - Inform patients to contact the Poison Control Center if they experience an overdose of INVOKANA (canagliflozin).
   - Inform patients to seek medical advice promptly if they experience symptoms of hypoglycemia or hyperglycemia.

32. Prescribing Information:

   - Inform patients to report any adverse reactions to their healthcare provider.

33. Contraindications:

   - Patients with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73 m²).
   - Patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²).
   - Patients with ESRD.
   - Patients treated with dialysis.

34. Warnings and Precautions:

   - Inform patients to report any adverse reactions to their healthcare provider.

35. Adverse Reactions:

   - Urinary Tract Infections: Inform patients of the potential for urinary tract infections in patients with severe renal impairment.
   - Gastrointestinal: Monitor for increased risk of gastrointestinal adverse events in patients with severe renal impairment.

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

37. Monitoring: Monitor patients with severe renal impairment for increased urine output, volume, and frequency.
California’s experience with Medicaid expansion highlights the importance of careful interagency planning. Horberg at Kaiser Permanente says coordination also is vital at the local level.

Lessons learned

“The HIV care program at Kaiser Permanente Santa Clara has worked closely with the VA, Stanford, and the PACE Clinic, which is the public AIDS clinic in San Jose. The case managers know each other. For a long time, there has been churn, where patients have to change insurance and go from one care system to another. But because of this close collaboration, not only do we make sure that a patient’s information is transferred, but there is confidence among the providers about the quality of care of the other providers. It’s pretty seamless, with a great deal of consistency.”

Even after people with HIV make the switch into commercial and public coverage, Ryan White programs, including ADAPs, will play a critical role, paying for services like transportation that are not covered by insurers.

They also can cover gaps in dental and vision coverage, or pay for part of the premiums for plans offered through the exchanges. Advocates say this compels payers and Ryan White programs to get to know one another.

“We don’t expect that Medicaid plans will completely understand the Ryan White system and its quirks,” says Mulhern-Pearson. “But knowing that it exists and that it is the payer of last resort and what that means would be important.”

Level of clarity varies

To ensure smoother transitions, advocates such as the AIDS Legal Council of Chicago steer clients toward plans that coordinate with ADAPs. The level of clarity about interaction, however, varies by state.

“There are many states where governors have ordered state agencies to have nothing to do with health care reform, so their ADAP agencies aren’t even supposed to look at this — which is ridiculous,” says Fisher. In other states, though, NASTAD’s Killelea has seen illustrations that specifically define where insurance coverage stops and Ryan White starts. “They go through your qualified health plan services, your Medicaid services, and your Ryan White and ADAP services in a very clear, visually representative way,” she says.

Killelea is optimistic that gaps in the treatment cascade can be narrowed in a “coordinated one-two punch” involving two systems that have grown up in silos.

“There is an incredible opportunity to strengthen — or in some cases, create from scratch — relationships between HIV/AIDS programs and the private insurance world. For many programs, that’s new. “There’s opportunity to figure out where the gaps in services are and, when people move on to a private insurance plan, how to make sure that the new systems of care we are building are accountable for quality.

“There are many opportunities for that conversation.”

Michael D. Dalzell is a freelance writer and a former managing editor of Managed Care.

The ACA and HIV

The Affordable Care Act includes several provisions of interest to people with HIV: guaranteed issue, elimination of lifetime and annual limits on coverage, an end to pre-existing condition clauses, and Medicaid expansion. The law also requires that U.S. Preventive Services Task Force “A” and “B” recommended services be offered at no cost to patients in new private health plans, Medicare, and Medicaid.

Michael Horberg, MD, is national director of HIV/AIDS at Kaiser Permanente and a member of the Presidential Advisory Council on HIV/AIDS, which had urged the USPSTF to develop its recommendation that people ages 15–65 be routinely screened for HIV. “This will end up being a very major way to identify people who need the care,” he says. “But remember, testing is only 50% of the thing. We have to lead them to care.”

The ACA transforms Medicaid into an income-based entitlement. Up to now, Medicaid eligibility has been based on categories: children, pregnant women, mothers with children, people with disabilities, and low-income seniors. Childless single males — who make up a substantial portion of HIV patients — have been excluded.

In states where Medicaid doesn’t expand, access to care will vary significantly. People with income below the federal poverty level aren’t eligible for exchange subsidies, as the Obama administration didn’t expect the Supreme Court to give states the choice not to expand Medicaid.

Feedback, Please!

Send your letters and comments to editors@managedcaremag.com
Q&A

A Conversation With David J. Brailer, MD, PhD

A New Age for IT

The former national health technology ‘czar’ says that as insurers’ business models change, information systems will be critical to success

The technology landscape is changing rapidly for insurers in particular, because their business models are changing, he says. Areas such as care management and consumer engagement have great potential, he adds, and Medicare Advantage plans are setting a strong example. But we have a long way to go before we’ll see the most significant changes health care information technology can enable, Brailer says.

“We’ve accomplished nothing if in the end we’ve simply converted paper to electronics and it doesn’t change the way treatment decisions are made, the way costs are managed, the way quality is improved, the way consumers engage, and the way people can begin having a broader health care experience. And that has yet to be seen.”

The new post that President Bush appointed him to was National Coordinator for Health Information Technology. He held it from 2004 to 2006.

Brailer is an Internet pioneer. Back in 1992 he founded CareScience, a company designed to bring Internet-based tools to health care, and began the health information technology program at the University of Pennsylvania’s Wharton School. He also practiced general medicine and taught health management and economics at the University of Pennsylvania.

He earned a bachelor’s degree in science and political science as well as his medical degree at West Virginia University. He completed an internal medicine residency and a fellowship in general medicine at the University of Pennsylvania School of Medicine, where he was a Charles A. Dana fellow and a Robert Wood Johnson clinical fellow. He earned his PhD in health economics at the University of Penn-
sylvania. Brailer spoke recently with Managed Care Senior Contributing Editor MargaretAnn Cross.

MANAGED CARE: We are close to 2014, 10 years after President Bush hired you to be the first health technology czar. How does the progress today compare with the expectations then?

DAVID J. BRAILER, MD, PhD: No one then would have guessed how far we’ve come. We have seen very little partisan bickering, and I think that in part is why it has moved forward so well. It also could not have been more well timed. The industry was clearly ready for this change.

MC: You talked a lot about connecting health systems together back then. Did the priorities evolve?

BRAILER: In July of 2004, we outlined the nation’s strategic plan for the decade of health IT. It outlined four things: point-of-care automation; widespread connectivity; a clinical research, discovery and public health enterprise; and transparency for pricing and purchasing. I think it’s fair to say that we’ve accomplished goal number one, but the other ones are lagging, and they are going to take some time to get done. We have all the basic infrastructure in place, and if it’s not quite there, it will be in the next year or two. Nearly every hospital has an electronic medical record in place or being installed. Almost all doctor groups of any size have one as well.

MC: So we have what we need to accomplish the other goals?

BRAILER: What we need is a reset of another decade of health IT to refresh these other goals. The promise is there, and it is tremendous. But they are still “to be done.”

MC: We understand that the investments being made by the government through the Affordable Care Act and the HITECH Act are perhaps the biggest commitment ever to health IT. How does that bode for the “to do” list?

BRAILER: This has been an area of debate. At the time the government stimulus occurred, the market was moving along very strongly. There has been steep growth in the rate of adoption by hospitals and doctors since 2004. When the government incentives were announced, that rate of adoption slowed tremendously; people were waiting on the government, saying that if the government is going to pay you to do something, why do it yourself?

MC: It changed the market?

BRAILER: Many health systems bought computer systems that are different from what they might have because of the government incentives. Certainly many organizations that wouldn’t have gone digital have, but we have to get back to a functioning marketplace where people do things because it is in their interest and has an ROI, as opposed to because they are required or paid to do it. We’re going to see a tremendous hangover from the binge we’ve been on with government financing and that will be very disruptive.

MC: What will that mean for the other goals, such as interoperability or getting consumers information about pricing?

BRAILER: We will see the market stumble along for a while until people wake up and say, “No one is going to pay me to do this. I have to do this if I want to get it done.” That is like someone going off of welfare and back to work. It’s a hard transition. But the market forces here are powerful, and there’s so much value created from the innovation and the technology that I am sure it will happen. It is just not going to be as linear as it would have been if the government had stayed out of the marketplace and not interfered. It’s just a question now of how to wean people off of this tremendous dependency mentality so they can get back to building their businesses.

MC: You have an economics background. How does the argument for better care at reduced costs hold up?

BRAILER: The research that demonstrates the value in productivity, efficiency, and transparency that comes from using information technology is very powerful. It has consistently shown that up to a third of health care spending is wasteful and driven by quality errors, and much of it could be eliminated. Having said that, technology alone will not be enough. Technology enables organizations to work smarter, be more proactive and preventive, and to work as a team, but if organizations don’t change the way doctors and nurses do things and the way they manage the care process, they are simply going to have an “electronic paper” chart. They are not going to see the financial, competitive, and better care benefits.

MC: Are you seeing organizations use information technology that way?

BRAILER: I have been very impressed, particularly in the last two years, by how the health care
system has taken on this charge. It will take a long time for these benefits to be fully realized because we are not talking about easy changes. We are talking about re-engineering a multi-trillion dollar health care sector. Remember that most of the cost in health care is tied up in hospitals and specialists, so information technology has a lot of work ahead of it before it can change these complicated and critical parts of the industry. Connectivity and health information exchange will begin by making the health care industry more seamless — we won’t get those benefits until we stitch this system of independent electronic medical records together into a cohesive, intelligent, portable information system that is as integrated as we want it to be.

Accountable care organizations are a publicity stunt created by Congress and the administration to make people feel like they were reforming care delivery when everyone knew they weren’t.

**MC:** Will accountable care organizations play a role in moving that forward?

**BRAILER:** Accountable care organizations are a publicity stunt created by Congress and the administration to make people feel like they were reforming care delivery when everyone knew they weren’t. You can’t create integrated care by having a trivial economic incentive for it in the face of a tsunami of disincentives. Nearly all Medicare payments reinforce disintegrated, volume-based care, so the little experiments that are called ACOs face a stark reality. We need economic incentives that are like ACOs but on a vastly larger scale, and to do that, we have to have the information infrastructure in place. It’s not that accountable care drives IT adoption, it’s the other way around. We will never be able to get there unless we have the information systems in place. We always saw IT as the ramp upon which we pull onto the integrated care highway, and from that perspective, we’ve got a lot of work to do. It’s up to the next iteration of IT to prove that it can work.

**MC:** How are health plans contributing?

**BRAILER:** My answer is different now from what it would have been two years ago. When I was in public policy, I spent a lot of time courting health plans, showing them the roles that they could take as aggregators of large groups of consumers and as regional care organizers. But with Obamacare, the role that insurers play in IT has changed dramatically. It is no longer a catalytic role to stimulate a better pool of care delivery. Now their role in IT is an absolute matter of necessity. What I mean is: Being a traditional insurer who makes money from underwriting is clearly a very bad strategy in this market. All health plans, other than Medicare Advantage plans, are running quickly to the exits. Where are they running to? They are either trying to become information technology and information exchange companies, trying to be really good at claims processing and the back office infrastructure, or beginning to manage care delivery or actually provide clinical services. Some of the biggest acquisitions of health information exchange companies have been by health plans.

**MC:** So they are becoming more than insurance companies?

**BRAILER:** Yes, some are becoming IT companies. Some are becoming providers. They are buying up hospitals and doctors and using their population approach to create a scaled, integrated care delivery system that will drive IT forward out of necessity. Or, insurers are trying to become consumer aggregation entities. Again, the information technology they need for that is vital to their survival. At this point I view the future of IT and the future of our insurance platform as being completely interwoven. It is no longer health plans pushing others to do the right thing and to help; it is now a vital necessity for them, too. That is one of the reasons I am optimistic that market forces are going to come raging back into the health IT economy once the government steps out of it.

**MC:** You mentioned Medicare Advantage plans not running for the exits.

**BRAILER:** It’s the one sector of insurance that has really thought hard about the role of IT, partially because of the way MA plans are paid, partially because of their population, partially because of their strategy, and partially because they are newer and more modern organizations. They represent a new life form and what insurance is going to look like in the future, particularly for the regional plans, which are being threatened by provider consolidation. Medicare Advantage plans, which fought for their existence against a very hostile Congress when ACA was passed, will make care delivery
reform unnecessary. MA plans will grow to become such a dominant share of Medicare that they will do the reform from the bottom up by making FFS irrelevant rather than from the top down the way we always expect health reform to happen.

MC: Are some health plans being left behind?

BRAILER: It is too chaotic to know who’s really ahead and who’s behind. But, one thing is clear: This is a game of scale and the bigger you are the more staying power you have. Smaller plans, while they can carve out a small niche market, are vulnerable to regional challenges and aren’t able to invest what they need to build their offerings to keep up. Smaller, more regional plans are still trying to figure out which direction to go. We are beginning to see the signs of a tremendous amount of experimentation going on.

MC: Are health plans exploring how to merge data from electronic medical records and claims systems?

BRAILER: I see a lot of interest from health plans in traditional electronic medical records, but I have not seen a lot of success yet. Plans are still trying to take claims data and then add lab results or prescription data that come from outside the EMR. Electronic medical record data are in the hands of many, many providers, so mapping and getting those data in the absence of a health information exchange is quite hard. Plus, this is really about how to amalgamate relevant data that you can use to manage care. A lot of the data in the EMR are simply there for medical management and for liability reduction, so they’re not very relevant to being able to manage future health status.

MC: If not EMR and claims data, what areas do have the most potential for better automation for health plans?

BRAILER: I mentioned the area of taking claims data and supplementing them in some way to get very precise, very actionable information to help a health plan manage the patient. That is significantly more productive than creating a huge mass of data from electronic records. We actually have a company that does that. CenseoHealth gets claims data and then figures out what additional data need to be collected about that patient to assess and manage certain risks. The information is then compiled into algorithms, and a number of predictive tools are applied to suggest what interventions would benefit the patient. That to me is the future: the ability to use data to manage a patient and to target medical interventions toward that. Medicare Advantage plans are uniquely positioned to do this and should be given room to let this mature. Another area that should be on plans’ radar screens is the ability to manage specific care episodes in real time, to know what’s going on with a patient so that they can intervene. Some of the best Medicare Advantage plans are doing this because they know that it doesn’t help them to figure out a month later when their patient started spiraling down. This is one area where regional plans can have a real toehold because it’s hard for national plans to develop the relationships necessary to collect this actionable data across the whole U.S., but if you are active in one market, you can do that.

MC: Any others?

BRAILER: A third area that is quite exciting is the ability to create consumer engagement around the care experience. There are companies that are trying to put a seamless front end on the insurance experience, the care provider experience, the financial experience — putting all of the pieces together. It is no different from having a single integrated interface for your bank. Consumers who are starting to age into certain conditions are very tech savvy. They are going to expect it. Health plans need to pay a lot of attention to this, because it’s an area where they really can flourish in terms of their aggregation of the consumer engagement brand experience.

MC: One of the goals of your investment firm is to help new products gain market share. How do things become standard in the industry?

BRAILER: New ideas in the health care industry don’t behave the way new ideas do in the tech industry or in consumer sectors, where a new idea can simply obliterate an old idea. In health care, old ideas fight back very hard — they don’t give up even if some other approach is demonstrably better. At the broadest level, where American health care has gone wrong is that we focus all our effort on salvaging patients once they are sick, not on preventing the illness.

Obesity and diabetes and other conditions are caused outside of the health care industry — a result of our ubiquitously available and cheap bad nutrition and other bad practices. The illness they create flows into the health care industry at an increasing pace, and this onslaught of uncontrollable demand
has pushed the health care industry further and further into salvage. Many good ideas for slowing disease progression or educating patients away from bad choices don’t have a business model in this health care market because the economy is based on treatment. The significant question is going to be when do Congress and Medicare recognize this and realize they are the root of the problem? Until that happens, the rest of the industry has no chance of reorienting itself toward prevention and away from salvage.

**MC:** Do you, then, say no to a lot of good ideas?

**BRAILER:** Investors like us say all too often, “That is a great idea. We need that. But you are going bankrupt because there is no money for it.” Unfortunately, that happens all of the time.

**MC:** What do you look for in a health IT company’s business model?

**BRAILER:** The first and most important thing is how the company creates value, not how it makes money. What does it do to fundamentally alter the way care is delivered or the results obtained? The second question is how does it monetize the value it creates? You can go wrong in both of those. There are companies that create very little value but can monetize it. For example, if I help a hospital collect its bills from consumers or from health plans, I have a very easy model. I can say, “You are collecting 70%, and I am going to collect 90%, and I am going to keep a third of that difference.” But that creates zero value. So we look for value creation. How does it create better care, better quality, better consumer engagement? How does it create a more efficient, more productive industry? How does it create alternatives to expensive treatments that are less expensive or more valuable? That’s primary value creation. But many of these companies can’t monetize their value because their success could be costly to their customers in this toxic marketplace.

**MC:** Have you seen innovative pricing models?

**BRAILER:** Yes, and they can look promising at first glance. The question is whether they monetize value in a legitimate, sustainable way. Often, a lot of companies are trying to monetize through advertising. That works for the tech industry, but I don’t think it is sustainable in health care. We look at a business model and ask how it translates the company’s value proposition into money? Who pays for what? And are they being paid for the value being created in a way that they can do it profitably? Often, a company is doing something that everybody knows is of value, but it doesn’t help a hospital’s bottom line that much, so they don’t get paid very much and can’t deliver that service profitably. There are many pitfalls in monetizing health care value creation, to say the least.

**MC:** Who is buying the most technology right now?

**BRAILER:** Hospitals are in a funk. They have figured out that a lot of the expenses for health care reform are going to be balanced on their books, so it’s a hard proposition to sell things to hospitals right now. The future of health care is going to come through doctors, yet doctor groups are still relatively small and difficult to organize. They are still in the primary stages of becoming sophisticated organizations, but they will grow up and become major clinical companies, but still have a ways to go. Health plans have a lot of hope. Some are just floundering around figuring out where the future is, but a lot of them have figured out where they are going and are working hard to put together that new platform. They are buying products and services that help them build. Health plans are really working against a timetable to get to a new place before their iceberg melts, so they are motivated. So are drug companies. They have been through their funk and are on the other side. Their pipelines are getting stronger again. They are dealing with the financial distress from the generic conversion wave, and they, too, show a lot of promise. Hospitals will come back at some point, probably as big corporate entities, but the hospital industry has to rebuild the core economic proposition of a hospital before anyone succeeds.

**MC:** Thank you.

**CALL FOR PAPERS**

**MANAGED CARE** is seeking article submissions. We welcome a wide variety of manuscripts, including drug class reviews, disease state management reviews, pharmacoeconomic analyses, strategies for coping with medication errors, outcomes research evaluations, DUEs, commentaries, book reviews, and letters to the editor. Please see our author guidelines at managedcaremag.com.

Interested? Write to managing editor Frank Diamond at fdiamond@medimedia.com.
Professional Networking

*For* Medical Directors

*By* Medical Directors

The first and only site that offers Medical Directors a verified, secure, closed-loop environment for peer-to-peer interaction.

The Medical Directors Forum offers a comprehensive resource library, discussion groups, calendar postings and alerts; giving Medical Directors the opportunity to network and share ideas on a robust site.


*Communicate. Connect. Rule your world…*
Could QALYs Help in Assessing High-Priced Cancer Treatments?

Other nations use ‘quality-adjusted life-years’ to measure the cost-effectiveness of drugs, but this tool has been anathema in the United States — so far

By Jack McCain

For doctors at Memorial Sloan-Kettering Cancer Center in late 2012, it was an easy call. The drug Zaltrap, new on the market (Bach 2012) for treatment of patients with metastatic colorectal cancer, promised to provide an overall survival benefit of 1.4 months compared with a standard chemotherapy regimen. But so did Avastin (bevacizumab) — and the two drugs had similar mechanisms of action, preventing the interaction of VEGF with its receptors. The chief difference was that Zaltrap, initially priced at $11,000 for one month of treatment, cost more than twice as much as Avastin. So the oncologists decided not to use this costly drug. And from the perspective of the cancer center, the story has a happy ending: The marketers of Zaltrap began offering the drug to hospitals at a 50% discount.

But other comparisons of oncology products are not so straightforward. A new drug may offer a modest improvement in overall survival quality of life in the absence of a survival benefit. What then? Outside the United States, policymakers turn to a measurement unit called the “quality-adjusted life-year,” (see “What’s a QALY?” on page 33), though with less enthusiasm than in years past to inform decisions on allocating resources to new drugs. And some experts think it may be time for QALY’s American debut.

**FIGURE 1**

Relationship between quality and quantity of life

Which intervention would you choose? Compared with Usual Care, Intervention A offers shorter length of life but improved quality of life. Intervention B provides higher quality of life than Usual Care but the same length of life; the triangle bounded by the sloping and vertical red lines and the sloping black line represents the incremental gain in quality afforded by Intervention B. Compared with Usual Care, the incremental gain in quality from Intervention B is less than that provided by Intervention A, however. Intervention C provides longer length of life than Usual Care or Intervention A or B but lower quality of life than those interventions or Usual Care. Intervention D initially offers actual improvement in quality of life followed by a steep decline, and although length of life is longer than with any other intervention or Usual Care the quality of life ultimately is greatly diminished.
To quantify value

In an essay in the New York Times, some prominent oncologists and cancer researchers set forth their prescription for improving cancer care (Emanuel 2013). By way of introduction, they said the FDA had approved 13 anticancer agents in 2012, each costing more than $5,900 per month — and that only one offered a survival benefit exceeding six months. The heart of the essay was a set of five recommendations (see box on page 34). Although the word wasn’t used, the thorny issue of value was implicit in each recommendation. Consumers commonly regard high price as an indication of high value whether they’re purchasing wine, automobiles, higher education or, alas, health care goods and services.

Perhaps that shouldn’t be terribly surprising because, as the health economist Tina Shih, PhD, points out, we really don’t know how to quantify value. Shih is an associate professor of medicine at the University of Chicago and director of its Program in the Economics of Cancer.

Health economists have various tools for evaluating interventions (Table 1), the simplest of which, in theory, is cost-minimization analysis. If two different therapies produce the same outcome, you just choose the less expensive one. Such was the call made by the Memorial Sloan-Kettering doctors at

What’s a QALY?

A quality-adjusted life-year is the bidimensional measure used in the form of cost-effectiveness analysis known as cost-utility analysis. QALYs capture quality and quantity of life in a single metric. QALYs are computed by asking patients or, preferably, members of the general public to weigh the utility (i.e., indicate their preference) for being in a given health state by assigning a numerical value to it; the values range from 0 (dead) to 1 (in perfect health). The time spent in the health state is multiplied by its assigned value, and the products are summed. (Some economists maintain that since few people ever report being in perfect health, average health might be a more meaningful upper end of the scale.) In a cost-utility analysis, the next step is to calculate the difference in mean costs between the intervention of interest and its comparator, generating the incremental cost, and the mean effectiveness of the intervention compared to the comparator, expressed as QALYs gained. (In other cost-effectiveness analyses, effectiveness might be expressed as life-years gained or, especially in oncology, by a surrogate outcome such as complete response rate or disease-free survival.) Dividing the incremental cost by the mean effectiveness yields the incremental cost-effectiveness ratio (ICER). In the example below, in which two interventions are compared for one year, the gain in QALYs provided by Intervention A is 0.20, and the incremental cost difference is $10,000, which works out to $50,000 per incremental QALY gained.

Ideally, health economists say, cost-utility analyses should be conducted from a broad societal perspective to capture all the direct and indirect costs and consequences associated with an intervention over the long term, but they frequently are conducted from the narrow perspective of a third-party payer concerned only with direct costs over the short term.

<table>
<thead>
<tr>
<th>Intervention A ($40,000 per year)</th>
<th>Intervention B ($30,000 per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Utility weight of health state</strong>*</td>
<td><strong>Time spent in health state</strong></td>
</tr>
<tr>
<td>0.9</td>
<td>0.25 y</td>
</tr>
<tr>
<td>0.8</td>
<td>0.25 y</td>
</tr>
<tr>
<td>0.7</td>
<td>0.25 y</td>
</tr>
<tr>
<td>0.6</td>
<td>0.25 y</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.750</strong></td>
</tr>
<tr>
<td><strong>Mean effectiveness</strong></td>
<td>0.200</td>
</tr>
<tr>
<td><strong>Incremental cost</strong></td>
<td>$10,000</td>
</tr>
<tr>
<td><strong>Incremental cost-effectiveness ratio</strong></td>
<td>$50,000</td>
</tr>
</tbody>
</table>

*The health states do not necessarily unfold in the order presented here. The actual order in which they do occur may be important to some patients, however, but a cost-utility analysis will not take this into account.
the time that Zaltrap was introduced. Combining length of life and quality of life in a single metric, the QALY enables comparisons of interventions in disparate diseases. In the U.K., the National Institute for Health and Care Excellence (NICE) mandates use of cost-utility analysis as a tool — but not the sole tool — to determine which interventions should be provided by the National Health Service. It’s a strike against a new intervention if its cost per QALY exceeds £30,000, the upper limit of NICE’s arbitrary range for cost-effectiveness. Shih says QALYs are best employed from a societal perspective, and not for making treatment decisions for individuals with a disease, especially in end-of-life situations.

Is end of life different?

Even NICE now makes exceptions for end-of-life treatments, largely in reaction to the furor that erupted in 2008 when it rejected some new cancer drugs because they weren’t deemed sufficiently cost-effective. The next year, NICE made major adjustments (http://bit.ly/nice-EOL), allowing drugs used in end-of-life care to exceed the threshold if the treatment is aimed at a small patient population and extends life by at least three months, compared with the current treatment, in patients whose life expectancy is less than 24 months.

None of the 2012 approvals represents a dramatic breakthrough, such as a new first-line treatment that

### TABLE 1

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Use</th>
<th>Metric</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of illness</td>
<td>Measuring the economic burden of a disease</td>
<td>Costs from perspective of interested party or parties (e.g., society, third-party payer, business, government)</td>
<td>Defining the illness may be complicated Inclusion of indirect costs generates controversy</td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Computing total costs and benefits of an intervention</td>
<td>$ gained or lost from the intervention</td>
<td>Difficult to quantify some components</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Comparing the costs &amp; benefits of interventions not expected to produce the same outcomes</td>
<td>$ per natural unit (e.g., life-years gained, duration of disease-free survival, response rate, mm Hg in BP reduction)</td>
<td>Unit of comparison may not be the most clinically relevant measure</td>
</tr>
<tr>
<td>Cost-minimization</td>
<td>Comparing interventions expected to produce the same outcome (e.g., generic simvastatin vs. branded Zocor)</td>
<td>Price differential</td>
<td>Not easy in most cases to demonstrate clinical equivalence Limited practical use</td>
</tr>
<tr>
<td>Cost-consequence</td>
<td>Comparing alternative interventions by computing the components of their incremental costs and consequences</td>
<td>List of each component</td>
<td>Doesn’t generate an aggregated result</td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Comparing disparate interventions employed in disparate diseases, for purpose of resource allocation</td>
<td>Incremental $ per QALY compared with alternative intervention</td>
<td>QALYs in different diseases may not be commensurate</td>
</tr>
</tbody>
</table>
adds years to cancer patients’ lives. Instead, they’re for patients already in dire straits — patients with metastatic disease for which second- or third-line treatments no longer are effective. Some of these drugs wouldn’t pass muster with NICE because they serve small populations and don’t extend life by at least three months.

**What oncologists think**

Even so, a recent survey of U.S. and Canadian oncologists suggests that the majority of oncologists wouldn’t balk at high prices for such drugs (Ubel 2012). When asked what treatment cost per life-year gained represented “good value for money,” about 70% selected an incremental cost-effectiveness ratio (ICER) of $100,000 or less. But when oncologists were randomly presented with hypothetical new drugs for metastatic cancer that cost either $50,000 or $125,000 more than standard chemotherapy costing $25,000, the median increase in life expectancy stipulated by oncologists to justify using the $75,000 drug was six months, which translates into $100,000 per life-year gained. The median survival benefit oncologists selected to support use of the more-expensive drug also was six months, but in this case the cost per life-year gained was $250,000.

Each is the best-case scenario for cost per QALY, because if the time is spent in less than perfect health, the cost per QALY would be even higher.

Although the study shows that oncologists seem to be rather inconsistent and illogical in their approach to the value of their drugs, the authors said their results shouldn’t be taken as criticism of oncologists, for several reasons:

- Oncologists aren’t trained to use cost-effectiveness data in decision-making.
- Oncologists aren’t comfortable using such data.
- Oncologists usually aren’t aware of the cost of the drugs they’re prescribing (other studies show they are concerned about the amount of a patient’s copayment, which in itself can adversely affect compliance with therapy).
- Oncologists are taught to just let policymakers deal with these matters.

In another study, oncologists at Massachusetts General Hospital and the Dana-Farber Cancer Institute were asked to identify the minimum survival benefit they’d need to prescribe a hypothetical new treatment for metastatic lung cancer if the new treatment cost $70,000 per year more than the standard-of-care treatment and if there was no difference in quality of life between the standard and the new...
treatment (Nadler 2006). The responses ranged from one day (ICER of $25.6 million) to one year or more (ICER of $70,000), with the median and mean responses being $280,000 and $319,000 respectively (Figure 2).

Suspicion

In the United States, QALYs often are regarded with suspicion, so much so that the Affordable Care Act forbids the Patient-Centered Outcomes Research Institute to use the cost per QALY “or similar measure that discounts the value of a life because of an individual’s disability as a threshold to establish what type of health care is cost effective or recommended.”

Peter Neumann, ScD, professor of medicine at Tufts University School of Medicine and director of Tufts’ Center for the Evaluation of Value and Risk in Health, speculates that the ambiguous language of this passage might permit ICERs using cost per QALY to be calculated but not compared with a threshold, but that it might also be construed as a broader ban on cost-utility analysis (Neumann 2010b). (Neumann has studied QALYs extensively and published numerous scholarly articles about their use in oncology among other areas.)

The fact that legislators saw fit to insert language in the Affordable Care Act to ban the use of QALYs may seem unfortunate and bizarre in a nation where there’s so much talk about the high costs of health care. Whatever the reasoning behind the legislation, it runs counter to what most oncologists apparently want. In a national survey of U.S. oncologists, 80% “strongly or somewhat agreed” that more use of cost-effectiveness data is needed in coverage and payment decisions for cancer drugs, and that more government research is needed on the comparative effectiveness of cancer drugs (Neumann 2010a). Well, good luck with that.

But while the oncologists said they’d like to see the government provide more comparative effectiveness research, only 21% thought government should determine whether a drug provides good value — and a mere 6% thought insurance companies should do so. Instead, they wanted value determinations to be made by physicians (60%), not-for-profit organizations, (57%) and patients (37%). Taken together, these studies suggest that if oncologists want to make value-based treatment decisions, at least some of them need guidance in evaluating cost-effectiveness data.

“QALYs are easy to criticize, but it’s hard to capture anything with a single number,” Neumann says. He cites the Dow Jones Industrial Average and the measurement of snowfall by inches as common metrics that tell us something interesting but hardly tell us everything needed to adequately assess the phenomena in question.

Likewise, he says, “The QALY has a place as a crude but imperfect measure of value. I recoil when it’s used rigidly.”

From the perspective of pharmaceutical companies, an objection to QALYs is that overreliance on them could stifle innovation. According to this argument, some drugs — especially first-in-class agents — merit a high price and a high cost per QALY in order to spur further research. Herceptin (trastuzumab), for example, was initially approved as first-line therapy for metastatic breast cancer, and for that indication its cost per QALY gained was calculated as at least $125,000. That’s far above the conventional threshold. But in the adjuvant setting, its cost per QALY was found to be only $26,000. Had the drug been rejected initially because of an unacceptably high cost per QALY, the opportunity to study it in the adjuvant setting might never have arisen. But Shih says such pharmacoeconomic analyses should be interpreted cautiously, because they often are just retrospective mathematical models that are subject to manipulation.

Comparisons are difficult

In the case of Zaltrap, oncologists had no need to call on QALYs to determine that the initial price of the new drug was far too high. Its value relative to a competing product was immediately apparent because the efficacy and safety of each drug were regarded as equivalent, and market forces (lack of demand) soon led to a downward adjustment in price.

Comparisons of other cancer drugs tend to be far more difficult because the products aren’t equivalent, in which case QALYs may be one tool that complements others to help policymakers, physi-
cians, and patients determine which drug offers the best value.

People like the freedom to use whatever drug they want, says Shih, but at some point we have to face the reality that resources are limited. If we don't want to use cost-effectiveness analyses to allocate resources, what process are we going to use, she asks, other than the random process employed right now?

Neumann says that to reject QALYs in the absence of a better metric is to implicitly argue that we're better off if the trade-offs revealed by QALYs remain hidden. Still, in the current environment, one person's quest for value may be perceived and portrayed by someone else as the imposition of rationing.

Jack McCain is an independent medical writer and editor who lives in Durham, Conn.

For further reading

| TABLE 3 |
| Common arguments against using QALYs in end-of-life situations |
| Argument against QALY | Counterargument |
| 1. Because it includes a time element, a QALY is inappropriate if an intervention provides no survival benefit | An intervention can enhance life (i.e., generate a gain in QALYs) even if it doesn’t extend life |
| 2. In comparison with other dimensions of quality of life, health status diminishes in importance at the end of life | • There’s no reason non-health domains can’t be incorporated in QALYs, if it is decided that they should be incorporated • The (not-so-simple) solution is finding out what is important to people at the end of life and measuring it |
| 3. Patients’ preferences for health states aren’t reliable at the end of life because their preferences change over time | Instability of preferences becomes a problem only when patients’ preferences are used, so a practical solution is to use the preferences of the general public |
| 4. When death is imminent, death is an invalid anchor point for preference-based measures of health status | • Problem diminishes when the general public is used instead of patients as the source of preferences for health states • However, this argument does have merit |
| 5. People value life differently at the end of life in comparison with other life stages | • This is the argument behind NICE’s decision to allow exceptions for end-of-life treatments that exceed the established cost-effectiveness threshold but meet certain criteria • It has not yet been demonstrated that individuals and society value end-of-life time greater than time at other stages of life |
| 6. Reliance on QALYs leads to rejection, on cost-effectiveness grounds, of some interventions that are acceptable to patients and the public | • Phenomenon is not unique to end-of-life care • Since thresholds are political determinations, thresholds are subject to political modification |

Source: Round 2012

Feedback Please! Send your letters and comments to editors@managedcaremag.com

MC_1312_QALY_v6FD_READER.indd 37
12/2/13 3:52 PM
Focused on Biologics

Next-Generation Sequencing Problematic, If Promising

Genomic profiling in cancer may open the door to the use of unproven therapies

By Thomas Reinke

Targeted cancer therapies have been one of the most important steps forward in personalized medicine — also called precision medicine. The value of these drugs is that they work in a high proportion of cancer patients who have a specific genetic alteration. Conversely, they may not work in patients without that mutation.

These medications are made possible by the existence of genetic biomarkers for the presence of a specific cancer-causing pathway. Pharmacogenetic tests for the biomarkers help clinicians know when to use a targeted therapy, thus reducing trial-and-error therapy and producing great benefits for patients.

Rapid advances in gene sequencing, specifically genomic profiling using next-generation sequencing, are providing new insight into the genetic heterogeneity of cancers by identifying additional alterations in cancers where they were not previously known.

However, genomic profiling is also leading to claims that targeted therapies, even conventional medications, may be candidates for off-label use for cancers for which they are not approved by the FDA. So while technology is propelling cancer diagnosis to the next level of understanding, it also potentially opens the door to unsupported therapy.

Genomic profiling defined

Genomic profiling looks at the alterations of all of the protein producing genes in the entire human genome, or at specific genomes like that of a cancer tumor. This spectrum analysis is powered by next-generation sequencing, NGS, which is a technologic leap into the future of precision medicine. Instead of looking for genetic alterations serially, gene by gene, NGS relies on high speed parallel processing of a library of small DNA segments to “read” different types of alterations.

The NIH says it would take years to sequence a person’s entire genome with earlier technology, compared to days or weeks with NGS. In addition, NGS is significantly more sensitive than previous technologies, so it also has the capability to find low frequency mutations that escaped earlier technologies.

The power of NGS has allowed research laboratories and upstart direct-to-consumer genetics labs to create panels of 200+ genes that they use to identify all types of genetic alterations.

In doing so they have created a new buzzword — clinically actionable targets — to claim that the addi-
tional alterations they find may be candidates for drugs outside of the cancers they are approved for, in spite of the lack of solid documentation of their effectiveness.

**Technology outpaces understanding**

“Most solid organ tumors have 60 mutations and 100 or so translocations [a chromosome breaks off and attaches to a different chromosome], most of which we do not understand the significance of,” says William Nelson, MD, PhD, director of the Johns Hopkins Kimmel Cancer Center and an expert on translational genetics. “The technology now is such that we can find all of the changes before we know what they mean.

“The big concern is not that genomic profiling will lead to increasing costs. The more important worry is that it will get less expensive and people will go off half cocked with information that isn’t truly worth acting on. Some labs are going to say that they have found one alteration among 200 others and that one small study said this particular drug might be related to this alteration.”

This is already happening. The website of a genetics lab, GeneKey, says its multi-gene panel “provides information to identify potential treatments that would not be considered otherwise. We search for options not only among known lymphoma treatments, but among the more than 2,000 FDA-approved drugs.”

Academic and research labs also use the term clinically actionable targets, although in that context it could mean there are opportunities to investigate new indications for existing drugs.

There is a very positive side to genomic profiling. “Drug development companies are totally enamored of this technology,” says Nelson. “There are hundreds of drug compounds in discovery. Next-generation sequencing simplifies and reduces the cost of drug development because it eliminates many of the steps in the former empiric drug development process. For example, it simplifies and reduces the cost of clinical trials.”

Genomic profiling via NGS is still in the process of proving its analytic validity, clinical validity, and clinical utility.

Analytic validity is the ability of profiling to accurately identify the intended genetic alteration target and to exclude false positive results. Clinical validity relates to how closely a genetic alteration is related to the presence or risk for a specific cancer. Clinical utility exists when a treatment or therapy is useful in decision making and improves patient outcomes.

The analytic validity of NGS is affected by complexity that does not exist for other tests. The starting point is the need to have high quality tumor samples that accurately represent the alterations that may be found. In addition, the traditional standards of sensitivity, specificity, and accuracy for the millions of repeated reads of genetic alterations come into play.

**FDA’s perplexed**

Genomic profiling is not regulated by the FDA, which has been wrestling with how it might regulate genomic tests. It has not figured out how to get it right — what will be regulated, how evaluations will take place, or when this oversight might kick in.

Each lab may freely develop tests and market them. Labs are usually certified by CMS under the Clinical Laboratory Improvement Act (CLIA), and by the College of American Pathologists (CAP). However, these certifications deal primarily with proficiency and reproducibility and do not encompass clinical validity.

Standards have been developed by the Next-Generation Sequencing: Standardization of Clinical Testing workgroup and the American College of Medical Genetics. The elements in these standards include specimen preparation, the method for “reading” alterations, and the software that interprets the significance of the reads of possible mutations.

“The analytic validity of genetic testing is extremely high. Everyone who has looked at it in any way has said that technical analysis is very good; when we find a mutation it is usually confirmed with an alternate sequencing technology, and the result is usually correct,” says Andrew Faucett, a director at Geisinger Health System’s genomic medicine institute. He served as a reviewer of an Institute of Medicine report on incorporating genomic information into clinical practice.

There is at least one potential limitation in the
procedures for confirming the analytical validity of NGS. “Next-generation sequencing can pick up alterations that Sanger sequencing, the former gold standard, would miss,” says Mark Rubin, MD, director of the institute of precision medicine at the Weill Cornell Medical College. “When we go to validate next-generation sequencing for regulatory purposes, we are asked to use older technologies which are less sensitive.”

A validation study
An October online article in the journal Nature Biotechnology describes the work of Foundation Medicine in demonstrating the analytical validity of its cancer profiling test. That test is a 287-cancer gene panel that examines 4,557 alterations. The validation study tested 2,221 samples of breast, lung, colorectal, head and neck, prostate, and other cancers. The studies validated the Foundation Medicine test against other testing methods.

Alterations were reported in 174 of 189 (92%) tested genes. Testing found 1,579 unique alterations with an average of 3.06 alterations per sample (range, 0–23). A tumor can harbor multiple alterations at any position in the DNA with a wide range of frequencies for each alteration. The validation study found clinically actionable alterations in 76% of the tumors with an average of 1.57 actionable alterations per patient sample, three times the number of actionable alterations detected by current diagnostic tests.

In summary, the profiling test found numerous alterations that would not have been identified by

“We are interested in tests that can clearly impact treatment decisions,” says Steve Perkins, MD, vice president for medical affairs at UMP Health Plan.

False hope for many patients
Genomic profiling is still in its infancy. Several health plans have said that they are not seeing claims for a large number of profiling tests. Some claims for genomic testing may be paid, although these tests are considered experimental.

“Our coding system does not allow us to identify specific types of genetic tests because tests are broken down into many components and the codes are very general,” says Donald Liss, MD, a medical director at Independence Blue Cross.

Liss explains how health plans will handle coverage decisions for profiling. “With new technologies like genomic profiling, we, and many other health plans consult with technology assessment firms,” says Liss. “We will look at the validity and utility of these tests, evidence from controlled trials, and other authorities such as the incorporation of the technology into clinical guidelines from places like the National Comprehensive Cancer Network.”

Rapidly evolving technologies such as genomic profiling may be easier to handle at health plans with integrated provider organizations such as the University of Pittsburgh Medical Center. “When it comes to the development of medical policy for new technologies at the health plan, we have the ability to create a dialogue with our clinicians and researchers to get a perspective on the value of a new technology that may not otherwise be available,” says Steve Perkins, MD, vice president for medical affairs at UMP Health Plan.

“We are interested in tests that can clearly impact treatment decisions. We ask if this particular test in this particular case is going to impact treatment decisions. If the answer is yes then coverage is feasible. The onus is on us to determine if the test is responsible,” says Liss. He adds, “The other area that is of interest to insurers is what is on the horizon. We need to be thinking about how technologies will impact the standard of care as we design our plans and project future medical claims costs.”

Over time the use of and coverage for genomic profiling may develop a twist in comparison to how diagnostic tests are used.

Profiling is likely to be considered experimental until its utility is proven and then prior authorization is likely to ensure its appropriate use.

After a while, profiling may evolve to limited use. “Genomic profiling will not be used universally. There are situations when you want to do a simple focused genetic test such as the companion diagnostics being approved for new targeted therapies,” says Rubin. “Then there will be other situations where it may make sense to do sequencing; it can come into play if the patient becomes resistant to first-line therapy, such as in lung cancer, because you are looking for the presence of several other targetable mutations.”
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.
In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In children receiving Synagis for a second season, one of the fifty-six children had transient, low level reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

A trial of high-risk preterm children less than or equal to 24 months of age was conducted to evaluate the immunogenicity of the lyophilized formulation of Synagis (used in Trials 1 and 2 above) in 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 point time 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 immunosensor 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
Gaithersburg, MD 20878
U.S. License No. 1799
1-877-633-4411

Revision Date: April 2013
Component No.: 10423A

Brief Summary of Prescribing Information SYNAGIS® (PALIVIZUMAB)

CONTAINMENTS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Cases of anaphylaxis and anaphylacthic 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 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 with thrombocytopenia or any coagulation disorders.

Risk Management Programs: SYNAGIS for intramuscular administration is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to children with thrombocytopenia or any 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 occur for 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.

The data described below reflect exposure to Synagis (n=1639) compared to placebo (n=1143) in children 3 days to 24.1 months of age at high risk of RSV-related hospitalization in two clinical trials. Trial 1 was conducted during a single RSV season and studied a total of 1502 children less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (less than or equal to 35 weeks gestation 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.
previous technologies. This information in the hands of desperate patients could create false hopes for additional therapy options.

The sheer volume of additional alterations identified through genomic profiling makes it difficult to determine the clinical validity of an individual alteration.

**Clinical validity**

“Clinical validity depends on the disease and the genetic alteration,” says Faucett. “We have a good understanding of the types of mutations in some diseases and there’s a much broader group of diseases and alterations that we’re learning about.”

Cancer genomes and entire human genomes contain many genetic alterations that are insignificant, not necessarily disease producing. “One category of genetic alterations is research-grade information; the alternation is read accurately so it is a true mutation, but its frequency is very limited and its impact is unknown,” says Rubin.

“These represent the largest percentage of what we find. Right now we’re struggling for a systematic approach to determine what are the important mutations that we should focus on developing the next treatment targets.”

The identification of previously unknown alterations complicates knowing if they are clinically valid.

“Herceptin for HER2 amplification in breast cancer works part of the time, which means we do not fully understand all of the cancer-causing alterations,” says Faucett. “But that biomarker was based on previous testing capabilities, and became the standard of care for Herceptin therapy. Today, though, health plans, as the result of finding additional alterations through next-generation sequencing, could say that alteration as a clinically actionable target is not supported by evidence.”

**Databases**

Experts say that databases of genomic profiles serve as key references to support efforts to determine the clinical validity and the utility of genomic profiling.

“One of the most important concepts for next generation sequencing and its relationship to precision medication is that we are developing a knowledge base,” says Rubin. “That knowledge base today includes information that is not actionable because we do not fully understand the identified alteration, but in five years some of that information will be found actionable.” There are many different types of reference databases — publicly funded cooperative databases, databases operated by various consortia, international databases, and databases at hospitals and research institutions. One challenge is the differences in information stored in the databases and finding an effective means for a researcher to share or easily access information.

“It would be interesting to develop something similar to crowdsourcing where questions or developments could be shared widely and quickly, especially on truly new or rare situations,” says Rubin.

**Genetic variants**

The 1,000 Genomes Project is the first project to sequence the genomes of a large number of people to provide a comprehensive resource on genetic variations. Its goal is to find most genetic variants that have frequencies of at least 1% in the populations studied.

The project provides information on population-wide variations that may or may not be related to specific diseases. It serves as a resource to determine the extent of natural variations in the population.

The Cancer Genome Atlas is specific to cancer. “It provides a static [one time] image of mutations in common tumors,” says Rubin.

A common limitation of genomic databases is that they do not provide information on subsequent development of diseases or the effects of treatment, says Nelson.

“Where we are really making inroads is in projects like the Stand Up to Cancer work in prostate cancer,” says Rubin. “Five institutions are participating in a study that tracks advanced castrate resistant patients. Mutations are sequenced before, during, and after treatment.

“Patients in this study are in a well-defined protocol so there’s the potential to learn about the development of mutations that lead to resistance, the weaknesses of existing drugs, and what additional drugs are needed to deal with resistance.”

---

**Genomic profiling via NGS is still in the process of proving its analytic validity, clinical validity, and clinical utility.**
October was just one nightmare after another for Ariad Pharmaceuticals. On October 9, Ariad stopped enrollment in one clinical trial for its leukemia drug, ponatinib (Iclusig), and reduced dosing in other trials after disclosing that real-world incidence of blood clots was higher than what the drug's label showed. That deflated Ariad's stock price from $17.14 to $5.83 in just a day.

Fast forward nine days. Ariad — which had achieved accelerated Food and Drug Administration approval for ponatinib last December on the basis of phase 2 data in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia and chronic myeloid leukemia — ended a phase 3 trial that was critical for ponatinib's survival. By Halloween — a mere six years after Ariad's new drug application was filed — ponatinib was off the market. In asking for Ariad to stop sales and marketing, the FDA said it "could not identify a dose level or exposure duration that is safe." Stock price: $2.20.

Investors aren't the only ones for whom Ariad has some explaining to do. Physicians and the FDA want answers. So do patients, for whom treatment options are limited. For physicians who want to keep treating patients who are doing well on ponatinib, the FDA has established access under an emergency investigational new-drug process. Ariad vows to get its $115,000-a-year therapy back on the market, but ponatinib's long-term future is uncertain.

"Yes," but with an asterisk

The FDA's Peripheral and Central Nervous System Drugs Advisory Committee held its nose in recommending Sanofi's once-a-year intravenous multiple sclerosis therapy, alemtuzumab (Lemtrada), for approval. Split between concerns about autoimmune disorder risks and worries over limited options for people with MS, the panel agreed to recommend approval for use in people who have failed other therapies. "Do I want to take this drug? No way!" committee chairman Nathan Fountain, MD, told Reuters. But, he added, for patients with no other options, "I wouldn't want to deny those people."

The committee agreed that alemtuzumab provided substantial evidence of effectiveness but concluded that studies were inadequately controlled. The FDA is not bound to its advisory committee's recommendations, and many analysts believe that the advisory group's concern about the quality of the phase 3 studies will result in an

Memo to P&Ts: Early approvals could be the new norm

P&T committees often wait six months to a year before fully evaluating a new drug. The Food and Drug Administration's new "breakthrough drug" designation doesn't change that, but the appellation will almost certainly force P&T committees to review those products earlier than they might otherwise have.

Whether P&Ts will have all the data they need, however, is an open question.

"Breakthrough" is a formal designation the FDA began bestowing this year on products it believes can make a real difference. The FDA hasn't explicitly spelled out what the "breakthrough" label means, but we may be seeing that one perk is speedy market approval. The first two biologics to pocket this designation were approved in November — far ahead of schedule.

Roche/Genentech's obinutuzumab (Gazyva) was the first to be labeled a breakthrough drug, back in May and shortly after the California biotech company filed its new-drug application (NDA). Obinutuzumab is a first among leukemia drugs: It attacks cancer cells and stimulates the body's immune system. Investors were taken by surprise and sales and marketing forces were left to scramble when it became apparent during the fall that the FDA would smile on Roche with an early decision. And early it was. When the FDA approved obinutuzumab on November 1, regulators were six weeks ahead of schedule.

Pharmacyclics/Johnson & Johnson's ibrutinib (Imbruvica) received approval 12 days later — just four months after its NDA filing. The second drug to gain the FDA breakthrough designation, ibrutinib wasn't expected to be reviewed until February. Regulators, however, quickly approved one of the two indications J&J sought — mantle cell lymphoma, which accounts for only 35,000 diagnoses a year — on the basis of phase 2 trial data. The FDA will revisit the other indication later, even as ibrutinib remains under study.

If P&T committees wanted to size up the two new products, the early approvals didn't leave them much to go on. Genentech was keeping mum about phase 3 data until December's American Society of Hematology Meeting. J&J hasn't established overall survival data for ibrutinib, and, unconventionally, the FDA didn't immediately release ibrutinib's label upon approval.
A complete response letter.

Another FDA advisory committee, meanwhile, glowed about two oral therapies for hepatitis C.

First up: Johnson & Johnson’s simeprevir, for treatment of patients with genotype 1, the most common form of hepatitis C. In three phase 3 studies, simeprevir had a collective 80% cure rate.

Next was sofosbuvir, for which Gilead seeks indications in all four genotypes. More important, sofosbuvir approval would create a new standard of care—an interferon-free regimen—for genotypes 2 and 3. The Antiviral Drugs Advisory Committee voted unanimously to recommend approval of both drugs.

“Game-changer”

Jean-Charles Soria knows how to work a room. The French lead investigator of Roche’s early-stage trial of MPL-3280 in patients with non–small-cell lung cancer (NSCLC) was positively persuasive about the drug’s 26% response rate in smokers. Normally, something that works in 1 in 4 people would be a disappointment, but the fact that the agent worked in only 10% of nonsmokers made the PD-L1 blocker, in Soria’s estimation, “a game changer.”

In NSCLC patients with a history of smoking, treatment is largely futile and survival rates are dismal. “And bingo, this is the first targeted agent that shows more activity in smokers than in nonsmokers,” Soria told reporters. By blocking PD-L1, MPL-3280 allows T-cells to recognize tumors and attack them.

Roche is in a race with Merck, whose PD-1 receptor inhibitor MK-3475 will probably make landfall next summer with a melanoma indication and is under study for lung cancer, and with Bristol-Myers Squibb, which is out with new data about its anti-PD-1, nivolumab. Completing an analysis of phase 1 data, BMS said two-year survival in previously treated patients was 24% — almost double what was reported when topline data were released last June.

Did you hear?

Researchers at Stanford are recruiting for a phase 2 trial of tricyclic antidepressants to treat small-cell lung cancer. Early research was encouraging, showing that imipramine induced apoptosis in tumors that had become resistant to chemotherapy...

Could resveratrol, the heart-protective chemical in red wine, be effective in fighting cancer? A study in Science Translational Medicine reported that a resveratrol metabolite slowed tumor growth in mice.

— Michael D. Dalzell

All clinical trials described in this column are phase 3, randomized, controlled studies unless otherwise specified.

**SELECTED FDA BIOLOGIC AND SPECIALTY DRUG APPROVALS, SEPT. 15–NOV. 14, 2013**

<table>
<thead>
<tr>
<th>Date (type)</th>
<th>Manufacturer</th>
<th>Drug (trade name); administration</th>
<th>Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct. 16 (BLA)</td>
<td>Novo Nordisk</td>
<td>Turoctocog alfa (NovoEight); no label information on administration available yet</td>
<td>Hemophilia A in adults and children for control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes</td>
<td>Recombinant coagulation factor VIII medication will not be launched in the United States until 2015.</td>
</tr>
<tr>
<td>Nov. 1 (NDA)</td>
<td>Roche/Genentech</td>
<td>Obinutuzumab (Gazyva); intravenous infusion</td>
<td>In combination with chlorambucil for treatment of patients with previously untreated CLL</td>
<td>“Next generation rituximab” was the first drug with FDA “breakthrough” designation to be approved; only 6 years passed from phase 1 to approval. Cost is $41,300 for 6-month course; Genentech says no patient will take it longer.</td>
</tr>
<tr>
<td>Nov. 13 (NDA)</td>
<td>Pharmacyclics/Janssen Biotech</td>
<td>Ibrutinib (Imbruvica); oral</td>
<td>Patients with MCL who have not responded to at least one prior therapy</td>
<td>Second FDA “breakthrough” agent to receive approval. Designation based on 65.8% ORR. Ibrutinib’s AWP is &gt;$90/tablet, or about $8,200/month.</td>
</tr>
</tbody>
</table>

_AWP = average wholesale price, BLA = biologics license application, CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, NDA = new-drug application_


_AWP = average wholesale price, BLA = biologics license application, CLL = chronic lymphocytic leukemia, MCL = mantle cell lymphoma, NDA = new-drug application_


**BIOLOGICS IN DEVELOPMENT**

On a hopeful note, another FDA advisory committee, meanwhile, glowed about two oral therapies for hepatitis C. First up: Johnson & Johnson’s simeprevir, for treatment of patients with genotype 1, the most common form of hepatitis C. In three phase 3 studies, simeprevir had a collective 80% cure rate. Next was sofosbuvir, for which Gilead seeks indications in all four genotypes. More important, sofosbuvir approval would create a new standard of care—an interferon-free regimen—for genotypes 2 and 3. The Antiviral Drugs Advisory Committee voted unanimously to recommend approval of both drugs.
3 ways biomarkers are changing drug development

Targeting a biomarker in drug development addresses the age-old problem of one-size-fits-all drugs working in half or fewer of patients, because response rates of drugs in patients with a corresponding biomarker are generally much higher. Here are three ways molecular discoveries are driving change in the way drugs and biologics are developed.

1 Biomarkers and drug-diagnostic combinations According to a 2010 report from the Tufts Center for the Study of Drug Development, in some therapeutic areas, half of active drug trials involve some sort of biomarker. The fruits of this research are beginning to hit the market. In 2011 and 2012, three personalized medications — defined as requiring the use of a companion diagnostic to identify appropriate patients — received Food and Drug Administration approval. In 2013, four such products had been approved by November 15. The speed of approvals can be expected to continue to increase; Roche, for one, has said that by next year, at least half of its approvals will be for drugs requiring a companion diagnostic.

Drug-diagnostic approvals in last 3 years

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug Name</th>
<th>Therapeutic Area</th>
<th>AWP (price/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug. 17, 2011</td>
<td>Zelboraf (vemurafenib)</td>
<td>Ovarian cancer</td>
<td>$11,055</td>
</tr>
<tr>
<td>Aug. 26, 2011</td>
<td>Xalkori (crizotinib)</td>
<td>Amyotrophic lateral sclerosis</td>
<td>$9,600</td>
</tr>
<tr>
<td>June 8, 2012</td>
<td>Perjeta (pertuzumab)</td>
<td>Small cell lung cancer</td>
<td>$6,000</td>
</tr>
<tr>
<td>May 29, 2013</td>
<td>ado-trastuzumab emtansine</td>
<td>Cervical cancer</td>
<td>$9,800</td>
</tr>
<tr>
<td>May 29, 2013</td>
<td>trameitinib (Mekinist)</td>
<td>Anthrax</td>
<td>$8,700</td>
</tr>
<tr>
<td>July 12, 2013</td>
<td>dabrafenib (Tafinlar)</td>
<td>Septic shock</td>
<td>$5,500</td>
</tr>
<tr>
<td>May 29, 2013</td>
<td>Perjeta (pertuzumab)</td>
<td>Sickle cell disease</td>
<td>$7,600</td>
</tr>
<tr>
<td>July 12, 2013</td>
<td>afatinib (Gilotrif); oral</td>
<td>Myasthenia gravis</td>
<td>$5,500</td>
</tr>
</tbody>
</table>

AWP = Average wholesale price
Sources: Manufacturers’ package information; Medical Marketing & Media, UBC/Express Scripts, Nature news blog, Seeking Alpha, Forbes.com

2 Unmet needs The advent of biomarkers has re-invigorated research into treatments for disease areas where therapy has not changed for a long time.

Medications in development for conditions with no approvals in 10 years

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Drugs in development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>158</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>61</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>41</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>28</td>
</tr>
<tr>
<td>Anthrax</td>
<td>27</td>
</tr>
<tr>
<td>Septic shock</td>
<td>26</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>19</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>7</td>
</tr>
</tbody>
</table>


3 Repurposing medications The average wholesale prices in the timeline above suggest that the cost of developing new personalized medicine is unsustainable. That, coupled with the potential for biomarkers to make treatment more effective in specific patients, led the National Institutes of Health to launch an initiative to see if old drugs or abandoned molecules could have utility in people with specific molecular profiles.

For a pilot NIH program, eight drug manufacturers donated 58 molecules that have undergone preclinical and, in some cases, human testing. Last June, NIH awarded nine grants totaling $12.7 million to see if these molecules can provide new benefits in certain subpopulations.

Diseases targeted under the NIH Discovering New Therapeutic Uses for Existing Molecules initiative

- Alcoholism
- Alzheimer’s disease
- Calcific aortic valve stenosis
- Duchenne muscular dystrophy
- Lymphangioleiomyomatosis
- Nicotine dependence
- Peripheral artery disease
- Schizophrenia

Source: National Institutes of Health–National Center for Advancing Translational Sciences, June 2013

— Michael D. Dalzell
Fixed-Dose Triple-Combination Treatments In the Management of Hypertension
C. Venkata S. Ram, MD

ABSTRACT
Hypertension remains uncontrolled in approximately 50% of patients with hypertension, which increases the risk of cardiovascular morbidity and mortality in these individuals. A key factor contributing to poor blood pressure (BP) control is nonadherence to prescribed antihypertensive medications. Improving patient adherence to antihypertensive therapy is the key to improving BP goal attainment. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend a stepwise treatment algorithm for patients with stage 1 hypertension, with initial treatment consisting of a single antihypertensive drug. For most patients, however, combinations of 2 or more antihypertensive agents are necessary for adequate BP control. Antihypertensive regimens that combine agents from different antihypertensive drug classes can facilitate attainment of BP goals and improve cardiovascular outcomes at lower drug doses compared with monotherapy. Patient adherence to antihypertensive therapy decreases with increasing number of pills in multiple pill regimens, but fixed-dose triple-combination treatments for hypertension provide a tool for addressing patient nonadherence associated with pill burden. For patients whose antihypertensive therapy includes multiple medications, the use of a single-pill, fixed-dose combination therapy can significantly improve compliance and thereby help patients achieve BP goals. In addition, single-pill combinations may reduce health care utilization and medical costs compared with multiple single-pill therapies. The purpose of this article is to review the role of novel single-pill, fixed-dose, triple-combination treatments for modern hypertension management.

Keywords: Hypertension, Drug Combinations, Medication Adherence, Treatment Outcome, Cost Savings

INTRODUCTION
The prevalence of hypertension (defined as systolic blood pressure [SBP] ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg) has increased over the past 2 decades, such that nearly one third of U.S. adults – about 78 million people ≥20 years of age – have high BP (Go 2013). The National Health and Nutrition Examination Survey (NHANES) 2007-2010 collected data showing that, among US adults with hypertension, 82% were aware of their condition, 75% were under treatment, and 53% had their hypertension under control (Go 2013). The prevalence of hypertension in the elderly is even higher: poor BP control is associated with an increased risk of cerebrovascular disease, ischemic cardiovascular disease, renal damage, and vascular dementia (Chobanian 2003, Law 2009, Lu 2009, Sharp 2011, WHO 2002). Coronary artery disease and heart failure (HF) were the costliest conditions studied in the Medicaid population, with per-patient medical and prescription expenses estimated at approximately $5,000 and $6,000 per year, respectively (Priest 2011). The American Heart Association projects that direct medical costs of treating hypertension in the U.S. will increase from $70 billion in 2010 (in 2008$) to over $200 billion in 2030, while the cost of hypertension as a risk factor for cardiovascular disease (a portion of the costs of complications associated with hypertension, including HF, coronary heart disease [CHD], stroke, and other cardiovascular disease) will increase from $131 billion in 2010 to $389 billion in 2030 (Heidenreich 2011).

The economic impact of hypertension is substantial. In a retrospective study of health care costs using a database of about 2.8 million Medicaid patients, annual disease-related costs for hypertension were estimated to be $587 per patient, including medical care and prescription costs (Priest 2011). The costs associated with secondary medical outcomes in patients with hypertension are even higher: poor BP control is associated with an increased risk of cerebrovascular disease, ischemic cardiovascular disease, renal damage, and vascular dementia (Chobanian 2003, Law 2009, Lu 2009, Sharp 2011, WHO 2002). Coronary artery disease and heart failure (HF) were the costliest conditions studied in the Medicaid population, with per-patient medical and prescription expenses estimated at approximately $5,000 and $6,000 per year, respectively (Priest 2011). The American Heart Association projects that direct medical costs of treating hypertension in the U.S. will increase from $70 billion in 2010 (in 2008$) to over $200 billion in 2030, while the cost of hypertension as a risk factor for cardiovascular disease (a portion of the costs of complications associated with hypertension, including HF, coronary heart disease [CHD], stroke, and other cardiovascular disease) will increase from $131 billion in 2010 to $389 billion in 2030 (Heidenreich 2011).

Treatments that effectively lower BP can reduce the risk of cardiovascular and cerebrovascular events and...
cardiovascular morbidity and mortality across a wide range of patient populations (Neal 2000, Ogden 2000, Verdecchia 2010). Most patients with hypertension can achieve BP goals (Cushman 2002), but clinicians must determine which antihypertensive drug or drug combination is appropriate for the individual patient.

Several classes of antihypertensive agents with different mechanisms of action — including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), and thiazide-type diuretics — have demonstrated efficacy for lowering BP (Chobanian 2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines recommend a stepwise treatment algorithm, generally initiating therapy with thiazide-type diuretics for patients with stage 1 hypertension (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg) (Chobanian 2003).

Switching to a drug in a different class or to a combination of 2 or more drugs is considered for patients who do not achieve adequate BP control with first-line therapy and for patients with stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) (Chobanian 2003). The American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention, and the Canadian Hypertension Education Program Recommendations Task Force also recommend the use of thiazide diuretics, ACE inhibitors, ARBs, or CCBs as first-line treatment, and a drug combination when target BP is not achieved with a single medication (Rabi 2011, Rosendorff 2007).

For most patients, combinations of 2 or more antihypertensive agents are necessary for adequate BP control (ie, <140/90 mm Hg). The investigators of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported that by treatment year 5, 62.5% of patients were using 2 or more drugs and 27.3% were using 3 or more (Cushman 2002). The ALLHAT investigators found that participating clinicians did not consistently intensify therapy when SBP remained >140 mm Hg, suggesting that an even greater percentage of patients in clinical practice will require multiple antihypertensive medications to achieve adequate SBP control (Cushman 2002).

The percentage of US patients with hypertension whose BP is controlled has increased over the past 2 decades as both awareness of the risks of hypertension and the number of treatment options have increased (Egan 2010). However, NHANES data indicate that BP still remains uncontrolled in approximately 50% of patients with hypertension (Egan 2010). Among the factors accounting for high rates of patients with inadequate control are clinical inertia, or the failure to increase antihypertensive drug dosage or prescribe additional medications, and nonadherence to the therapy prescribed (Chobanian 2003). Finding ways to improve patient adherence to antihypertensive therapies is a critical step in bringing more patients to BP goals. The aim of this article is to review the role, benefits, and clinical trial data of 3 single-pill, fixed-dose, triple-combination treatments for hypertension management.

**Combination therapy for hypertension**

**Clinical benefits of combination therapy**

Extensive data from randomized controlled trials and population-based studies have demonstrated that combination therapy regimens can reduce BP, facilitate attainment of BP goals, and improve cardiovascular outcomes compared with a mono-therapy approach (Corrao 2011, Feldman 2009, Lv 2010, Wald 2009). Combining BP-lowering medications from drug classes that act on different physiological pathways involved in BP regulation can yield additional reductions by blocking complementary pressor mechanisms and preventing compensatory response to any single drug class (Elijovich 2009, Escobar 2010, Gradman 2010b).

JNC 7 and guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI), and the American Diabetes Association (ADA) recommend combination antihypertensive drug therapies as first-line treatment for patients with stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) (Chobanian 2003) and for patients with complicating comorbidities including HF, CHD, diabetes, and chronic kidney disease (Wright 2011).

These recommendations are based on the fact that combination therapies are associated with quick and safe achievement of BP goals. Compared with monotherapy, drug combinations can bring patients to BP goals more rapidly than single-drug therapies (Weir 2007, Weir 2011). In the large, double-blind, placebo-controlled Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) trial, patients with mild to severe hypertension (N=1490) randomly assigned to receive olmesartan/amldipine combination therapies achieved greater reductions in SBP and DBP at week 8 compared with patients administered olmesartan or amlodipine monotherapy (Chrysant 2008a). Differences between the combination vs. monotherapy groups were evident by week 2, and response plateaued by week 4 (Chrysant 2008a, Chrysant 2008b).
Fixed-dose Triple-Combination Hypertension Treatments

Lowering BP rapidly can reduce the risk of cardiac events and stroke. In clinical trials, treatment groups that achieved a lower BP earlier in treatment had lower risk of myocardial infarction, HF hospitalizations, stroke, composite cardiac mortality and morbidity, and all-cause death (Julius 2004, Staessen 2004), and risks were lower particularly during the early time period when BP differences between the groups were greatest (Julius 2004).

The recommendations also take into account that specific antihypertensive drug classes offer increased target organ protection and reduce morbidity and mortality beyond that accounted for by BP reduction alone (Lindholm 2002, Okin 2003, Parving 2008). Table 1 lists the classes of antihypertensive drugs recommended for patients with compelling conditions according to JNC 7. Table 2 summarizes guidelines and expert consensus statements on combination therapy in patients with hypertension.

The ACC/AHA guidelines mention that most patients will require more than 1 antihypertensive agent to achieve BP control and that pharmacotherapy should begin with known outcome-improving agents. These guidelines recommend addition of a β-blocker, ACE inhibitor, ARB, and/or long-acting CCBs to a thiazide diuretic for treating hypertension in patients with unstable angina and non–ST-segment elevation myocardial infarction (Wright 2011). The ADA and American Association of Clinical Endocrinologists state that multidrug therapy (2 or more agents) is generally required to achieve BP targets in patients with hypertension and diabetes (Arauz-Pacheco 2004; Handelsman 2011). The ADA recommends initial drug therapy with ACE inhibitors, ARBs, β-blockers, CCBs, or diuretics for treating patients with BP >140/90 mm Hg (Arauz-Pacheco 2004). All patients with diabetes and hypertension should be treated with either an ACE inhibitor or an ARB (Arauz-Pacheco 2004, Handelsman 2011). ACE inhibitors are recommended to delay progression of diabetic nephropathy and ACE inhibitors and ARBs to delay progression of macroalbuminuria. If BP targets are not being met, a thiazide diuretic should be added (Arauz-Pacheco 2004).

The KDOQI guidelines include the use of ACE inhibitors or ARBs in combination with a diuretic for treating hypertension in patients with diabetes (NKF 2007); CCBs and β-blockers also are considered effective therapies. A position paper from the American Society of Hypertension states that single-pill combinations may be used as initial treatment in a patient in whom multimdrug therapy is likely to be needed, in a patient partially controlled on monotherapy, or as a substitute for independently titrated doses of individual components. It also is acknowledged that it is easier for a patient to comply with an antihypertensive treatment regimen that includes fewer pills (Gradman 2010b).

Combining medications from different classes can provide added protective effects on the cardiovascular system, reducing the risk of cardiovascular and cerebrovascular events (Aronow 2011). In a meta-analysis of SBP reductions in 42 trials (N=10,698), each of 4 classes of antihypertensive drugs (thiazide diuretics, ACE inhibitors, β-blockers, and CCBs) was compared with pairwise combinations among the classes (Wald 2009). The reductions in SBP for each class were additive when drugs from 2 classes were combined, and the combination of any 2 medications from different BP-lowering drug classes was approximately 5 times more effective than doubling the dose of a single drug.

Finally, antihypertensive drug combinations can improve tolerability compared with monotherapy. Similar or greater BP reduction achieved with antihypertensive drug combinations means that lower drug doses are required to reach BP goals compared with a single, higher-dose drug (Aronow 2011; Neutel 1999). Furthermore, one component of an antihypertensive combination therapy can reduce the occurrence of adverse events caused by a second component. Patients with uncomplicated hypertension treated with the CCB

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Target organ protection: benefits of antihypertensive drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td><strong>JNC 7-recommended Classes of Antihypertensive Drugs</strong></td>
</tr>
<tr>
<td>Heart failure</td>
<td>Diuretics, β-blockers, ACE inhibitors, ARBs, aldosterone antagonists</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>β-blockers, ACE inhibitors, aldosterone antagonists</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>Diuretics, β-blockers, ACE inhibitors, CCBs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diuretics, β-blockers, ACE inhibitors, ARBs, CCBs</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACE inhibitors, ARBs</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>Diuretics, ACE inhibitors</td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme; ARBs=angiotensin receptor blockers; CCBs=calcium channel blockers.

Adapted with permission from Chobanian et al (Chobanian 2003).
Fixed-dose Triple-Combination Hypertension Treatments

amlodipine 10 mg/d experienced statistically significant increases in 2 objective measures of ankle edema, ankle foot volume (AFV), and pretibial subcutaneous tissue pressure (PSTP) (Fogari 2007). Patients who were administered valsartan 160 mg/d in addition to amlodipine, however, experienced no changes in edema from baseline and had significantly lower AFV and PSTP compared with the amlodipine monotherapy group.

**Antihypertensive treatment adherence**
Persistence with antihypertensive medications has been estimated to be approximately 60% to 75% after 1 year, declining to approximately 55%

<p>| TABLE 2 Recommendations for antihypertensive combination therapy in patients with hypertension |</p>
<table>
<thead>
<tr>
<th>Guidelines/expert consensus statement</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report (Chobanian 2003)</td>
<td>Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with a drug from another class (ACE inhibitors, ARBs, β-blockers, CCBs) also demonstrated to be beneficial in randomized controlled outcome trials. Adding a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve BP goal. When BP is &gt;20/10 mm Hg above goal, consider initiating therapy with 2 drugs. If BP goal is not reached, additional drugs can be added until goal is achieved.</td>
</tr>
<tr>
<td>ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly (Aronow 2011)</td>
<td>Thiazide diuretics are recommended for initiating therapy. If BP response is inadequate after reaching “full dose” (not necessarily maximum recommended dose), a second drug from another class (β-blockers, CCBs, ACE inhibitors, ARBs) should be added. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching full doses of 2 classes of drugs, a third drug from another class should be added. When BP is &gt;20/10 mm Hg above goal, therapy should be initiated with 2 antihypertensive drugs.</td>
</tr>
<tr>
<td>2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Wright 2011)</td>
<td>Pharmacotherapy should begin with known outcome-improving medications (primarily thiazide diuretics as first choice, with the addition of β-blockers, ACE inhibitors, ARBs, and/or long-acting CCBs). (Primary prevention patients with high BP should be treated according to JNC 7 recommendations.)</td>
</tr>
<tr>
<td>Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease: KDOQI (NKF 2007)</td>
<td>Hypertensive patients with diabetes and CKD stages 1-4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic.</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (Handelsman 2011)</td>
<td>Initially, antihypertensive agents are selected on the basis of their ability to reduce BP and to prevent or slow progression of nephropathy and retinopathy; ACE inhibitors or ARBs are the preferred choice in patients with diabetes mellitus. The use of combination therapy is likely required, including CCBs, diuretics, combined α/β-adrenergic blockers, and newer-generation β-adrenergic blockers in addition to agents that block the renin-angiotensin system.</td>
</tr>
<tr>
<td>Hypertension Management in Adults With Diabetes: American Diabetes Association (Arauz-Pacheco 2004)</td>
<td>Initial drug therapy should be with a drug class demonstrated to reduce CVD events in patients with diabetes (ACE inhibitors, ARBs, β-blockers, diuretics, CCBs). All patients with diabetes and hypertension should be treated with a regimen including either an ACE inhibitor or ARB. If BP targets are not achieved, a thiazide diuretic should be added.</td>
</tr>
</tbody>
</table>

ACC=American College of Cardiology; ACCF=American College of Cardiology Foundation; ACE=angiotensin-converting enzyme; AHA=American Heart Association; ARBs=angiotensin receptor blockers; BP=blood pressure; CCBs=calcium channel blockers; CKD=chronic kidney disease; CVD=cardiovascular disease; KDOQI=National Kidney Foundation-Kidney Disease Outcomes Quality Initiative.

48  MANAGED CARE / DECEMBER 2013
after 3 years and 40% after 10 years (Perreault 2005, van Wijk 2005). Nonadherence is associated with reduced BP goal achievement (Bramley 2006, Fung 2007, Ho 2008, Yiannakopoulou 2005) and a higher risk of CHD, cerebrovascular disease, HF, and death (Bailey 2010, Cherry 2009, Dragomir 2010, Kettani 2009, Perreault 2009). Patient nonadherence to antihypertensive medication was significantly associated with uncontrolled BP in several retrospective studies of pharmacy and BP records from U.S. managed care databases (Bramley 2006, Fung 2007, Ho 2008). In a prospective assessment of long-term adherence to antihypertensive treatment and its effect on BP outcomes, decreases in SBP and DBP were proportional to rates of persistence with treatment (Veronesi 2007). Improving adherence to hypertension treatment regimens thus is likely to increase the number of patients with hypertension who meet the recommended BP goals.

The costs of nonadherence, in terms of patient outcomes and health care utilization, are high. Because better antihypertensive medication adherence is associated with higher levels of BP goal attainment (Bramley 2006, Fung 2007), improving adherence can save lives and substantially reduce health care utilization in patients with hypertension. In a retrospective cohort study in which 61% of patients were nonadherent to antihypertensive medication (i.e., took <80% of prescribed drugs based on Medication Refill Adherence), it was estimated that approximately 200,000 lives could be saved over a 5-year period by increasing adherence for patients with hypertension to ≥80% (Bailey 2010). Patients adherent to prescribed antihypertensive medications have fewer emergency department visits, hospitalizations, inpatient hospital days, and consequently lower health care costs (Dragomir 2010, Pittman 2010). Estimated excess hospitalization costs associated with nonadherence in approximately 19,000 Canadian patients with hypertension were $25.2 million from 1999 to 2002 (Dragomir 2010).

The advantages of single-pill combination therapies for hypertension may be offset by the negative effect on adherence of a regimen composed of multiple single pills. Patients may find that managing multiple pills daily is cumbersome and confusing. Indeed, adherence to hypertension therapy is reduced as the number of pills in a regimen increases (Fung 2007): in a historical cohort study of 84,929 Medicare beneficiaries aged ≥65 years who were prescribed antihypertensive medications, Fung and colleagues assessed patient adherence to at least 1 hypertension medication and to the full prescribed hypertension treatment regimen by number of drugs prescribed. They observed that the percentage of patients who were adherent to the full treatment regimen decreased with increasing number of prescribed antihypertensive medications (Figure 1). Notably, among patients who were not fully adherent to the multiple-medication regimen, partial compliance increased with the number of medications prescribed—that is, the more medications in the regimen, the more likely patients were to take at least 1 of their pills (Figure 1) (Fung 2007). Findings from this study suggest that, even in patients motivated to adhere to the hypertension treatment plan, multiple medication regimens can be a barrier to full compliance. In an effort to reduce pill burden and increase compliance, single-pill, fixed-dose combination therapies for hypertension have been introduced.

**Single-pill, fixed-dose combination therapy for hypertension**

An extensive range of antihypertensive drug combinations are available as single-pill, fixed-dose medications, most including a diuretic plus a second antihypertensive drug from a different class. Fixed-dose, single-pill combination therapies reduce pill counts and thereby improve adherence to hypertension treatment regimens (Gradman 2010). Several retrospective studies of pharmacy...
records from large medical administrative databases have demonstrated that prescribing fixed-dose combination pills can lead to increased adherence to antihypertensive medications compared with the use of multiple individual-component pills (Brixner 2008, Dezii 2000, Dickson 2008, Panjabi 2013, Yang 2010, Zeng 2010). Adherence or compliance rates ranged from approximately 63% to 73% for single-pill combination drugs and 28% to 61% for patients prescribed the individual components (Brixner 2008, Dezii 2000, Dickson 2008, Yang 2010).

A meta-analysis of 6 studies, including 30,295 patients prescribed antihypertensive medications, reported a statistically significant 29% increase in compliance with fixed-dose combination pills compared with free-drug combinations (Gupta 2010). A second meta-analysis of 12 retrospective database studies published between 2000 and 2010 found that, in the 7 studies reporting medication possession ratios and in the overall meta-analysis, patients prescribed single-pill, fixed-dose antihypertensive combination therapy had significantly higher treatment adherence compared with patients prescribed free-drug combinations (Sherrill 2011). The pooled risk ratio for persistence in the meta-analysis was 2.1 (95% confidence interval [CI], 1.1-4.1), favoring the single-pill combination therapy. Persistence with single-pill compared with free-drug combinations is shown in Figure 2 (Sherrill 2011).

Although the use of fixed-dose combination therapies offers several advantages, some disadvantages are associated with them: branded fixed-dose combinations may be more expensive than equivalent free-dose combinations; the duration of action of individual components may not be equivalent, and this may not justify a single daily dosing of the combination; the use of fixed-dose combinations results in less flexibility in modifying the doses of individual components; and patients may be exposed to unnecessary therapy (Angeli 2012).

**FIGURE 2**
Persistence with antihypertensive therapy regimens; single-pill combination therapy vs free-drug combinations.
Persistence was defined as the percentage of patients meeting a predefined threshold (depending on the study) during a 12-month follow-up period (Sherrill 2011).

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.0</td>
<td>68.7</td>
<td>70.0</td>
<td>57.4</td>
<td>59.3</td>
<td>55.5</td>
</tr>
<tr>
<td>19.1</td>
<td>57.9</td>
<td>12.9</td>
<td>14.9</td>
<td>20.9</td>
<td>19.1</td>
</tr>
</tbody>
</table>

**Potential economic benefits of single-pill combinations**

Single-pill combinations increase adherence to antihypertensive therapy and, as expected, reduce health care costs compared with multiple-pill therapies (Dickson 2008, Panjabi 2013, Yang 2010). Prescription drug costs sometimes (but not always) are higher for single-pill combination therapies compared with the component drugs (Brixner 2008), yet reduced health care utilization in patients prescribed single-pill combinations results in lower overall medical service expenditures. In a retrospective study using data from a large, nationwide medical administrative database, the reduction in medical services expenditures for patients with hypertension receiving single-pill combination therapy over 6 months of treatment (compared with a 6-month pre-treatment baseline) was $208 (95% CI, $114-$302) greater per patient compared with the reduction in medical services expenditures for patients receiving the individual component drugs (Figure 3) (Yang 2010). In the meta-analysis of 12 retrospective database studies, single-pill, fixed-dose combination therapy was associated with lower overall and hypertension-related medical costs compared with free-drug combinations (Sherrill 2011).

**FDA-APPROVED TRIPLE-COMBINATION TREATMENTS FOR HYPERTENSION**

A triple combination treatment (reserpine, hydralazine, and hydrochlorothiazide) was first utilized in the 1960s (VACSG 1967), but sequential monotherapy was recommended over drug combinations in practice at that time (Black 2009). The use of multiple-drug treatments is now common for patients who do not achieve BP goals with a single antihypertensive medication, have stage 2 hyperten-
Fixed-dose Triple-Combination Hypertension Treatments

FIGURE 3
Change from baseline in health care costs in patients with hypertension using either a single-pill combination or free-drug combination.

Changes in health care costs were calculated as the costs incurred during the 6-month post-index period minus those incurred during the 6-month baseline period. Reproduced with permission from Yang et al (Yang 2010).
CI = confidence interval; CV = cardiovascular.

TABLE 3
U.S. FDA-approved triple-combination antihypertensive treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exforge HCT</th>
<th>Tribenzor</th>
<th>Amturnide</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval date</td>
<td>April 30, 2009</td>
<td>July 23, 2010</td>
<td>December 21, 2010</td>
</tr>
<tr>
<td>Components</td>
<td>Valsartan (ARB*)</td>
<td>Amlodipine (CCB†)</td>
<td>Olmesartan (ARB*)</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide (thiazide diuretic)</td>
<td>Hydrochlorothiazide (thiazide diuretic)</td>
<td>Amlodipine (CCB†)</td>
</tr>
<tr>
<td>Pivotal trial</td>
<td>Calhoun 2009a</td>
<td>Oparil 2010</td>
<td>Lacourciere 2012</td>
</tr>
</tbody>
</table>
| *AT receptor subtype; †Dihydropyridine class.

sion, or have cardiovascular or cerebrovascular comorbidities (Chobanian 2003). Consequently, numerous single-pill, 2-drug combinations are available, and 3 single-pill triple-combination therapies recently received FDA approval (Table 3): the combination of valsartan, amlodipine, and hydrochlorothiazide (Exforge HCT) in 2009; olmesartan, amlodipine, and hydrochlorothiazide (Tribenzor) in 2010; and aliskiren, amlodipine, and hydrochlorothiazide (Amturnide), also in 2010.

The single-pill, triple-combination therapies are indicated for patients whose BP is uncontrolled with dual-combination therapy. The use of single-pill, fixed-dose triple-combination therapy would be appropriate in patients with uncontrolled hypertension who are taking 2 separate drugs, a 2-drug combination, or 3 separate drugs (Elijovich 2009,
Fixed-dose Triple-Combination Hypertension Treatments

Gradman 2010a, Gradman 2010b), with the choice of triple-combination pill based on the currently prescribed components and patient comorbidities. No head-to-head trials among the 3 triple combinations have been published to date.

Valsartan/amlopidine/hydrochlorothiazide

The first triple combination approved by the FDA, valsartan/amlopidine/hydrochlorothiazide (10/320/25 mg), was associated with greater SBP and DBP reductions (last observation carried forward) compared with the component dual-combination therapies (amlodipine/valsartan, amlodipine/hydrochlorothiazide, valsartan/hydrochlorothiazide) in an 8-week, randomized, double-blind, parallel-group trial (N=2271) (Calhoun 2009a). The study included a single-blind, placebo run-in period followed by double-blind treatment for 8 weeks; patients were randomly assigned to 1 of 4 groups titrated to valsartan/amlopidine/hydrochlorothiazide 320/10/25 mg, valsartan/hydrochlorothiazide 320/25 mg, amlopidine/valsartan 10/320 mg, or amlopidine/hydrochlorothiazide 10/25 mg once daily (Calhoun 2009a).

Beginning at screening and continuing throughout the study, each patient took 2 tablets and 2 capsules except on days when clinic visits were scheduled. Placebo was administered as either a tablet or capsule to maintain blinding. Greater BP reductions were observed for the triple combination compared with the dual combinations regardless of age, sex, race, or ethnicity. In addition, the proportion of patients achieving BP control (<140/90 mm Hg) at study end point was significantly greater with the triple combination (70.8%) compared with the dual combinations (44.8–54.1%).

In a secondary analysis of data from that study, significant differences between the triple combination and all dual combinations were observed by week 3, after patients in the triple-dose arm had received all 3 components for 1 week (Calhoun 2009b). Valsartan/amlopidine/hydrochlorothiazide efficacy also was assessed in a subset of patients who received 24-hour ambulatory BP monitoring at baseline and after 8 weeks of therapy (Lacourciere 2011). In this subset, the triple combination was significantly more effective than any of the dual combinations, reflecting the results of the total study population.

The percentages of patients reporting at least 1 adverse event ranged from 45% to 48% in the total study population, with no differences observed between treatment groups (Calhoun 2009a). An adverse event was the most common reason for discontinuation from the double-blind treatment phase. The most common adverse events (≥2%) reported by patients administered the triple combination were dizziness (7.7%), ankle edema (4.5%), and headache (4.3%) (Calhoun 2009a).

In a 52-week, open-label safety and tolerability study enrolling patients with mild to moderate hypertension, 17% of patients reported peripheral edema at the 10/160/12.5 mg dose (Domenech 2010).

Olmesartan/amlopidine/hydrochlorothiazide

The triple-combination treatment olmesartan/amlopidine/hydrochlorothiazide (40/10/25 mg) was compared with the component dual-combinations (olmesartan/amlopidine, amlopidine/hydrochlorothiazide, and olmesartan/hydrochlorothiazide) in a phase 3, 12-week, randomized, double-blind, parallel-group efficacy and safety trial (TRINITY, the Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study) that enrolled 2492 patients with BP ≥140/100 mm Hg or ≥160/90 mm Hg off antihypertensive treatment (Oparil 2010). Participants were randomized (stratified by age, race, and diabetes status) at the start of the study to a treatment sequence that led to their final treatment assignment: either 1 of the 3 component dual-combination treatments or the triple-combination treatment (olmesartan/amlopidine/hydrochlorothiazide 40/10/25 mg, olmesartan/amlopidine 40/10 mg, olmesartan/hydrochlorothiazide 40/25 mg, or amlopidine/hydrochlorothiazide 10/25 mg). Patients could be newly diagnosed with hypertension; not be receiving current antihypertensive therapy (ie, no antihypertensive medication for at least 3 weeks); or be undergoing a washout of current antihypertensive therapy.

The study consisted of a 3-week washout period with no study medication and a 12-week double-blind treatment period. Patients received a total of 5 tablets per day, each of which looked different, corresponding to either the active treatment or placebo image. Adherence to study medication was similar across treatment groups, ranging from 98.0% to 98.5%.

Patients administered olmesartan/amlopidine/hydrochlorothiazide achieved significantly greater mean reductions in SBP and DBP at week 12 compared with each of the dual combinations. A greater percentage of patients in the olmesartan/amlopidine/hydrochlorothiazide group reached BP goal (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes, chronic kidney disease, or chronic cardiovascular disease) compared with each dual combination at weeks 6, 8, 10, and 12 (week 6 represented the treatment effect 2 weeks after patients received the triple-combination treatment). At week 12, 70% of patients administered olmesartan/amlopidine/hydrochlorothiazide achieved a BP target of <140/90 mm Hg com-
pared with 41% to 53% of patients receiving the dual combinations.

The percentages of patients reporting at least 1 treatment-emergent adverse event ranged from 52% to 59%, with no differences observed between treatment groups. The most common treatment-emergent adverse events (≥3%) reported by patients administering the triple combination were dizziness (9.9%), ankle edema (7.7%), headache (6.4%), fatigue (4.2%), nasopharyngitis (3.5%), muscle spasms (3.1%), and nausea (3.0%) (Oparil 2010). In an open-label, long-term extension of an efficacy study for amlodipine/olmesartan, 56% of 440 patients who received olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg reported adverse events; the drug-related treatment-emergent adverse event of edema occurred in 10.7% of patients receiving olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg (Chrysant 2009).

**Aliskiren/amlodipine/hydrochlorothiazide**

The triple combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) was compared with the component dual combinations (aliskiren/amlodipine, amlodipine/hydrochlorothiazide, aliskiren/hydrochlorothiazide) in a randomized, double-blind, 8-week trial enrolling patients with moderate to severe hypertension (Lacourciere 2012). Eligible patients entered a 1–4-week single-blind placebo run-in period to establish baseline BP and eligibility for randomization based on the entry criteria, followed by an 8-week double-blind treatment period (Lacourciere 2012). Patients administered aliskiren/amlodipine/hydrochlorothiazide had significantly greater reductions in SBP and DBP compared with patients receiving the dual combinations. BP control (<140/90 mm Hg) was achieved by 62.3% of patients receiving triple-combination treatment compared with 33.1% to 41.3% receiving dual-combination treatments.

Most adverse events were mild or moderate, with the overall incidence comparable in the 4 treatment groups: 33.4% (aliskiren/amlodipine), 32.3% (aliskiren/hydrochlorothiazide), 33.6% (amlodipine/hydrochlorothiazide), and 36.2% (aliskiren/amlodipine/hydrochlorothiazide). Peripheral edema was the most frequently reported adverse event (Lacourciere 2012).

The Aliskiren Amlodipine HCTZ in Minority Patients with Stage 2 Hypertension (ASCENT) study evaluated the efficacy of aliskiren/amlodipine/hydrochlorothiazide vs. the dual combination of aliskiren/amlodipine in 412 self-identified minority patients (black, Hispanic/Latino) (Ferdinand 2011). In this study, the triple combination also resulted in greater mean BP reductions and goal achievement (<140/90 mm Hg) compared with aliskiren/amlodipine.

**SUMMARY**

There is a clinically desirable role for single-pill, fixed-dose triple combination therapies in bringing patients with hypertension to BP goals and reducing cardiovascular and cerebrovascular events. Nonadherence to antihypertensive therapy is a substantial barrier to effective BP control (Bramley 2006, Fung 2007) and has been associated with poor cardiovascular outcomes and increased medical costs (Bailey 2010, Dragonir 2010, Perreault 2009). Reducing pill-count burden is one step clinicians can take to improve adherence in patients prescribed multiple medications for hypertension and related comorbidities. Patients prescribed single-pill combination therapies have higher rates of treatment compliance and are more likely to achieve BP goals compared with patients taking the individual component drugs (Fung 2007). Further, overall and hypertension-related medical costs are significantly lower for patients taking single-pill combinations (Dragomir 2010). Improving patient adherence with the use of triple-combination therapy has the potential to save lives and reduce health care costs in patients with uncontrolled BP (Bailey 2010, Dragomir 2010).

**Acknowledgments**

Research funds for the preparation of the manuscript were provided by Daiichi Sankyo, Inc, Parsippany, New Jersey. Editorial support for this article was provided by Vrinda Mahajan, PharmD, of Peloton Advantage, LLC, Parsippany, New Jersey. The opinions expressed in the current article are those of the author. The author received no honorarium/fee for service or other form of financial support related to the development of this article.

**REFERENCES**


Fixed-dose Triple-Combination Hypertension Treatments


Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trials'
Fixed-dose Triple-Combination Hypertension Treatments


December 2013 / Managed Care 55


Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Associa-


Clinical pathways becoming widespread

Payers who intend to improve patient outcomes while decreasing inappropriate drug utilization in oncology care are positioned to implement clinical pathways now more than ever before. Prior authorization is a commonly used management strategy that is effective to a certain degree, but there is still room for improvement. Payers and practitioners alike agree that the ideal management strategy should enable practitioners to take the wheel in selecting a patient’s pharmacotherapy, which prior authorization can inhibit.

Pathways to prior authorization goals

- Practice according to FDA label, guidelines, and compendia
- Make treatment decisions based on prior treatment failure and diagnostic tests
- Prescribe correct dose and duration
- Efficacy, safety, and cost drive pathway treatment options
- Dosages are provided by pathways
- Evidence-based medicine is foundation of pathways

Clinical pathways can help to reduce the need for prior authorization as a management strategy while satisfying oncologists’ needs. The figure “Pathways to prior authorization goals” shows how goals of prior authorization can be met by clinical pathways.

The 50% of plans across the nation that have already implemented pathways or plan to do so soon see that the greatest return on investment of clinical pathways is for cancer diagnoses that are most prevalent and/or are associated with the highest drug cost.

The figure below and at right shows the most common tumor types for which pathways have been developed by health plans.

—Krishna R. Patel, PharmD, RPh

Tumor types that are most often addressed by clinical pathways

Source: “Payers Working Collaboratively With Providers to Adopt Clinical Pathways and New Care Delivery Models,” Journal of Oncology Practice, Vol. 9, issue 2

Reprints available

Major articles are reviewed by appropriate members of MANAGED CARE’s editorial advisory board and/or other qualified experts. Reprints of these copyrighted articles may be a useful tool for your company.

To obtain information concerning the purchase of professionally printed copies, please contact:

Lisa Gardineer
Phone: 267-685-2789
E-mail: lgardineer@medimedia.com
An aging population that includes too many people who are obese or overweight will drive up the costs associated with heart disease substantially by 2030, says a study in *Health Affairs*. One of the problems is that the health care system will be victim to the success of treatments that will keep heart disease patients alive longer. Society should focus more on prevention, the researchers argue.

“The question of whether to make treatment or prevention of cardiovascular disease a higher priority had often been debated, and most researchers have suggested balanced approaches,” they write in “More Americans Living Longer With Cardiovascular Disease Will Increase Costs While Lowering Quality of Life,” in the October issue of *Health Affairs*. “However, our findings suggest that substantial reductions in incidence are crucial: Otherwise, improvements in mortality from cardiovascular disease (along with aging and obesity trends) will lead to a troubling increase in prevalence.”

The average 10-year risk of heart disease will rise to about 15% for men and 9% for women by 2030, from a baseline of 12.7% and 6.8% in 1991, the study states. Researchers used data from the National Health and Nutrition Examination Surveys to make their forecast.

In addition, they relied on meta-analyses of cholesterol and blood pressure treatment. “Physical activity was not included as a risk factor because a high proportion of relevant data was missing and definitions of physical activity changed....”

The authors add that “improvements in treatment of cardiovascular disease and smoking rates have not outweighed (and will not outweigh) the influence that rising age and obesity have had on increasing total risk of cardiovascular disease.”

**Disturbing forecast**


<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>2002</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>2004</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>2006</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>2008</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2030</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Linear trend lines added for trend analysis (solid lines) and projections (dotted lines). Lighter shaded points for years 2015–30 are projections.

SOURCES “More Americans Living Longer With Cardiovascular Disease Will Increase Costs While Lowering Quality of Life,” *Health Affairs*, October 2013.