FALL 2017

biosupplytrends
QUARTERLY

SPECIAL FOCUS:
INNOVATION

Patient Engagement

Trends in Digital Health Technology

OPTIMIZING PATIENT CARE
High-Tech Apps and Instruments

CHALLENGING PUZZLE
Central Pain Syndrome

TRENDING HEALTHCARE MODEL
Concierge Medicine

MYTHS AND FACTS
E-Cigarettes

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8 Critical Steps

Purchasing

At FFF, we only purchase products from the manufacturer–never from another distributor or source. This means the integrity of our products is never in question from tampering or mishandling.

Storage

We store and transport viable protein compounds that are sensitive to temperature variations. Temperature controlled, monitored 24/7, and supported with backup generators in the event of power loss.

Specialty Packaging

We use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

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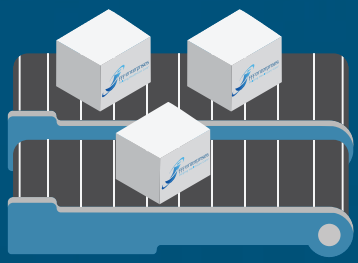
Assures responsible, demand-based distribution of critical-care products in challenging market conditions. Reduces potential for gray-market purchasing to accommodate critical demand issues.



To Guaranteed Channel Integrity™

Delivery

We deliver only to facilities with a state-issued license, and only to the address on the license. We make no exceptions. It is our commitment to do everything in our power to prevent products from entering a secondary distribution channel.

Methods of Delivery

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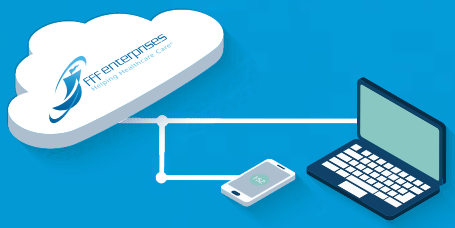

Verification

In compliance with DSCSA requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History and Transaction Statement.

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

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Features

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About BioSupply Trends Quarterly

BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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From Technologies to Models: A Changing Medical Landscape

ADVANCES IN medical technologies and models are rapidly changing the way healthcare is practiced. Indeed, in the next 10 or 20 years, medicine promises to evolve tremendously, greatly benefiting the value and quality of patient care and modernizing practices. That's the focus of this innovation-themed issue: modern tools of medicine and how they will shape the future of healthcare.

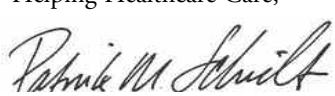
Digital technologies are blazing full speed ahead. With so much innovation in this arena, it would be impossible to capture all the progess in one issue. So, we're previewing a few of the more interesting technologies. Our article "Increasing Patient Engagement Through Online Digital Health Records and Apps" reports on the evolution of electronic health records (EHRs), a concept first introduced in the 1960s to automate patients' health records. While the initial goal of EHRs was to incentivize providers to deliver better patient care, it wasn't until the last decade or so that EHRs have truly made inroads. Today, personal health records (PHRs) and healthcare apps interface with providers' EHRs, allowing patients to enter real-time information that feeds into them. With this synchronization, providers can track patient stress levels, blood pressure, glucose, etc., as a means to promote greater adherence and oversight to treatment plans. And, while it's not always easy to convince patients to use these new tools (a poll shows only 20 percent of U.S. adults access their medical records online), we provide some marketing strategies physician offices can implement to help patients overcome technological barriers and show them the value of participating in their own care.

Other technological developments that aim to improve patient care are modernizing the way medicine is practiced. In our article "Revolutionizing Patient Care with Digital Technologies," we feature a number of leading-edge digital platforms both in development and in use in the classroom, clinical trials and practice. These include a tool that provides surgical students with a 3-D model of conducting surgery rather then the standard 2-D textbook model currently in place; the use of Apple's ResearchKit platform in combination with mobile apps that provide more accurate data about patients in clinical trials; and apps that remind patients to take their medications so they stay on track, and offer providers real-time data about medication adherence.

This increased interest in better patient outcomes has launched a new medical practice model known as concierge medicine that focuses on quality rather than quantity. The idea for concierge medicine, launched in 1996 by a company named MD2, has since burgeoned throughout the country. The reason? As we explain in our article "Concierge Medicine: Reinventing Primary Care," physicians are frustrated with high patient loads preventing them from spending adequate time with patients, increasing overhead costs and cutbacks in insurance reimbursement. While there are different levels of concierge medicine, all operate like a "private club," with patients paying a fee for enhanced personal care, including timely appointments, access to physicians via phone, longer office visits, reduced costs for some services and coordinated care for those with more complex medical needs. Under this up-and-coming model, physicians can limit the number of patients they see and, in some instances, operate on a cash-only basis. It could well be a win-win for many patients and providers.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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Supreme Court Rules in Favor of Faith-Based Hospitals' Exemption from ERISA

In June, the U.S. Supreme Court unanimously ruled that faith-based hospitals' pension plans qualify for the "church plan" exemption from the Employee Retirement Income Security Act (ERISA), which means they will not have to pay premiums to the Pension Benefit Guaranty Corp. or fully fund their pensions to meet ERISA requirements. The ruling came after three federal appeals courts ruled against dozens of other faith-based health systems that faced lawsuits from current and former employees alleging they are not entitled to the church-plan exemption.

Under ERISA, all private employers except faith-based organizations must fully fund their pensions, pay premiums to the Pension Benefit Guaranty Corp. and comply with the law's disclosure requirements. In the 1980s, Congress expanded the church plan exemption to include the pension plans of church-affiliated organizations. According to the Supreme Court justices, Congress's intention when it amended ERISA in the 1980s was not to extend the exemption to only church-established pension plans.

While all eight justices unanimously upheld the exemption (Justice Neil Gorsuch was not yet on the bench when the case was heard), Justice Sonia Sotomayor said she was "troubled" by the outcome because she is concerned that many employees will be left without federal pension protections, and large faith-based corporations don't have to comply with the same regulations as their secular competitors. ❖

Teichert E. Supreme Court Backs Faith-Based Hospitals' ERISA Exemptions. *Modern Healthcare*, June 5, 2017. Accessed at www.modernhealthcare.com/article/20170605/NEWS/170609959?utm_source=modernhealthcare&utm_medium=email&utm_content=20170605-NEWS-170609959&utm_campaign=am.

More Small Practices Exempt from MACRA Under New Draft Rule

Under a new draft rule, the Centers for Medicare and Medicaid (CMS) would exempt physician practices with less than $90,000 in Medicare revenue or fewer than 200 unique Medicare patients per year from complying with the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015. The original threshold was $30,000 or fewer than 100 Medicare patients. Combining this new rule with the exemptions already in place, a total of approximately 834,000 more clinicians are excluded from complying with the quality reporting program under MACRA. While CMS estimates only 37 percent of 1.5 million Medicare clinicians now billing under Medicare will be complying with the quality reporting system under MACRA, experts say the move should not be viewed as CMS undermining value-based care. "This should not be taken as a sign that physicians are going to go back to the fee-for-service way of doing business," said Christopher Stanley, director of the healthcare practice at consulting firm Navigant.

Under MACRA, physicians can avoid penalties by following one of two payment tracks: the Merit-based Incentive Payment System (MIPS) or advanced alternative payment models like accountable care organizations (ACOs). Currently, there has been little interest in the MIPS option. However, CMS estimates the number of participating clinicians in alternative payment models will double next year, totaling 180,000 to 245,000, because more doctors are expected to participate in ACOs. ❖

Dickson V. CMS Gives More Small Practices a Pass on MACRA. *Modern Healthcare*, June 20, 2017. Accessed at www.modernhealthcare.com/article/20170620/NEWS/170629988?utm_source=modernhealthcare&utm_medium=email&utm_content=20170620-NEWS-170629988&utm_campaign=am.

Report Shows Hospital-Acquired Conditions Continue to Decline

The Agency for Healthcare Research and Quality has released a preliminary update to the National Scorecard on Rates of Hospital-Acquired Conditions that show a 21 percent reduction in hospital-acquired conditions from 2010 to 2015. This means nearly 125,000 fewer patients died, more than three million adverse events were avoided, and more than $28 billion in healthcare costs were saved.

Many of the hospital-acquired conditions, such as adverse drug events, catheter-associated urinary tract infections, central line-associated bloodstream infections, surgical site infections and ventilator-associated pneumonias, are priorities in the National Action Plan for Adverse Drug Event Prevention and the National Action Plan to Prevent Health Care-Associated Infections. Both plans highlight the importance of coordinating surveillance resources to gather more accurate and timely data, sharing tools to help with implementing evidence-based recommendations, creating incentives to drive high-quality care and facilitating research to understand better prevention strategies. ❖

New Report Shows Continued Reduction in Hospital-Acquired Conditions. Office of Disease Prevention and Health Promotion press release, Jan. 24, 2017. Accessed at health.gov/news/announcements/2017/01/new-report-shows-continued-reduction-in-hospital-acquired-conditions.

NIH Awards Grant to Study the Connection Between Autism and Autoimmunity During Pregnancy

The National Institutes of Health has awarded a $3 million grant to Feinstein Institute for Medical Research scientists Betty Diamond, MD, and Peter K. Gregersen, MD, to study the relationship between a mother's autoimmunity during pregnancy and the risk of autism spectrum disorder (ASD) in her child. Specifically, the study will look at whether women with autoimmune inflammatory disorders have increased levels of antibodies and are, therefore, at an increased risk of having children with ASD. In previous research,

Drs. Diamond and Gregersen discovered an antibody can lead to abnormal brain development and ASD symptoms.

The study, titled Prenatal Autoimmune and Inflammatory Risk Factors for Autism Spectrum Disorders, will follow 4,500 pregnant women who deliver at Northwell Health hospitals and their offspring for two years. The mothers will be given a blood test during pregnancy to identify the presence of autoimmune disease, immune activation and increased cytokine levels. After birth, researchers will monitor their offspring to see if they exhibit signs of ASD. ❖

Feinstein Institute Researchers Awarded $3M Grant for Autism Research. Feinstein Institute for Medical Research, Sept. 23, 2016. Accessed at www.feinsteininstitute.org/2016/09/feinstein-institute-researchers-awarded-3m-grant-autism-research.

HHS Renames AIDS.gov to HIV.gov

The U.S. Department of Health and Human Services (HHS) has officially changed the name of AIDS.gov, the federal government's source for information about HIV, to HIV.gov. The name change coincides with the 36th anniversary of the Centers for Disease Control and Prevention's first report of the initial cases of what would become known as AIDS, and "reflects major scientific advances that have transformed an almost universally fatal disease to a condition that, if diagnosed and treated early and continuously, can be controlled and prevented from progressing to AIDS."

"Much progress has been made in HIV/AIDS research since the disease was first recognized in 1981. Today, lifesaving antiretroviral therapies allow those living with HIV to enjoy longer, healthier lives — an outcome that once seemed unattainable," said Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases. "The website AIDS.gov has been a valuable resource for those seeking information about HIV/AIDS, and its name change to HIV.gov appropriately reflects our evolution in transforming the pandemic, even as work remains to bring about an end to HIV."

More than eight million people used the AIDS.gov website and its social media channels to find information about HIV or to find HIV-related programs and services in 2016, including HIV testing, medical care and treatment. The name change also embraces the way most people now search online for information about the disease. "HIV" is a much more common Internet search term than "AIDS." ❖

More Than a Name Change: AIDS.gov Becomes HIV.gov. U.S. Department of Health and Human Services press release, June 5, 2017. Accessed at www.hhs.gov/about/news/2017/06/05/more-name-change-aids gov-becomes-hivgov.html.

How Proposed 2018 OPPS Payment Rules Impact Pharmacy

THE OUTPATIENT Prospective Payment System (OPPS) determines how the Centers for Medicare and Medicaid Services (CMS) pays for Medicare patients treated in outpatient settings. For 2018, the proposed changes to the OPPS rules have been published in the Federal Register, the comment period has ended, and the final rules will be decided before the year's end. The impact of changes to the rules is broad since the scope of "outpatient" includes a vast array of clinics, infusion centers, treatment and diagnostic areas and emergency rooms. Payment for drugs, biologics and radiopharmaceuticals in these areas is covered under the Medicare Part B medical benefit. It's important to differentiate these from 1) drugs used in the ambulatory setting that fall under Medicare Part D and are part of the pharmacy benefit, and 2) those not billable because they are considered self-administered.

This column addresses how payment for drugs and biologics works, the effect Medicare decisions have on private payers and the proposed drastic reduction in payments for 340B drugs in settings covered by OPPS.

CMS Payment for Part B Drugs Under OPPS

CMS pays for Part B drugs in five different ways divided into two categories: those that are separately payable and those that are bundled or packaged.

Drugs that are separately payable have line-item reimbursement. These are:

1) New drugs not yet assigned a unique Healthcare Common Procedure Coding System (HCPCS) code (no proposed change)

2) New pass-through drugs, biologics and radiopharmaceuticals (several proposed changes)

3) Specified covered outpatient drugs (proposed threshold change)

Payable drugs with no line-item reimbursement because they are bundled or packaged are:

4) Lower-cost packaged products costing less than $120 per day (proposed threshold up from $110 per day in 2017)

5) Products used in policy packaged services, regardless of cost (no proposed change)

Payment for all policy packaged drugs, biologics and radiopharmaceuticals is included in the services and procedures with which they are reported. These are non-pass-through drugs, biologics and radiopharmaceuticals, including:

- All diagnostic radiopharmaceuticals
- All contrast agents
- Anesthesia drugs
- Implantable biologics that are surgically inserted or implanted in the body through a surgical incision or natural orifice
- Drugs, biologics and radiopharmaceuticals that function as supplies when used in a diagnostic test or procedure
- Drugs and biologics that function as supplies or implantable devices in a surgical procedure

Regardless of which category a drug falls into, every drug must be billed. Neglecting to bill will automatically cancel a request for payment for drug administration fees. It will also report inaccurate data to the payer and the big data pool, which will lead to artificially lowered reimbursement for bundles/packages in subsequent years.

Table 1. Status Indicator Definitions

Status Indicator	Item/Code/Service	OPPS Payment Status
G	Pass-through drugs and biologics	Paid under OPPS; separate APC payment includes pass-through amount
K	Non-pass-through drugs and biologics; brachytherapy sources; blood and blood products	Paid under OPPS; separate APC payment
N	Items and services packaged into APC rates	Paid under OPPS; payment is packaged into payment for other services, including outliers; therefore, no separate payment

Proposed 2018 Changes for Separately Payable Drugs

Transitional pass-through/non-pass-through separately payable drugs are currently paid at average sales prices (ASP) plus 6% minus 2% sequestration. These drugs move from annual to quarterly pass-through expiration status for devices, drugs and biologics ending in the quarter that is as close to three full years as possible after the products were first covered with a pass-through payment. The 2018 proposal lists 38 drugs with new/continuing pass-through status and 15 that lose pass-through status and move from status indicator (SI) G (pass-through) to SI K (separately payable). Four drugs lose pass-through status and move from SI G (pass-through) to SI N (items and services packaged into ambulatory payment classification [APC] rates).

Drugs and biologics are first eligible for pass-through status the quarter following application approval, and CMS will calculate the offset amount for pass-through payments at the HCPCS code level rather than the APC code level.

Drugs and biologics that are separately payable will continue to be paid at ASP plus 6% minus 2% sequestration under the statutory default payment policy adopted in 2013. CMS will pay all non-pass-through separately payable therapeutic radiopharmaceuticals at ASP plus 6% minus 2% sequestration as well. However, radiopharmaceutical manufacturers are not required to submit ASP. While some manufacturers voluntarily submit ASP, CMS will use that for a "patient-ready" dose. If ASP is not available, CMS will base payment on mean unit cost from its claims data.

To prepare for these proposed changes, pharmacy providers should work with their revenue cycle team to ensure all drugs with SIs G, K and N are billed regardless of whether they are separately payable. They should also update their list of waste billing drugs. And, they should remove the four pass-through drugs that are moving from SI G to SI N, as well as lower-priced drugs that no longer meet the threshold and will move from SI K to SI N and will no longer be eligible for waste billing as of Jan. 1, 2018. Table 1 provides a list of SI definitions.

Table 2. 2018 Preparation for 340B Sites

Drug Purchase	Patient Coverage Status	Treatment Location	CMS Payment	Payment Rules	Line Item Modifier Required?
Drug A bought at 340B price	Medicare	Outpatient setting	Reimbursed at ASP - 22.5%	OPPS	No
Drug A bought on regular contract	Medicare	Outpatient setting	Reimbursed at ASP + 6%	OPPS	Yes
Drugs bought at 340B price	Medicare	Ambulatory setting	No change proposed yet	Part D	No
Drugs bought at 340B price	Other payers	Outpatient setting	No change yet proposed by other payers		No
Drugs bought at 340B price	Other payers	Ambulatory setting	No change proposed yet	Part D	No

Proposed Payment Rate Changes for Certain Medicare Part B Drugs Purchased by Hospitals Through the 340B Program

For certain Medicare Part B 340B program drugs, the proposal is to cut reimbursement for 340B facilities from ASP plus 6% to ASP minus 22.5% minus 2% sequestration. CMS also is proposing that a modifier be added to each line item billed to a Medicare patient in an OPPS setting when a 340B drug is being used so it can identify which drugs will be reimbursed at that rate. This proposal is based on MedPac recommendations, and they apply only to Medicare patients treated in an OPPS setting. Others may adopt them as time goes on, but this is the limit as of now. CMS is requesting comments on how it can best implement this proposal to pass savings on to beneficiaries and providers, and to allow seniors to save money on drug costs. See Table 2.

Limited to Separately Payable Drugs

Only separately payable drugs are affected by this proposed ruling and only when used for Medicare in outpatient settings. According to CMS, "We believe that any payment changes we adopt should be limited to separately payable drugs under the OPPS, with other additional exclusions. These exclusions include 1) drugs on pass-through status, which are required to be paid based on the ASP methodology, and 2) vaccines, which are excluded from the 340B program." In addition, CMS is soliciting comments on whether other types of drugs such as blood clotting factors should be excluded from the reduced payment. ❖

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

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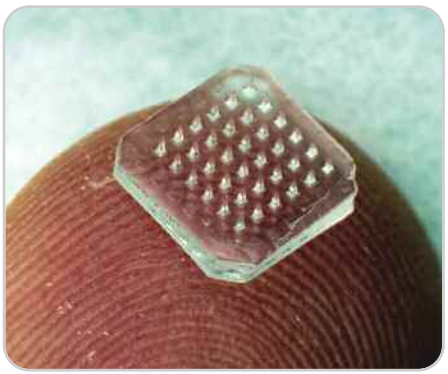
Research

Study Shows Microneedle Patch Influenza Vaccine Is Effective and Painless



A new study shows that microneedle patches provide an alternative to conventional needle-and-syringe immunization, potentially offering improved immunogenicity, simplicity, cost-effectiveness, acceptability and safety. In the Phase I randomized, partly blinded, placebo-controlled clinical trial, conducted at Emory University in Atlanta, Ga., 100 nonpregnant adults aged 18 years to 49 years were randomly assigned to four groups. One quarter of the adults received a single dose of inactivated influenza vaccine by microneedle patch by a healthcare worker; another quarter received a single dose of inactivated influenza vaccine by intramuscular (IM) injection by a healthcare worker; another quarter received a placebo by microneedle patch by a healthcare worker; and the last quarter received a single dose of inactivated influenza vaccine by microneedle patch that was self-administered by participants. Acceptability of the vaccine was rated slightly higher for the two microneedle patch vaccine groups (4.5 to 4.8 on a 5-point scale) than the conventional IM injection group (4.4 out of 5). Ninety-six percent of subjects who received the patch reported no pain, versus 82 percent of subjects receiving the IM injection. However, erythema (40 percent versus zero) and itching/pruritis (82 percent versus 16 percent) were reported much more frequently by subjects in the patch groups than the IM injection group.

The "peel-and-stick" microneedle patch penetrates the upper layer of the skin, and the tiny vaccine-filled needles dissolve rapidly as they deliver the vaccine. It was developed by lead investigator Mark Prausnitz, PhD, and his team at the Laboratory for Drug Delivery at the Georgia Institute of Technology and is licensed for development and commercialization to Micron Biomedical. ❖

Rouphael NG, Paine M, Mosley R, et al. The Safety, Immunogenicity, and Acceptability of Inactivated Influenza Vaccine Delivered by Microneedle Patch (TIV-MNP 2015): A Randomised, Partly Blinded, Placebo-Controlled, Phase 1 Trial. *The Lancet*, dx.doi.org/10.1016/S0140-6736(17)30575-5. Accessed at www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30575-5/fulltext.

Research

BCG Vaccine Could Permanently Reverse Type 1 Diabetes

Results of a new clinical trial show that the bacillus Calmette-Guerin (BCG) vaccine could permanently reverse advanced type 1 diabetes in mice, as well as help to restore proper immune response to insulin-producing beta cells. The BCG vaccine, which is based on a harmless strain of bacteria related to one that causes tuberculosis (TB) and is also approved in the U.S. to treat bladder cancer, is used in China, Africa and South America to vaccinate against TB, but it is not given to children in the U.S. because TB isn't common.

According to Denise Faustman, PhD, director of the Massachusetts General Hospital Immunobiology Laboratory that led the clinical trial, the BCG vaccine could induce a permanent gene express that restores regulatory T cells

(Tregs) that help to prevent the immune system attack that characterizes type 1 diabetes. "Repeat BCG vaccination appears to permanently turn on signature Treg genes, and the vaccine's beneficial effect on the host immune response recapitulates decades of human co-evolution with mycobacteria, a relationship that has been lost with modern eating and living habits," said Dr. Faustman.

Dr. Faustman and her team were the first to document type 1 diabetes reversal in mice, as well as in a subsequent successful Phase I trial among humans, for which long-term data is expected to be published later this year. Currently, a Phase II, 150-person trial is recruiting to assess whether repeat BCG vaccination can improve or even reverse advanced type 1 diabetes in adults. Belgian biotech company Imcyse announced it will begin human trials across Europe of a separate type 1 diabetes vaccine, with results expected in 2018. ❖

Woodfield J. BCG Vaccine Could Restore Proper Immune Response in Type 1 Diabetes. Diabetes.co.UK, June 12, 2017. Accessed at www.diabetes.co.uk/news/2017/jun/bcg-vaccine-could-restore-proper-immune-response-in-type-1-diabetes-92725826.html.

Medicines

FDA Approves First Drug to Treat Giant Cell Arteritis

The U.S. Food and Drug Administration (FDA) has approved Roche's Actemra (tocilizumab), the first treatment for adult patients with giant cell arteritis (GCA), a rare autoimmune condition. Also known as temporal arteritis, GCA can cause severe headaches, jaw pain and visual symptoms that, if left untreated, can lead to blindness, aortic aneurysm or stroke. The approval is based on the positive outcome of a Phase III study that showed Actemra, combined with a six-month steroid (glucocorticoid) regimen, more effectively sustained remission of GCA than a placebo.

This is the sixth FDA approval of Actemra since the medicine was launched in 2010. It is also being investigated in a Phase III study for patients with systemic sclerosis, or scleroderma, and was designated a breakthrough therapy for this indication in June 2015. ❖

FDA Approves Genentech's Actemra® for Giant Cell Arteritis. Vasculitis Foundation, *May 22*, 2017. Accessed at www.vasculitisfoundation.org/fda-approves-genentechs-actemra-for-giant-cell-arteritis.

Industry

ADMA Biologics Acquires Biotest's Therapy Business Unit

ADMA Biologics, which develops, manufactures and commercializes specialty plasma-based biologics for the treatment of immune deficiencies and prevention of certain infectious diseases, has acquired Biotest Pharmaceuticals' Therapy Business Unit (BTBU). As a result, ADMA has acquired Nabi-HB (hepatitis B immune globulin, human) and Bivigam (immune globulin intravenous, human), as well as the manufacturing and testing operations that consist of two facilities in Boca Raton, Fla.

ADMA plans to file a biologics license application for its lead product candidate RI-002, a specialty plasma-derived, polyclonal, intravenous immune globulin to treat patients with primary immunodeficiency disease. ❖

ADMA Biologics Completes Acquisition of Biotest's Therapy Business Unit Assets. ADMA Biologics press release, June 6, 2017. Accessed at www.nasdaq.com/press-release/adma-biologics-completes-acquisition-of-biotests-therapy-business-unit-assets-20170606-01125.

Industry

Sanofi Pasteur Acquires Protein Sciences

Sanofi Pasteur has acquired Protein Sciences, a privately held vaccines biotechnology company based in Meriden, Conn. Protein Sciences received U.S. Food and Drug Administration approval in October 2016 for its Flublok quadrivalent influenza vaccine, the only recombinant protein-based influenza vaccine. The acquisition will allow Sanofi to broaden its flu portfolio. "Protein Sciences was actively looking for an opportunity to grow its business, particularly in the U.S.," said Manon M.J. Cox, president and chief executive officer of Protein Sciences. "As part of Sanofi Pasteur, we expect our Flublok influenza vaccine to benefit from Sanofi Pasteur's expertise in the field of influenza vaccines." ❖

Sanofi to Acquire Protein Sciences. Sanofi press release, July 11, 2017. Accessed at globenewswire.com/news-release/2017/07/11/1042282/0/en/Sanofi-to-acquire-Protein-Sciences.html.

Research

Recombinant Quadrivalent Flu Vaccine More Effective in Older Adults

A clinical trial comparing the protective efficacy in older adults of a quadrivalent recombinant influenza vaccine (RIV4) with a standard-dose, egg-grown quadrivalent inactivated influenza vaccine (IIV4) during the A/H3N2-predominant 2014-2015 influenza season showed RIV4 provided better protection against confirmed influenza-like illness among older adults.

In the randomized, double-blind, multicenter trial of 9,003 participants aged 50 and older, 8,855 (98.4 percent) received a trial vaccine and underwent an efficacy follow-up (the modified intention-to-treat population), and 8,604 (95.6 percent) completed the per-protocol follow-up (the modified per-protocol population). Among RIV4 recipients, the reverse-transcriptase polymerase-chain-reaction-confirmed, protocol-defined, influenza-like illness attack rate was 2.2 percent (96 cases among 4,303 participants) in the modified per-protocol population, and 2.2 percent (96 cases among 4,427 participants) in the modified intention-to-treat population. Among IIV4 recipients, the attack rate was 3.2 percent (138 cases among 4,301 participants) in the modified per-protocol population and 3.1 percent (138 cases among 4,428 participants) in the modified intention-to-treat population. A total of 181 cases of influenza A/H3N2, 47 cases of influenza B and six cases of nonsubtypeable influenza A were detected. These results show the probability of influenza-like illness was 30 percent lower with RIV4 than with IIV4. The safety profiles of the vaccines were similar. ❖

Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age and Older. *New England Journal of Medicine*, 2017; 376-2427-2436. Accessed at www.nejm.org/doi/full/10.1056/NEJMoa1608862?query=featured_home.

Research

New Study Supports CDC Recommendation for Two-Dose HPV Vaccine in Children

A new study conducted at the Boston Medical Center (BMC) is the first to support new recommendations by the Centers for Disease Control and Prevention adopted this year for a two-dose HPV vaccine to prevent genital warts in kids younger than 15 years old. The study looked at nearly 400,000 girls from around the country to find the rate of genital warts based on the number of vaccine doses received. Findings showed that receiving two or three doses of the vaccine was effective at providing protection against genital warts compared with one dose or not receiving the vaccine. According to Rebecca Perkins, MD, obstetrician at BMC and the study's leader author, "This study validates the new recommendations and allows us to confidently move forward with the two-dose schedule for the prevention of genital warts." However, said Dr. Perkins, "The data supporting a two-dose schedule is encouraging, but it only reports on genital warts, not cervical dysplasia or cancer outcomes. Collecting that long-term data is paramount." ❖

Two-Dose HPV Vaccine Effective in Preventing Genital Warts, Study Finds. Boston University Medical Center, May 15, 2017. Accessed at www.sciencedaily.com/releases/2017/05/170515122145.htm.

Medicines

Novo Nordisk's Rebinyn Approved by FDA to Treat Hemophilia B

The U.S. Food and Drug Administration (FDA) has approved Novo Nordisk's Rebinyn (coagulation factor IX [recombinant], glycopegylated) to treat hemophilia B in adults and children. Rebinyn, brand name for nonacog beta pegol (N9-GP), is indicated for on-demand treatment and control of bleeding episodes and the perioperative management of bleeding. It is not indicated for routine prophylaxis or for immune tolerance induction in patients with hemophilia B. Approval was based on the efficacy and safety evaluation of 115 patients across the four paradigm clinical trials.

"We would like to thank the patients who participated in the clinical studies that led to this decision. Thanks to their commitment, we are able to continue to provide new medicines for people with hemophilia," said Bill Breitenbach, vice president of biopharmaceuticals portfolio at Novo Nordisk. "We are committed to the hemophilia community and will continue on our path to bring this new extended half-life treatment to patients who need it." ❖

FDA Approves New Novo Nordisk Treatment for Patients with Hemophilia. Novo Nordisk press release, May 31, 2017. Accessed at press.novonordisk-us.com/2017-05-31-FDA-Approves-New-Novo-Nordisk-Treatment-for-Patients-with-Hemophilia.

Medicines

Octapharma USA's NUWIQ Receives FDA Approval for Expanded Vial Strengths

The U.S. Food and Drug Administration has approved new product strengths for Octapharma's NUWIQ, offering added convenience by potentially reducing the number of vials needed for hemophilia A patients. Approval is for new single-dose vial strengths of 2,500, 3,000 and 4,000 international units (IUs), which became available in the U.S. in September. These are in addition to the already available 250, 500, 1,000 and 2,000 IUs. NUWIQ is the only recombinant factor VIII providing patients a wide array of vials with the lowest diluent volume of 2.5 ml. "The new vial options will benefit patients, physicians and healthcare professionals by providing greater treatment flexibility and convenience," said Octapharma USA President Flemming Nielsen. "The variety of vial options will be particularly beneficial to patients who previously may have needed more than one of the lower-strength vials." ❖

Octapharma USA Announces FDA Approval of NUWIQ New Product Strengths, Expanding Hemophilia A Patient Treatment Options. Business Wire, Aug. 22, 2017. Accessed at www.tmcnet.com/usubmit/2017/08/22/8598748.htm.

Research

Public Attitudes Toward Unvaccinated Children and Their Mothers Depends on Motivation Not to Vaccinate

A study conducted at the University of British Columbia (UBC) found that mothers are viewed negatively if their child hasn't been vaccinated, regardless of the reason; however, mothers who refuse to vaccinate their children are viewed in a harsher light compared with those who delay vaccine because of safety concerns or due to time constraints.

In the study, researchers used data collected from an online survey conducted from June 29, 2015, through July 2, 2015, that involved 1,469 U.S. respondents randomly assigned to read one of four scenarios: 1) a mother who has concerns about vaccinations and has refused to vaccinate her child; 2) a mother who has concerns about vaccinations and has decided to delay; 3) a mother who has no concerns about vaccinations but her job and family demands have made it difficult to stay up to date with medical appointments; and 4) a mother who has no concerns and has ensured her child always receives recommended vaccines. After reading the scenarios, respondents were asked questions that measured their attitudes such as blame toward the mother if the child or others became sick and how willing respondents would be to make friends with the mother or let their children socialize with the undervaccinated child. The survey also measured respondents' support for public policies that aim to boost vaccination rates such as providing greater vaccination education and services or banning undervaccinated children from school.

In addition to stigmatizing both the mother and her undervaccinated child regardless of the reason, respondents were also more likely to support stricter public policies like banning undervaccinated children from schools to increase vaccination rates. "Child vaccination rates are a complex problem that pose significant health consequences for the child and the community," said Nicholas Fitz, co-author of the study and recent UBC sociology graduate. "If health officials want to effectively address low child vaccination rates, it's important to understand not only the parents' motivations but also how the general public views both undervaccinated children and their parents." ❖

Parents' Reasons for Not Vaccinating Children Influence Public Attitudes Toward Them. University of British Columbia, May 23, 2017. Accessed at www.eurekalert.org/pub_releases/2017-05/uobc-prf051917.php.

Research

Study Shows Influenza May Increase Risk of Developing Parkinson's

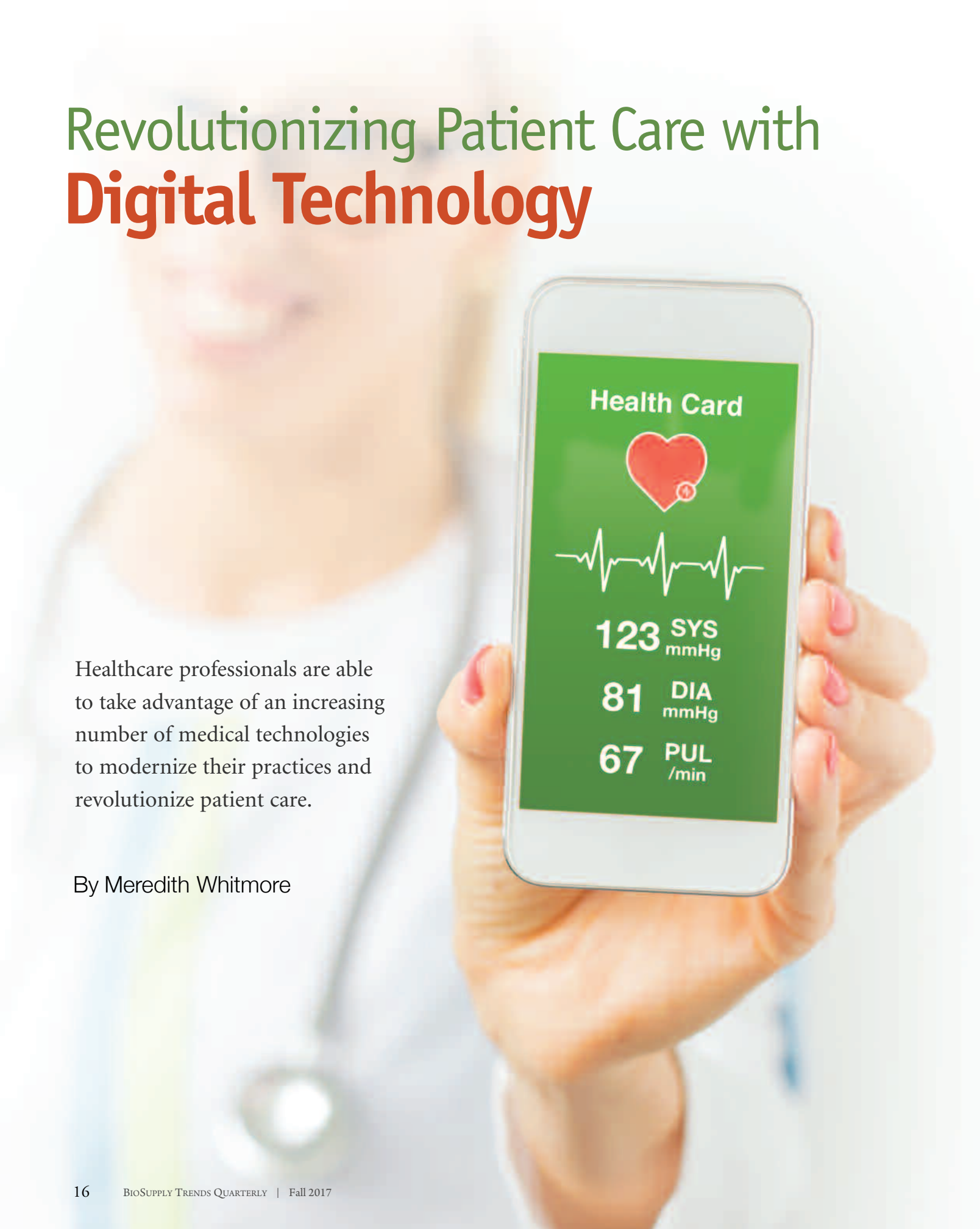
New research suggests a certain strain of influenza virus predisposes mice to developing pathologies that mimic those seen in Parkinson's disease. This new study built on previous research at St. Jude Children's Research Hospital in Memphis, Tenn., that showed a deadly H5N1 strain of influenza (bird flu) that has a high mortality rate (60 percent) was able to infect nerve cells, travel to the brain and cause inflammation that would later result in Parkinson's-like symptoms in mice. In the new study, researchers looked at a less-lethal strain, H1N1 (swine flu), that does not infect neurons, but still causes inflammation in the brain via inflammatory chemicals or cytokines released by immune cells involved in fighting the infection. Using a model of Parkinson's disease in which the toxin MPTP induces Parkinson's-like symptoms in humans and mice, they found that mice infected with H1N1, even long after the initial infection, had more severe Parkinson's symptoms than those who had not been infected with the flu. And, when mice were vaccinated against H1N1, or were given antiviral medications at the time of flu infection, the increased sensitivities to MPTP were eliminated.

"The H1N1 virus that we studied belongs to the family of type A influenzas, which we are exposed to on a yearly basis," said Richard J. Smeyne, PhD, professor of neuroscience in the Sidney Kimmel Medical College at Thomas

Jefferson University and director of the Jefferson Parkinson's Disease Center in the Vickie and Jack Farber Institute for Neuroscience. "Although the work presented here has yet to be replicated in humans, we believe it provides good reason to investigate this relationship further in light of the simple and potentially powerful impact that seasonal flu vaccination could have on long-term brain health." ❖

Infection with Seasonal Flu May Increase Risk of Developing Parkinson's Disease. Thomas Jefferson University, May 31, 2017. Accessed at https://www.sciencedaily.com/releases/2017/05/170531084502.htm.

Revolutionizing Patient Care with **Digital Technology**



Healthcare professionals are able to take advantage of an increasing number of medical technologies to modernize their practices and revolutionize patient care.

By Meredith Whitmore

SCIENCE FICTION IS becoming more of a reality as medical technologies accelerate to levels people could only dream of a few years ago. From robots and artificial intelligence in practices and devices that help physicians gather patients' health data, such tools, and many other highly technological instruments, are increasingly coming to fruition. Indeed, products are revolutionizing doctor offices and patient health. As technology progresses at breakneck speed, healthcare providers may occasionally feel outmoded. Today, even modern practices and industries must step up their game simply to remain proficient. To help providers stay apace, here is a glimpse at various developments.

Improving Anatomy Classes

Patient well-being begins with educating healthcare providers more effectively. A common problem among surgeons in training, for example, is shifting from the 2-D images of a textbook to a 3-D surgical environment. To address this, among other needs, 3D4Medical is developing Project Esper, an artificial intelligence textbook and a mixed-reality anatomy project. According to Irene Walsh, head of design at the Dublin-based medical tech company, "You can work with it in a really intuitive way with a 3-D representation of the body — just right there in front of your eyes, reach out and touch it. And it would be a breathing model, a living creature that can offer so much more than a cadaver in a lab."[1]

The company hopes its immersive, highly detailed and accurate anatomical models will eventually offer students and healthcare providers more mobility, allowing them to simulate dissections and possibly procedures, even from a dorm room or office. Such technology will also help patients understand their own physiology and health conditions, allowing them to visualize how their bodies should work, as opposed to how various illnesses cause damaging effects.[2]

Medical Activism … of a Sort

In 2016, Apple released a software update to its iPhone health information app installed on every smartphone with a feature to register as a donor with Donate Life. Apple CEO Tim Cook said he was inspired to add the feature by former-CEO Steve Jobs' "excruciating" wait for a donated liver in 2009, with the goal of addressing the organ donor shortage.[3] Donation advocates hope younger generations who use their smartphones for virtually everything will use the app. "Younger Americans are not registering [for donation] at the same rate as they have in the past," said David Fleming, chief executive of Donate Life America.[3]

Facebook has also implemented organ donation sign-up features. In 2012, the social media giant made it possible for users to display they are registered organ donors. In a single day, there was a 21-fold increase in donors, Johns Hopkins researchers found.[4]

Improving Clinical Trials

Platforms such as Apple's ResearchKit and other wireless, mobile-health (mhealth) devices could eliminate the tedious, paper-laden, visit-based treatment processes that sometimes produce more frustration than quality clinical research. And, pharmaceutical companies, among others, are teaming up with various organizations to conduct clinical trials using the technology.

Pfizer recently joined a clinical trial with the Lupus Research Alliance using ResearchKit as a platform to enable patients to connect with their healthcare providers through their iPhones.[5] "Traditional patient assessments in lupus are unfortunately done in a very arcane way; [they] require the patient to come to the clinic and complete a paper form," said Albert Roy, executive director of the Lupus Clinical Investigators Network. "Lupus patients don't come to the clinic every week unless they are very sick, so they have to recall weeks and weeks of how they felt and address the question in the most accurate way. We wanted to reduce this burden on the patients and see if we could translate all these instruments from paper into an electronic format. Running the mobile app is an opportunity for patients to do the assessment on their own, in the comfort of their homes and on a smartphone. We could get more accurate data since they would be able to answer these questions once or twice a week versus once a month."[5]

In 2016, Apple released a software update to its iPhone health information app installed on every smartphone with a feature to register as a donor with Donate Life.

According to Kenneth M. Farber, co-CEO and co-president of the Lupus Research Alliance, "This is an important step in demonstrating that mobile technology can improve how and what patients report to their care teams about subjective but serious symptoms of lupus such as debilitating fatigue. This app may enable more frequent and consistent reporting from patients, thus providing better information for care teams and

empowering patients to take a larger role in developing future therapies."[5]

Parexel and Sanofi are using ResearchKit as well for a clinical trial they call the patient sensor solution — but with the addition of a wearable device that gathers patient data. In an ongoing single-site study, data is being collected remotely via multiple devices patients wear. Not only can wearables potentially improve a trial's execution by increasing patient participation and engagement, they provide decentralized trial sites. Parexel and Sanofi are striving to determine how wearables can further drug development and boost study performance, since data from devices could potentially be simplified into a single, scalable data system that could help pharmaceutical development.[6]

"Our objective is to demonstrate the relevance of data collected remotely and the overall feasibility of utilizing wearables in clinical trials," said Lionel Bascles, global head of clinical sciences and operations at Sanofi. "Wearables are a core component of Sanofi's digital trials strategy, and represent an important approach to automate patient processes using the latest technologies to bring new therapies to patients sooner."[6] According to Xavier Flinois, Parexel Informatics president, "We believe the use of wearables to collect data from trial participants represents a breakthrough in the digital transformation within the industry. Working with Sanofi, we believe we have a strong opportunity to streamline and automate data collection from multiple devices, collect high-quality data remotely and generate meaningful results, all while reducing burden on patients and sites, as well as lowering costs."[6]

Perhaps one of the biggest problems that can be addressed with medical technology is patient adherence.

GlaxoSmithKline (GSK) has also ventured into using new medical technologies. It launched its PARADE (Patient Rheumatoid Arthritis Data from the Real World) study in 2016 using Apple ResearchKit for its clinical study. GSK's chief medical officer, Murray Stewart, says the company made the technology easily downloadable for patients through the App Store. "Within 48 hours, we had over 200 downloads," he said. "Our hope was that we would not just receive data but insightful information from patients."[7]

The app and its instructions are simple. First, users are asked whether they have rheumatoid arthritis. If they say yes, they are asked if they would be willing to use the app. Those who agree are then asked to do several things, including putting their phone in their pocket and walking with it, and holding their phone and moving it to monitor wrist movement. The app also asks them several additional questions.[7]

Moses Zonana, CEO of Compliance Meds Technologies (CMT), a startup medical tech company that focuses on patient adherence, believes clinical trials could benefit greatly from such technology by helping patients communicate with healthcare providers and researchers. "Pharmaceutical companies don't have a good way of correlating use patterns of patients to efficacy," he says. "So many medications might have been rejected because patients, during the course of the research, did not take them the way they were supposed to be taken. Many times, the medication could have been efficacious had the patients remained on track. While research statistics adjust somehow for those errors, it's not perfect."[8]

A device that encourages patient adherence such as CMT's CleverCap, which records dates and times of bottle access, among other data, could help researchers gauge efficacy much more efficiently and accurately. CleverCap and its various iterations could also aid in the opioid crisis by acting as a deterrent. "One of the features of our technologies is it can control and dissect when an overdose occurs, before it's too late," explains Zonana. "There are technologies to deter abuse, to monitor it and to curb it. We need to create awareness about that."[8]

Patient Adherence

Perhaps one of the biggest problems that can be addressed with medical technology is patient adherence. As many healthcare providers are aware, people are not always compliant with treatment plans. Indeed, more than 40 percent of patients sustain significant risks by misunderstanding, forgetting or ignoring physicians' healthcare advice.[9] Their inattentiveness to medical instructions, in fact, causes at least 125,000 preventable deaths per year and can cause significant economic burden as well.[10] The yearly cost of poor compliance to the pharmaceutical industry alone is $250 billion. And $300 billion each year is wasted in hospital admissions, avoidable emergency room visits, additional physician visits, etc.[11] With increasing costs ravaged by a broken healthcare system, the country is taking notice of patient nonadherence. *Forbes* went so far as to call it "one of the greatest cost drivers in healthcare," claiming that patient noncompliance costs an additional $300 billion in healthcare expenses since people who do not follow treatment plans often need emergency room visits or hospital stays.[12]

Medical tech companies such as CMT are addressing these problems. They have developed and continue to create easy-to-use

solutions that help doctors care for patients more effectively — and help patients live healthier by allowing them to participate in, even if passively, their own care. "These devices provide visual or audio cues to patients to remind them to take their medication," explains Zonana. "The patients can also utilize our app to stay connected with their provider with different engagement tools. All of the dosing information is recorded, real time, and uploaded into our cloud-based analytic system. The information is made available to providers that care about ensuring patients get better outcomes. The idea behind all of our solutions is to connect different stakeholders in the continuum of care with one goal in mind: Help patients stay on track with their therapies."[8]

Helping patients follow instructions is a tremendous factor in treatment efficacy, of course, and Zonana explains how his company's technology can make doctors' and patients' lives easier: "One of the issues with some medications is that they have side-effect profiles or they have certain characteristics that patients might [cause them to] drift away from a proper adherence pattern. In some cases, it may have to do with having a complex regimen or the medication creating a particular side effect. By the information being captured real-time in the outpatient setting, where people dispense their drugs on a daily basis, then the medical provider, being either the prescriber or the pharmacist, can anticipate if a patient is drifting into low adherence or anticipate some erratic potential patterns of use that might create a clinical complication. And by anticipating such problems, they can reach out to the patient to help them remain on therapy as they should to get the proper outcomes."[8]

Besides this benefit, Zonana says such technology also helps ensure a medication is given a fair chance, so to speak. "Many medical professionals today are pretty much in the blind sometimes, trusting what the patient says. Typically, the patient doesn't really remember details, so there's a high level of overstatement — patients saying they're taking their medications better than they are," he says. "Often, the doctor relies on that information and thinks that a particular treatment is not being efficacious on that basis. Then, he or she may overprescribe by resorting to a second-line therapy instead, or a third-line therapy instead. In many cases, the first-line therapy would have been as effective if the patient had taken it as prescribed. So, it may be creating toxicity or it may be creating additional problems by not having a better understanding of those patterns of utilization. While using our devices might cause a few more minutes of work for a doctor on the front end, they save many additional hours of work and cost down the road by keeping patients safe."[8]

Growing in Efficacy and Efficiency

Keeping patients safe and keeping providers better informed are the two biggest goals for much of the latest medical technology. While no one device or system can ensure patient compliance, comprehensively train a medical student or flawlessly record every single byte of trial data, medical technology is steadily growing in its efficacy and efficiency. Hopefully, it will eliminate currently labored processes and streamline data, and increasingly educate both providers and patients. And someday, perhaps soon, it will all seem less foreign than it does to many patients and providers now. The medical technology industry is growing so fast that in 10 years, the healthcare community will look back on today's most cutting-edge products and wonder how they ever managed. ❖

Keeping patients safe and keeping providers better informed are the two biggest goals for much of the latest medical technology.

MEREDITH WHITMORE is an English professor and freelance journalist in the Northwest.

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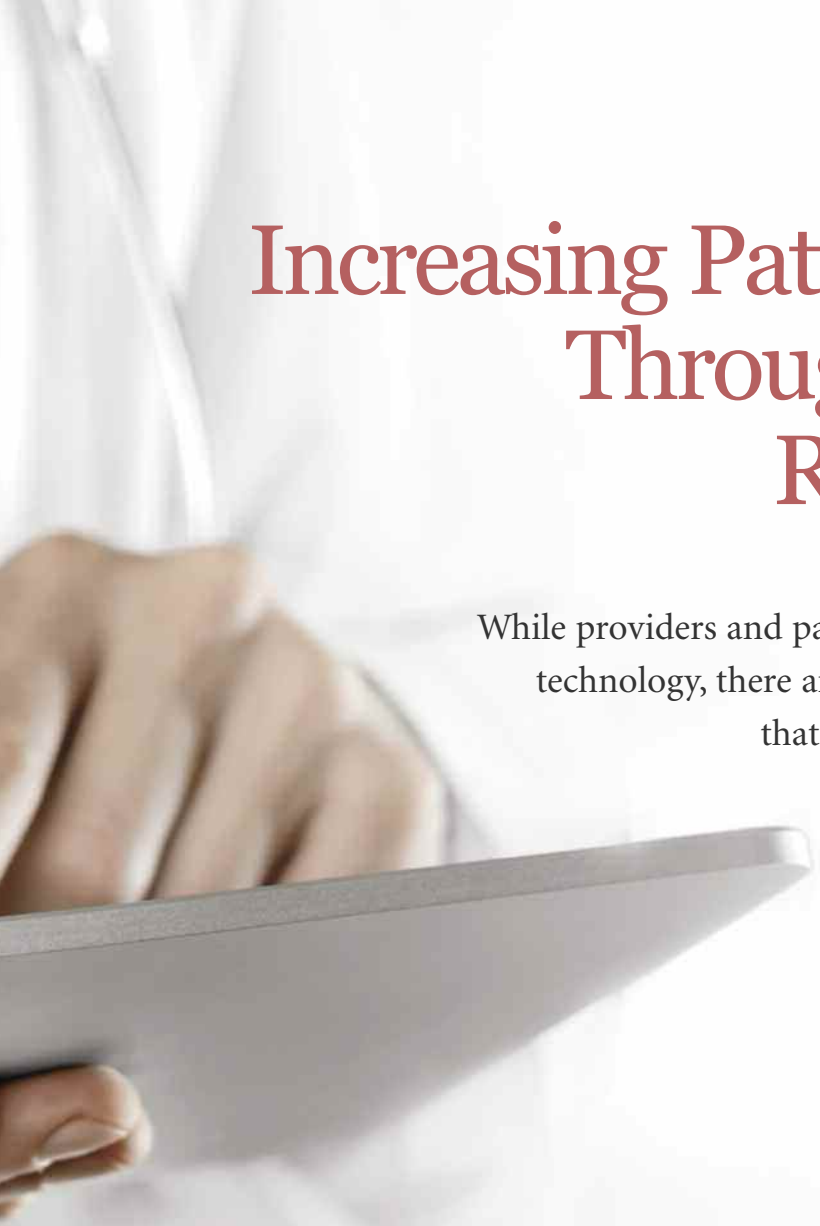


Increasing Patient Engagement Through Online Health Records and Apps

While providers and patients are gradually embracing digital health technology, there are still barriers to be overcome and strategies that could be adopted to increase its application.

By Amy Scanlin, MS

AS THE DEFINITION and metrics of "meaningful use" pertaining to electronic health records (EHRs) progress, physician and patient engagement is progressing as well. Providers are in a unique position since EHRs can provide talking points and encouragement to help patients get involved with using technology to enhance their own care. This includes making and canceling appointments online, opting in on automated reminder calls and texts for appointments and medications, and utilizing newer patient engagement technologies such as medical apps and personal health records (PHRs) — all of which provide them with data and the ability to work with their doctors to meaningfully use it. "Meaningful use initially was [created] to incentivize and provide quality checks on the [providers'] installation and initial use of EHRs," says John Sharp, senior manager of Consumer Health IT with the Personal Connected Health Alliance at Healthcare Information and Management Systems Society (HIMSS). "As it has evolved, there has been more emphasis on patient engagement." And, while interest in these technologies is higher for some patients than others, the sometimes steep patient learning curve can be lessened through staff and provider interaction and teaching tools in providers' offices.

Technology Continuum

Software designers offer a wealth of options for a wide range of interests and access to health and wellness information. Even the simplest technologies such as a text message reminder can be effective. For instance, researchers at HealthCrowd working with patients in New York's Healthfirst Medicaid Managed Care program found that 32 percent of beneficiaries who were sent text messages as part of a two-and-a-half-month pilot program took at least one suggested action when contacted about prenatal care, wellness visits for children and/or vaccinations. The study authors predict that had the pilot program lasted a year, they ultimately would have had an 86 percent response rate.[1]

Easy-to-access and -use healthcare apps linked to smartphones and tablets are another option that continues to gain popularity. Many apps allow patients to feed real-time data about their conditions into their PHRs, which feed that information into their providers' EHRs. From tracking stress levels, blood pressure readings and glucose monitoring, providers can be alerted in the event of an out-of-range report, and patients can send secure messages to providers with specific questions regarding their care.

These apps can promote greater adherence to recommended care plans, as well as greater understanding of how patients' actions concerning topics such as nutrition, exercise and pharmaceutical interventions can affect their health.

Physicians, 80 percent of whom use smartphone technology, have information like never before at their fingertips. This includes clinical reference apps that provide access to pertinent medical studies, public health apps that deliver alerts and diagnostic tools, biosurveillance data provided by the Centers for Disease Control and Prevention that tracks real-time population health, and diagnostic apps that, through algorithms, offer assistance with treatment decisions.

When coupled with apps requiring patient participation such as passively wearing a monitor or actively providing input, providers and patients capture even more data to help with treatment plans. Telehealth and disease management apps help patients and providers actively manage chronic conditions,[2] fitness and nutrition apps provide data about how wellness choices impact health, stress management apps check in with users throughout the day to assess stress levels and provide relaxation techniques, and sleep tracker apps log patients' restfulness and sleep patterns and provide referrals.

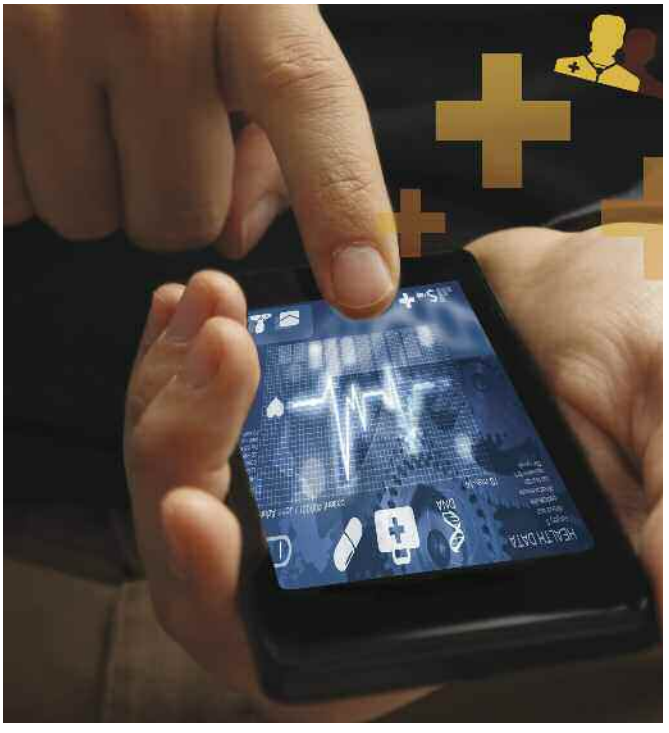
Hospitals are also taking advantage of new technology. A 2016 HIMSS survey found 52 percent of hospitals are using three or more connected health technologies, and 69 percent of respondents who use a mobile-optimized patient portal say the technology extensively supports their hospital's secure data exchange strategy.[3]

Meeting Patients Where They Are

Becoming comfortable using new technology is challenging enough for many physicians, but now they are challenged with engaging patients as well. This requires putting in place the right mix of support, environment and reminders for patients to register for health records or apps and, once registered, to actively use them.

What motivates each individual differs. As would be expected, age may correlate with interest, but this is not always the case. Sometimes, a more urgent health need will spur individuals to engage. For example, the Harris Poll found millennials are much more likely to actively use medical apps, as are those with chronic conditions that require monitoring.[4] They also found 60 percent of those polled who had been diagnosed with hypertension were very interested in monitoring their blood pressure through a smartphone app, and 63 percent of those diagnosed with heart disease were interested in checking their heartbeat for irregularities on a mobile device.

But, interest doesn't always translate to action as found in a California Health Care Foundation survey that showed that, although 80 percent of Americans who have online access to their health information use it, only 20 percent of all U.S. adults currently have access to their medical records online.[5]



EHR Barriers

How can providers interest patients in managing their health electronically? And, what is the right mix of face-to-face versus digital communication? The answer depends on the patient. For those with multiple chronic conditions, there is a lot of interest and benefit to continuous monitoring. For healthier people who see their doctors infrequently, says Sharp, there may be fewer reasons for accessing online records and more utility in wellness apps. For example, a fitness tracker may be of more value to patients in an employee wellness program. Of course, for apparently healthy people, a challenge for the physician is what to do with all the data.

While it is easy to blame lack of interest in apps and technology on age and a "non-techy" mind-set, infrastructure can be a barrier. Many people lack Internet access, and many don't have a smartphone or tablet. Infrastructure challenges at the provider level can include technologies that don't readily talk to each other. This is a problem for patients who may have multiple providers and multiple portals with which they must connect, and for providers who may have systems that don't talk to patients' other providers. While the goal eventually is a common language where portals can more readily communicate, that is not yet in place.

Rural areas with limited or no broadband are a hindrance (though many communities have or are applying for grants to remedy that). Broadband requirements are crucial for telehealth, especially with a shortage of physicians in many isolated communities.

Language and literacy are also barriers, though pilot programs are underway to look at various ways to address this. One pilot is examining the effectiveness of a texting program targeted toward Hispanics who are diabetics that offers suggestions for eating right and monitoring blood glucose. And, some senior centers are testing the ability to educate their residents about computers, while at the same time instructing them on how to access their PHRs.

Strategies for Engagement

With so many opportunities and benefits, two strategies stand out as most successful for encouraging patients to access their health information online: repetition and patience. "A full-out recruitment marketing strategy is needed," says Sharp.

Much like any marketing strategy where multiple touch points are key, multiple messaging may be required to help patients realize access is not only available, but useful. Posters and informational videos in waiting rooms can alert patients to the opportunity, as can communication with reception staff, medical technicians and even billing departments at check-out. For instance, researchers in Virginia found patient engagement in technology increased 139 percent when patients were invited to log into their portal during their office visit versus sending a direct mail invitation to do so.[6] Sharp also suggests physicians use the word "portal" as a verb. Providers can say to patients at the end of a visit: "If you think of any questions, portal me." "That's most effective," he says. "It is saying to patients: 'I use this all the time, and so should you.'"

Taking extra time to invite patients to register while at the office by having a dedicated staff person available to walk them through the process can make huge strides in getting patients to take the first step. This can reinforce patient understanding of what types of information they'll find in their PHRs and how access can be beneficial. Once registered, patients will need help to understand where various pieces of information are found, including test results and health education materials. They also need to learn how to create appointments, request prescriptions and send secure messages to their providers.

Once patients are comfortable online, providers can invite them to view their own and their family's health history in their PHR where they can fill in any lacking pertinent details. They can also show them where lifestyle information is found and how to either manually or automatically download information found in monitoring apps.

Developing an officewide strategy for patient engagement should include all staff, particularly those who have frontline patient interaction who can encourage registration and use of online records and apps. Staff should revisit talking points and other strategies at regular intervals to discuss what is working for patients and what can be improved.

Offices concerned with the logistics of a big rollout can start small with a focused group of providers and patients to better understand how their patients will use the apps and to get feedback. Or, they can begin with a few accessible features within the PHR that can be slowly expanded on so it is not overwhelming for patients and staff.

Much like any marketing strategy where multiple touch points are key, multiple messaging may be required to help patients realize access is not only available, but useful.

The End Result

The trend toward digital health is working, however slowly. According to an Office of the National Coordinator for Health Information Technology Data Brief, in 2014, nearly half of patients were offered online access to their PHRs with about one in 10 accessing their records six or more times during the year. Seven out of 10 patients who accessed their health information online also used it to monitor their health, and 12 percent transmitted their data to a third party such as a medical app or a PHR.[7]

It's not a matter of if, but when, the digital health bandwagon will pick up speed. And when it does, improved access to health information will translate to improved communication and, hopefully, better health for everyone. ❖

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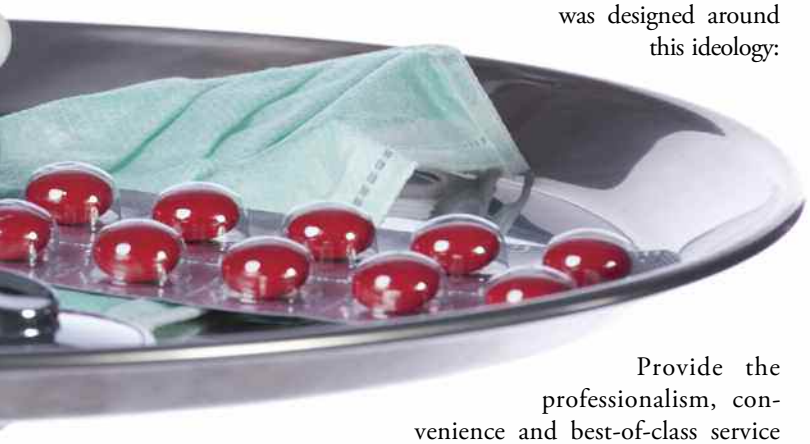
Concierge Medicine: Reinventing Primary Care

Is the concierge practice model the future of healthcare?

By Trudie Mitschang

IMAGINE A PATIENT-CENTERED practice that allows ample time to really get to know each patient. A practice model that prioritizes quality of care over caseload quantity. And a payment system that runs on a cash-up-front method with no need for pre-authorizations or claim forms. A couple of decades ago, this concept was little more than a utopian pipe dream. That is, until a Seattle-based physician named Howard Maron, MD, and his partner, Scott Hall, MD, established a practice based on this very premise.

MD2 (pronounced MD squared) was founded in 1996 with an ambitious goal of offering unlimited access to top-notch medical care to a maximum patient roster of just 50 families. Little did they know, the almost-instantly popular concept would birth a whole new treatment trend that became known as "concierge medicine."[1] "I never expected that by opening my one practice an entirely new category of healthcare would be created. It's amazing for me to see all the different levels of concierge medicine that are now available to people," said Dr. Maron, former team doctor for the Seattle SuperSonics. "Our practice was designed around this ideology:



Provide the professionalism, convenience and best-of-class service you expect from every service provider in your life. The very nature of these relationships necessitates we limit our practice to so few. It's what sets us apart."[2]

Understanding the Business Model

Concierge medicine is sometimes referred to as direct primary care (DPC), membership medicine or cash-only medicine. Although there may be structural differences in the business models (based on insurance inclusion), the distinguishing characteristic for a concierge practice is the patient pays an annual fee or retainer in exchange for an enhanced level of personalized care. There is also a hybrid concierge model in which physicians charge a monthly retainer or membership fee for services that Medicare and insurers do not cover. These services may include email access, phone consultations, newsletters, annual physicals, prolonged visits, and comprehensive wellness and evaluation plans. For all covered services, providers bill Medicare and insurance companies for patient visits and services covered by the plans.[3] This model allows physicians to continue to see their nonretainer patients while charging a fee to their concierge patients for special levels of care.

In most cases, when a practice opts for a cash-only or DPC model, it does not accept insurance. The advantage for these practices is that overhead and administrative costs remain low so that the practice can potentially offer affordable healthcare to a larger number of paying patients. "A lot of people like to compare concierge medicine to DPC and say, 'DPC is the less-expensive alternative.' But the data, the patient interviews and the industry service offerings say something completely different. The distinguishing factor differentiating DPC and concierge care is not price; it's insurance participation of the doctor, monthly billing (seen at most DPC clinics) and the amount of services offered," says Michael Tetreault, editor of *The DPC Journal* and *Concierge Medicine Today*. "In both concierge care and DPC, people have inherent, not ascribed value. There's no class order — no first class or second class, just people for whom doctors serve each day. They've built clinics for children, families and people who are sick — and it is these visioneering physicians who are drawing attention to the cost of healthcare across the country and designing ways for it to be available and affordable for anyone."[4]

From a patient perspective, the concierge model provides an experience akin to being in a private club with exclusive member benefits. Some concierge doctors make house calls, give out their cell phone numbers for speedy contact and provide healthy lifestyle counseling. Other common perks include:

- Same-day or next-day appointments
- 24/7 access to the physician by phone or email
- Annual physicals that last 60 minutes or more
- Reduced costs for routine tests such as blood work or scans
- Appointments that last 30 minutes or more
- Coordinated care for treatment from a specialist or at a hospital

This enhanced level of care can allow patients, particularly those with complex disease management needs, to get more personalized service and potentially better outcomes. Some studies suggest it may even help patients prevent more serious complications or diseases in the future.

Improving the level of care was a primary motivation for Celeste Amaya, MD, a board-certified internal medicine specialist who transitioned her Palm Desert, Calif., practice to a concierge model several years ago. "As a traditional internal medicine physician, I was responsible for over 5,000 patients and, every day, unless you were the first patient on the morning schedule or the first patient on the afternoon schedule, you would be waiting over an hour to see me. It created frustration for everyone. I simply couldn't rush the care," she says. "Moreover, with continued

cutbacks in insurance reimbursement and continued increases in malpractice insurance and other overhead expenses, I was forced to secure a high volume of patients each day in order to meet those demands. My ability to practice medicine the way it should be was compromised, which influenced my transition to concierge."

Counting the Cost

Rising healthcare costs and new mandatory insurance laws have influenced many physicians to jump on the concierge medicine bandwagon. Like MD2 founder Dr. Maron, who began his career catering to wealthy athletes, Samir Qamar, MD, also got started in concierge medicine by serving as house physician to the rich and famous at an upscale resort in Northern California. At the time, it was not unusual for clients to pay Dr. Qamar as much as $550 for an office visit and $30,000 for a monthly retainer. But in 2012, Dr. Qamar decided to abandon high-end concierge medicine in favor of a no-frills version that offers a subscription-based care model at an affordable cost. MedLion Direct Primary Care was founded in 2009 with a monthly membership cost of $59, and Dr. Qamar says the goal was to help frustrated doctors enjoy the practice of medicine without the hassles of insurance. To date, the practice has operations in 25 states and is currently the largest DPC group in the country.[5]

Rising healthcare costs and new mandatory insurance laws have influenced many physicians to jump on the concierge medicine bandwagon.

Dr. Qamar is not alone. He's part of a new and growing generation of concierge doctors who, in the wake of healthcare reform, are seeing and meeting a need among middle-class families and frustrated practitioners. And, it's a trend on the uptick. Of the estimated 5,500 concierge practices nationwide, about two-thirds charge less than $135 a month on average, up from 49 percent three years ago, according to *Concierge Medicine Today*, a trade publication that also runs a research collective for the industry.[6] Inexpensive practices are driving growth in concierge medicine, which is adding offices at a rate of about 25 percent a year, according to the American Academy of Private Physicians. In fact, while the vast majority of family physicians and general practitioners have not yet made the switch, a study conducted for The Physicians Foundation in early 2013 showed that almost one in 10 practitioners are considering converting to a private or concierge model.[7]

Unlike high-end concierge practices, which typically bill insurers for medical services on top of collecting retainer fees, the lower-end model charges patients directly for treatment along with membership, often posting menu-style prices for services and requiring payment up front. Eliminating insurance billing cuts 40 percent of the practices' overhead expenses, enabling them to keep fees low.[5]

Also fueling the trend is a little-known clause tucked into the healthcare law that allows DPC to count as Affordable Care Act-compliant insurance, as long as it is bundled with a "wrap-around" catastrophic medical policy to cover emergencies. "All of a sudden, our market went from the uninsured to everybody," says Dr. Qamar.[5]

The Case for Concierge

It is easy to see how patients benefit from paying a fee for more personalized access to a physician, but how do physicians benefit from implementing this model? While some people think the move is motivated by higher income, that is generally not the case, as studies have shown the average income for a private doctor is virtually the same as other primary care physicians. So if money is not the motive, what is? For some, it is simply the prospect of more satisfying work.

For physicians who became general practitioners because they wanted to build that strong doctor-patient relationship, concierge medicine offers an almost idyllic scenario. Private physicians can promise same-day or next-day access (while some patients often wait weeks or even months to see their nonconcierge physician), along with all of the personalized perks. "A major advantage for me is being able to spend more time with each patient, and in the majority of the time, I can avoid prescribing yet another pill," says Dr. Amaya. "The concierge practice model gives my patients 24/7 access to me or my staff. I can work in patients on the same day for urgent visits and see them as often as I need to. This accessibility keeps my patients' health at its best and has dramatically reduced my hospitalizations annually."

With the ability to really get to know patients on a personal level, as well as provide such a comprehensive approach to their medical care, doctors find they are better able to address concerns than with the prevailing model. Dr. Amaya says she is able to spend as much as one hour with each patient, unheard of in a traditional practice. "As a physician, I have always believed that achieving a cure is not synonymous with healing," she explains. "Now, having a concierge practice allows me not only to cure my patients, but also to take their hand as they journey on further to complete healing."

Another perk of a smaller patient load and a model based on membership fees is the potential reduction in overhead costs. With fewer patients, physicians can often operate a practice with fewer support staff. Plus, with the reduction in bureaucratic red tape from insurance companies and government programs, the time spent on daily paperwork is greatly reduced.

A Look at the Cons

Derisively dubbed "wealth care" at its inception, concierge medicine was accused of promoting a two-tiered health system that favored the wealthy while burdening the middle and lower class with a higher cost of insurance. Detractors contended that while this approach was lucrative for select physicians and certainly benefited patients who could afford it, it remained inaccessible for patients who could not drum up the needed membership fees.[6]

For private physicians eyeing a concierge model, there are several potential pitfalls to keep in mind. For example, concierge practices provide a comprehensive array of services for their patients, and if the practice has a small staff, it may be challenging to meet all those obligations without hiring outside help. Other concerns to be mindful of include:

- *Pricing error risks.* An inherent risk exists in computing an incorrect price point. The result is a less-profitable bottom line.
- *Loss of patients.* Because many patients are familiar with the standard healthcare model, transitioning to concierge medicine may result in patient attrition.
- *Extra services.* Providing flat-fee visits is not enough to justify membership costs for many patients. That means private physicians will need to include extra services to make concierge medicine worth the price.
- *Insurance regulations.* Although most concierge medical practices are cash-based, that does not mean insurance should be ignored since it does offer an additional income stream. Incorporating insurance into the concierge practice, however, can create a risk for double billing by charging for care submitted to the insurance company or Medicare in addition to charging the concierge fee. Keeping track of those nuances can prove tricky.
- *Increased marketing.* At minimum, concierge practices will need a well-positioned website that explains their pricing and services, a strategic plan to reach new patients and a means for connecting with referral partners.

There may also be concerns regarding managing expectations from patients who grow to demand more from their pay-for-service arrangement. "Since transitioning into the concierge model, my patients have come to expect the same attention and treatment at other offices. They become spoiled, so to speak. And, if they have to wait for more than 10 minutes, they figure, well, that's too long, so they complain to us and demand a referral to a different specialist. We try to encourage them to be patient while educating them about the economic reality of practicing medicine today," says Dr. Amaya. "What patients sometimes don't realize is that our costs and expenses are significant with rent, malpractice insurance, supplies, etc. Some patients are under the impression that if they pay high premiums for their health insurance, we as physicians must be receiving a significant portion of that, but the reality is we don't."

What Does the Future Hold?

The healthcare landscape is continuing to evolve, particularly in the area of primary care. With a new administration in the White House contemplating overhauling or completely replacing the Affordable Care Act, coupled with the new Medicare Access and CHIP Reauthorization Act (MACRA) that went into effect last fall, it remains to be seen what impact these changes will have on the long-term viability of the concierge practice model. But, one thing is certain: Change is in the air, and the concierge practice, in all of its variations, may very well offer attractive benefits to both practitioners and patients looking for a new way to deliver primary care.

> For physicians who became general practitioners because they wanted to build that strong doctor-patient relationship, concierge medicine offers an almost idyllic scenario.

"It is time to stop tinkering around the edges of the current payment system. It needs to change conceptually and completely to a new paradigm where that the primary care physician is paid directly by the patient. DPC (membership, retainer and concierge) is one such new paradigm," says Stephen C. Schimpff, former CEO of the University of Maryland Medical Center, senior advisor to Sage Growth Partners and author of *The Future of Health-Care Delivery: Why It Must Change and How It Will Affect You*. "The cost is reasonable, the care is better, doctor frustrations come down, patient satisfaction goes up and total healthcare costs come down. It is time for a change."[7] ❖

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Addressing Central Pain Syndrome

Central pain syndrome affects several million people worldwide, yet this condition wasn't fully understood until recently, and there are still many challenges concerning diagnosis and treatment.

By Dana Henry

JUST A FEW years ago, Radene Marie Cook was busy balancing demanding careers. She was a professional actor, dancer and singer. She was also a popular on-air personality whose resume includes being an "On the Spot" news and airborne traffic reporter for KFWB in Los Angeles, Calif. But Cook's life changed when, while on assignment, her plane was involved in an accident after being hit by a microburst. "The midair collision with the winds moving straight down at nearly 200 miles per hour was like the force of an 18-wheeler slamming into a Soap Box Derby car," she says.[1]

Cook sustained serious injuries to her head and back, but that wasn't the worst of it. Her workers' compensation program required her to have a discogram as part of her rehabilitation. This invasive procedure is designed to help physicians determine the anatomical source of a patient's back pain. During a discogram, dye is injected into the center of one or more spinal discs to pinpoint which ones are causing pain. The injection can reproduce back pain in the affected disc or discs. The dye also makes cracks in the exterior of discs visible on an X-ray or CT scan.[2]

The procedure is controversial in part because it's not always effective and in part because of potential complications.[2] In Cook's case, the needle punctured her spinal cord lining, which resulted in adhesive arachnoiditis, a condition characterized by complete encapsulation of the nerve roots. Adhesive arachnoiditis has been described as a life sentence of unremitting pain,[3] and Cook wasn't spared that outcome. After the discogram, her central pain syndrome symptoms appeared. As time passed without a proper diagnosis or treatment, her symptoms proliferated and also increased in severity. "The longer the pain went undertreated, the worse my overall health got," she says. "First, the symptoms themselves got more severe. Then, there were more of them."

Cook says it took three years before she was diagnosed with central pain syndrome and numerous associated conditions. Along the way, she received several misdiagnoses and encountered physicians who told her they had no idea what was going on. In her words, they "just threw up their hands." The correct diagnosis came from a neurologist in Alabama who specializes in detecting difficult-to-diagnose spinal issues.

What Is Central Pain Syndrome?

First described in 1891, central-type pain was believed to be caused by stroke-related damage of the thalamus. It was later believed to be caused by a thalamic syndrome that included a pain component. Until recently, thalamic pain was the prevailing understanding of central pain.[4,5]

According to the National Organization for Rare Disorders, researchers now understand that damage to the pain-conducting pathways anywhere along the neural axis, from the spinal cord to the sensory cortex, can cause central pain syndrome, which can be broken down into central pain of brain or brain stem origin or central pain of spinal cord origin.[4] The term "central pain syndrome" reflects the fact that damage to various areas of the central nervous system (CNS) can cause central pain and that a stroke is not necessarily the primary cause. Brain or spinal cord trauma, epilepsy, multiple sclerosis, Parkinson's disease and tumors can also cause central pain syndrome.[6] (See Causes of Central Pain Syndrome for additional causes.)

Sarah Dominguez, a specialty physical therapist who treats central pain syndrome and owner of Foundational Concepts in Kansas City, Mo., says central pain syndrome is different from chronic pain since it's caused by an insult to the CNS rather than pain that develops over time from an old injury such as one to the back or knee. "The pain originates from the CNS, not from the nerves in the periphery. It is similar to chronic pain as they both cause changes to the CNS, making the brain and nerves more sensitive to movement, thus enhancing the pain experience," she explains.

Adhesive arachnoiditis has been described as a life sentence of unremitting pain, and Cook wasn't spared that outcome.

Because there are a variety of causes, the syndrome differs from person to person. Some experience pain over a large portion of the body, while others may have pain in a specific area. Though each person is different, the pain is typically constant and moderate to severe. Touch, movement, emotions, temperature changes and other factors can affect the level of pain.[6] The type of pain may be aching, burning, freezing, lacerating, pressing, shocking or tearing in nature — or what can best be described as pins and needles. Brief bursts of sharp pain can also occur, as can numbness in the areas affected by the pain.[5,6] Central pain syndrome often begins shortly after the injury or damage occurs, but months or even years can pass before the pain starts, according to the Central Pain Foundation.[6]

Along with intense, unrelenting, multifaceted pain, Cook experienced pain in parts of her body that had not been injured, hyperhidrosis and hypothalamus dysfunction, and allodynia (central pain sensitization following painful, often repetitive, stimulation). "I had sharp, electric, lancinating-type pain anywhere and everywhere — my legs, my sides, my arms, everywhere, especially in bizarre places like the one that would wake me up in the middle of the night: the sides of my tongue," she says. "It would feel like someone had attached a jumper cable to the middle of my tongue, then hooked that jumper cable to the nearest electric chair."

The allodynia affected her from head to toe. The hyperhidrosis made her sweat in strange patterns. The hypothalamus dysfunction made her feel nauseated at 85 degrees and led her to pass out at temperatures higher than 98 degrees. "Honestly, you

could mix the electric chair pain with invisible knife wounds and throbbing pressure, and you pretty much have the pain range I am describing," she says. In fact, Cook's pain is so severe that she has to lie on a mattress in the back of a van when traveling to and from doctor appointments. Sitting for long distances is out of the question.

Causes of Central Pain Syndrome[5]

More Common

- Cancer
- Epilepsy
- Multiple sclerosis
- Parkinson's disease
- Spinal cord injury
- Stroke
- Traumatic brain injury

Less Common

- AIDS, especially end-stage
- Aneurysm
- Arachnoiditis
- Arteriovenous malformation
- Bacterial and viral infections (e.g., shingles and encephalitis)
- Cauda equina syndrome
- Cervical myelopathy
- Charcot-Marie-Tooth disease
- Chemical toxicity
- Cluster headaches
- Gunshot wounds
- Lead neuropathy
- Meralgia paresthetica
- Mercury toxicity
- Myelomalacia
- Neurofibromatosis
- Posterior myelitis
- Post-polio syndrome
- Prion disorders
- Radiation exposure
- Reflex sympathetic dystrophy syndrome
- Spinal cord infarction
- Surgical accidents
- Syringomyelia
- Tethered cord syndrome
- Transverse myelitis
- Vascular malformation
- Vitamin B-12 deficiency
- Any condition that causes nerve demyelination or other nerve or brain damage

A Difficult Diagnosis

Dominguez says a major impediment to early diagnosis and treatment is that symptoms can lag behind injury for years. Healthcare providers are traditionally trained to treat acute onset of pain or symptoms, not delayed symptoms. In addition, there are no ideal diagnostic tests to detect CNS hypersensitivity, which further inhibits diagnosis.

Beyond that, the system itself can hamper diagnosis, she says. She describes one scenario for illustration: Patient X begins having burning pain in his hands. He goes to his primary doctor, who prescribes some sort of pain medication and refers him to a specialist. It takes two to three months to get an appointment, giving Patient X's CNS more time to continue forming bad habits regarding sensitivity. The specialist needs tests and procedures. This takes more time. Meanwhile, Patient X's feet are now burning along with his hands, and his brain is racing to solve this pain puzzle by itself. This causes anxiety, worry and fear, which only increase pain sensitivity in the CNS. The procedures finally come, but show nothing, so Patient X is referred to another specialist (e.g., neurology, rheumatology, orthopedic), which takes another month or two, and the cycle continues until Patient X has spent three years just getting to a diagnosis.

This all-too-common scenario is very similar to the one Cook experienced on her own three-year quest for medical answers and appropriate treatment.

Dominguez adds that, while knowledge about central pain syndrome has been building over the past decade, clinical practice often lags behind research: "Many therapists simply have not learned how to best approach these types of patients. Our role as a physical therapist (PT) is to educate our patients about pain physiology, utilize our knowledge of the nervous and musculoskeletal systems, and work with movement to restore function." She adds that a PT's job is to avoid setting unachievable goals. The goal isn't to make people with chronic pain pain-free, she says, because that's not realistic. Instead, the focus is on function, recreation and quality of life — elements all healthcare providers can focus on with regard to the care they provide.

Lynn R. Webster, past president of the American Academy of Pain Medicine, echoes Dominguez's statement about avoiding the goal of making patients pain-free: "Clinicians should assess and treat underlying disorders that cause pain, and they should work to eliminate the pain, but they should also understand that, for some patients with some types of pain, eradicating all underlying causes or the pain itself may not be possible."

Why Treatment Matters

Webster says that, despite the inability to remove all causes of pain in all patients, pain must be addressed and prioritized.[7] To

do otherwise, he says, is to "put patients at risk for a host of complications, the most serious of which is the progression to pain as a chronic destructive pathology."

In an effort to prevent chronic pain from developing in the first place, Webster says pain should be assessed in patients as frequently as vital signs are assessed. Unfortunately, some providers don't quite know what to do with pain, including central pain syndrome, when it does present in a patient. This stems in part, says Dominguez, because central pain syndrome is hard to see, difficult to reproduce and a challenge to treat. Others might be reluctant to treat complex forms of pain because opioid addiction is on the rise. Some healthcare providers assume opioids are the only way to treat chronic pain, and they don't want to manage that class of medications. They might even think patients with central pain are drug-seeking or have emotional or mental health issues that are causing their pain.[5] Yet, delays in treatment because of these misperceptions only make central pain syndrome worse.

Cook's current therapy is high-dose opioids along with several supplements to help her body fight the constant onslaught of pain. This regimen has allowed her to live in a way that's plugged in — not checked out — to her creativity, to her spirit and to her purpose.

According to Dominguez, the appropriate treatment matters a great deal, especially from the standpoint of physical therapy. "The current research shows that when we educate patients about the physiology of pain, they feel better. Why? Because when they have a better understanding of their pain, the brain calms down, stops worrying and does not fear what it does not know," she says. She also says it's important for healthcare providers to develop a team approach to central pain syndrome: "One provider alone will not have all the answers. A physician who understands the condition, a mental health provider, physical therapy and often many alternative therapies are important parts of the team."

A Healing Journey

Pain patients aren't lost causes. Their pain can be addressed, and they can learn to live with it, not in spite of it. Take Cook, for example. These days, she's touching people's lives in a new way. The former actor and news reporter spends her time working as an advocate for people who suffer from chronic pain. Along with other outreach work, she has put a face to pain through the INvisible Project, a program of the U.S. Pain Foundation that uses portraits of people living with chronic pain to educate others about these complex conditions. "Although I am still in pain, my life is improving significantly," her profile states. "It is because I have access to the opioid treatment appropriate for me, and because of the individualized treatment plan worked out between me and my doctor, that I can again have a quality of life that overshadows the pain — something I could not have when left to 'fail-first' treatment plans."[1]

This portrait is one of many that is part of the U.S. Pain Foundation's INvisible Project that puts a face to pain.

Her words say it all. Appropriate diagnosis and treatment, a patient-centered plan of care and the understanding that there's no quick fix are essential when treating people with central pain. Within this framework, healthcare providers can come alongside their patients — and stay beside them — as they reclaim their health and their lives. ❖

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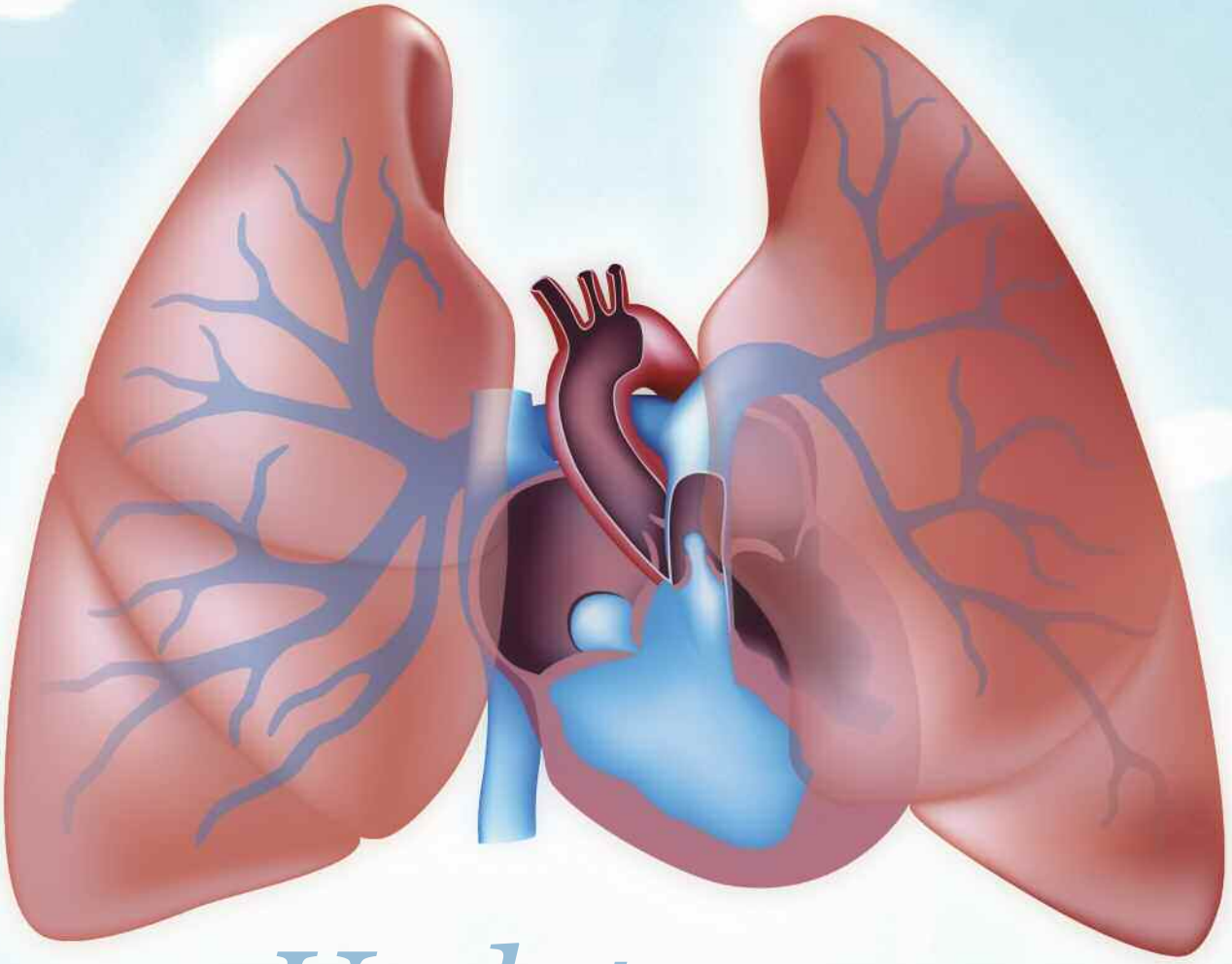

Update on Pulmonary Arterial

This disease is caused by multiple factors, most prominently other health conditions. And, while it is incurable, symptoms can be eased with treatment.

By Jim Trageser

Hypertension

WHILE HIGH BLOOD pressure is well understood as the single most prevalent cause of early mortality in the U.S. and Europe, a specific subset, pulmonary arterial hypertension (PAH), is a little-known yet deadly condition in which high blood pressure is confined to or focused on the lungs. It is chronic and progressive, and the eventual outcome is heart failure.

What Is PAH?

PAH is an incurable disease in which the arteries in the lungs become constricted (either through narrowing or internal blockages), causing increased pressure on the right side of the heart. It is one of five categories of the larger disease group known as pulmonary hypertension,[1] and it is subcategorized based on the likely cause of the disease. Most cases will fall into one of the first four categories, but there are even more rare cases as well:

- Associated PAH (APAH)
- Drug- and toxin-induced PAH
- Heritable PAH (HPAH)
- Idiopathic PAH (IPAH)
- Persistent pulmonary hypertension of the newborn (PPHN)
- Pulmonary veno-occlusive disease (PVOD)
- Pulmonary capillary haemangiomatosis (PCH)

While exact numbers of patients with PAH are not available,[2] estimates range from 15 to 50 cases per million in the U.S. for the larger pulmonary hypertension disease group known as APAH.[3] Women are more likely than men to develop PAH, and it generally manifests between the ages of 20 years and 60 years. Being overweight is also correlated with developing PAH, as is a family history of the disease. Those living at high altitude are also at higher risk.[2]

Survival rates for those diagnosed with IPAH (the form in which no cause can be determined) range from 68 percent at one year down to a five-year rate of just 34 percent.[4] (However, these numbers are not adjusted for patient age or how far the disease had progressed at time of diagnosis.)

Causes of PAH

More than half of PAH cases are thought to be caused by another condition that strains the body. These disparate conditions are grouped together as APAH, with underlying causes ranging from connective tissue diseases (lupus, scleroderma), liver disease (including cirrhosis and portal hypertension), HIV, sickle cell disease, lung disease (emphysema, chronic obstructive pulmonary disease [COPD]) and congenital heart disease. These connective tissue diseases are associated with roughly 30 percent of all PAH cases.[5]

Scleroderma (also known as systemic sclerosis, or SSc) and lupus can lead to APAH by scarring the blood vessels in the lungs.[6] Up to 12 percent of all patients with SSc will develop PAH, with only a 50 percent three-year survival rate.[7]

Cirrhosis and other liver diseases, including portal hypertension, are thought to cause PAH through elevated sodium levels left in the bloodstream by a weakened liver, leading to higher blood pressure.[8]

The specific mechanisms by which HIV leads to PAH are not fully understood, but researchers believe the statistical correlation is too high to be coincidence.[9]

Sickle cell disease can lead to PAH through the general deterioration of tissue, including arterial walls, associated with the genetic disease.[10]

Researchers believe that the lung diseases emphysema and COPD can trigger PAH through the inflammation and hypoxia affecting the tissue in the arteries.[11]

Congenital heart disease can trigger PAH through overcirculation, causing lesions to form on the arterial walls. Researchers believe other factors also come into play, but don't fully understand the mechanisms that can trigger PAH.[12]

Another leading cause of PAH in developing areas of the world is schistosomiasis, a parasitic infection of the Trematoda freshwater flatworm.[13] It is found in the Caribbean, and travelers who have been to tropical locations in other parts of the world may bring the infection home. About 4.6 percent of those with schistosomiasis will develop PAH.[6]

Drugs and poisons can also lead to the development of PAH. These are sometimes included with APAH, while other researchers and practitioners place them in their own category. Substances that have a high correlation with PAH and are thought to play a role include illegal street drugs such as cocaine and methamphetamine (which both constrict blood vessels and can cause scarring on the internal walls),[14] as well as since-removed prescription weight-loss drugs fenfluramine and dexfenfluramine (which had a high correlation between their use and later development of PAH).[15]

HPAH is sometimes referred to as familial PAH. It is tied to an inherited genetic mutation that is thought to either cause development of, or make it more likely to develop, PAH. The

two genes thought to be associated with PAH are bone morphogenetic protein receptor type 2 and activin receptor-like kinase 1.[6] There is a correlative tie with PAH, but the causative function that leads the mutation to bring about PAH is not yet understood. Some 15 percent to 20 percent of all PAH patients have HPAH.[5]

When doctors are unable to determine a likely cause of PAH, it is then diagnosed as IPAH. This is likely the second-largest group of cases, behind APAH.

Drugs and poisons can also lead to the development of PAH.

Infants born with PAH are described as having PPHN. The specific trigger is not understood, but it is thought to be a failure of the normal circulation transition that occurs immediately after birth as infants begin processing their own oxygen via the lungs rather than via the placenta.

Lastly, two closely related diseases to PAH generally included in the PAH classification under the World Health Organization's (WHO) pulmonary hypertension descriptions are PVOD and PCH. PVOD is a condition in which the small veins in the lungs become obstructed with new tissue growth.[16] PCH is considered a pretumorous growth of capillaries that typically manifests in children and young adults, and generally progresses to PAH.[17] The causes of these are also unknown.

Symptoms and Progression of PAH

Patients with PAH can be asymptomatic in the earliest stages of disease.[18] Initial symptoms of PAH are generally identical to those of other forms of hypertension:

- Shortness of breath (especially following physical activity)
- Excess fatigue
- Dizziness or fainting
- Racing pulse
- Chest pain or pressure

Depending on the progression of PAH, symptoms may also include:

- Swollen arms, legs or face due to edema
- Cough
- Hoarseness
- Low blood pressure

Late-stage PAH patients may exhibit blue coloration on lips or skin, particularly the extremities, due to low oxygen levels in the blood. Some patients may also develop Raynaud's disease, which causes fingers and toes to feel cold or grow numb.[5]

WHO has created a functional status classification to assist physicians in treating patients with all forms of pulmonary hypertension, including PAH:[19]

- No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, fatigue, chest pain or presyncope [lightheadedness, muscular weakness, blurred vision and feeling faint]
- Mild limitation of physical activity; no discomfort at rest, but normal activity causes increased dyspnea, fatigue, chest pain or presyncope
- Marked limitation of activity; no discomfort at rest, but less than normal physical activity causes increased dyspnea, fatigue, chest pain or presyncope
- Unable to perform physical activity at rest; may have signs of right ventricular failure; symptoms increased by almost any physical activity

Regardless of the initial cause or trigger (if known), once PAH has developed, disease progression will typically follow the same general path: increasing fatigue as the lungs struggle to oxygenate the blood, and then a gradual weakening of the heart as the right side tries to make up for resistance in the pulmonary arteries. The disease is progressive and, ultimately, fatal. Progression tends to be rapid — years rather than decades. There is some statistical evidence that the condition of patients with HPAH will deteriorate more rapidly than patients with other forms of PAH.[20]

Diagnosing PAH

Given the similarity of PAH symptoms to other forms of hypertension, and that many cases of PAH are caused by a pre-existing lung or heart condition that will also manifest the same symptoms, a specific diagnosis can be challenging. In fact, it is thought that it typically takes more than two years from a patient's initial symptoms to disease diagnosis.[21]

Because of the lack of unique initial symptoms, a PAH diagnosis is usually one of exclusion.[6] In 1999, a group of associations (American Heart Association, American College of Chest Physicians, American Thoracic Society and the Pulmonary Hypertension Association) developed a standardized sequence of tests and procedures to assist physicians in correctly diagnosing PAH and similar diseases.[22] The sequence follows typical best practices: an initial physical examination and review of patient history (particularly noting any family history of PAH, as well as any conditions linked to APAH such as liver disease, connective tissue disease, HIV, etc.), followed by blood tests, chest X-ray, electrocardiogram, echocardiography and possible angiogram or polysomnography, with each step a process of elimination to help narrow the possibilities. Other tests included in the sequence include lung function, right heart catheterization and a lung ventilation/perfusion scan.[23] Genetic

testing may also be ordered if HPAH is suspected.

PPHN is diagnosed by measurement of right-to-left shunt coupled with a lack of congenital heart disease.[24]

PVOD may result in a negative reaction to normal PAH treatment. It can be definitively identified by microscopic examination of the veins in a sample of lung tissue taken during a biopsy, although due to the risks involved and that the prognosis for both diseases is short-term, this is rarely done.[25]

Because sudden death is a high risk for PCH patients, the risks of a biopsy may be warranted for a definitive diagnosis.[26]

Treating PAH

There is presently no cure for PAH, PVOD or PCH, but treatments can be used to ease symptoms and prolong patient quality of life. A lung or heart-lung transplant is the only option to extend a patient's life more than a few years. The one exception is PPHN, which can be successfully treated, usually with oxygen therapy (CPAP, hood or ventilator), medications to control blood pressure and, possibly, antibiotics if there is an associated infection.[27]

There are two main approaches to treating all other cases of PAH, depending on the type. For APAH, the underlying cause (whether it's liver disease, connective tissue disease or lung or heart disease) will be treated at the same time the symptoms of PAH are addressed. With SSc-PAH, the use of intravenous immune globulin has recently been shown to reduce fibrous scarring and overall inflammation.[28] And, with schistosomiasis, the parasite can be effectively treated with praziquantel.[29]

In all other cases, whether drug-induced, hereditary or idiopathic, treatment is focused on maintaining as much quality of life as possible given the progression of disease. WHO recommends using its functional status classification to help devise the appropriate treatment and how much activity a patient can reasonably tolerate.

Calcium channel blocking drugs are one treatment option to control the symptoms of PAH. These can help smooth the interior of blood vessels to ease resistance from the heart. Some popular options include amlodipine (Norvasc), diltiazem (Cardizem, Tiazac), felodipine (Plendil) and isradipine (Dynacirc).[30]

Endothelin receptor blockers such as bosentan (Tracleer) and ambrisentan (Letairis) are another treatment option that has been effective in addressing PAH symptoms. Endothelin is a natural substance produced by the body that causes blood vessels to tighten. Using an endothelin receptor blocker can help maintain higher blood flow.[4]

A third class of drug that has shown effectiveness in easing symptoms is synthetic prostacyclin. Prostacyclin is produced by the body and dilates blood vessels. Examples of this drug are epoprostenol (Flolan), administered via IV, treprostinil (Remodulin), administered subcutaneously, and iloprost (Ventavis), taken via inhaler.[4]

Phosphodiesterase type 5 inhibitors have been found effective in restoring some mobility, as well as in decreasing the pressure in the pulmonary artery.[5] These drugs include sildenafil (Revatio) and tadalafil (Adcirca). A similar drug is riociguat (Adempas).

Finally, last year, the U.S. Food and Drug Administration approved the use of selexipag (Uptravi), which works by relaxing the muscles in blood vessels.[5]

Oxygen will often be called for as the disease progresses. And, most PAH patients will be prescribed diuretics to help reduce fluid buildup.[18]

Still, all of these treatments can, at best, ease symptoms and, perhaps, slow progression. The only way to extend a patient's life beyond a few years is a single- or double-lung transplant, or a heart-lung transplant. Early referral to a nearby transplant center to begin analyzing a patient's potential suitability is often recommended.[31]

For the two PAH-related diseases, PVOD and PCH, the only proven treatment is a lung transplant.[26,32] In fact, studies show these two conditions are generally worsened by the drugs used to treat PAH symptoms.

As with any end-of-life diagnosis, ensuring patients have appropriate emotional and family support is crucial to maintaining the highest quality of life for their remaining time.

> Because of the lack of unique initial symptoms, a PAH diagnosis is usually one of exclusion.

Preventing PAH

There is no inoculation to prevent onset of PAH. However, for APAH, early diagnosis and treatment of the underlying causes can help prevent its onset. Avoiding the use of cocaine and methamphetamine will prevent drug-induced PAH. Other types of PAH have no prevention, as their cause is not known.

Maintaining positive general health and avoiding smoking and use of illegal or dangerous recreational drugs can help lower one's risk of developing PAH. And, those with HPAH are encouraged to avoid living at altitude if possible.

Ongoing Research

Hundreds of studies are currently being conducted for PAH, as well as thousands more for the related conditions that can

trigger or contribute to PAH (such as sickle cell disease, connective tissue disease, liver disease, etc.).

Because the underlying biochemical reactions that cause or trigger PAH are not yet fully understood, the National Heart, Lung and Blood Institute (a branch of the National Institutes of Health) is funding basic research designed to further knowledge of how this disease occurs.[33]

On the practical side, much of the research currently listed at ClinicalTrials.gov (861 active and recent PAH-related trials as of this writing) is focused on whether existing drugs approved for other treatments will also work on easing symptoms of PAH. A successful example is the use of phosphodiesterase type 5 inhibitors, which were originally brought to market to treat erectile dysfunction. Now, those same active ingredients under different brand names are being used to treat symptoms of PAH.

This deadly, incurable disease will continue to be a challenge for physicians for decades to come.

Some of the more interesting studies include one looking at the presence of antibodies to endothelial cells in patients with SSc-PAH.[34] Others are exploring whether the kinase-inhibiting leukemia drug imatinib might relieve PAH symptoms. And a beta blocker already approved for use in treating congestive heart failure is being tested to see if it can provide relief for PAH patients.[35]

The subjects of other studies include the role of regular exercise in slowing the progression of PAH and technological advances in angiogenic imaging to allow for more accurate diagnosis and treatment planning.[36] Another in France is recruiting test subjects to determine if denervation of the pulmonary arteries will provide relief.[37] And, yet another is testing whether specific biomarkers in the blood can be used for a quicker definitive diagnosis.[38]

Looking Ahead

With disparate identified causes and triggers for PAH, including genetic predisposition, drug use and underlying medical causes ranging from sickle cell disease to SSc, and with many causes not yet understood, this deadly, incurable disease will continue to be a challenge for physicians for decades to come. Current research may bring to market new treatments that improve a patient's prognosis within a few years, but for now, transplant surgery is the only hope for most patients. ❖

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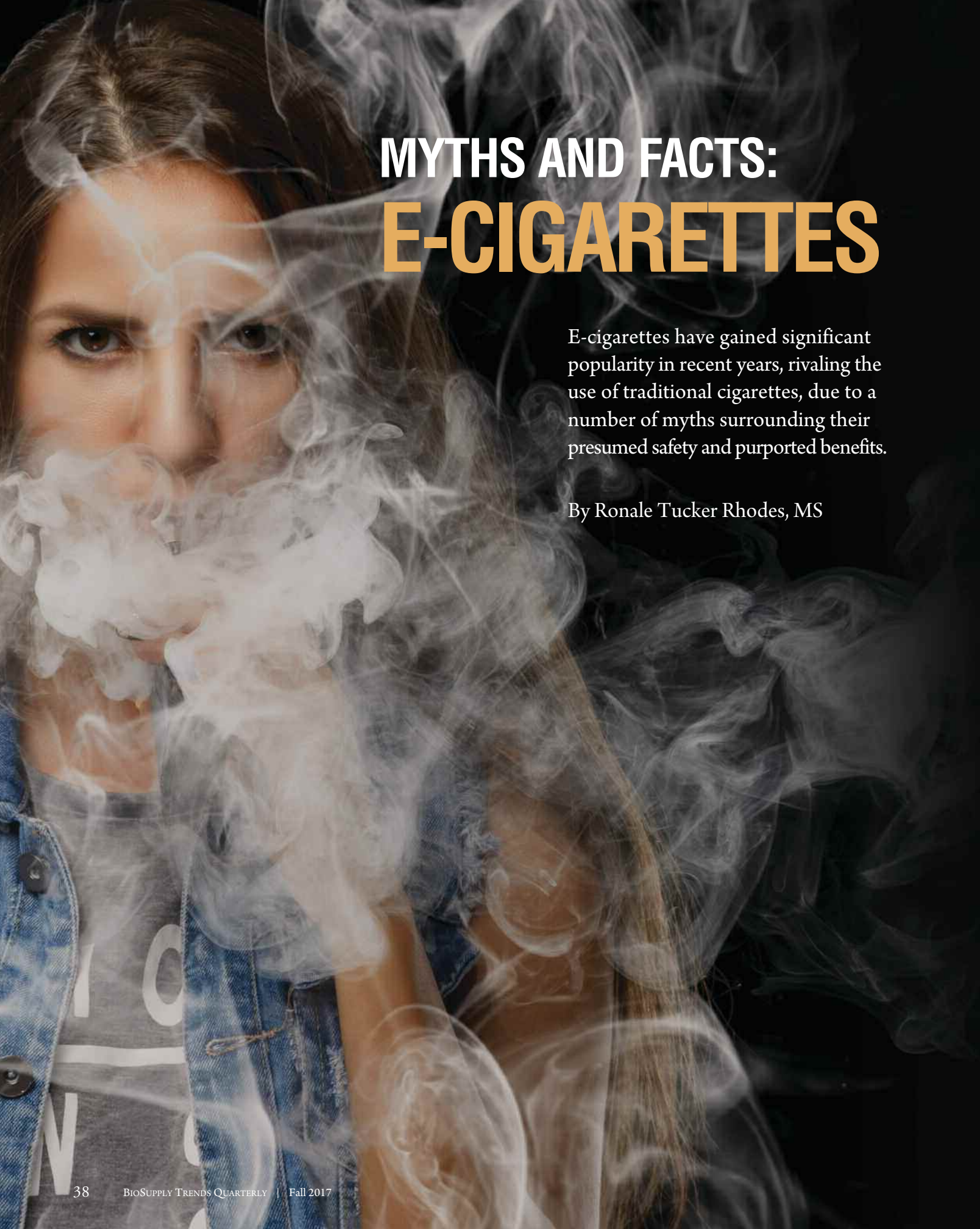

MYTHS AND FACTS: E-CIGARETTES

E-cigarettes have gained significant popularity in recent years, rivaling the use of traditional cigarettes, due to a number of myths surrounding their presumed safety and purported benefits.

By Ronale Tucker Rhodes, MS

TOBACCO IS ONE of the most abused substances in the world. According to the Centers for Disease Control and Prevention (CDC), cigarette smoking is the leading cause of preventable disease and death in the U.S., accounting for more than 480,000, or one of every five, deaths each year. CDC estimates that in 2015, 15 of every 100 U.S. adults aged 18 years or older (15.1 percent) smoked cigarettes, which translated to about 36.5 million adults.[1]

Fortunately, cigarette smoking is on the decline, with a 6 percent drop in the number of smokers from 2005 to 2015.[1] Furthermore, a high number of current smokers would like to quit, which is no surprise. Quitting means reduced cancer risk, improved physical health, lower insurance premiums, cost savings and elimination of unwanted side effects such as wrinkles, yellow teeth and loss of taste. Yet, because tobacco is such an addictive substance, quitting is far from easy. So, when e-cigarettes debuted in the U.S. in 2007, many looked to them as a possible solution.

Although the first non-tobacco cigarette was patented in 1963, it wasn't until 2003 that the first prototype e-cigarette was developed by Hon Lik, a Chinese pharmacist, who marketed the product as a way to enjoy smoking without the risks.[2] Today, most e-cigarettes consist of three components: 1) a cartridge that holds a liquid solution containing varying amounts of nicotine, flavorings and other chemicals; 2) a heating device (vaporizer); and 3) a power source (usually a battery). Puffing on the e-cigarette activates the heating device, which vaporizes the liquid in the cartridge. The resulting aerosol, or vapor, is then inhaled, which is known as vaping.[3] Today's higher-end models allow users to adjust the voltage from the battery, which regulates the intensity of the heating element. As the solution gets hotter, it intensifies the effect of the nicotine.[4] E-cigarettes don't replace the actual smoking experience, particularly when it comes to the delivery of nicotine; however, rather than getting into the bloodstream through the lungs, nicotine travels through the soft tissue of the buccal mucosa (the mucous membranes lining the inside of the mouth).[2]

Today, more than 250 different e-cigarette brands are on the market, with the leading producers in the U.S. including Reynolds American Inc., Fontem U.S. and Logic, reporting total sales of $795 million for the 52 weeks ending Nov. 2, 2014.[5] Although e-cigarettes were originally touted as risk-free, much has been learned about their "so-called" safety and purported benefits. Therefore, it would be prudent for smokers who are looking for a better alternative to the tobacco cigarette to choose e-cigarettes only after understanding the facts about them.

Separating Myth from Fact

Myth: The ingredients in e-cigarettes are safe.

Fact: The primary component of e-cigarettes is the liquid contained in the cartridges. To create the liquid, nicotine is extracted from tobacco and mixed with a base (usually propylene glycol) along with flavorings, colorings and other chemicals.

Nicotine is addictive and can lead to negative health impacts, including heart disease, stroke, cancer and decreased adolescent brain development. The more nicotine a person uses, the greater potential for addiction.[6] Aside from the danger of inhaling nicotine, liquid nicotine (which is contained in the e-cigarette's cartridge, many of which are refillable) is extremely toxic when swallowed. Robert Basset, MD, medical toxicologist and emergency medicine physician at Philadelphia's Einstein Medical Center, said that while nicotine is perceived as safe, it can be fatal when taken in high doses. According to Dr. Basset, "Nicotine mistakenly has this reputation for being safe because it is purchased over the counter." But, he says, one teaspoon of liquid nicotine is enough to kill a 200-pound person.[2] Indeed, bottles of liquid nicotine are available for individual purchase, some of which may contain as many as 36,000 milligrams of nicotine, which is enough to kill 500 people.[7]

One teaspoon of liquid nicotine is enough to kill a 200-pound person.

Poisoning from liquid nicotine can occur by ingestion, inhalation or absorption through the skin or eyes. Reports of poisoning due to e-cigarette liquids is rising, with the number of calls to poison centers increasing from one per month in September 2010 to 215 per month in February 2014, according to a CDC study. More than half (51.1 percent) of calls to poison centers due to e-cigarettes involved young children under age 5, and about 42 percent of calls involved people aged 20 years and older.[8]

Many studies show the substances used in the mix with liquid nicotine could be toxic. While marketers claim flavors used are safe because they have FEMA GRAS status, that status applies only to food, meaning it's safe to eat, but it doesn't apply to inhaling through e-cigarettes. [FEMA is the group of independent experts that evaluates flavor ingredients to determine whether they are generally recognized as safe, or "GRAS," under conditions of intended use.] One flavoring sometimes used is diacetyl, a

buttery flavored chemical often added to food products such as popcorn, caramel and dairy products, which is known to cause a serious and irreversible lung disease commonly known as "popcorn lung."

Other chemicals are also of concern. In 2009, the U.S. Food and Drug Administration (FDA) conducted lab tests that found detectable levels of toxic cancer-causing chemicals, including an ingredient used in antifreeze, in two leading brands of e-cigarettes and 18 various cartridges. In another review of studies, it was found that levels of toxins in e-cigarette aerosol varied considerably within and among brands. In 2014, a study found aerosol from e-cigarettes with a higher voltage level contains more formaldehyde, another carcinogen that can potentially cause cancer.[9] Another study found that increasing the voltage from 3.2V to 4.8V while using an e-liquid with glycerin and propylene glycol solvents produced almost as much formaldehyde as a traditional cigarette, which is suspected as being carcinogenic when inhaled. And, while the study also found that at lower voltages, e-cigarettes produced up to 800 times less formaldehyde than a cigarette, the size of the vapor particles can travel deep into the lungs and heavily impact the risk of disease.[4] In fact, another study in 2014 found that using e-cigarettes has the same short-term effects on the lungs as smoking tobacco cigarettes.[10]

Finally, a study in 2015 found that e-cigarettes reduce the body's ability to fight off infections from strep and flu germs. In the study, mice exposed to e-cigarette vapors for two weeks had an increase in inflammation and susceptibility to infections.[10]

Even some products that claim not to have any nicotine in them may still contain it.

Myth: Some e-cigarettes don't contain nicotine.

Fact: Even some products that claim not to have any nicotine in them may still contain it. In the 2009 FDA lab tests, cartridges labeled as nicotine-free had traceable levels of nicotine. And, they found little consistency between the amount of nicotine delivered by e-cigarettes of the same brand and strength.[9] Indeed, nicotine levels in e-cigarette juice have been found to be significantly higher or lower than the labels claim. Consequently, users face nicotine intake that is higher than what they're used to, which can cause mild overdose and feelings of jitteriness and nausea, or lower than what they're addicted to, causing withdrawal and cravings.[7]

Myth: E-cigarettes don't produce dangerous secondhand emissions.

Fact: Breathing secondhand vapor is not totally harmless. While the amount of toxic levels is smaller compared to secondhand smoke, e-cigarettes have the same amount of tiny particles of heavy metals and other substances that can affect the lungs.[2] Two studies have found formaldehyde, benzene and tobacco-specific nitrosamines (all carcinogens) coming from secondhand emissions. Other studies have shown that chemicals in the emissions contain formaldehyde, acetaldehyde and other potential toxins. As such, the U.S. surgeon general concluded that e-cigarette aerosol is not harmless and can contain harmful and potentially harmful chemicals, including nicotine.[9]

Myth: E-cigarettes help smokers quit the habit.

Fact: While some people use e-cigarettes for the purpose of quitting, and some even vouch for its effectiveness, whether they do help is unclear. Worth noting, FDA's Center for Drug Evaluation and Research has not approved any e-cigarette as a safe or effective method for quitting. In fact, according to a 2015 CDC survey, 58.8 percent of people who recently used

e-cigarettes also currently smoked conventional cigarettes.[9] In addition, a 2016 report from the World Health Organization also claimed there was not enough evidence to show e-cigarettes actually help people stop smoking.[10]

Myth: E-cigarettes aren't marketed to children.

Fact: According to former CDC Director Tom Frieden, MD, "The same advertising tactics the tobacco industry used years ago to get kids addicted to nicotine are now being used to entice a new generation of young people to use e-cigarettes."[11] And, they're doing so with aggressive industry tactics such as cartoon characters and candy flavors, including bubble gum, Froot Loops, chocolate and strawberry.[6] A joint study by FDA and the National Institutes of Health showed that from 2013 to 2014, about 80 percent of youth tobacco users reported using a flavored tobacco in the past 30 days, with the availability of flavors being the primary reason for use.[12] Discouragingly, a study published in *JAMA Pediatrics* showed kids can easily buy e-cigarettes online.[9]

In 2015, FDA reported that three million middle and high school students were using e-cigarettes.[12] And, according to a report by the U.S. surgeon general, e-cigarette use among youth and young adults is a major public health concern, with e-cigarettes now the most commonly used form of tobacco among youth in the United States. From 2011 to 2015, usage grew an astounding 900 percent among high school students.[13]

Myth: E-cigarettes are not regulated.

Fact: Upon their introduction to the U.S. in 2007, e-cigarettes were not regulated. But, on May 5, 2016, FDA extended the Family Smoking Prevention and Tobacco Control Act of 2009 to regulate e-cigarettes along with other tobacco products.[12] This means manufacturers of e-cigarettes will have to show the products meet the applicable public health standard set forth in the law and receive marketing authorization from FDA.[14] While the regulations are not scheduled to go into effect until FDA has time to fully evaluate e-cigarettes, manufacturers were required to register with FDA by August 8, 2016, after which they have an additional two years to submit an application to remain in the marketplace.[9] During that time, FDA will conduct a review process to evaluate ingredients, product design and health risks, as well as their appeal to youth and nonusers. FDA will then issue an order granting marketing authorization where appropriate.[14]

In addition, under the new FDA regulation, the age requirement for purchasing e-cigarettes as of May 5, 2016, is now 18.[12] And, beginning in 2018, product packages and advertisements of e-cigarettes and other regulated tobacco products must bear the following warning statement: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." If the tobacco product manufacturer submits a self-certification statement to FDA that the tobacco product does not contain nicotine (and the manufacturer has data to support this assertion), an alternate statement must be used on product packages and advertisements: "This product is made from tobacco."[15]

In 2015, FDA reported that three million middle and high school students were using e-cigarettes.

Dispelling the Myths Now

The bottom line: E-cigarettes are a tobacco product, and no tobacco products are safe. Until FDA's evaluation of the 250 brands and 7,700 flavors of e-cigarettes is completed, they will remain on the market, and there are few ways for anyone other than the manufacturers to know what chemicals are contained in e-liquids or how e-cigarette use might affect health in the short- and long-term. For now, understanding the facts surrounding e-cigarettes is the best and only way to decide whether the risks and purported benefits are worth their use. ❖

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Flublok:
A Potent New Weapon Against the Shape-Shifting Influenza Virus

By Keith Berman, MPH, MBA, and Luke Noll

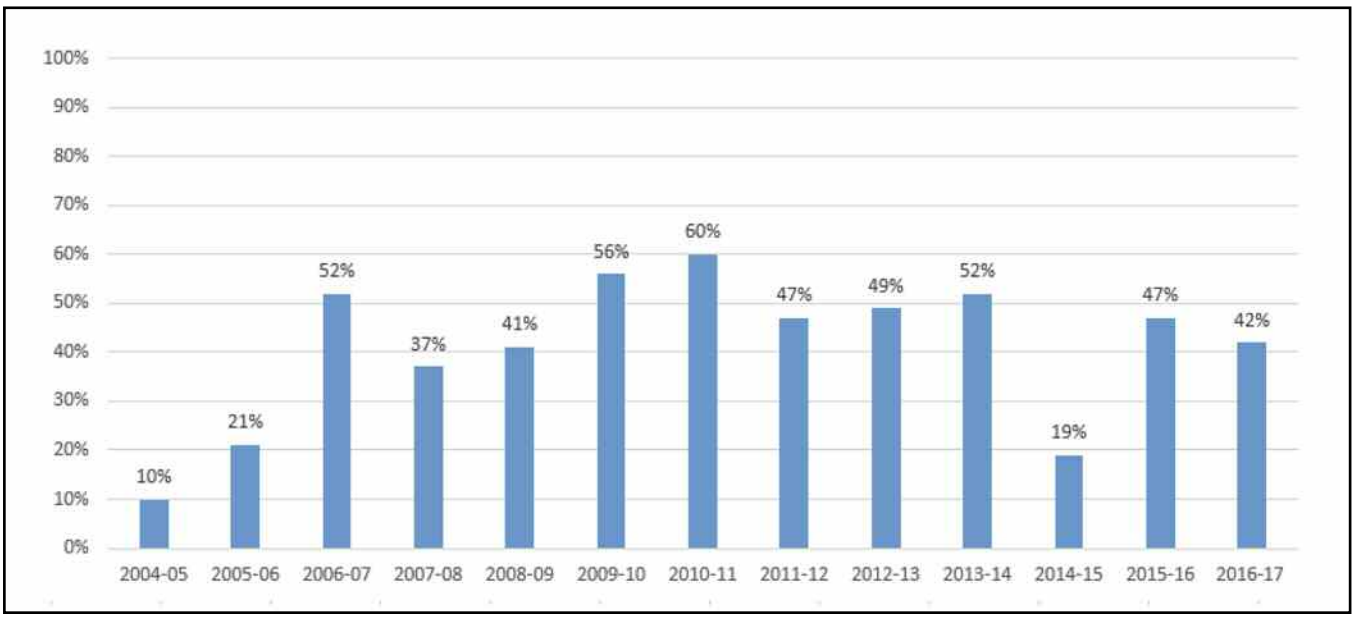
RAPID GENETIC MUTATION is the evolutionary strategy that, year after year, enables influenza viruses to evade antibody-mediated defenses and newly infect people who have had the flu or received flu immunizations many times in the past. A "universal" flu vaccine that can provide broad multi-seasonal protection against new emergent strains by targeting conserved antigenic sites on the virus still exists only in our imaginations. Our best line of defense remains immunization with new flu vaccines prepared annually against emergent influenza strains identified as the likeliest to produce the next seasonal flu epidemic.

But its propensity to continually mutate makes the influenza virus a moving target for vaccine manufacture. Mutations in the gene encoding hemagglutinin (HA) — the surface glycoprotein antigen against which we mount an antibody response — reduce the match between surface HA antigen in virus strains selected each February by the World Health Organization (WHO) and HA antigen that appears on circulating epidemic strains that finally arrive in the fall and winter. This "antigenic drift" in turn reduces vaccine effectiveness.

Atop gene mutations caused by "antigenic drift" are additional mutations introduced by genetic manipulations of selected vaccine virus strains to produce "high-growth reassortments" that yield more HA antigen in embryonated chicken eggs. In the 2016-2017 flu season, egg-based flu vaccines accounted for about 95 percent of the roughly 160 million doses distributed in the U.S. last year.

In flu seasons when epidemic influenza strains are more closely matched to the WHO-selected vaccine strains, immunization can reduce the risk of contracting laboratory-confirmed influenza by as much as 50 percent to 60 percent. But other years when more mutations occur due to combinations of antigenic drift and egg-adaptive reassortment, flu vaccine effectiveness can drop precipitously (Figure 1). The

Figure 1. Adjusted Vaccine Effectiveness (VE) Estimates for Influenza Seasons 2005-2017[11]

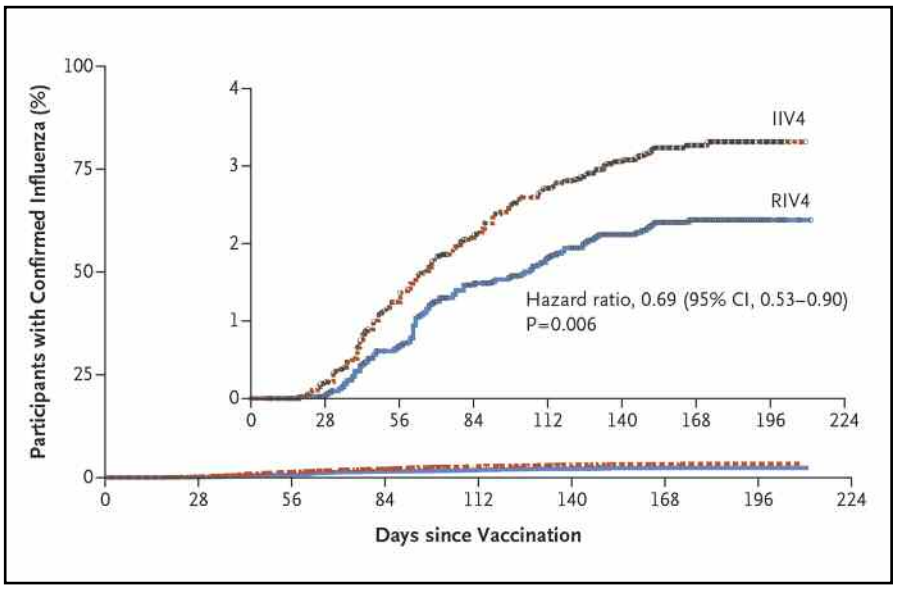


relationship is brutally straightforward: the poorer the genetic match between the selected vaccine strains and the strains that become epidemic that fall and winter, the less protection it confers against influenza attack and the higher the incidence of flu-related illness, hospitalizations and death.

Entirely apart from vaccine potency, impaired or declining immune function of the vaccine recipient can also account for diminished vaccine protection. To boost flagging vaccine responsiveness in persons aged 65 years and older — the age group that also accounts for most flu-related deaths — Sanofi Pasteur introduced Fluzone High-Dose in 2009, an inactivated influenza vaccine (IIV) featuring four times the standard 15 micrograms (µg) of HA antigen for each A and B strain. In 2015, the U.S. Food and Drug Administration (FDA) approved the first adjuvanted IIV, Seqirus' Fluad, also indicated for persons aged 65 years and older. Both represent important innovations proven to reduce the incidence of influenza-like illness in older adults. But just like standard-dose non-adjuvanted IIVs prepared with the same candidate vaccine virus strains, their protective benefit is much diminished in flu seasons when there is a poor antigenic match between vaccine strains and circulating flu strains.

Could we one day see an influenza vaccine that is both highly and more consistently immunogenic against seasonal influenza virus, and thus able to provide better year-to-year protection against the ravages of the disease? Backed by an expanding body of evidence, there is good reason to believe that such a vaccine already exists. It is Protein Sciences' Flublok, a recombinant quadrivalent product recently approved for adults aged 18 years and older.

Figure 2. Frequency of Confirmed Influenza in 8,604 Study Participants Randomized to Receive Quadrivalent Flublok (RIV4) or Inactivated Influenza Vaccine (IIV4)



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More Antigen Boosts Flublok Immunogenicity

In persons 65 years of age and older, it is well documented that standard dose IIV induces a less-robust neutralizing antibody response than in younger adults.[1] A large randomized trial of Fluzone High-Dose proved that simply increasing the administered dose of each HA antigen by four-fold, from 15 µg to 60 µg, both boosts hemagglutinin inhibition titers and reduces the influenza attack rates in seniors.[2] Flublok is formulated with 45 µg of recombinant HA antigen per strain, three times the quantity in standard-dose IIVs.* Pre-licensure hemagglutinin inhibition studies in subjects 65 years of age and older demonstrated significantly higher seroconversion rates and higher postvaccination geometric mean titers (GMT) for both the A/H1N1 and A/H3N2 subtypes following immunization with Flublok compared to immunization with a standard egg-based IIV (Fluzone).[3] Flublok was approved for use in 2013 based on its excellent immunogenicity and safety profile.

Earlier this year, results of a double-blind, multicenter trial finally addressed whether Flublok's superior immunogenicity profile compared to standard-dose IIV translates into better flu protection.[4] Just over 9,000 U.S. adults aged 50 years and older were randomized to receive the new quadrivalent form of Flublok or standard-dose egg-based quadrivalent IIV (IIV4) (Fluarix Quadrivalent, GlaxoSmithKline). Flublok immunization was associated with a 30 percent reduction in the cumulative incidence of laboratory-confirmed influenza-like illness (ILI) compared to IIV4 throughout the influenza season (95% confidence interval, 10 to 47; P=0.006) (Figure 2).

**Studies conducted by Protein Sciences found there is a limit to the boost in immunogenicity that can be attained by increasing Flublok's HA antigen content: Doses more than three-fold higher than the standard 15 µg amount in IIV do not appreciably increase anti-HA antibody titers (Treanor JJ, Schiff GM, Couch RB, et. al.* J Infect Dis *2006; 193:1223–8).*

Surprisingly, in this study's younger 50- to 64-year-old age cohort, the incidence of ILI in participants receiving quadrivalent Flublok was 42 percent lower than in those vaccinated with IIV4 — comparable to the 30 percent overall reduction for all participants age 50 years and older. While high-dose IIV has been shown to be marginally more immunogenic than standard-dose IIV in the 50- to 64-year-olds,[5] no previous study has documented improved protection of high-dose vaccine against contracting ILI in the middle-aged adult population. Yet to be answered is what accounts for Flublok's superior protection against ILI, including the 50- to 64-year-old age cohort in whom standard-dose IIV can still induce a reasonably robust antibody response.

> "Could we one day see an influenza vaccine that is both highly and more consistently immunogenic against seasonal influenza virus, and thus able to provide better year-to-year protection against the ravages of the disease?"

Flublok and the Hemagglutinin (HA) Stalk Domain

The large majority of influenza-related deaths — up to 90 percent — occur in persons older than 65 years of age, the result of immunosenescence, as well as a higher prevalence of existing comorbidities. Yet, paradoxically, older adults have much lower flu attack rates than younger adults and children. A recent study in the Netherlands, for example, found that the A/H1N1 attack rate was by far the highest in children (35 percent), lower in adults age 20 to 39 years (6.6 percent) and lower yet in adults age 40 and older (2.8 percent).[6]

The puzzle of lower influenza attack rates in seniors might be explained in part by a very recent finding that titers of broadly neutralizing IgG antibodies against the conserved stalk region of HA are very low in children, but increase with age.[7] Likely because the stalk domain of the HA glycoprotein is embedded in the viral membrane, egg-based seasonal flu vaccines usually do not induce these types of anti-stalk antibodies at significant levels. Further, while possibly less potent than antibodies against the exposed globular HA head, stalk-reactive antibodies have been shown to confer robust antivirus protection in vivo. Thus, some researchers speculate that the lower influenza attack rate with advancing age may at least in part be the result of repeated exposures to influenza viruses over many years, which prime broad protective antibody-based immunity against the conserved HA stalk domain of new seasonal virus strains.

As conventional split-virion IIV vaccines are known not to meaningfully induce anti-stalk antibodies against the highly conserved HA domain, investigators were surprised to discover that healthy middle-aged adults mounted a moderately strong antibody response to the stalk domain of HA in Flublok.[7] Why?

First, the stalk domain of this highly purified HA may be more exposed than membrane-embedded HA in split-virion vaccines. Second, the recombinant HA in Flublok is produced in insect cells, which attach smaller N-linked glycans to proteins than do mammalian or avian cells. Less glycosylation of HA antigens could correlate with a broader immune response and better viral neutralization activity; thus, the lesser glycosylation of Flublok HA than split-virion HA may permit a more robust antibody response to Flublok's HA stalk antigens.

Could Flublok Ameliorate Mismatch Due to Antigenic Drift?

The complex and cumbersome 70-year-old egg-based flu vaccine development and production cycle extends over the better part of a year (Figure 3). To ensure enough doses can be delivered ahead of the upcoming flu season starting in September/October, candidate vaccine virus strains must be decided upon at the WHO vaccine composition meeting in February. These selections follow complex analysis of isolates collected from the preceding few months by National Influenza Centers (NICs) throughout the world.

Thus, between February and the start of the influenza season, ever-mutating influenza virus strains in circulation have many months to undergo enough antigenic drift to at least partially escape vaccine-mediated neutralization.

This is exactly what occurred during the 2014-2015 flu season. After an A/H3N2

virus was selected for vaccine manufacture, a number of variant A (H3N2) viruses emerged. These late variant viruses were not well neutralized by antisera to the WHO-selected A/H3N2 vaccine virus. Unfortunately, these late-emerging A/H3N2 strains predominated during the 2014-2015 flu season, resulting in very low vaccine effectiveness.

A Centers for Disease Control and Prevention (CDC) lookback at the progression of test findings is instructive. During the preceding 2013-2014 flu season during which an A/H1N1 strain predominated, CDC characterized 86 A/H3N2 viruses, all of which were vaccine-like. In February 2014, less than 1 percent of A/H3N2 viral isolates tested by CDC exhibited a reduced titer to the selected A/H3N2 vaccine virus sera. But by April, the corresponding figure for reduced titers had increased to 11 percent, then jumped to 31 percent in May.

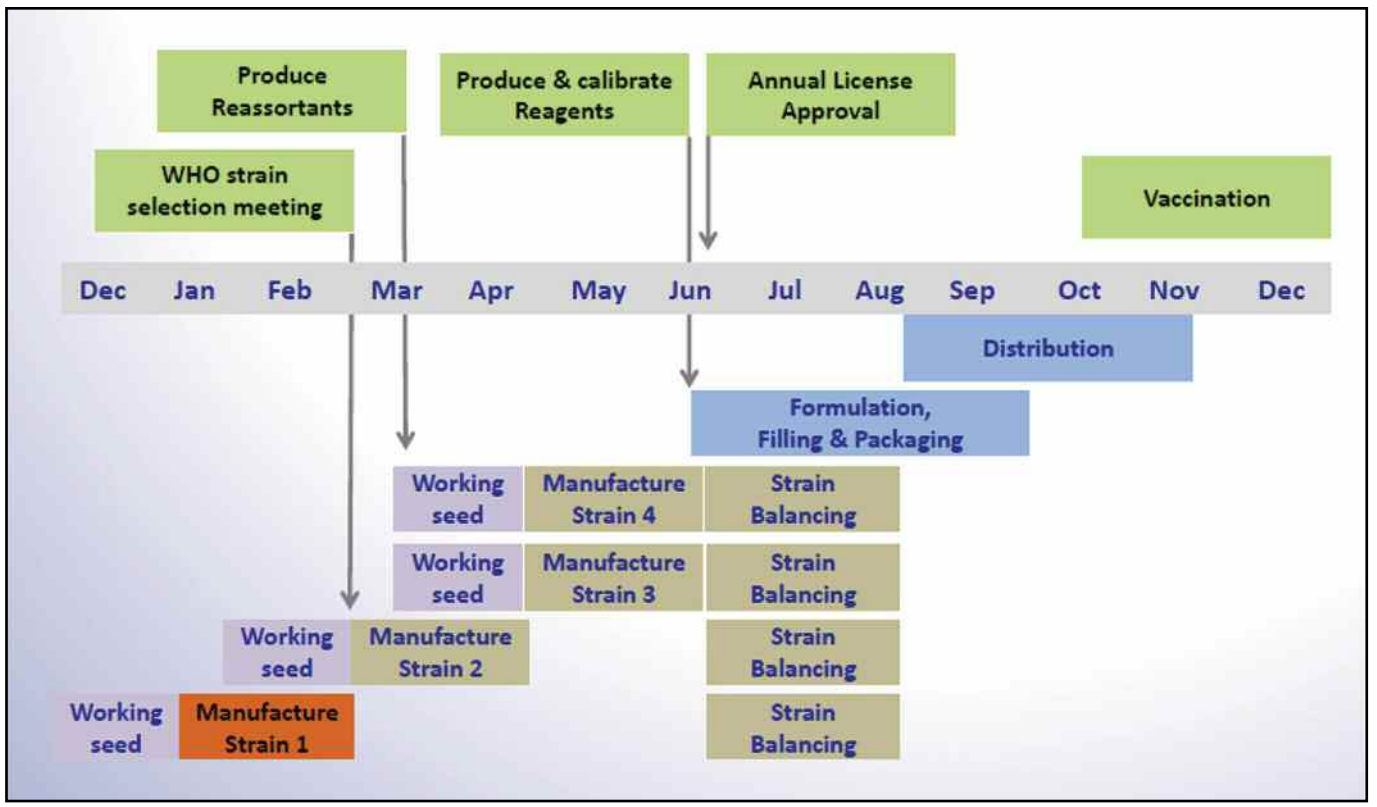
By September 2014, 49 percent of isolates tested by CDC had reduced titers to the vaccine antisera. The result of this antigenic drift and consequent antigenic divergence between vaccine and circulating viruses: an overall vaccine effectiveness of just 19 percent for the 2014-2015 flu season. For adults aged 65 years and older, the flu-related hospitalization rate reached the highest level since record keeping started in 2005-2006.

To try to address this problem of late-emerging flu virus variants, U.S. health officials explored scenarios involving delaying the vaccine virus decision from February to mid-April, or revising virus selection to allow a changed recommendation for one vaccine virus as late as mid-June. It became apparent that, given the long timeline for egg-based vaccine production, delaying the virus strain selection beyond mid- to late-March would adversely impact vaccine availability, and thus was not feasible.[8]

As noted earlier, significant mutations are also generated when selected wild-type vaccine viruses — in particular the H3N2 subtype — are genetically adapted to improve their growth rate in embryonated eggs. In the process of producing these egg-adapted "high-growth reassortants" optimized for egg-based vaccine manufacture, new mutations may be introduced in the HA antigen that again can further diminish the immunogenicity of inactivated reassortant vaccine virus against the wild-type epidemic virus strain.

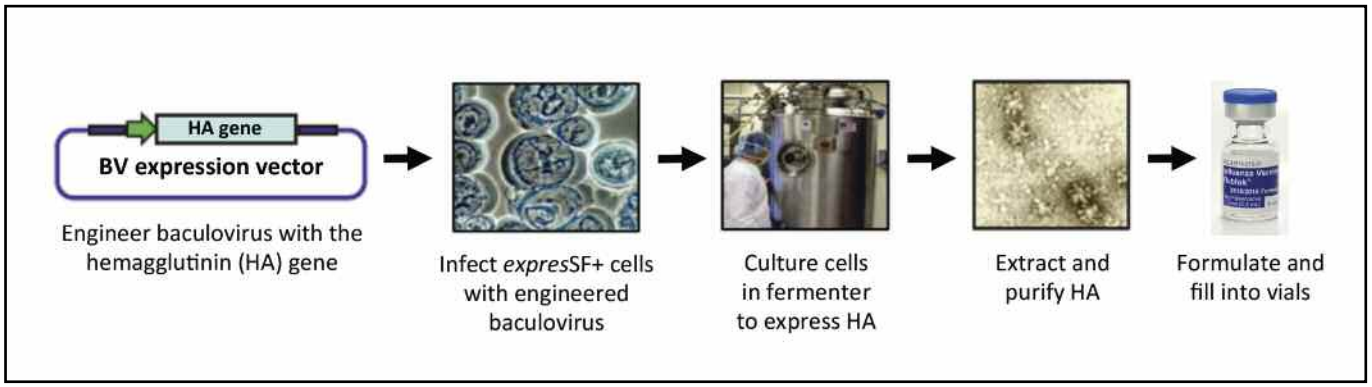
In contrast, Flublok is manufactured without growing influenza virus at all

Figure 3. The Manufacturing Cycle for Egg-Based Quadrivalent Influenza Vaccines



Reprinted from Ampofo WK et al. *Vaccine* 2015 Aug 26;33(36):4368-82.

Figure 4. Gene to Vaccine: Basic Steps in Manufacture of Flublok Quadrivalent



(Figure 4). As a result, there is no risk of introducing mutations of the kind caused by replication of the influenza virus to improve growth in eggs. Influenza viral RNA encoding each of the four full-length HA proteins (from four selected A and B influenza subtypes) is reverse transcribed to produce a cDNA that is cloned into a baculovirus expression vector. The recombinant baculovirus vector is then combined with host insect cells in large-scale bioreactors. The baculovirus-infected cells are then cultured, harvested and HA antigens are extracted, purified, blended together and filled into single-dose prefilled syringes.[9] A licensed human papillomavirus vaccine (Cervarix; GSK) is manufactured using a very similar baculovirus expression system.

From receipt of HA genetic sequences from WHO-selected and FDA-approved vaccine virus strains, large-scale production of Flublok can be completed in about eight weeks — several months faster than egg-based IIV production. It is for this reason that development of Flublok has received critical support from the U.S. government's Biomedical Advanced Research and Development Authority (BARDA), which strongly values the ability of this manufacturing strategy to expedite production and distribution of vaccine in the event of a severe flu pandemic.**

Currently, WHO Collaborating Centers convene in February to analyze data from as many as 200,000 respiratory specimens supplied by NICs in more than 90 countries between the preceding September and January to select from some 5,000 unique viral strains thought most likely to be predominantly circulating when the flu season starts eight months later.[10] Very shortly thereafter, FDA makes its final strain selections that are used in vaccine development by all manufacturers — including Protein Sciences.

But the short Flublok manufacturing cycle raises an intriguing "what if" scenario with a potential payoff in improved and more consistent year-to-year flu vaccine effectiveness:

*Could WHO Collaborating Centers conduct a supplemental analysis of viral isolates collected several months closer to the start of flu season — perhaps as late as May or June — to select candidate strains specifically for Flublok vaccine production with potentially closer match to strains that later emerge to become epidemic?****

It seems reasonable to expect that A and B flu strains selected from viral isolates that have propagated and genetically drifted for several months after WHO-selected strains in February are apt to be a better match to circulating strains that ultimately account for the fall/winter seasonal flu epidemic. Figure 5 presents this concept in graphic form.

Putting Flublok's Differentiating Features to the Test

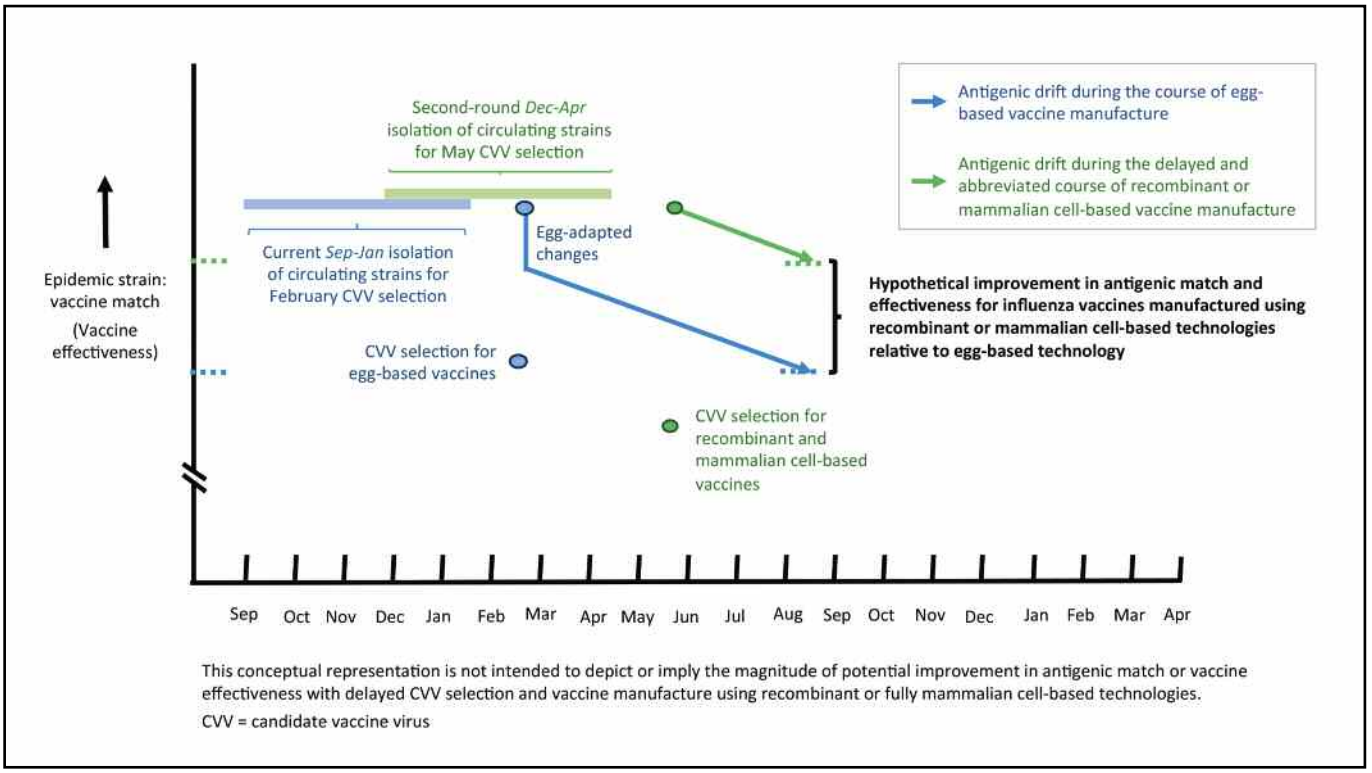
The HA antigens in Flublok are not subject to reassortment-related mutations that can occur when selected vaccine strains are subjected to egg adaptation. Reduced HA glycosylation peculiar to expression in insect cells could translate into improved effectiveness through induction of neutralizing antibody to the protein's more exposed stalk region. Flublok Quadrivalent is formulated with three times the quantity of each of the four HA antigens as standard IIV4s to optimize its immunogenicity.

Could Flublok — manufactured from the same selected vaccine viruses as egg-based vaccines or more ideally prepared using less antigenically drifted flu strains selected months later in a second round

** *BARDA has also supported development of Flucelvax (Seqirus), an influenza vaccine that grows whole virus in mammalian (MDCK) cells rather than eggs. Similar to Flublok, the Flucelvax manufacturing cycle is much shorter than for egg-based flu vaccines.*

*** *This supplemental vaccine virus strain selection process could apply as well to Seqirus' Flucelvax, which also features a much shorter production cycle than egg-based vaccines.*

Figure 5. Hypothetical Improved Recombinant and Mammalian Cell Influenza Vaccine Effectiveness Associated with Delayed Selection of Vaccine Virus Strains and Elimination of Genetic Reassortment Required for Egg-Based Viral Culture



— be more effective than egg-based vaccines in reducing seasonal influenza attack rates and flu-related complications? Of course there is a way to find out: well-designed head-to-head clinical trials in elderly, nonelderly and immunocompromised adults over multiple flu seasons, variously evaluating Flublok against standard-dose, high-dose and adjuvanted IIVs.

Large-scale influenza vaccine efficacy trials of this nature are notoriously expensive to conduct, and positive outcomes are certainly not assured. But far higher are the yearly costs in influenza-related illness, lost work days, hospitalizations and deaths for the continued failure of currently licensed vaccines to more fully protect the American public from seasonal influenza.

No manufacturer is more intimately familiar with the limitations of today's flu vaccines than vaccines giant Sanofi Pasteur, which agreed to acquire Protein Sciences in July. "As part of Sanofi Pasteur, we expect our Flublok influenza vaccine to benefit from [its] expertise in the field of influenza vaccines," said Protein Sciences president and CEO Manon M.J. Cox, who led development of the product. Given Sanofi Pasteur's resources and its demonstrated commitment to influenza vaccines research, the future for this first-ever recombinant influenza vaccine — and potentially millions of people who continue to be at risk for flu-related complications — is promising indeed. ❖

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Since being diagnosed with multiple conditions, Jamie Stewart has continued-care telemedicine visits with his doctor every six months to avoid a 400-mile round-trip drive to his doctor's office.

Telemedicine:
A Patient's Perspective

By Trudie Mitschang

AT A TIME when convenience is a leading motivator in consumer decisions, telemedicine has evolved as one of the fastest-growing trends in the healthcare industry. The concept offers round-the-clock physician access via phone or video consultation, and even includes access to prescription medications. Telemedicine is often touted for eliminating the waiting room experience and improving access to care for those who live in remote or rural areas. According to a 2015 report by market intelligence firm Tractica, telemedicine video visits are expected to soar from 19.7 million visits in 2014 to 158.4 million visits annually in 2020.[1]

For Jamie Stewart, telemedicine has helped manage a number of chronic conditions without the added stress of a long commute for doctor visits. Stewart's diagnoses include chronic inflammatory demyelinating polyneuropathy (CIDP), small fiber neuropathy and secondary adrenal insufficiency. He is currently retired due to his medical conditions, and he accesses his physician via telemedicine twice a year.

Q. What technology or device do you use to connect with your doctor?

A. My telemedicine is through the Department of Veterans Affairs (VA). Its telemedicine system offers access through a secure software program. The system allows me to actually see my doctor on my computer screen, and I feel like I am seated in her exam room. I have never experienced any type of malfunction.

Q. When did you first use telemedicine?

A. My first experience was in 2013. As someone who lives 400 miles round trip from my VA neurologist, telemedicine allows me to see my doctor without having to spend an entire day driving.

Q. What were you seen/treated for?

A. Telemedicine is often utilized for continued care of CIDP. The agreement my doctor and I have is that as long as things remain stable, I can continue to utilize telemedicine. We both are aware if things change that I could be required to be examined in person. I have a telemedicine session at least once every six months.

Q. For patients with concerns about telemedicine, what advice would you offer?

A. There are a few considerations concerning the use of telemedicine. First is security. For instance, what technology is being utilized, and is this technology secure? I would suggest patients ask providers for as much information as possible so they can research and determine if the software/hardware being used is, in fact, secure.

The second consideration is more practical and has to do with hearing clearly during medical visits. Patients need to make sure the speakers and microphone they're using are of good quality and provide enough volume and clarity so they can understand their doctor and their doctor can understand them. Visually, they want to make sure the camera and monitor allow them to see one another clearly. Video resolution should allow them to "show" something, if necessary, to their doctor. The only other consideration is the network connection if using a computer. A high-speed Internet connection is key to ensuring a satisfactory telemedicine experience. Without a high-speed connection, there could be instances of buffering, lags, jitters or disconnections.

Q. How long are most of your telemedicine visits?

A. Since a telemedicine session is essentially an office visit, time is critical. Anything that can cause delays will make for a poor experience. My provider allows for possible complications due to technology. My session is always scheduled for 30 minutes versus the normal office visit, which is typically 20 minutes.

Q. How does telemedicine work with your health insurance?

A. I have only used telemedicine through the VA, so I am unaware if my health insurance company would have issues with a provider using this technology.

Q. Do you think this method of seeing patients is as effective as in-person visits?

A. I feel a telemedicine session is a great use of time and resources when the appointment is a follow-up or does not require the provider to employ touch diagnostics to diagnose. Since my appointments are to discuss any changes in my chronic condition, my provider doesn't need to employ touch diagnostics. But, both provider and patient need to be aware of any technology limitations, and they need to embrace it. Patience and understanding are essential. ❖

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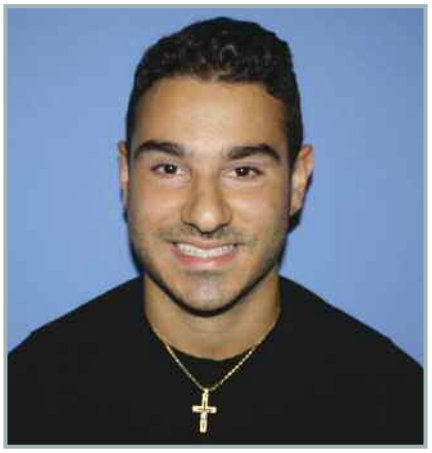


Telemedicine:
A Corporate Perspective

JEFFERY KHOURY is the CEO of Doctor Pocket, an iOS and Android app that connects users to a network of medical specialists from Harvard, Yale, Johns Hopkins and McGill. The app lets individuals select a specialist of their choice and meet in a virtual consult through an instant messaging platform. For a fee set by the specialist, users can get their medical questions answered without a time limit on the consultation. Named IBM Global Entrepreneur competition winner for 2017, Khoury launched the app last year while he was a first-year finance student at John Molson School of Business at Concordia University in Montreal.

BSTQ: Tell us about your inspiration for Doctor Pocket.

JK: The idea came to me when I was traveling abroad. I got sick multiple times and would visit a local doctor, and the experience was not what I was used to at all. I didn't have comfort or the peace of mind that I would have whenever I left a doctor's clinic back in Montreal. And, since half of my family is in the medical field, I would always message my cousin for medical advice. I would send him voice messages and pictures, and say: "Listen, this is what is wrong with me. I went to see the doctor and he gave me this and this. I'm still not feeling better. What should I do?" This was a recurring scenario, so I decided to analyze the telemedicine market to see whether there was any need for a service like Doctor Pocket. That's when I found our major competitor and realized that they had a great idea but they had missed the mark on many things. For example, they didn't treat their users as actual patients, and their users weren't allowed to pick their doctor, features I feel are important for a telemedicine app. Doctor Pocket will allow anybody with a smartphone to choose a neurologist from Harvard and have a consult with no time limit. Instead of selling a service, our team is focused on providing a solution. Then, and only then, will they end the consultation.

> **Ultimately, individuals have the convenience of picking whichever doctor they want.**

BSTQ: How does the app work?

JK: Users log into the app, where they can view all of our doctors. They can then search doctors based on their specialty and their availability; you can also search based on location. After choosing a doctor, his or her profile opens to show the image of the doctor and the times he or she is available and a brief description. Ultimately, individuals have the convenience of picking whichever doctor they want, as well as a date and time of their choice. The app offers a global network of medical doctors to any user around the world. These doctors are specialists; there's no other app out there that lets people go in and connect with any doctor on a global scale. We don't want users to come, fill in a form and automatically be linked to a doctor and then be treated as just a number. We really want the user to feel confident using our service.

BSTQ: How can telemedicine benefit the tourist industry?

JK: Since it's a global application, we've been targeting the tourist market, specifically people who are staying in hotels and become ill but don't want to visit a local doctor in whatever region they are in. With the app, they can choose to connect with a doctor they are familiar with from their own city.

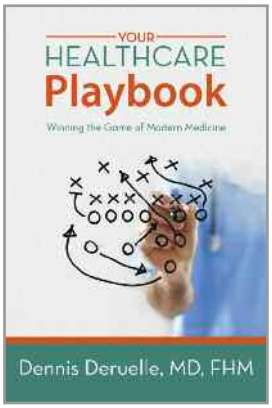
BSTQ: What's next for telemedicine?

JK: The main issue of telemedicine is addressing the physical barrier between patient and doctor. Offering a telemedicine service where the doctor is talking to you from halfway across the world, but everything he or she would need to look at during the exam such as the analytics and vitals is available in real-time during the virtual consultation. Our goal is to integrate medical devices to capture heart rate, blood pressure, body temperature, blood sugar, blood oxygen and customized integrated earphones to hear the heartbeat and lung functions. We are currently in the process of soliciting potential manufacturers for the integration of all these metrics. That is where the future of telemedicine is headed. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Your Healthcare Playbook: Winning the Game of Modern Medicine

Author: Dennis Deruelle, MD, FHM



With more than 20 years in practice, Dr. Deruelle authored this book as a nonpartisan explanation of healthcare policy to help patients navigate their way through the "confusing mess of paperwork, decisions and insurance." According to him, teams are the future of healthcare. Many of the new changes are similar to the best practices of the National Football League (NFL), which he considers the "Rosetta Stone that could help people translate and eventually win the game of medicine." Dr. Deruelle uses the NFL to break down the information about healthcare so it's easy to understand. Included are insights from key members of the NFL, as well as some of the foremost doctors and safety experts.

www.simonandschuster.com/books/Your-Healthcare-Playbook/Dennis-Deruelle/9781682612422

Clinical Research Manual, 2017 Edition

Author: U.S. Food and Drug Administration

This manual provides guidance on everything from pharmacokinetics and study design to recruitment, monitoring and statistics to ensure clinical trials stand up to regulatory scrutiny. Focusing on the U.S., Europe and Asian markets, it has been completely updated to make it the most current and comprehensive resource available. The updated version includes six new chapters: 1) Dosage Form Design, 2) Clinical Trials Organization, 3) Product Registration in the U.K. and Europe, 4) Clinical Trials of Medicines in Children, 5) Clinical Trials of Medicines in the Elderly and 6) Using Patient-Reported Outcomes as Tools for Clinical Practice.

www.fdanews.com/products/54130

Zika Virus Resources

Author: California Department of Public Health (CDPH)

The CDPH has published new and revised Zika virus resources for physicians on its website. The resources include 1) a CDPH Zika screening algorithm; 2) CDPH Zika virus information for healthcare providers; 3) Zika virus exposure patient self-assessment, English and Spanish; 4) evaluation and follow-up procedures for suspected congenital Zika virus infection — fetus, newborn and infant; 5) risk-based testing for local Zika virus transmission; and 6) patient educational materials. In addition to these California-specific materials, CDPH is highlighting a Centers for Disease Control and Prevention program called Zika Care Connect (ZCC), a new resource being developed by the agency in collaboration with March of Dimes. ZCC establishes a network (searchable online) of specialized healthcare providers who can care for patients and families affected by the Zika virus.

www.cdph.ca.gov/Programs/CID/DCDC/Pages/Zika.aspx

Code of Federal Regulations: Food and Drugs

Author: U.S. Food and Drug Administration

The Nine-Volume Title 21 CFR (Code of Federal Regulations) Set for 2017 has been updated through April 1, 2017. The latest additions and revisions govern food and drugs used in humans and animals, biologics, cosmetics, medical devices, radiological health and controlled substances.

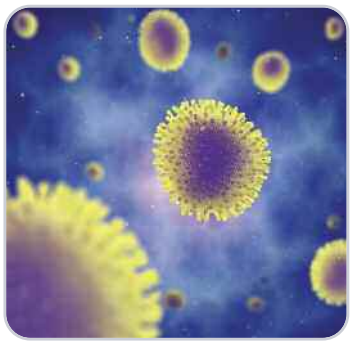
www.fdanews.com/products/54195

IVIG Highly Protective in Ferrets After Challenge with Severe Pandemic pH1N1 and Avian H5N1 Influenza Strains

Australian investigators tested the ability of intravenous immune globulin (IVIG) to protect against potential pandemic influenza virus in outbred ferrets, which are naturally susceptible to human influenza viruses and considered a relevant small animal model of human influenza infection. Two hours prior to intranasal challenge with the 2009 wildtype pH1N1 pandemic influenza virus, animals were administered IVIG prepared from donor plasma. A negative control group was given diluent only, and a positive control group was given homologous (pH1N1) hyperimmune serum by the intraperitoneal route. All animals were euthanized, and virus content was titrated from homogenates taken from 10 different lung sites.

Compared to diluent control animals, there was a marked reduction in the number of sampled lung sites containing pH1N1 virus in ferrets that were administered either IVIG or pH1N1 hyperimmune serum, indicating that IVIG acted to prevent deep lung viral replication.

In a separate ferret study, IVIG was intraperitoneally administered in varying doses, or a similar volume of diluent as a control, to ferrets at the time of challenge with the wild-type avian H5N1 influenza virus strain. Reactivity of IVIG (Privigen) against this lethal influenza strain in a standard hemagglutinin inhibition assay was found to be below detection limits. Nevertheless, while all eight diluent control animals not receiving IVIG succumbed to H5N1 infection, only one of seven animals given the highest IVIG dose (0.5 g/kg) succumbed to infection. Three of four ferrets that received 0.25 g/kg of IVIG survived lethal H5N1 challenge with little or no impact on activity. In the 0.125 g/kg treated group, two of the four animals survived.



To investigate the mechanism by which IVIG conferred protection against lethal H5N1 challenge, F(ab′)2 or Fc fragments derived from IVIG (equimolar to 0.5 g/kg) were administered at the time of challenge with H5N1. Overall, eight out of 10 (80%) of the F(ab′)2-treated animals survived, significantly greater than the Fc-treated and diluent control groups with only three out of 18 (17%) and one out of 10 (10%) survivors respectively. "Our data suggest that following exposure through either vaccination or infection, a level of endogenous antibody cross reactivity to highly pathogen influenza strains occurs in the community … these studies in the ferret model suggest that human IVIG may be effective in preventing serious influenza infection and provides a possible alternative treatment option requiring confirmation in human clinical trials," the authors concluded.

Rockman S, Lowther S, Camuglia S, et al. Intravenous immunoglobulin protects against severe pandemic influenza infection. EBioMedicine *2017 May;19:119-27.*

Co-Administration of Albumin with Lactulose Reverses Hepatic Encephalopathy and Reduces Mortality in Liver Cirrhosis

A multidisciplinary team of investigators based in New Delhi randomized 120 patients with liver cirrhosis and overt hepatic encephalopathy (HE) to receive oral lactulose therapy (to reduce high blood ammonia levels that are the proximate cause of HE) or oral lactulose plus 1.5 g/kg/day of human albumin, until either complete recovery of HE or a maximum of 10 days. The primary study endpoint was complete reversal of HE; secondary endpoints included mortality and length of hospital stay.

Forty-five of 60 patients (75%) who received albumin therapy experienced complete reversal of HE, compared to 32 of 60 patients (53.3%) who received lactulose therapy alone (P = 0.03). Mortality was also significantly lower in the lactulose plus albumin group: 11 deaths (18.3%) versus 19 deaths (31.6%) in the lactulose-only group. Additionally, the mean hospital stay for patients receiving concomitant albumin therapy was more than two days shorter than for patients receiving lactulose only: 6.4 ± 3.4 versus 8.6 ± 4.3 days (P = 0.01). "The combination of lactulose plus albumin is more effective than lactulose alone for treatment of overt hepatic encephalopathy in patients with cirrhosis," the investigators concluded.

Sharma BC, Singh J, Srivastava S, et al. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. J Gastroenterol Hepatol *2017 Jun;32(6):1234-9.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective Oct. 1, 2017, through Dec. 31, 2017

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$68.56	$67.46
IVIG	FLEBOGAMMA	Grifols	J1572	$59.67	$58.71
IVIG	GAMMAGARD SD	Shire	J1566	$68.56	$67.46
IVIG	GAMMAPLEX	BPL	J1557	$82.16	$80.84
IVIG	OCTAGAM	Octapharma	J1568	$73.24	$72.06
IVIG	PRIVIGEN	CSL Behring	J1459	$77.01	$75.78
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$79.57	$78.29
IVIG/SCIG	GAMMAKED	Kedrion	J1561	$77.89	$76.64
IVIG/SCIG	GAMUNEX-C	Grifols	J1561	$77.89	$76.64
SCIG	CUVITRU	Shire	J3490 / J3590 / J7799	**	**
SCIG	HIZENTRA	CSL Behring	J1559	$98.13	$96.56
SCIG	HYQVIA	Shire	J1575	$131.36	$129.25

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

** CUVITRU does not yet have Medicare rates.

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	CARIMUNE NF Lyophilized	CSL Behring	PI, ITP	6 g, 12 g
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g, 10 g, 20 g
IVIG	FLEBOGAMMA 10% DIF Liquid	Grifols	PI	5 g, 10 g, 20 g
IVIG	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Shire	PI, ITP, B-cell CLL, KD	5 g, 10 g
IVIG	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g
IVIG	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g
IVIG	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Shire	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
IVIG/SCIG	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 5 g, 10 g, 20 g
			SCIG: PI	
IVIG/SCIG	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUVITRU Liquid, 20%	Shire	PI	1 g, 2 g, 4 g, 8 g
SCIG	HIZENTRA Liquid, 20%	CSL Behring	PI	1 g, 2 g, 4 g, 10 g
SCIG	HYQVIA Liquid, 10%	Shire	PI	2.5 g, 5 g, 10 g, 20 g, 30 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease

2017–2018 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
AFLURIA (IIV3)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older*	90656
AFLURIA (IIV3)	SEQIRUS	5 mL MDV	5 years and older*	90658/ Q2035
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUVIRIN (IIV3)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90656
FLUVIRIN (IIV3)	SEQIRUS	5 mL MDV	4 years and older	90658/ Q2037
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	18 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	18 years and older	90688
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	3 years and older	90686
FLUBLOK (ccIIV4)	PROTEIN SCIENCES	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	Q2039/90756***
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST** (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE INTRADERMAL (IIV4)	SANOFI PASTEUR	0.1 mL prefilled microinjection 10-BX	18-64 years	90630
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine.

Afluria may be used in persons aged ≥9 years.

** For the Advisory Committee on Immunization Practices' latest intranasal influenza vaccine recommendations, please visit www.cdc.gov/vaccines/acip/index.html.

*** Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

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