Fall 2014

BioSupply Trends

Special Focus: INNOVATION

Quarterly

21ST CENTURY MEDICINE

PIONEERING CUTTING-EDGE THERAPIES

Personalized Medicine: The End of "One-Size-Fits-All"

Regenerative Medicine: Harnessing the Power of the Body

The Emerging Age of Telemedicine

Can Alzheimer's Disease Be Stopped?

Myths & Facts: von Willebrand Disease

A Leap Forward in Long-Acting Factor Concentrates — Page 48

Flublok®

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Pure Safe Effective, by design

ACIP recommended for those with egg allergies

Approval in 50+ expected this Fall

100% egg-free

No influenza virus

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Protein Sciences CORPORATION

CPT Code 90673

Flublok (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok safely and effectively. See full prescribing information for Flublok available at www.Flublok.com.

INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

DOSAGE AND ADMINISTRATION

A single 0.5 mL dose for intramuscular injection.

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5mL single dose vials.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks.

ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (>37%); the most common (≥10%) solicited systemic adverse reactions were headache (>15%), fatigue (>15%) and myalgia (>11%).

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older.
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Revised: October 2013

Manufactured by:
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450
(203)686-0800 • www.proteinsciences.com

FB13017-2

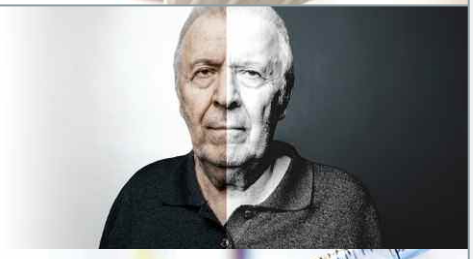
www.Flublok.com

BioSupply Trends Quarterly

Fall 2014

Features

Special Focus: Vaccines



Up Front

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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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Healthcare Solutions: Peering Into the Future

MEDICINE IS ABLE to do more for the human body today than at any other time in history. Treatments that were once thought to be at the forefront of innovation are now looked back on as shocking and, oftentimes, barbaric. Consider, for instance, how mental illness was once treated with electroshock therapy that caused violent seizures and brain damage, bullet removal had a 71 percent chance of death, and the common cold was treated with bloodletting leeches, scarificators and carbolic smoke balls. Now, as we peer into the not-too-distant future, is it possible that some of the treatments that seem so innovative today will also be looked back upon as unsophisticated?

In this annual innovation-themed issue of *BioSupply Trends Quarterly*, we look at medicine and medical technology that are advancing at an impressive rate to prevent, treat and cure disease from all angles — showing promise to vastly improve medical care for patients and save billions of dollars in healthcare costs.

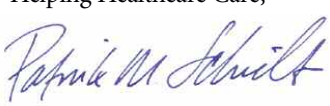
Personalized medicine is being hailed as the end of the "one-size-fits-all" approach to medical care. In our article "21st Century Medicine: Now It's Personal," we discuss customized, patient-tailored therapy approaches that will help to "identify the right drug for the right patient at the right time." These approaches include predictive tests to determine if a patient might be at high risk of disease onset to allow him/her to take measures to prevent the disease and even reverse it before it has progressed, as well as biomarker-based diagnostic tools and pharmacogenomics to determine if a patient will respond to a drug or experience side effects. In some instances, it may be possible to tailor the treatment to eliminate undesirable outcomes. Personalized medicine hopes to revolutionize the way medicine is practiced by eliminating cookie-cutter treatments, potentially a win-win for patients and practitioners.

With the electronic age in full swing, enter "The Age of Telemedicine." In this article, we explore the growing trends of doctor-patient televisits in which patients meet with doctors via videoconferencing from the comfort of their homes, telepresence robots in hospitals that help doctors who remotely care for patients, surgeons who perform minimally invasive robotic-assisted surgeries such as laparoscopic hysterectomies from afar, and nursebots that assist patients with everyday tasks. Spurred by the threat of a declining number of physicians in an era when the numbers of patients are increasing, televisits and telesurgeries are the norm today, with televisits predicted to top 1.8 million by 2017 and telesurgeries being performed across state lines and even internationally.

Perhaps one of the most innovative areas in the spotlight today is regenerative medicine, widely hailed as the future of medicine. In our article "Regenerative Medicine: Are We There?" scientists report discovering that rather than replacing tissue and organs, they can regrow them using the patients' existing organs and synthetic materials. Regenerative medicine, which relies on the use of stem cells, is being practiced today with "spray-on" skin, the regrowth of cartilage and muscle, and the first human implants of organs grown in the laboratory, including bladders and a bio-engineered windpipe. But, scientists are merely on the cusp of harnessing the power of the body to heal itself, and it is hoped that regenerative medicine will one day eliminate the need for organ donor transplant lists.

In this and every issue of *BioSupply Trends Quarterly*, we continue to provide you with updates on progressive medical practices and breakthrough technologies. As always, we hope you enjoy this issue and find the content educational. We welcome your comments.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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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ACA Insurance Subsidies Struck Down by D.C. Appeals Court

A federal appeals court has struck down subsidies provided under the Affordable Care Act (ACA) for federally run insurance exchanges. According to the three-judge panel, the law forbids income-tax subsidies for low- and middle-income Americans who use one of the federally run insurance exchanges based on a 2012 interpretation of the law by the Internal Revenue Service (IRS). If upheld, it could end insurance subsidies in as many as 36 states. However, the Justice Department will file for an en banc review of the decision either to the D.C. Circuit Court or directly to the Supreme Court, which will trigger an automatic stay because the ruling cannot have legal force until after the full panel of the Circuit Court has a chance to reconsider the case.

The text of the ACA says the sliding-scale tax credits are only available for coverage purchased "through an exchange established by the state," which only 16 states have established. IRS officials claim that the imprecise wording of the law contradicted Congress' overall intent to expand insurance coverage as widely as possible. But, the IRS argument did not sway the appeals court. "Because we conclude that the ACA unambiguously restricts the section 36B subsidy to insurance purchased on exchanges 'established by the state,' we reverse the district court and vacate the IRS regulation," the two-member majority wrote.

Nearly seven million people used the exchanges to buy coverage in 2014, and more than 80 percent of them qualified for a tax credit that averaged about $2,900 per enrollee. According to legal experts, the high court will rule in the matter in the spring of 2015. ❖

Round Two Recipients Chosen for Health Care Innovation Awards

Thirty-nine recipients from 27 states and the District of Columbia have been chosen by the Department of Health and Human Services to receive Health Care Innovation Awards that total as much as $360 million to test care models designed to deliver better healthcare and lower costs. The prospective (not yet final) awards range from an expected $2 million to $23.8 million over a three-year period.

The awards are made possible by the Affordable Care Act and are for round two of the Health Care Innovation Awards program. This round will include five awards focusing on improving emergency care; ten awards focusing on improving care for children; four awards focusing on promoting prevention and improving management of cardiovascular disease; seven awards focusing on promoting better rural care coordination and telehealth; seven awards focusing on improving care for frail elderly patients or providing support for aging in the community; and two awards focusing on promoting better care for persons living with HIV/AIDS.

In 2012, 107 organizations located in urban and rural areas, all 50 states, the District of Columbia and Puerto Rico received awards through round one of the initiative. The second round differs from the first round because the Centers for Medicare and Medicaid Services specifically sought innovations in four areas: rapidly reducing costs for patients in outpatient hospital and post-acute settings; improving care for populations with specialized needs; testing improved financial and clinical models for specific types of providers; and linking clinical care delivery to preventive and population health.

More information about the Health Care Innovation Awards program can be found at innovation.cms.gov/initiatives/Health-Care-Innovation-Awards/Round-2.html. ❖

CMS Proposed Rule Will Extend EHR Incentive Program

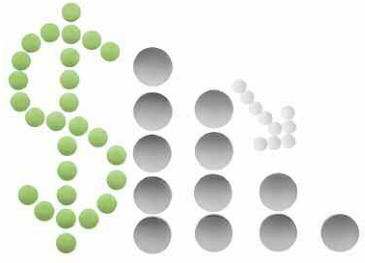
Under a proposed rule by the Centers for Medicare and Medicaid Services (CMS), healthcare providers will have an extra year to use 2011 edition software in their electronic health record systems under the federal incentive program for health IT. This will provide hospitals, physicians and other eligible professionals trying to meet the program's stage 1 meaningful-use criteria more flexibility.

CMS and the Office of the National Coordination for Health Information Technology cited the slow delivery and implementation of the upgraded 2014 edition software as the reason for the delay. "Through letters to CMS, public forums, listening sessions and public comment at CMS meetings, many provider associations have expressed concern that, although 2014 edition (technology) may be available for adoption, there is a backlog of many months for the updated version to be installed and implemented so that providers can successfully attest for 2014," the rule writers said. "We also understand that the delay in availability may limit a provider's ability to fully implement 2014 edition (technology) across the facility." ❖

Lower Medicare Spending Means Enhanced Financial Future

According to the 2014 annual report from the Medicare program's boards of trustees, a substantial decrease in Medicare spending as a result of improvements made by the Affordable Care Act (ACA) will result in the Medicare Trust Fund lasting until 2030, as well as no increase in projected Part B premiums for 2015. The ACA improvements include changes to promote value-based payments, reduce waste and fraud and strengthen the program's benefits, which have reduced hospital spending on preventable readmissions, helping to lower hospital costs — a significant portion of trust fund spending.

The per capita growth rate for Medicare spending over the 2009 through 2012 period was just one-third of its rate over the 2000 through 2008 period, falling from 6.3 percent per person to 2 percent per person. In 2013, that rate fell to nearly zero, and so far in fiscal year 2014, growth in per person Medicare spending is at or below zero. The dramatic decline in spending has generated $116 billion in savings over the four years from 2009 to 2012.



In 2009, the trustees projected the trust fund would not be able to pay its bills in 2017. But, it will now last an additional 13 years, until 2030. The actuarial imbalance, which measures the gap between the trust fund's income and expenditures over the next 75 years, is just 0.87 percent of taxable payroll, down by more than 75 percent since 2009, before the passage of the ACA.

And, lower Medicare spending means lower cost sharing and lower premiums for Medicare beneficiaries. For the second year in a row, Medicare Part B premiums are projected to stay the same in 2015 as in 2013 and 2014. This means seniors are expected to keep more of their annual Social Security cost-of-living adjustment. ❖

HHS to Enforce Orphan Exclusion Rule for 340B Drug Discounts

The Department of Health and Human Services (HHS) will allow certain hospitals to receive discounts on orphan drugs when they are used for non-orphan conditions, despite a ruling by the U.S. District Court for the District of Columbia that HHS did not have the authority to do so. In June, HHS said in a court filing that it planned to either appeal the federal ruling or issue guidance that would replace the rule and continue to require drugmakers to provide the discounts.

The rule applies to four types of hospitals that participate in the 340B drug program, which gives discounts on covered outpatient drugs to healthcare providers that serve large numbers of low-income or indigent patients. The Health Resources and Services Administration, the HHS agency that administers the 340B program, urged providers and manufacturers to "attempt to work out any issues in good faith" prior to the start of the new quarter July 1. Manufacturers that do not comply may be required to refund covered hospitals or have agreements terminated.

Providers in the 340B program do not have access to discounts on orphan drugs when used to treat designated orphan diseases or conditions — those that affect fewer than 200,000 people in the U.S. Orphan drugs are some of the costliest drugs on the market, and many have multiple indications, including some for orphan diseases or conditions and others for common issues that affect a broader number of patients. ❖

Specialty Pharmacies and Delivery Models

The words "specialty pharmacy" can incite a range of emotions and opinions among healthcare practitioners. The specialty medications these pharmacies provide are expected to continue to be the biggest driver of branded drug spending. (This will also be true of biosimilars once they reach the U.S. market.) A recent report by the IMS Institute for Healthcare Informatics, titled *Medicine Use and Shifting Costs of Healthcare*, notes that specialty drugs represented 29 percent of spending on medicines in 2013 (up from 23 percent in 2008), averaged 10 percent growth in the last five years and grew by 9 percent in 2013. In addition, spending on biologics rose 9.6 percent in 2013, representing 28 percent of the total, which was up from 21 percent in 2008. Specialty therapies play a very important role in oncology, asthma, chronic obstructive pulmonary disease, cystic fibrosis, HIV, other viral diseases including hepatitis C, rheumatoid arthritis, and conditions treated with immunostimulants, immunosuppressants and interferons. Although these chronic conditions can sometimes be treated with oral or self-administered specialty medications, some of these products are injectable and need to be administered in infusion centers.

Shifting Benefit Design

Specialty medicines are currently paid for under Medicare Parts B and D.

Part B drugs are tied to physician services and fall under the medical benefit. They're usually injectables furnished incidental to a physician's service and not usually self-administered. Part D drugs generally are prescription drugs prescribed and dispensed for self-administration, but they also include biological products; insulin and medical supplies associated with insulin injection; and certain vaccines not covered under Medicare Parts A or B.

A growing trend is to move expensive specialty drugs out of the medical benefit and into the drug benefit. The next steps often are to move these into new payment tiers and place them under the control of specialty pharmacies.

What Is a Specialty Pharmacy?

A specialty pharmacy is a pharmacy service model that provides patient-focused care to optimize outcomes of specialty drugs for chronic and low-incidence medical conditions. It integrates medication management and clinical and fulfillment functions with disease management principles and practices. And, it provides a framework to manage medication necessity, efficacy, cost and the pipeline. Proponents say a specialty pharmacy is designed to help ensure appropriate medication use, help avoid unwarranted drug expenditure and optimize adherence to medication therapy.

Medicare Part D defines "specialty" as any drug with a negotiated monthly price of $600 or more, whereas the Academy of Managed Care Pharmacy defines it using a commercial payer's threshold of $1,200 per month or more. Typically, specialty biologic- or biotech-based formulations that may require additional supervision, monitoring and handling are those that are oral, injectable, infused or inhaled. These products can be administered at home, in a physician office, infusion center or outpatient hospital area.

In addition to the high cost of specialty pharmaceutical products, the delivery model — the way the drugs are handled, acquired and distributed — as well as the restrictions being placed on them by payers, often differs from the traditional model. The traditional model, which is the normal open-distribution model, allows product to be available from regular/routine drug wholesalers with wide distribution. The manufacturer bears the cost of increased inventory, outdated merchandise, frequent returns and special packaging, shipping or storage. But, with the restricted drug distribution system (RDDS) model by which specialty drugs are often delivered, the costs of inventory are reduced, and outdated merchandise and frequent returns are eliminated. In addition, specialty pharmacies provide special packaging, shipping and storage to preserve and deliver these delicate medicines in high-tech, cold-chain and just-in-time delivery systems.

The healthcare setting is a complex environment in which patients are being seen and treated in a multiplicity of outpatient clinics and treatment sites — all designed to keep the patient ambulatory and to avoid hospitalization unless absolutely necessary. That has spurred the growth of the specialty pharmacy industry, which is governed by the same regulations as distributors that follow the traditional delivery model. The specialty pharmacy industry has created an entirely new dimension in the procurement and distribution of specialty pharmaceuticals whose costs are staggering compared with traditional medications used at home. The RDDS model, with its potential for better therapy efficacy, safety and convenience of administration, justifies the extra distribution cost of specialty medicines that often present logistical and financial challenges to the healthcare facility or practice that struggles with issues of patient safety, institutional liability and reimbursement.

Making It Work

Moving to a new healthcare delivery model has accelerated the need for change, cooperation and coordination between sites of care. So, what are some options to help practitioners and pharmacists manage this change? White or brown bagging.

White bagging is the practice of having patient-specific medications or supplies delivered directly to the practice setting. That setting may be an outpatient infusion center, a physician's office or a hospital, but the common link is that the drug is intended for use by a specific patient and must be stored and used only for that patient. Discontinued medications are not returnable, cannot be used for another patient and must be destroyed at the expense of the site. As the medications may be prepaid or complimentary, no billing for these products/supplies transpires. However, billing for the clinic visit where the drugs are administered and for the drug administration itself still brings income to the facility or practice site. Brown bagging is essentially the same as white bagging with the exception of the delivery location. Medications are delivered to the patient's home, and the patient brings the medication with him or her to the appointment for administration.

For white bagging, the Centers for Medicare and Medicaid Services (CMS) has specific requirements for how this transpires. Thus, following the guidelines determined by the Medicare administrative contractor or fiscal intermediary is essential. Basically, the drug is billed at a zero charge to indicate that it was given; this, then, allows the drug administration fee to be processed. Maximum payments depend on the reimbursement team understanding the nuances of proper coding for these drugs. One key point to remember: Common procedural terminology (CPT) codes are used to describe and bill for services/tasks performed, while Healthcare Common Procedure Coding System codes are used to describe and bill for drugs and other items. There are no fewer than 40 CPT codes that are used to bill for drug administration. Some are specific to the type of drug administered, with more complex administrations receiving considerably higher reimbursement. Both private payers and Medicare reimburse for drug administration using these codes. Therefore, it's important to look at the CPT definition of drug administration, which includes the use of local anesthesia; starting the IV; access to IV, catheter or port; routine tubing, syringe and supplies; preparation of the drug; flushing catheters at completion; and hydration fluid.

In the case of brown bagging, CMS is not as clear. CMS acknowledges that medical societies are opposed to brown bagging and "continues to urge them to reinforce this message with their members."[1] Part D plan sponsors may contractually specify medications are only covered when administered in the home setting. Billing for administration of medications provided under brown bagging would follow the same approach as white bagging.

Changing Perceptions

Perhaps the most difficult part of implementing a white-bagging or brown-bagging program for specialty pharmaceuticals at a facility is to understand how well and easily this process works. A facility or practice can generate revenue by handling these drugs, and concerns about product integrity and storage can be allayed by understanding the process. White-bag medications are sent directly from the specialty pharmacy to the hospital or other practice site, and the drugs are sent in their original packaging with appropriate shipping, packaging and usually insurance due to their high cost. This is similar to patient-assistance drugs or routine wholesaler shipments; the drugs do not go to the patient. Brown-bag medications are delivered to the patient and may or may not be in their original packaging. Concerns about product storage are significantly different than with white bagging, but can be overcome by working with specialty pharmacies accredited by The Joint Commission, Accreditation Commission for Health Care, Community Health Accreditation Program or Utilization Review Accreditation, which require validation of delivery processes.

With today's evolving healthcare delivery models, healthcare providers should develop an organized, careful multidisciplinary approach that supports the use of pre-paid or complimentary specialty medications. To achieve success, they should comprehensively assess how these models work with their practice, and ensure staff understand the billing methodology. ❖

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.*

Reference

1. Medicare Prescription Drug Benefit Manual. Chapter 6 – Part D Drugs and Formulary Requirements – Appendix C Medicare Part B versus Part D Coverage Issues.

Ask Our Experts

Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.

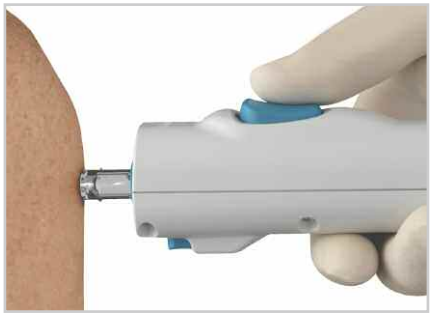
Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

New Technology

FDA Approves Needle-Free Injector for Afluria Flu Vaccine

The U.S. Food and Drug Administration (FDA) has approved PharmaJet Inc.'s Stratis 0.5mL Needle-Free Jet Injector for delivery of bioCSL Inc.'s AFLURIA influenza vaccine for individuals ages 18 to 64 years. This is the first needle-free delivery system approved by FDA for the administration of an inactivated influenza vaccine. In addition to AFLURIA, the injector is intended to deliver various medications and vaccines either intramuscularly or subcutaneously.

The PharmaJet injector delivers the vaccine by means of a narrow, precise fluid stream that penetrates the skin in about one-tenth of a second. No external power sources are required, and each needle-free syringe is sterile, auto disabling and cannot be reused. According



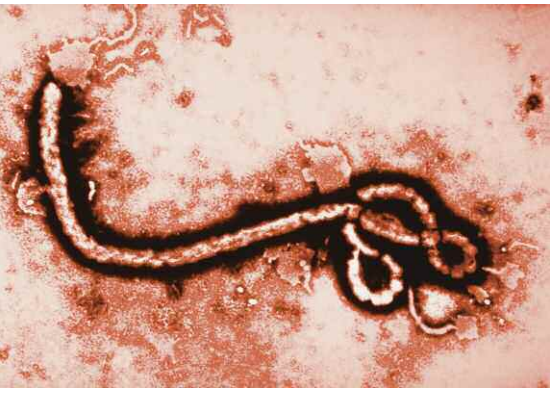
to Pharmajet's website, needle-free technology significantly reduces patient fear and anxiety associated with getting a needle injection. There is an audible click when the vaccine is delivered, and many report a preference for this technology. In a recent study, 89 percent of people receiving a needle-free injection indicated that they would choose the PharmaJet device for their next injection.

Needle-free technology eliminates needlestick injuries to healthcare workers, greatly reduces the need for sharps disposal, and eliminates the possibility of cross-contamination. "The PharmaJet injection technology is an especially important innovation for the millions of individuals who suffer from fear of needles and who consequently forego their annual flu vaccine," says Ron Lowy, PharmaJet CEO and co-chairman. "We believe this is a significant step forward in the effort to improve public health through broader immunization coverage, as well as improved safety of caregivers."

To view the video demonstrating how the injectors works, go to www.pharmajet.com. ❖

Vaccines

Ebola Vaccine to Be Tested in Humans



With the spread of Ebola in West Africa on the rise, a vaccine developed by the National Institutes of Health began testing in humans in a Phase I clinical trial in September. If approved, the vaccine could be ready for use by mid to late 2015. However, even if deemed safe, it may not end the spread of Ebola.

During the trial, scientists will not expose the subjects to Ebola; instead, they will examine the subjects' antibodies as they develop to see if their immune system creates defensive antibodies to fight Ebola the same way primate test subjects did. They also will monitor the subjects' health to ensure the vaccine is safe to use. If the study goes well, a larger study will follow. Yet, despite the outcome of a larger study, the vaccine's effectiveness in protecting people from the virus won't likely be fully known until it's tested in the field such as during an outbreak.

The Ebola virus spreads through bodily secretions, including blood and urine, making it particularly dangerous to those caring for Ebola patients. As of this writing, more than 4,000 people have died from the virus, according to the World Health Organization. ❖

Vaccine Update

bioCSL, formerly CSL Biotherapies, has announced the donation of more than 700,000 doses of its **influenza** vaccine to the Partnership for Influenza Vaccine Introduction, an innovative program — spearheaded by the U.S. Centers for Disease Control and Prevention and the Task Force for Global Health — that helps low- and middle-income countries reduce annual morbidity and mortality from influenza. The program helps eligible countries create or expand public vaccination program infrastructures within their borders. This year marks the second consecutive year that bioCSL has donated vaccine to the program. ❖

Medicines

FDA Approves Baxter's HYQVIA for Treatment of PI

The U.S. Food and Drug Administration (FDA) has approved HYQVIA (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase), Baxter's subcutaneous treatment for adult patients with primary immunodeficiency (PI). HYQVIA is the first subcutaneous immune globulin (IG) treatment approved for PI patients with a dosing regimen requiring only one infusion up to once per month (every three to four weeks) and one injection site per infusion to deliver a full therapeutic dose of IG. "The availability of HYQVIA has a significant impact on the treatment of PI, allowing for effective delivery of a full therapeutic dose of IG less frequently than other subcutaneous treatments (up to once a month), while maintaining the efficacy, safety and tolerability profile that is most important for patients," said Ludwig Hantson, PhD, president of Baxter BioScience. "This approval highlights the support of the patient community for new treatment options."

HYQVIA was approved in Europe in 2013 for aduts 18 years and older with PI and myeloma or chronic lymphocytic leukemia with severe secondary hypogammaglobulinemia and recurrent infections. It is currently available in several European countries, including Germany, Netherlands, Sweden, Norway, Denmark, Ireland and Italy. ❖

Initiative

Site Advocacy Group Initiative Launched for Clinical Research

The Society for Clinical Research Sites (SCRS) and TransCelerate BioPharma Inc. have launched the Site Advocacy Group (SAG), an initiative that enables clinical investigators and site professionals to interact directly with senior industry leaders in the exchange of perspectives and experiences on innovative ideas, processes, tools and technologies. SCRS members representing a broad spectrum of site professionals and clinical research sites will partner with TransCelerate workstream members to exchange feedback on various topics. In return, industry leaders will share with the sites their key priorities and initiatives to elevate the industry. Outcomes from the SAG initiative will help to inform collaborative initiatives within the industry aimed at enhancing safety, efficiency and innovations. Results from the SAG initiative will also be poised to enhance operational and business performance for the sites.

TransCelerate is a nonprofit organization focused on advancing innovation in research and development (R&D), identifying and solving common R&D challenges and improving patient safety, with the goal of delivering more high-quality medicines to patients. "This SAG program will provide TransCelerate workstreams direct access to the voice of investigative sites around the world, gather timely input and feedback on projects and further optimize the impact we can make on clinical trials efficiency," said Dalvir Gill, PhD, chief executive officer of TransCelerate.

More information can be obtained from SCRS at myscrs.org. ❖

Research

New Therapy Requires Less Frequent Dosing for Hemophilia B Patients

Interim Phase II/III and III findings of a study conducted by CSL Behring demonstrate an improved pharmacokinetic profile of recombinant fusion protein linking coagulation factor IX with recombinant albumin (rIX-FP) among hemophilia B patients in all age groups. The Phase II/III study of patients ages 12 years to 61 years and the Phase III study of patients ages 1 year to 11 years compared the change in frequency of spontaneous bleeding events between on-demand and weekly prophylaxis regimen in patients previously receiving only on-demand treatment and the number of patients developing inhibitors against factor IX as primary outcome measures. It also compared multiple prophylaxis regimens of seven-day and 14-day treatment intervals. The treatment allows a prolonged routine prophylaxis treatment interval of 14 days or potentially longer compared with the current standard of two to three times per week.

"Patients with hemophilia B and treating physicians are eager for innovative products that are able to decrease the dosing frequency while being effective and reliable in the prevention or treatment of bleeding episodes," said Elena Santagostino, MD, PhD, lead investigator of the study. "Our interim PK data from two Phase III studies, combined with the Phase I and I/II results, demonstrate that rIX-FP has the potential to satisfy this unmet need by offering a longer dosing interval and fewer injections." ❖

Research

CSL Enrolls First Patient in Study of rVIII-SingleChain

CSL Behring has enrolled its first patient in the pivotal pediatric Phase III study to evaluate the efficacy, safety and pharmacokinetics of its novel investigational recombinant factor VIII single chain (rVIII-SingleChain) for the treatment of previously treated children (up to 11 years) with severe hemophilia A. The study site for the first enrollment is Malaysia, and there will be a minimum of 25 previously treated subjects from 6 years to 11 years of age and at least 25 subjects under 6 years of age who have undergone more than 50 exposure days with a previous factor VIII product. Subjects will be assigned to either an on-demand or prophylaxis treatment regimen for the treatment of bleeding episodes and will receive rVIII-SingleChain at a dose to be determined by the investigator. Hemostatic efficacy will be assessed by the subject or caregiver and the investigator, who will assess overall efficacy by a four-point scale.

In an earlier study, rVIII-SingleChain showed improved pharmacokinetics over octocog alfa, the comparator, and demonstrated a safety and efficacy profile that supported advancement to late-stage clinical development. CSL Behring, in collaboration with its parent company, CSL Limited, is developing rVIII-SingleChain for the treatment of hemophilia A as part of the AFFINITY clinical trial program. ❖

Research

rFVIII Treatment for Hemophilia A Receives Positive Results

Baxter's Phase III clinical trial of BAX 855, an investigational, extended half-life recombinant factor VIII (rFVIII) treatment for hemophilia A based on ADVATE (Antihemophilic Factor [Recombinant]), has met its primary endpoint in reducing annualized bleeding rates (ABR) in the prophylaxis arm compared with the on-demand arm.

The multi-center, open-label study evaluated BAX 855 among 138 adolescent and adult patients with previously treated hemophilia A. Patients received prophylaxis treatment twice weekly (45 IU/kg) or on-demand, and were followed for six months. Patients in the prophylaxis arm experienced a 95 percent reduction in median ABR compared with those in the on-demand arm (1.9 vs. 41.5, respectively). BAX 855 was also effective in treating bleeding episodes, 96 percent of which were controlled with one or two infusions. The half-life of BAX 855 was 1.4 to 1.5 times that of ADVATE, consistent with the findings from the Phase I study. No patients developed inhibitors to BAX 855, and no treatment-related serious adverse events, including hypersensitivity, were reported. The most common (three patients) product-related adverse event was headache.

Baxter expects to submit a Biologics License Application for BAX 855 to the U.S. Food and Drug Administration before the end of 2014 and will present additional data in the coming months. In addition to an ongoing continuation study for patients who have completed the pivotal trial, the company is initiating a Phase III prospective, open-label, multi-center study to evaluate the safety and efficacy of BAX 855 among 60 previously treated patients under age 12 with severe hemophilia A. ❖

Research

Study Finds Vaccine Side Effects Extremely Rare

An analysis of 67 research studies published in the July 1 edition of *Pediatrics* has found that serious complications related to vaccines are very rare, and there is no evidence that immunizations cause autism. The analysis comes as many vaccine-preventable diseases are making a comeback. According to the Centers for Disease Control and Prevention (CDC), at least 539 people across 20 states have been infected with measles this year. "This report should give parents some reassurance," says pediatrician Courtney Gidengil of Rand and Boston Children's Hospital and co-author of the study.

According to a report in April by CDC, vaccines given to infants and young children over the past two decades will prevent 322 million illnesses, 21 million hospitalizations and 732,000 deaths over the course of their lifetimes. ❖

Vaccines

ACIP Urges Nasal Spray Flu Vaccine for Children

The Advisory Committee on Immunization Practices voted 15 to 0 to recommend a preference for the inhaled live attenuated influenza vaccine, FluMist Quadrivalent, for healthy children ages 2 years through 8 years. The recommendation still must be approved by the Centers for Disease Control and Prevention director, incorporated into the flu prevention and control recommendations and published in *Morbidity and Mortality Weekly Report* before it becomes official policy. But, the committee also said that if the nasal vaccine isn't available, children should get the flu shot rather than miss vaccination.

The recommendation was based on a data review that suggested the nasal spray vaccine provides better protection than flu shots against laboratory-confirmed, medically attended flu illness. According to Catherine Dundon, MD, a Nashville-area pediatrician and consultant to MedImmune, the maker of FluMist Quadrivalent, the recommendation is not likely to change practice. "Most pediatricians are already using FluMist or at least have it in their offices," she said. ❖

Vaccines

Vaccination Coverage Among Kids 13-17 Rises

An analysis by the Centers for Disease Control and Prevention (CDC) has found that vaccination coverage among adolescents ages 13 to 17 years rose between 2012 and 2013. CDC analyzed data from the 2013 National Immunization Survey-Teen and found that coverage increased for each of the vaccines routinely recommended for adolescents, which includes tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) from 84.6 percent to 86 percent; meningococcal conjugate (MenACWY) from 74 percent to 77.8 percent; human papillomavirus (HPV) among females from 53.8 percent to 57.3 percent; and HPV among males from 20.8 percent to 34.6 percent. Coverage varied by state and local jurisdictions and by U.S. Department of Health and Human Services region. Healthy People 2020 vaccination targets for adolescents ages 13 to 15 years were reached in 42 states for Tdap, 18 for MenACWY and 11 for varicella (a catch-up vaccine). ❖

People and Places in the News

FDA has approved Iroko Pharmaceuticals' Tivorbex (indomethacin), a low-dose painkiller for adult patients. The drug is a nonsteroidal anti-inflammatory drug approved at 20-mg and 40-mg doses for the treatment of **mild to moderate acute pain**. It contains indomethacin as submicron particles that are approximately 20 times smaller than their original size, providing an increased surface area, leading to faster dissolution. The approval follows FDA's OK of Iroko's Zorvolex (diclofenac) capsules, developed using the same technology, for the treatment of mild-to-moderate acute pain in adults. ❖

Research

CDC Announces Recent Flu Season Numbers

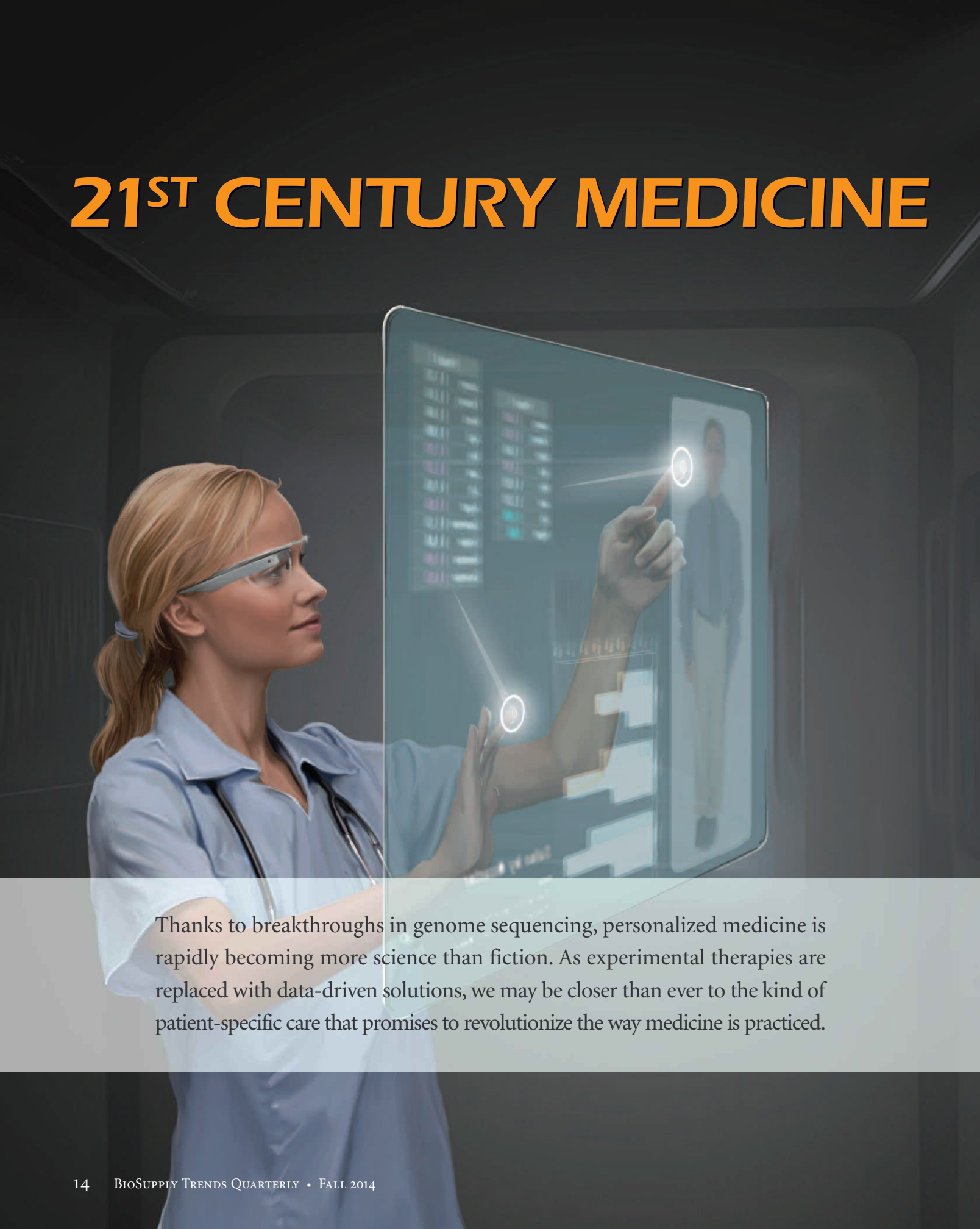
The Centers for Disease Control and Prevention (CDC) has released the nation's numbers for the 2013-2014 influenza season, which show Americans were hit particularly hard due to the return of the H1N1 virus that caused the 2009 swine flu pandemic.

The flu season peaked in late December and January, and the highest death rate from flu and pneumonia was 8.7 percent of all reported deaths at the end of January. Similar to 2009, the flu season hit young and middle-aged adults fairly hard, but flu also killed at least 96 children and many elderly people as well. "The highest hospitalization rates were among adults 65 years or older, which is consistent with previous influenza seasons," said a team from CDC that writes in the agency's weekly report on death and disease. But, "hospitalization rates among those aged 50 to 64 years were significantly higher than in all years since the 2009 pandemic."

According to the U.S. Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee, the available vaccines in the 2013-2014 season matched the circulating flu viruses well. "Influenza A viruses predominated until late March, and influenza B viruses became the most commonly identified viruses nationally during the week ending March 29," the report says.

While this is a national report, CDC figures come from 30 states, New York City and Chicago, so they are not complete numbers for the nation. ❖

21ST CENTURY MEDICINE



Thanks to breakthroughs in genome sequencing, personalized medicine is rapidly becoming more science than fiction. As experimental therapies are replaced with data-driven solutions, we may be closer than ever to the kind of patient-specific care that promises to revolutionize the way medicine is practiced.

Now It's Personal

By Trudie Mitschang

Two patients present with identical symptoms and diagnoses. Each is prescribed the same medication, and several weeks later, the first patient is responding well with improved symptoms and minimal side effects. The second patient, however, experiences debilitating side effects and escalating symptoms, and actually seems worse after taking the medication as prescribed. Two patients. One diagnosis. Same medication. Dramatically different results. This scenario is increasingly the norm for practitioners across the country, indicating that the "one-size-fits-all" approach to medical care is both outdated and ineffective.

Historically, healthcare practitioners were faced with the dilemma of offering cookie-cutter treatments to patients whose age, lifestyle and health history make their outcomes far from predictable. With recent research, scientists have discovered that even a person's genes can influence their response to medication, and these findings are driving an entire industry toward a new age of patient-specific care. Is the long-predicted age of personalized medicine finally on the horizon?

Pioneering the P4 Approach

An old folktale describes what happens when a group of blind men encounter an elephant. Each man touches a different part of the elephant and gives a description of what he believes an elephant is. The first person touches the elephant's trunk and claims the elephant is a snake. The second person touches the elephant's leg and declares it is a tree. The third reaches out and touches the elephant's ear and confirms it is a sail. The moral of the story is that if the three men had collaborated and holistically examined the elephant, its true identity would have been revealed. This is the concept behind a new approach to medicine called P4.

The P4 medical approach hinges on four pillars: predictive, preventive, personalized and participatory. This approach is intended to help identify the right drug for the right patient at the right time, thereby avoiding the prescription of costly and ineffective drugs and preventing potentially harmful side effects. Some say the practice of P4 medicine may be achievable in the next five to 10 years, and at the forefront of this concept is biologist and researcher Leroy E. Hood, MD, PhD, co-founder of Seattle's Institute for Systems Biology.[1] "P4 medicine will provide actionable opportunities and revolutionize medicine. It will save billions of dollars in healthcare costs, and [it] will force a reluctant healthcare system to accept a radical change in how we deal with medicine," said Dr. Hood in a recent interview.

P4 systems medicine, as Dr. Hood conceptualizes it, uses a holistic approach and new computational tools to analyze large amounts of molecular, cellular, phenotypic and medical data for specific patients. In other words, it evaluates the entire elephant. The first step in the process is to generate clouds of billions of data points for each person. As Dr. Hood described in a *Science Translational Medicine* editorial, "Medicine will be informed by computational analyses that reduce high-dimensional data to actionable hypotheses designed with the intent of optimizing wellness and minimizing disease in individual patients."

The P4 medical approach is intended to help identify the right drug for the right patient at the right time.

The next step in this approach integrates the data clouds in technologies and strategies designed to optimize wellness and minimize disease. Over the next three to five years, Dr. Hood will embark on a comprehensive study involving 100,000 healthy patients. The study will continue for 20 to 25 years and review six different data sets to generate data clouds for analysis. Analysis will involve various body systems and functions, including the brain, heart, colon, lymphatic systems, liver, lungs, chromosomes and insulin levels.

Because the project involves a large number of patients who will be in good health when the study begins, the generated matrix will quantitatively define wellness. But, as the project proceeds, the data clouds will display when and how individuals transition from good to poor health. If scientists can identify both the transition point to disease early on and the earliest mechanism of disease, the theory is they could then intervene

and reverse the disease before it has time to progress.[1]

The P4 collaboration between genetic knowledge and clinical studies is expected to contribute significantly to advances in preventive and prospective medicine. Perhaps the biggest concern is that the developers of molecular diagnostics are still not well-aligned with the pharmaceutical manufacturers whose products might be affected by diagnostics. Experts say more collaboration is needed between the diagnostic test developers, who are focused on targeting early drug development efforts, and the pharmaceutical companies that manufacture and sell the drugs.[2]

Despite the hurdles, P4 medicine has the potential to minimize the increasing costs of medical care, a goal shared by most stakeholders. Some predict P4 could become the foundation of future global healthcare, and, in a perfect world, would allow the focus of medicine to shift from curing disease to maintaining wellness, affecting everything from the economic cost of sick-leave pay to general population productivity.[2]

Biomarker-Based Diagnostics

Studies similar to the one being embarked upon by Dr. Hood have spurred the beginning of a major paradigm shift in healthcare away from "one-size-fits-all" approaches toward customized, patient-tailored therapies. In recent years, pharmaceutical companies have begun focusing on biomarker-based diagnostics and companion diagnostic tests that identify a patient's likelihood of responding to a drug or experiencing side effects. Biomarkers, molecular substances in the body that can be used to indicate health or disease, can be found in tissue, blood, urine and other body fluids. Prostate and ovarian cancers are two examples of how the use of biomarkers are currently being used for individualized diagnosis and treatment.[2]

In recent years, pharmaceutical companies have begun focusing on biomarker-based diagnostics and companion diagnostic tests.

As with all new theories and treatment approaches, the challenge is to find the balance between patient benefits, economic value and clinical merit. The two main groups of companion diagnostics include tests developed after a drug has come to market and tests simultaneously developed as a companion to the drug. Today, a majority of drugs in the developmental pipeline are accompanied by associated biomarker programs, and that number is expected to increase. Such companion diagnostic tests can improve research productivity by decreasing trial sizes, increasing the speed to market and supporting higher drug prices.

These types of diagnostic tests are also showing potential in significantly reducing the costs of clinical trials. A recent report estimates more than $130 million in savings for pharmaceutical companies per approved compound.[2] Realistically, scientific and clinical factors place limits on the pace of such developments. In many cases, the current scientific knowledge is insufficient to select for specific biomarkers at early stages of a disease. In other instances, there is no immediate clinical need for companion diagnostics. And, from an economic standpoint, the prospect of generating greater market value for a product after it launches is more important for pharmaceutical and biomedical companies than investing in technology that would make the development itself more effective.[2]

Additionally, pharmaceutical companies are more likely to invest in diagnostics and technologies that impact larger groups, such as infectious diseases, immunology and oncology, with the latter being the most advanced field for personalized medicine to date. In contrast, disease states where incentives are not significant enough to encourage investment, despite technical feasibility and clinical need, include categories like antipsychotics and anticoagulants.[2]

Predictive Medical Care

With healthcare costs at an all-time high, the prospect of diagnosing disease before it strikes, and prescribing interventional therapy to prevent it rather than treating it, is intriguing. In a recent study, scientists were able to predict that a man was at a higher risk for developing type 2 diabetes and over a two-year period tracked his health as he developed the disease. Even better, because they caught it so early, they were able to reverse the diabetes with lifestyle changes. This man's glucose levels have since returned to normal.[3]

Despite widespread skepticism, there are already several proven applications of personalized medicine making headlines. Physicians are currently using predictive testing for certain cancers to determine who might be in a high-risk category. It's been proven that mutations of the BRCA-1 and BRCA-2 genes can heighten a woman's risk of developing breast and/or ovarian cancers.[4] Patients who have a family history of these cancers can now request a genetic test that would look for mutations of those specific genes. A positive test allows the patients to consider preventive options such as precancer mastectomy or hysterectomy. Lifestyle changes, as in the case with the prediabetic patient, could also be considered to mitigate risk factors.

Colon cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death in men and women combined in the U.S. Lynch syndrome, an inherited

illness linked to colorectal cancer, has several genetic links, and if a patient tests positive for this gene, a physician may recommend getting colonoscopies earlier than the current "over 50" guidelines, tailoring the screening regimen to the patient rather than the general population.

All diseases have a genetic component, whether inherited or resulting from the body's response to environmental stresses such as viruses or toxins. Ultimately, the goal is to learn how a faulty gene might cause disease, and then use this information to treat, cure or even prevent various diseases. Of course, some information garnered from genetic testing is only beneficial from a research perspective; at this point, knowing certain patients have a likelihood of developing Alzheimer's disease still leaves them powerless to do anything about it.

The Quest for Pharmacogenomics

Another emerging form of personalized medicine is called pharmacogenomics, which uses genetics to predict an individual's response to a drug. Proponents of pharmacogenomics say this is the future of pharmaceuticals, since people's genetic makeups can impact how and whether they respond to medications. Supporters argue that using genes to guide drug use would lead to more effective therapies, while detractors say the science simply is not refined enough to help most patients.

Pharmacogenomics is already being used for some commonly prescribed medications, and recently, two large prescription drug companies announced plans to offer in-pharmacy genetic testing as part of the prescription-filling process. Under this process, certain prescriptions would trigger physician notification about available genetic testing, which would then be offered as an option to the patient. The testing would presumably help physicians customize prescriptions to fit individual needs, ward off undesirable side effects and optimize patient outcomes.[5]

Tests are now available that can help predict whether people with cancer or other diseases are likely to have good responses or bad reactions to certain medications. One such test looks at a group of enzymes that are responsible for breaking down and eliminating more than 30 types of medications, including antidepressants, chemotherapy drugs and heart medications. Due to their genetic makeup, some people aren't able to break down these medications fast enough. The medications can then build up in the body and cause severe side effects. Conversely, some people break down these medications too quickly, before they have a chance to work. Genetic testing can identify people with these genetic variations to enable doctors to make more informed prescribing decisions, thus increasing the likelihood of treatment success and minimizing the risk of side effects.[6]

Supporters of pharmacogenomics say it has the potential to improve patient safety and decrease overall healthcare costs. It may also provide an opportunity to advance the field of genetic study by collecting data on genetic testing results and drug effectiveness. However, critics argue that we don't yet understand enough about the human genome (and how it interacts with the environment and other factors) to routinely use genes as the basis for medical decisions. And, since pharmacogenomics is a relatively new science, insurance companies may not reimburse for the cost of genetic testing.[7] "There are still a relatively small number of drugs where pharmacogenomics actually plays a role, but this could drastically expand over the next five years," said Scott Weiss, a physician at Harvard Medical School and interim director of the Partners Healthcare Center for Personalized Genetic Medicine. "Antidepressants, asthma meds, anti-arrhythmia drugs, lipid-lowering drugs — some of the biggest sellers in terms of drug use nationally — could potentially have pharmacogenetic implications."[8] ❖

Despite widespread skepticism, there are already several proven applications of personalized medicine making headlines.

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

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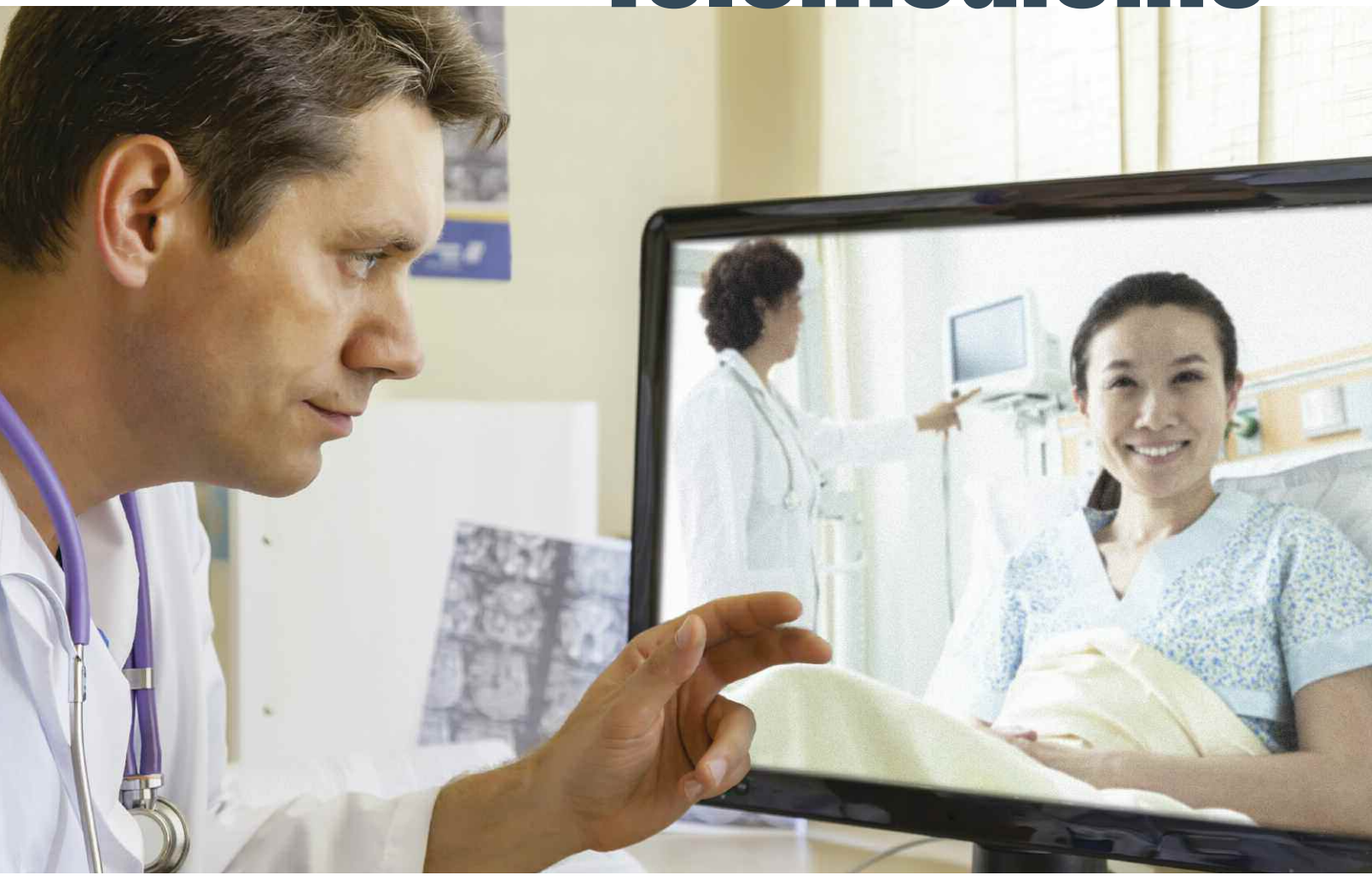
The Age of Telemedicine



Medicine has come into the electronic age with telemedicine, which provides wider reaching care in an era when there is a projected doctor shortage.

By Amy Scanlin, MS

With aging baby boomers, increased numbers of patients due to the Affordable Care Act and a shrinking pool of doctors, there is a fear there won't be enough healthcare providers for the care that is needed. Enter telemedicine, which has endless applications for the healthcare industry. Telemedicine is a rapidly developing practice of clinical medicine where medical information is transferred through the phone or the Internet, and sometimes other networks, for the purpose of consulting and, increasingly, remote medical procedures and examinations.[1] Today, patients are able to remotely connect with doctors, have their gallbladders removed from an ocean away and receive help, reminders and guidance by a friendly face, even if that face is just on a screen.

Care at a Distance

Telehealth visits seek to improve a patient's health by permitting two-way, real-time interactive communication between the patient and the physician or practitioner at a distant site. Many insurance companies have contracted with a host of telehealth providers that provide access to a doctor or nurse practitioner who is able to diagnose and prescribe — all at a price of about $50.

And, the trend is growing, with more than 400,000 doctor-patient televisits in 2013, which is more than double that in 2011.[2] Indeed, by 2017, it is predicted that 1.8 million patients will be treated via televisits worldwide, a sign of the growing acceptance of remote medical services.[3] Doctors who provide services through televisits must be licensed in the patient's state, must obtain informed consent and must document the patient's visit. On the patient end, they either set up a time for a "visit" or just make a cold call and get in queue for one. The American Telemedicine Association is even developing a specific accreditation program for telehealth visits.

From a patient standpoint, the convenience of meeting with a doctor from the comfort of their home for routine questions is making the lack of in-person attention an acceptable trade for many. However, there are some concerns. Namely, because the patient and doctor don't meet in person, it's possible that a diagnosis may be incorrect or inconclusive, or that a patient could be overprescribed or underprescribed a medication. Because of these concerns, the Federation of State Medical Boards is establishing guidelines that will hold virtual visits to the same standards as an office visit, including a full medical history and informed consent, and will allow patients to choose among participating doctors. The group also is finalizing a plan to make it easier for doctors to practice across state lines.[4]

Taking telemedicine a step further, telepresence robots are being used in some hospitals and are another growing trend in hospital medicine — especially in rural areas where there is a shortage of doctors. The videoconferencing robots have a large video monitor, camera, speakers, microphone and wheels and are able to travel through the halls of a hospital and check on resident patients.

One such robot is RP-VITA, developed by InTouch Health and iRobot Corp., which is approved for hospital use by the U.S. Food and Drug Administration (FDA) and is helping doctors remotely care for patients in about 1,000 hospitals internationally.[5] With the help of a nursing assistant who is in the room with the patient, a doctor from a remote location can log into the RP-VITA by using a computer, laptop or iPad, and he or she can see, hear and speak to the patient, as well as have access to clinical data and medical images. This allows doctors to make assessments and provide instructions from miles, if not thousands of miles, away.

Robotic-Assisted Surgeries

Since FDA's approval of robotic-assisted (RA) devices for laparoscopic surgeries of cardiac, colorectal, gynecologic, urologic, head and neck and thoracic general procedures, much has been said about their benefits, challenges and costs.

RA surgeries, during which a surgeon performs minimally invasive procedures through robotic or mechanical arms affixed to a cart next to the patient's bed, are praised by many for shorter pre- and post-operative recovery times, as well as the ability to facilitate minimally invasive surgeries — particularly in areas of the body that are difficult to reach. In a 2009 study at Stanford University of the da Vinci Surgical System (developed by Intuitive Surgical), researchers compared RA laparoscopic hysterectomy with a matched control group of standard laparoscopic hysterectomy. They found that the RA surgery had a similar outcome to the standard therapy, and they concluded that the device held exciting promise, particularly in the area of telesurgery.[6]

Today, surgeries are being performed across state lines and even countries. The first transoceanic telesurgery was performed in 2001 in Strasbourg, France. The surgeon was at an office in New York manipulating robotic arms of a device called the ZEUS System (manufactured by Computer Motion) using dedicated asynchronous transfer mode (ATM) telecommunication technology. The patient's gallbladder removal was carried out in 54 minutes, without complications and with a constant time delay of 155 milliseconds throughout the procedure. All surgeons involved rated the safety of the procedure a "10."[7]

Yet, some criticize the idea of RA surgical devices due to errors in surgery or even malfunctions of the machines. In fact, every person involved in the administration of an RA surgery has the potential to introduce error, which is why the training and education from setup of the machine through breakdown and maintenance is so critical. Machines like da Vinci and the ZEUS System are approved by FDA; however, training, education and accreditation of surgeons and medical staff using the equipment are not regulated by FDA, as it says the training is the responsibility of the manufacturer, physicians and the healthcare facilities.

FDA did conduct a post-market evaluation survey through the Medical Product Safety Network of experienced physicians who use the da Vinci Surgical System after receiving increased medical device reports related to computer-assisted surgical systems.[8] In the survey, surgeons reported no serious issues with using the device even though the depth of their training requirements varied.

Impact of Robots on Nursing

Nurses also face new challenges with RA surgeries. A spring 2011 summary report of the McKee Medical Center on the use

of robotics technology in gynecologic surgery stated that nurses and nurse circulators are becoming as specialized as the surgeons with use of robotic technology. According to Dr. John Crane, a gynecologist who performed McKee's first robotic surgery, "At no time has the nurse's role been more prominent and necessary than now as we take a robotics program to a higher level of efficiency."[9]

RA surgeries require more nursing and surgical tech staff to assist in setting up the robot prior to surgery, a unique anticipation of surgeon needs during surgery, the skill to undock the robot from the patient post-surgery, as well as the knowledge of how to inventory and complete medical charts.

Nurses must also be trained in the area of post-operative education, including instructions and the timing of those instructions. With patient stays shortened, nurses have to make sure patients and their caregivers understand the tools they need to manage the first days at home. And, they must be in tune with the patients' and caregivers' readiness to hear and understand the instructions post-surgery, when they may be overwhelmed by the amount of information and responsibility bestowed on them. They also must assess patients' and caregivers' capabilities of working through the transition back to pre-operative lives.[10]

Today, surgeries are being performed across state lines and even countries.

Nursebots

Nursebots, personal robotic assistants, are designed to supplement, though not replace, nursing care. Pearl, a four-foot nursebot, was conceived back in 1998 and is being developed by scientists at the University of Michigan, University of Pittsburgh and Carnegie Mellon University as an option to help improve the quality of life of patients, as well as help them maintain their independence.[11] Pearl was tested at the Longwood Retirement Community in Oakmont, Pa., as a way of helping the elderly with routine activity reminders such as eating and drinking, using the bathroom and taking medications, as well as providing walking assistance (the slow pace of patients makes assisting them while walking one of the most labor-intensive requirements of nursing home staff). Pearl can also interact with clients through a touch-screen interface that allows for direct communication.[12]

Researchers view Pearl as a way to augment, rather than replace, human interaction with services that a robot would be able to provide. "Robotic technology can be a way to augment nursing care — high-tech devices taking care of low-tech jobs (delivering trays, linens, lab specimens, etc.)," says Linda Hollinger-Smith, RN, PhD, vice president of the Mather Lifeways Institute on Aging in Evanston, Ill. "It allows nurses to get back to high-touch care."[11]

Additional nursebot prototypes are being tested. Japan is seeing huge challenges to its healthcare industry as its aging population far outnumbers those who are able to care for them, and the country is at the forefront of nursebot production. In 2010, Japan's Ministry of Health, Labor and Welfare estimated two million healthcare workers would be needed for nursing homes and hospitals, and by 2025, it is estimated four million will be needed.[13] Researchers there have also been testing robot nurse prototypes to assist with everyday tasks such as lifting patients out of beds, taking vital signs and interfacing between doctors and patients, an idea that could save Japan $2.1 billion in healthcare costs.[14]

What the Future Holds

When healthcare providers interact with patients, they ask questions and formulate recommendations based on patient feedback. If patients are not compliant with instructions, healthcare providers can ask why and perhaps formulate a new plan based on the patients' responses. As exciting as robots are, today's technology doesn't autonomously allow robots to do this. However, when robots are able to process right from wrong, use "computational meta-ethics" and algorithms to determine what information is missing from their decision-making tree, as well as how best to get that information, technology will be that much closer.[13]

One research center working to help robots make that transition is Memorial Sloan-Kettering Cancer Center in New York, which is working with Watson, IBM's supercomputer, to develop complex decision-making skills. Watson is learning to make sense of dictated and written notes in medical records, articles published in medical journals and raw data published by public health departments. When making a diagnosis, Watson lists not only strong possibilities, but its own level of confidence in each possibility. It is even theorized that Watson will be able to help with complex issues such as cancer, as well as everyday primary care diagnoses, where a mistake can be equally costly.

Dr. Marty Kohn, an emergency room physician and a clinical leader of the IBM team training Watson, says that about one-third of medical mistakes come from focusing too much on just a few bits of information that he calls "anchoring bias." A doctor may inadvertently focus on this information at the exclusion of other information and miss a crucial detail, or he or she may have the right diagnosis but not realize it is incomplete and not treat the whole condition. Dr. Kohn says Watson can help. As scientists learn more about medicine,

Why Risk VTE From Low Antithrombin (AT) Levels?

AT Level	61-75 IU/dL	45-60 IU/dL
Unprovoked* VTE Risk	6x Risk	23x Risk

*Data reflect events that occurred in the absence of transient risk factors (ie, surgery, trauma, prolonged bed rest [>1 week], pregnancy/puerperium, and combined oral contraceptive use). Risk assessed in comparison to patients with normal AT levels (or levels >100 IU/dL).[2]

Do You Test for Hereditary AT Deficiency?

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FOR PATIENTS WITH HEREDITARY ANTITHROMBIN DEFICIENCY[1]

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- Replaces antithrombin normally present in the body
- In clinical use for over 20 years

Important Safety Information

Thrombate III® (antithrombin III [human]) is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

In clinical studies, the most common adverse events were dizziness, chest discomfort, nausea, and dysgeusia.

The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III is made from human plasma. Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. No cases of transmission of viral disease or CJD have ever been identified for Thrombate III.

Please see brief summary of Thrombate III complete Prescribing Information on adjacent page.

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Thrombate III®
antithrombin III (human)

BRIEF SUMMARY
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FOR INTRAVENOUS USE ONLY

DESCRIPTION

Antithrombin III (Human), THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III (ATIII).

THROMBATE III is prepared from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn. When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pH of 6.0–7.5, a sodium content of 110–210 mEq/L, a chloride content of 110–210 mEq/L, an alanine content of 0.075–0.125 M, and a heparin content of not more than 0.1 IU heparin/IU ATIII. THROMBATE III contains no preservative and must be administered by the intravenous route.

Each vial of THROMBATE III contains the labeled amount of antithrombin III in international units (IU) per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.

The capacity of the THROMBATE III manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties. There are two dedicated virus inactivation/removal steps included in the THROMBATE III manufacturing process: a heat treatment step at 60°C ± 0.5°C for not less than 10 hours for virus inactivation and a nanofiltration step for effective removal of viruses as small as 18 nm.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

An individual production step in the THROMBATE III manufacturing process has been shown to decrease TSE infectivity of that experimental model agent. The TSE reduction step is the Effluent I to Effluent II + III fractionation step (6.0 $\log_{10}$). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL PHARMACOLOGY

Antithrombin III, an alpha$_2$-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by ATIII occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on ATIII. ATIII is also capable of inactivating other components of the coagulation cascade including factors IXa, Xa, XIa, and XIIa, as well as plasmin.

The neutralization rate of serine proteases by ATIII proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect in vivo of heparin is mediated by ATIII, heparin is ineffective in the absence or near absence of ATIII.

The prevalence of the hereditary deficiency of ATIII is estimated to be one per 500 to 5000 in the general population. The pattern of inheritance is autosomal dominant. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with ATIII levels of 40%–60% of normal. These episodes usually appear after the age of 20, the risk increasing with age and in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary ATIII deficiency during pregnancy has been reported to be 70%, and several studies of the beneficial use of Antithrombin III (Human) concentrates during pregnancy in women with hereditary deficiency have been reported. In many cases, however, no precipitating factor can be identified for venous thrombosis or pulmonary embolism. Greater than 85% of individuals with hereditary ATIII deficiency have had at least one thrombotic episode by the age of 50 years. In about 60% of patients thrombosis is recurrent. Clinical signs of pulmonary embolism occur in 40% of affected individuals. In some individuals, treatment with oral anticoagulants leads to an increase of the endogenous levels of ATIII, and treatment with oral anticoagulants may be effective in the prevention of thrombosis in such individuals. In clinical studies of THROMBATE III conducted in 10 asymptomatic subjects with hereditary deficiency of ATIII, the mean in vivo recovery of ATIII was 1.6% per unit per kg administered based on immunologic ATIII assays, and 1.4% per unit per kg administered based on functional ATIII assays. The mean 50% disappearance time (the time to fall to 50% of the peak plasma level following an initial administration) was approximately 22 hours and the biologic half-life was 2.5 days based on immunologic assays and 3.8 days based on functional assays of ATIII. These values are similar to the half-life for radiolabeled Antithrombin III (Human) reported in the literature of 2.8–4.8 days.

In clinical studies of THROMBATE III, none of the 13 patients with hereditary ATIII deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with THROMBATE III for high thrombotic risk situations (11 surgical procedures, 5 deliveries) developed a thrombotic complication. Heparin was also administered in 3 of the 11 surgical procedures. Eight patients with hereditary ATIII deficiency were treated therapeutically with THROMBATE III as well as heparin for major thrombotic or thromboembolic complications, with seven patients recovering. Treatment with THROMBATE III reversed heparin resistance in two patients with hereditary ATIII deficiency being treated for thrombosis or thrombo embolism.

During clinical investigation of THROMBATE III, none of 12 subjects monitored for a median of 8 months (range 2–19 months) after receiving THROMBATE III became antibody positive to human immunodeficiency virus (HIV-1). None of 14 subjects monitored for ≥ 3 months demonstrated any evidence of hepatitis, either non-A, non-B hepatitis or hepatitis B.

INDICATIONS AND USAGE

THROMBATE III is indicated for the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

Subjects with ATIII deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease.

The diagnosis of hereditary antithrombin III (ATIII) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma ATIII levels, and the exclusion of acquired deficiency.

ATIII in plasma may be measured by amidolytic assays using synthetic chromogenic substrates, by clotting assays, or by immuno assays. The latter does not detect all hereditary ATIII deficiencies.

The ATIII level in neonates of parents with hereditary ATIII deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of ATIII are lower in neonates than adults, averaging approximately 60% in normal term infants. ATIII levels in premature infants may be much lower. Low plasma ATIII levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

CONTRAINDICATIONS

None known.

WARNINGS

Because THROMBATE III is made from human plasma, it may carry a risk of transmitting infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for THROMBATE III. Inform patients that THROMBATE III is made from human plasma and may contain infectious agents that can cause disease. While the risk that THROMBATE III can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by inactivating or removing pathogens during manufacturing, patients should report any symptoms that concern them. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics Inc. [1-800-520-2807].

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary ATIII deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

PRECAUTIONS

General

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. THROMBATE III, once reconstituted, should be given alone, without mixing with other agents or diluting solutions.
4. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted THROMBATE III product in accordance with biohazard procedures.

The diagnosis of hereditary ATIII deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma ATIII levels, and the exclusion of acquired deficiency.

Laboratory Tests

It is recommended that ATIII plasma levels be monitored during the treatment period. Functional levels of ATIII in plasma may be measured by amidolytic assays using chromogenic substrates or by clotting assays.

Drug Interactions

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary ATIII deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to THROMBATE III. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established. The ATIII level in neonates of parents with hereditary ATIII deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of ATIII are lower in neonates than adults, averaging approximately 60% in normal term infants. ATIII levels in premature infants may be much lower. Low plasma ATIII levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

ADVERSE REACTIONS

In clinical studies involving THROMBATE III, adverse reactions were reported in association with 17 of the 340 infusions during the clinical studies. Included were dizziness (8), chest discomfort (3), nausea (3), dysgeusia (3), chills (2), pain (cramps) (2), dyspnoea (1), chest pain (1), vision blurred (1), intestinal dilatation (1), urticaria (1), pyrexia (1), and wound secretion and hematoma (1). If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

CAUTION

Rx only

U.S. federal law prohibits dispensing without prescription.

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biomarkers and how technology can help to aggregate and filter information, robots like Watson will become more and more invaluable because the complexity of the information and the decision making will become overwhelming. In an example of the high hopes for robots in medicine, WellPoint, the insurance company, has already begun testing Watson as a support tool for nurses who make treatment-approval decisions.[15]

Cost Challenges

Cost is always an issue when developing new technology. Developers have to balance the costs of development, the purchase of equipment, training (not only the surgeons but other healthcare workers) and the price charged to the patient.

Today, robots and RA surgical equipment are quite expensive. Da Vinci, for example, costs between $1.5 million and $2 million per machine, and the average cost of a hysterectomy is $8,868 using da Vinci compared with $6,679 to perform a laparoscopic hysterectomy. Medicare and private insurers reimburse the same amount no matter which type of surgery a patient has.[16]

With telesurgery, another significant cost challenge is the telecommunications system. Each end of the surgical system must have the ATM communication lines required for this type of surgery. Yet, at present, most hospitals are not equipped to handle ATM communications. It is estimated that a one-year cost of ATM technology availability could be $100,000 to $200,000. So, for those looking at RA surgery from purely a cost standpoint, it may be prohibitive. That's why others suggest looking at this type of surgery from the standpoint of bringing improved surgical capabilities to all corners of the world.[7]

Telemedicine Is Moving Forward

Costs aside, the momentum toward robotic-enhanced healthcare and technology in general is moving forward. Since 2000, more than 1,370 hospitals have purchased a da Vinci Surgical System,[16] and half of physicians surveyed plan to add a robotic system in the next two years. In addition, there was a 60 percent jump in the total number of RA surgeries performed between 2010 and 2013.[17] And, the American Medical Association reports that the number of RA hysterectomies has jumped from 0.5 percent to 10 percent in three years.[18]

One clear sign that the medical establishment is transforming toward telemedicine is the demand for IT workers. The Bureau of Labor and Statistics reports that IT healthcare industry job advertisements tripled between 2009 and 2010, and it estimates that healthcare IT jobs will grow by 20 percent in the next decade, though even that may not be enough to meet demand.[15]

As our healthcare systems continue to evolve and become more autonomous, there appears to be significant potential for improved medical care enabled by the new emerging technology, even if the care is not performed by (or entirely by) a human. However, it remains to be seen how the transition will be implemented, the costs absorbed and what health improvements would result, especially in answer to the growing physician shortage, not only in the U.S. but worldwide. ❖

AMY SCANLIN, *MS, is a freelance writer and editor specializing in medical and fitness topics.*

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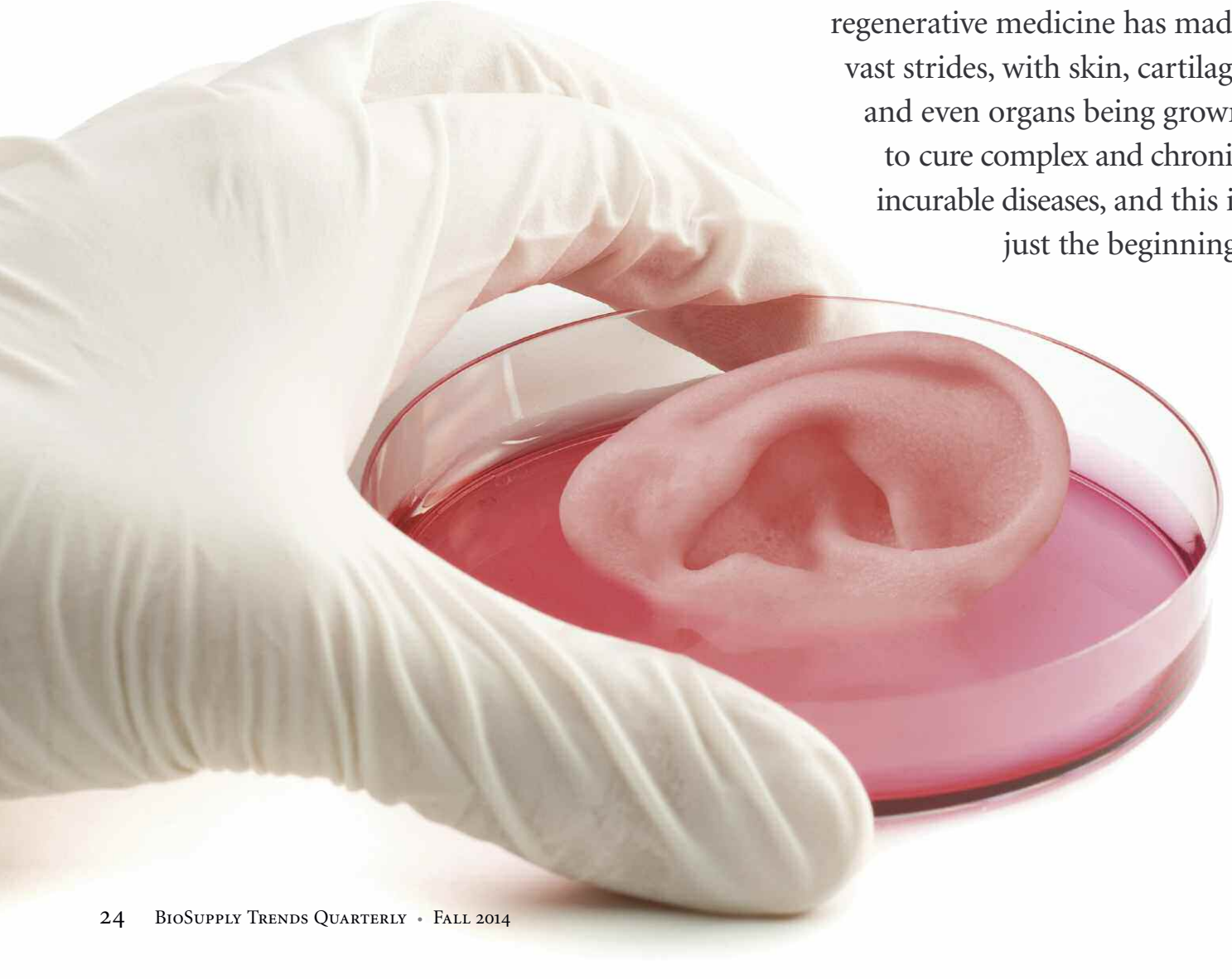
Regenerative Medicine: ARE WE THERE?

By Ronale Tucker Rhodes, MS

During the past two decades, regenerative medicine has made vast strides, with skin, cartilage and even organs being grown to cure complex and chronic incurable diseases, and this is just the beginning.



More than 84,000 people in the U.S. are waiting for organ transplants.[1] Is it possible that within the next couple of decades, transplant waiting lists could be eliminated? That's the goal of the promising new field of regenerative medicine. Up until now, medicine has been all about replacements. If your kidney isn't working, replace it with another one. But, with regenerative medicine, the cause is treated, and structure and function are restored to damaged tissues and organs using tissue from synthetic materials and patients' own existing organs. While this new science is just on the cusp of changing the treatment landscape, organs are already being grown in the laboratory and implanted into patients today. Regenerative medicine is all about harnessing the power of the body to heal, dramatically improving medical care for millions and saving millions in medical costs.

Regenerative Medicine Defined

Regenerative medicine evolved from the field of tissue engineering, which is the "practice of combining scaffolds, cells and biologically active molecules into functional tissues." Regenerative medicine includes tissue engineering but also incorporates research on self-healing, using the body's own systems, sometimes with the help of foreign biological materials, to recreate cells and rebuild tissues and organs. Both focus on cures instead of treatments for complex, often chronic, diseases.[2]

In 2006, the National Institutes of Health defined regenerative medicine as "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects."[3] The field encompasses three separate approaches to augment, repair, replace or regenerate organs and tissues: cell-based therapies, small molecules and biologics and synthetic and bio-based materials. With cell-based therapies, living cells replace damaged or diseased cells and/or tissue, stimulate healing and regeneration in diseased tissue, and deliver small molecule therapies to targeted areas. The use of chemicals and cellular components in small molecules and biologics induce dormant cells to regain regenerative properties. Synthetic and bio-based materials are implanted into the body for reconstructive purposes such as joint replacement, bone repair, artificial ligaments and tendons, dental implants, heart valves and wound repair. These materials work in partnership with native cells to support reconstruction and healing.[4]

A Growing Industry

In 2012, the Alliance for Regenerative Medicine (ARM), the national voice for regenerative medicine, estimated the industry to include more than 700 companies in the fields of biology, chemistry, engineering and physical sciences. Forty-three percent of these companies are developing regenerative medicines (cell- and tissue-based therapies: 65 percent; regenerative compounds and devices: 25 percent; biopharmaceuticals: 10 percent). Another 48 percent are developing tools and non-therapeutic products. And, 9 percent are companies providing services and manufacturing.

Also in 2012, there were approximately 300 cell- and tissue-based therapeutics commercially available or in clinical development around the world. Fifty-five of the available products are described and marketed as regenerative medicine products. Products commercially available are for musculoskeletal/orthopedic (38 percent), wound/noncardiac ischemic (26 percent), skin/soft tissue (15 percent), ocular (11 percent), cardiac (4 percent), oncology (3 percent) and diabetes (3 percent). And, all but one of the top-15 regenerative medicine products are for skin, wound, bone or cartilage repair, used to treat more than 500,000 patients through the end of 2011.

Regenerative medicine is all about harnessing the power of the body to heal.

The United States boasts the greatest number of companies developing regenerative medicine products, as well as has the greatest number of those products in ongoing trials. The greatest number of products are in Phase II clinical trials (45 percent). Those in late-stage trials (Phase II/II, III and pivotal) include musculoskeletal/orthopedic products (34 percent), oncology (27 percent), wound/noncardiac ischemic (15 percent), cardiac (15 percent), ocular (2 percent) and other (7 percent).[4]

The Role of Stem Cells

Stem cells — key components of regenerative medicine — are self-renewing primitive cells that are able to develop into functional, differentiated cells. In other words, they are able to branch out and change. The two broad categories of stem cells are adult stem cells and embryonic stem (ES) cells. Adult stem cells are referred to as "multipotent" (also known as mesenchymal) cells because they can develop into multiple, but not all, types of cells in the body. ES cells, which are derived from pre-implantation embryos, are unique because they are "pluripotent," meaning they can develop into all cells and tissues in the body, and they self-renew indefinitely in their undifferentiated state.[5]

Regenerative medicine researchers are studying both ES and adult stem cells. They are also looking at various types of progenitor cells, described as "oligopotent," meaning they can

differentiate to form one or more kinds of cells but cannot divide and reproduce indefinitely, which means they are more limited than stem cells. Also under study are bioengineered cells called "induced pluripotent" stem cells.[6]

The most common regenerative therapies using stem cells begin with a patient's own cells. Once collected, these cells are grown in large quantities in the lab and injected back into the patient. A number of products developed with stem cells are currently on the market, including Provenge (Dendreon) for prostate cancer, Apligraf (Novartis) to treat diabetic foot ulcers, Carticel (Genzyme) to replace knee cartilage, Gintuit (Organogenesis) to promote healing after gum surgery and Fibrocell (Fibrocell Science) to replace fibroblasts. In addition, some of the most advanced clinical trials of products developed with stem cells involve treating congestive heart disease and regrowing muscles in soldiers who were wounded in explosions.[7]

In hopes of creating new therapies, scientists have been searching for ways to control how stem cells develop into other cell types. Recently, researchers at the National Institute of Biomedical Imaging and Bioengineering discovered that confining the growth of pluripotent cells in different types of defined spaces triggered very specific gene networks that determined the ultimate fate for the cells, which may help to harness stem cells for medical uses.[2]

From Skin to Organs

Since the first derivation of primary embryonic stem cells in 1995 and the first cloning of a mammal (Dolly the sheep) in 1996, this new field has achieved promising breakthroughs.

The most common regenerative therapies using stem cells begin with a patient's own cells.

In 2007, the Armed Forces Institute of Regenerative Medicine (AFIRM) was created by the U.S. Army Medical Research and Materiel Command to lead the efforts to develop advanced regenerative medicine techniques for injured U.S. military personnel. Dr. Rocky Tuan, founding director of the Center for Military Medicine Research at the University of Pittsburgh and co-director at AFIRM, says the institution currently has more than 60 projects in its portfolio. One of these is skin regeneration, which includes treating burns and scars that are common among injured service personnel. Regenerative medicine does away with skin transplants and instead allows skin to grow back naturally using the patient's own cells. With the "spray-on" skin, doctors harvest a small piece of skin (smaller than what is required for grafts) that is broken down using an enzyme solution and sprayed back onto the damaged skin. The product, ReCell (marketed by Avita Medical), is one of a limited number of regenerative procedures.[8]

Another project at AFIRM involves regenerating cartilage. Osteoarthritis, a degenerative joint condition often associated with older generations, is becoming prevalent among soldiers due to the physical demands of operational tours, including carrying heavy loads over long distances. Earlier this year, Dr. Tuan unveiled a procedure for 3D print cartilage grown from human stem cells. Creating the artificial cartilage requires stem cells, biological factors to make the cells grow into cartilage and a scaffold. The 3-D printing extrudes thin layers of stem cells in a solution that retains its shape (acting as a scaffold) and provides growth factors.[8] The 3-D technology to grow cartilage was first developed by researchers at St. Vincent's Hospital Melbourne, part of the University of Wollongong-headquartered Australian Research Council Centre of Excellence for Electromaterials Science (ACES). Their product uses scaffolds fabricated on 3-D printing equipment to grow cartilage over a 28-day period from stem cells extracted from tissue under the knee cap.[9] Prior to this, the only product on the market for cartilage damage was Carticel (Genzyme), the first and only cell therapy that uses the patient's own cartilage cells, called

chondrocytes, and implants them into the damaged area that then grows to form new cartilage.[8]

Regrowing muscle on patients with leg injuries is also part of AFIRM's projects. Dr. Stephen Badylak, a regenerative medicine specialist at the University of Pittsburgh, is testing implants of "extracellular matrix" (connective tissue that holds cells together) to boost muscle mass. The material, supplied by ACell Inc., comes from pigs and is thought to release chemical signals that promote regrowth of healthy tissue instead of scar tissue. A study of the treatment is measuring changes in strength and muscle volume, and in early testing, patients have shown up to 10 percent to 20 percent improvement in strength of the muscle after treatment.[10]

Using scaffold seeded with a patient's own cells is a growing area of research. Scientists at the McGowan Institute at the University of Pittsburgh Medical Center are working on a method to encourage the growth of healthy tissue instead of scar tissue to reconstruct the esophagus and trachea (part of the food tube). In early studies, a damaged section of the food tube was replaced with a specially formed scaffold constructed from a material already being used in humans, and within 90 days, the scaffold was replaced with functional tissue. They are also developing scaffolds made of U.S. Food and Drug Administration (FDA)-approved biodegradable polymers and protein beads to help the peripheral nervous system regrow. The scaffolds act as guides for axons, the long arms of nerve cells, to grow longer and in the right directions. In early studies, a nerve guide seeded with stem cells derived from fat restored some hind leg mobility in paralyzed rats.[11]

Much more other research in regenerative medicine is ongoing. Scientists at the University of Pittsburgh and Rice University are working on growing bone to fix jawbone and other facial defects. Researchers at Massachusetts General and Rutgers University are trying to grow eyelid muscles.[10] And, in August, FDA gave approval to Asterias Biotherapeutics Inc. to begin a clinical trial of its stem cell therapy in patients with spinal cord injury. The Phase I/IIa clinical trial is a follow-on to the California Institute for Regenerative Medicine-funded trial begun by Geron Corp. in 2010, which was halted. This new trial will involve doses of stem cells up to 10 times greater than the initial study in which follow-up studies of the five patients have shown no serious side effects, and in four of five patients, MRI scans have shown that the actual injury site had shrunk and that the cells may have had some positive effects in reducing the deterioration of spinal cord tissue.[12]

The first success of regenerative medicine of organs in humans occurred in 2006 when scientists at Wake Forest University successfully implanted bladders grown in a laboratory into patients with bladder disease. Last year, a bioengineered windpipe was implanted into a 2-year-old girl, the youngest person ever to receive a lab-grown organ and only the sixth operation of its kind in the U.S.[8]

Other artificial organs are also being studied. In 2011, researchers at Japan's RIKEN Center derived a working pituitary gland from mouse stem cells. To grow a working pituitary gland, a hypothalamus is needed. To overcome this, the researchers created a 3-D cell culture and tried combinations of signaling factors until it worked. They then implanted the lab-grown glands into mice with pituitary defects, and the mice quickly showed restored levels of key pituitary hormones, and behavioral symptoms of pituitary problems disappeared.[13]

Using scaffold seeded with a patient's own cells is a growing area of research.

This year, British scientists at the University of Edinburgh became the first in the world to grow a fully functional organ — a thymus — from scratch by transplanting cells originally made in a cell. They converted connective tissue cells from a mouse embryo directly into a completely different cell strain by flipping a genetic switch in their DNA. The resulting thymic epithelial cells were mixed with other thymus cell types and transplanted into mice, where they spontaneously organized themselves and grew into a whole structured organ. According to Professor Clare Blackburn of the Medical Research Council Centre for Regenerative Medicine at the University of Edinburgh: "The ability to grow replacement organs from cells in the lab is one of the 'holy grails' in regenerative medicine. But the size and complexity of lab-grown organs has been limited. By directly reprogramming cells, we've managed to produce an artificial cell type that, when transplanted, can form a fully organized and functional organ."[14]

Policy and Legislation

Over the years, FDA has offered courses in regenerative medicine, including a two-day interactive course in 2006 titled "FDA's Regulation of Regeneration Medicine including Stem Cell Treatments, Tissue Engineering and Gene Therapies" and its Regenerative Medicine Program, a multi-center fellowship in regenerative medicine.[15,16]

FDA is the key gatekeeper for the regulatory pathway for regenerative medicine products. It rates each product by deconstructing the key components of each to determine which ones are most important in providing benefit to the patient. For example, if the regenerative medicine product consists of living cells that are delivered to the patient, it would

be regulated as a cellular therapy. If it consists of cells that are genetically modified outside of the body and given to the patient, it would be considered gene therapy. If it consists of cells that are combined with a natural synthetic biomaterial, it would be regulated as a biologic-device combination product.[17]

In 2010, the National Institutes of Health established the NIH Center for Regenerative Medicine (NIH CRM), which according to its website, is currently "at a transition point." In May, it held a workshop with leaders in the field to help prioritize challenges to be addressed. The goal of NIH CRM is to work through hurdles to the development of induced pluripotent stem cell therapies.[18]

Regenerative therapies are now being hailed as the future of medicine.

In March, ARM introduced the Regenerative Medicine Promotion Act of 2014 in the U.S. Senate. Major provisions of the bill include creation of a multi-agency Regenerative Medicine Coordinating Council within the Department of Health and Human Services, and calling for a detailed assessment of federal activities in regenerative medicine, as well as progress compared with national programs in other countries. The goal of the bill is to outline a coordinated effort to allow the U.S. to "advance toward innovative, life-saving therapies and create the regulatory infrastructure necessary to encourage private investment in promising regenerative medicine research," said Morrie Ruffin, managing director of ARM. "Dovetailing with this bill, ARM has outlined a national strategy for regenerative medicine and is seeking rapid implementation of these programs," said Michael Werner, executive director of ARM. "To date, ARM has worked with the White House, the U.S. Food and Drug Administration, National Institutes of Health, National Institute of Standards and Technology and members of Congress to further define and promote adoption of this proposed strategy."[19]

The Future of Medicine

Regenerative therapies are now being hailed as the future of medicine. According to ARM, "the promise of regenerative medicine is that altering the course of disease will eliminate the need for daily therapies, reduce hospitalizations and avert expensive medical procedures, thus enabling patients to lead healthier and more productive lives." Much has been accomplished in the last two decades, with significant growth in the number of companies focused on regenerative medicine and considerably more research being conducted than mentioned in this article. "Regenerative medicine is not just a future hope," says ARM. "It's a reality today."[4] ❖

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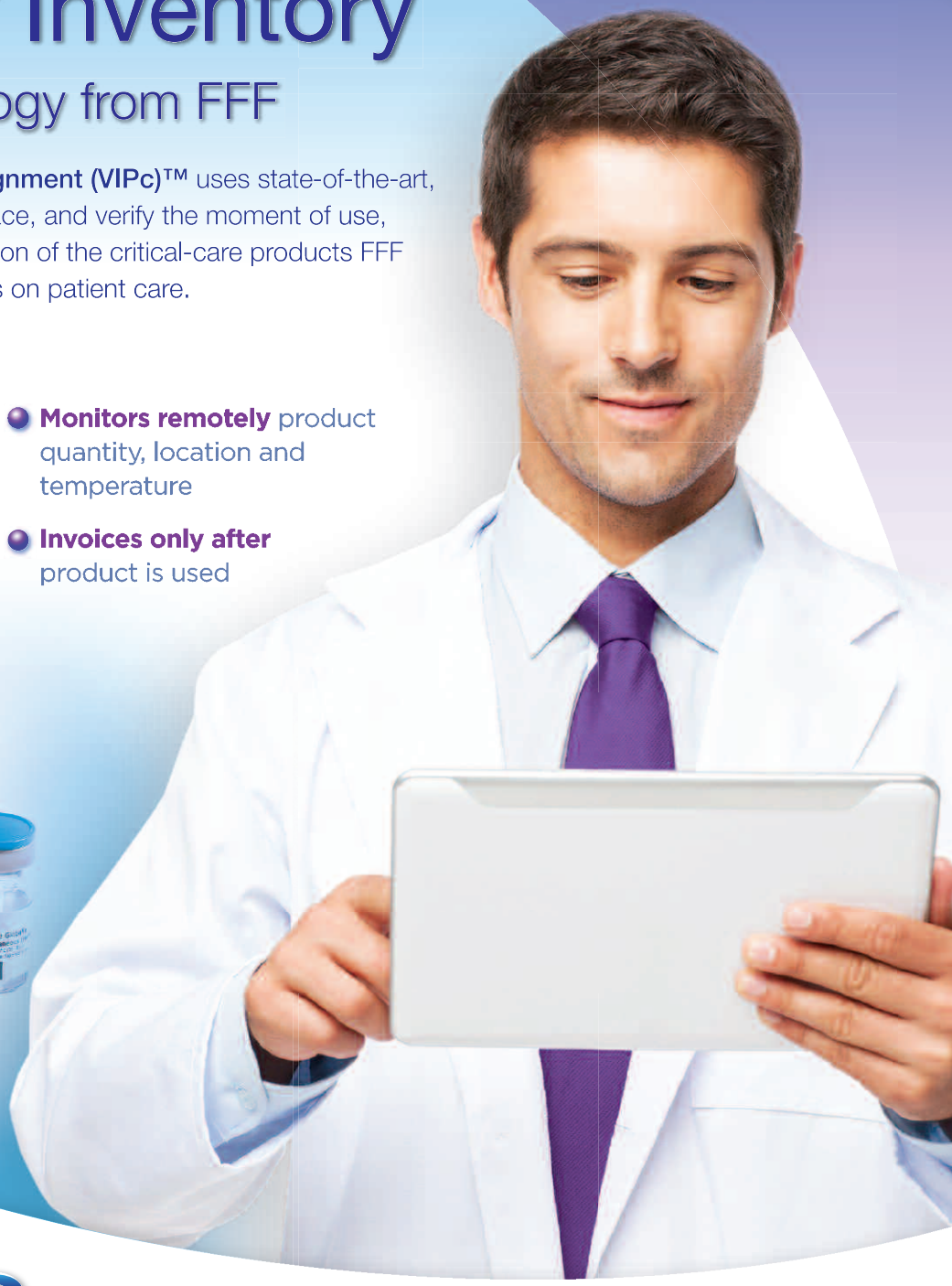

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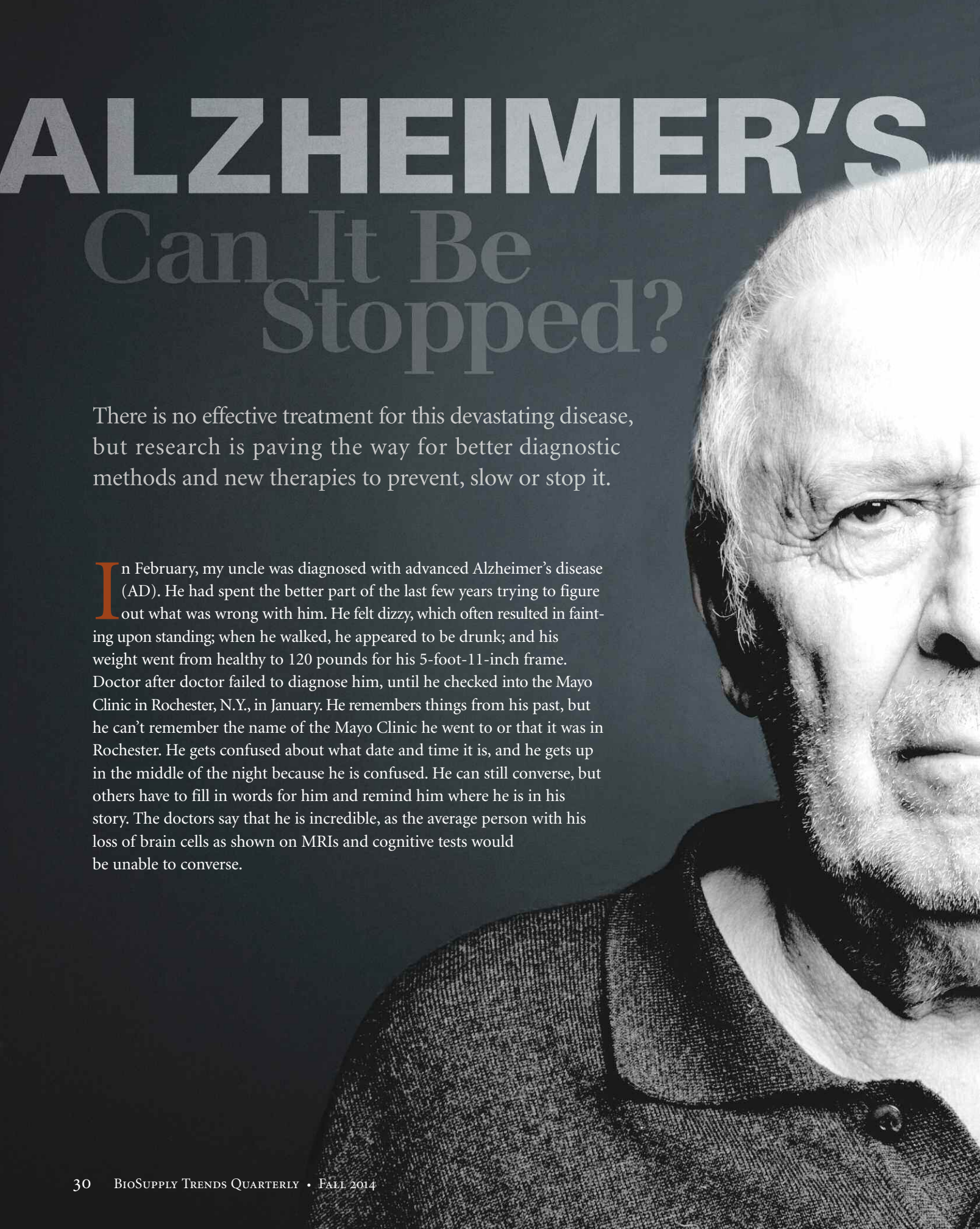
ALZHEIMER'S
Can It Be Stopped?

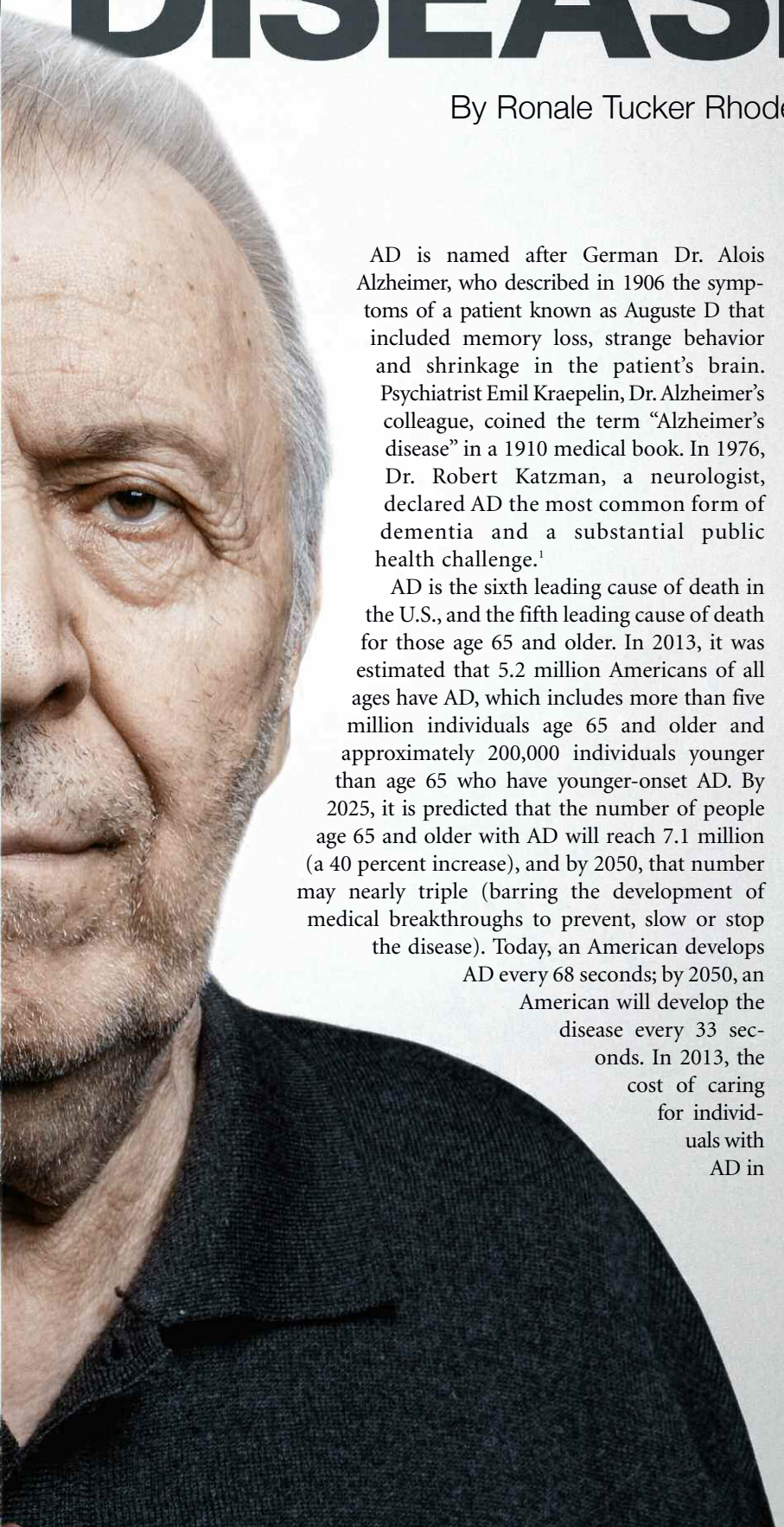
There is no effective treatment for this devastating disease, but research is paving the way for better diagnostic methods and new therapies to prevent, slow or stop it.

In February, my uncle was diagnosed with advanced Alzheimer's disease (AD). He had spent the better part of the last few years trying to figure out what was wrong with him. He felt dizzy, which often resulted in fainting upon standing; when he walked, he appeared to be drunk; and his weight went from healthy to 120 pounds for his 5-foot-11-inch frame. Doctor after doctor failed to diagnose him, until he checked into the Mayo Clinic in Rochester, N.Y., in January. He remembers things from his past, but he can't remember the name of the Mayo Clinic he went to or that it was in Rochester. He gets confused about what date and time it is, and he gets up in the middle of the night because he is confused. He can still converse, but others have to fill in words for him and remind him where he is in his story. The doctors say that he is incredible, as the average person with his loss of brain cells as shown on MRIs and cognitive tests would be unable to converse.



DISEASE

By Ronale Tucker Rhodes, MS



AD is named after German Dr. Alois Alzheimer, who described in 1906 the symptoms of a patient known as Auguste D that included memory loss, strange behavior and shrinkage in the patient's brain. Psychiatrist Emil Kraepelin, Dr. Alzheimer's colleague, coined the term "Alzheimer's disease" in a 1910 medical book. In 1976, Dr. Robert Katzman, a neurologist, declared AD the most common form of dementia and a substantial public health challenge.[1]

AD is the sixth leading cause of death in the U.S., and the fifth leading cause of death for those age 65 and older. In 2013, it was estimated that 5.2 million Americans of all ages have AD, which includes more than five million individuals age 65 and older and approximately 200,000 individuals younger than age 65 who have younger-onset AD. By 2025, it is predicted that the number of people age 65 and older with AD will reach 7.1 million (a 40 percent increase), and by 2050, that number may nearly triple (barring the development of medical breakthroughs to prevent, slow or stop the disease). Today, an American develops AD every 68 seconds; by 2050, an American will develop the disease every 33 seconds. In 2013, the cost of caring for individuals with AD in America is estimated at $203 billion, and the cost is predicted to increase to $1.2 trillion by 2050.[2]

AD is perhaps one of the most devastating and frightening diagnoses a person can receive. There is no cure, and the future is certain: a cognitive decline so great that the individual's brain essentially dies, eventually rendering that person incapable of remembering anyone or anything or of having a simple conversation.

AD is the sixth leading cause of death in the U.S., and the fifth leading cause of death for those age 65 and older.

What Is AD?

AD is the most common form of dementia — a general term for loss of memory and other intellectual abilities serious enough to interfere with daily life — accounting for 50 percent to 80 percent of dementia cases. It is not a normal part of aging, despite the fact that age is the greatest known risk factor and the majority of people with AD are 65 and older. Only 5 percent of people with AD have early-onset AD, which usually occurs in people in their 40s and 50s.[3]

Scientists first linked amyloid plaques to AD more than 100 years ago, when Dr. Alzheimer documented unusual protein knots in the brain of his patient during an autopsy. By the mid-1980s, scientists determined that the plaques are made up of a protein they named beta-amyloid, which healthy neurons produce plenty of, but which the purpose of is still unknown. It is known that in the early stages of AD

and other neurodegenerative disorders, beta-amyloid proteins begin to behave strangely by sticking together to form larger and larger clumps.[4]

These clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles) are two of the main features of AD. The third is the loss of connections between nerve cells (neurons) in the brain. This damage to the brain starts a decade or more before problems typically appear. During the preclinical stage of AD, individuals are free of symptoms but toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain, causing once-healthy neurons to begin to work less efficiently. Eventually, those neurons lose their ability to function and communicate with each other, and they die. After that, the damage spreads to a nearby structure in the brain called the hippocampus, which is essential in forming memories. And, as more neurons die, affected brain regions begin to shrink. By the final stage of AD, damage is widespread, and brain tissue has shrunk significantly.[5]

What Causes AD?

What causes AD is not known, but risk factors have been identified, including age, family history and heredity. Age is the greatest known risk factor, and after age 65, the likelihood of developing AD doubles about every five years. After age 85, the risk reaches nearly 50 percent. Those who have a parent, brother, sister or child with AD are more likely to develop the disease, and the risk increases if more than one family member has AD.

The Alzheimer's Association has broken the symptoms of AD into seven stages.

When diseases tend to run in families, it is believed that either heredity or environmental factors, or both, may play a role. Scientists know that genes play a role in AD. There are two types of genes that can affect whether a person develops AD: risk genes and deterministic genes. Risk genes increase the likelihood of developing AD, but don't guarantee it. The risk gene with the strongest influence is E-e4 (APOE-e4), with estimates that this gene may be a factor in 20 percent to 25 percent of AD cases. Everyone inherits a copy of some form of APOE from each parent. While scientists aren't certain how APOE-e4 increases risk, they do know that those who inherit the gene from one parent have an increased risk of AD, and those who inherit it from both parents have an even higher risk. In addition, the APOE-e4 gene may make AD symptoms appear at a younger age. Genetic tests are available for this gene, but they are not recommended.

Deterministic genes directly cause a disease. Anyone who inherits one of the three deterministic genes for AD — amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2) — will develop autosomal dominant AD (ADAD), also known as familial AD. Symptoms nearly always develop before age 60, and may appear in the 30s or 40s. It should be noted that deterministic AD variations have been found in only a few hundred extended families worldwide, accounting for less than 5 percent of cases.[6]

There are a few other theories about what causes AD that are being investigated. One theory centers on chemicals. Studies of AD patients' brains have uncovered diminished levels of various neurotransmitters (the chemicals that allow white brain cells to communicate with one another) that are thought to influence intellectual functioning and behavior. An alternate chemical theory is aluminum since increased deposits of the metal have been found in AD brains.[7] However, while aluminum emerged as a possible suspect in causing AD during the 1960s and 1970s, studies have failed to confirm any role.[6]

Other theories being studied are that AD is an autoimmune disease in which the body's immune system attacks itself; a slow virus theory, which has been identified as a cause of some brain disorders that closely resemble AD; and a blood vessel theory in which there are defects in blood vessels supplying blood to the brain.[7]

Symptoms of AD

The Alzheimer's Association has broken the symptoms of AD into seven stages. In stage one, there is no impairment and no symptoms. In stage two, there is very mild cognitive decline, which may be either normal age-related changes or early signs of AD, but no symptoms of dementia can be detected during a medical exam or by friends or family.

In stage three, there is mild cognitive decline (known as early-stage AD) that friends or family begin to notice, including noticeable problems coming up with the right word or name, trouble remembering names when introduced to new people, having noticeably greater difficulty performing tasks in social or work settings, losing or misplacing a valuable object, and increasing trouble with planning or organizing. At this stage, doctors may be able to diagnose AD in some people.

In stage four, there is moderate cognitive decline, also known as early-stage AD, and symptoms include forgetfulness of recent events, impaired ability to perform mental arithmetic, greater difficulty performing complex tasks (e.g., planning dinner for guests or paying bills), forgetfulness about one's own personal history, and becoming moody or withdrawn. A careful medical interview should be able to detect clear-cut

symptoms of AD at this stage.

In stage five, there is moderately severe cognitive decline, known as moderate or mid-stage AD. At this stage, individuals show noticeable symptoms, including the inability to recall their own address or telephone number, becoming confused about where they are or what day it is, trouble with less-challenging mental arithmetic, needing help choosing proper clothing and remembering significant details about themselves and their family. However, while they need help with day-to-day activities, they still require no assistance with eating or using the toilet.

In stage six, there is severe cognitive decline, known as moderately severe or mid-stage AD. At this stage, the individual's memory begins to worsen, personality changes may take place, and they may need extensive help with daily activities. Symptoms include losing awareness of recent experiences and their surroundings, remembering their own name but having difficulty with their personal history, distinguishing familiar and unfamiliar faces but having trouble remembering the name of a spouse or caregiver, needing help dressing properly, experiencing major changes in sleep patterns, needing help handling details of toileting, having increasingly frequent trouble controlling their bladder or bowels, experiencing major personality and behavioral changes, and tending to wander or become lost.

Stage seven is the last stage in which there is very severe cognitive decline, known as severe or late-stage AD. This is the final stage of the disease during which individuals lose their ability to respond to their environment, carry on a conversation and, eventually, to control movement. At this stage, the individual may also lose the ability to smile, to sit without support and to hold their heads up. Their reflexes become abnormal, their muscles grow rigid, and their swallowing is impaired. In this final stage, the patient is bedridden.[8]

One symptom that is not listed in the seven stages and is being investigated as an early sign of AD is weight loss. In a study published in the *Archives of Neurology*, the researchers found that a subtle speeding up of weight loss that can accompany aging may be a very early warning sign of AD. Older people in the study who were followed for an average of six years lost twice as much weight in the year before the first signs of dementia appeared as people who did not develop Alzheimer's-related dementias — 1.2 pounds compared with 0.6 pounds per year. While the study's authors said the acceleration in weight loss was too small to help physicians identify AD earlier in individual patients, they did think the finding may help researchers better understand the disease.[9]

More recently, a study found that non-overweight individuals in their late 60s, 70s and early 80s who have no outward symptoms of Alzheimer's are more likely than their heavier peers to have biological markers of AD. In the study, researchers looked at 101 people who underwent brain scans designed to identify the plaques and abnormal tangle of proteins thar are the hallmark of AD, and another 405 people whose cerebrospinal fluid was analyzed for fragments of the beta-amyloid peptide and tau proteins. Each group included some people with AD, some with mild cognitive impairment and some with no signs of mental deterioration. There was no connection between body mass index (BMI) and AD biomarkers in the patients who had AD. But, in the other two groups, lower BMI was associated with higher levels of biomarkers and a higher likelihood of having brain plaques and tangles. For instance, among people

There are some new biomarkers that are being investigated for diagnosing AD.

with mild cognitive impairment, 85 percent of non-overweight individuals had signs of these brain abnormalities compared with just 48 percent of those who were overweight or obese. According to the researchers, the finding raises the possibility that weight loss or a low BMI later in life may be an early warning sign of mental decline. Jeffrey M. Burns, the lead author of the study and the associate director of the University of Kansas Alzheimer's Disease Center, said that well before memory loss and other symptoms appear, AD may trigger metabolism changes that promote weight loss. "In general, we think of Alzheimer's as a brain disease," Burns said. "But, this is evidence that there are systemic problems throughout the body in the early stages of Alzheimer's."[10,11]

Another symptom that also is not included in the seven stages and that is being investigated to identify AD patients at high risk of rapid cognitive decline is balance. In a study published in the *Journal of Alzheimer's Disease*, 686 AD patients were evaluated by a geriatrician every six months for up to two years to measure their degree of cognitive impairment. At the same time, a "one-leg balance" test was given during which participants were asked to stand on one leg for as long as possible. The test was considered abnormal when the participant was unable to stand on one leg for five seconds or more. At the outset, roughly 15 percent of the study subjects had an abnormal one-leg balance test, and these patients were significantly older and had significantly more severe cognitive impairment. In analyses taking into account factors that might influence the results, the researchers found that subjects with an abnormal one-leg balance test had significantly greater decline in memory and thinking at 12 months, 18 months and 24 months. "Our results reinforce, in an Alzheimer's disease population, the

growing evidence suggesting a link between physical performance and cognitive decline," said study chief Dr. Yves Rolland of the University of Toulouse III in France. "If these results are confirmed by other data, the one-leg balance test could be adopted in clinical practice to identify Alzheimer's disease patients at risk of rapid decline."[12]

Diagnosing AD

The only way to make a definite diagnosis of AD is to determine whether there are plaques and tangles in the individual's brain tissue, which can only be done in an autopsy. Therefore, doctors must make a possible or probable AD diagnosis. Fortunately, at specialized centers such as the Mayo Clinic, doctors can correctly diagnose AD up to 90 percent of the time. To do this, they utilize several tools: a complete medical history, which includes information about the person's general health, past medical problems and any difficulties the person has carrying out daily activities; medical tests such as tests of blood, urine and spinal fluid, which help discover other possible diseases causing the symptoms; neuropsychological tests that measure memory, problem solving, attention, counting and language; and brain imaging studies using magnetic resonance imaging (MRI) or positron emission tomography (PET). It's important for physicians to rule out other possible causes of the person's symptoms using information from the medical history and test results. For instance, thyroid problems, drug reactions, depression, brain tumors and blood vessel disease in the brain — all of which can be successfully treated — can cause AD symptoms.[13]

There are some new biomarkers that are being investigated for diagnosing AD. In the past 10 years, scientists have developed sophisticated brain scans that can estimate the amount of plaque in the brain while people are still alive. These scans have proved useful in studying the earliest stages of AD before overt symptoms appear. One such scan is called Amyvid, which was approved in 2012 by the U.S. Food and Drug Administration (FDA). Amyvid was built on an approach developed a dozen years ago at the University of Pittsburgh. In that approach, researchers injected patients with a small, benign amount of a radioactive dye they named Pittsburgh compound B, or PiB. The dye traveled through the blood to the brain and clung exclusively to clusters of amyloid protein. Scanning the brain with a PET machine then produced images that highlighted any plaques by detecting radiation in the form of gamma rays emanating from the dye. Scientists at Philadelphia-based Avid Radiopharmaceuticals then developed a longer-lasting dye that gave clinicians more time to scan their patients, and the result was Amyvid, which Eli Lilly bought in 2010 for $300 million. Today, the test is available in more than 450 imaging centers at a cost of $3,000 or more.

But, the use of Amyvid is under debate. Officially, the test has been approved primarily to exclude AD as a diagnosis for someone who already has cognitive impairment, which can be particularly helpful when causes are unclear. But, in January 2013, an expert task force convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging published guidelines that advised limiting the test's use to patients with unexplained, persisting mild cognitive impairment and to those who either have developed dementia unusually early or have dementia with atypical symptoms such as hallucinations or delirium. It also advised against amyloid scans for people with no cognitive impairment. Because there is no treatment for AD, panelists worried that amyloid-positive results might send some vulnerable individuals into depression or perhaps suicide, and that it might make it harder for an individual to get long-term care

insurance or renew a driver's license. A clinical trial began last November to quell the controversy. The study at 60 U.S. medical centers aims to screen 3,000 healthy senior citizens to identify 1,000 amyloid-positive individuals who will receive either a drug therapy for AD called solanezumab or a placebo for three years. But, the study is accepting only participants who are "capable of handling uncertainty and, potentially, what could be construed as bad news if they learn that they are amyloid-positive on imaging." The trial's results are not expected until 2018.[4]

Blood tests are another new method being investigated for diagnosing AD earlier than the current brain scans and cognitive tests. In a recent trial at Saarland University and Siemens Healthcare, scientists compared and contrasted 140 microRNAs (non-coding genetic molecules) of a sample group of 202 people made up of AD patients and a healthy control group. They found that 12 of the microRNAs differed significantly between the AD patients and the healthy group. By using those 12 as biomarkers, the technique accurately identified the presence of AD 93 percent of the time. It also distinguished AD from similar neurodegenerative diseases such as Parkinson's and early-onset dementia. Researchers now need to ensure the accuracy of the biomarkers and get the test approved for clinical use.[14]

Even better, in March, researchers at Georgetown University in Washington, DC, developed a blood test that identifies 10 chemicals in the blood associated with the disease two to three years before symptoms start, and it might be able to predict Alzheimer's decades earlier. The researchers studied 525 people age 70 and older for five years who showed no signs of mental impairment at the start of the study. Each year, the team performed a detailed cognitive examination and took blood samples from all participants. During that time, 28 people developed Alzheimer's or mild cognitive impairment, which is thought to be the earliest noticeable sign of dementia. An analysis of the participants' blood highlighted 10 metabolites that were depleted in those with mild cognitive impairment who went on to get Alzheimer's compared with those who didn't. In subsequent trials, the team showed these chemicals could predict who would go on to get Alzheimer's within the next three years with up to 96 percent accuracy. Once verified in a larger group, the test should provide a cheap and quick way of predicting Alzheimer's. And, because the brain changes associated with Alzheimer's begin many years before symptoms occur, "these metabolic changes might occur 10 or 20 years earlier," says team member Mark Mapstone at the University of Rochester Medical Center in New York. "That would give us a real head start on predicting the disease."[15]

Researchers at Georgetown University Medical Center (GUMC) and the University of Hong Kong also have found a new biomarker for possibly diagnosing AD by simply screening for changes in the eyes. In their study, the scientists showed how the thicknesss of a particular layer of retinal cells may serve as an indication of AD progression. They analyzed the thicknesses of the six layers of retinas in a group of mice that had been genetically engineered to develop AD. They found that there was significant loss in thickness to both the inner nuclear layer, which experienced an average 37 percent loss of neurons, and the retinal ganglion cell layer, which experienced an average 49 percent loss. "The retinas have neurons themselves that send projections straight to the brain," said Dr. R. Scott Turner, director of the Memory Disorder Program at GUMC. "Those nerve cells are directly connected to the brain via the optic nerve.… So, when looking at the retina, it's the easiest place to see the brain and its neurons." The next step is to see if the biomarker translates to humans with AD. If similar changes in retinal thickness occur in people, then a simple, noninvasive procedure known as optical coherence tomography can be used to measure loss of neurons in these layers.[16]

Last, a new clinical test to confirm a diagnosis of early-stage AD is being examined at the University of Florida. In a small pilot study, patients who were coming to the university's College of Medicine's department of neurology to be tested for AD also sat down with a clinician who had 14 grams of peanut butter, which equals about 1 tablespoon, and a metric ruler. With the patients' eyes and mouth closed and one nostril blocked, the clinician opened the peanut butter container and held the ruler next to the open nostril while the patient breathed normally. By moving the peanut butter up the ruler 1 cm at a time during the patient's exhalation, the researcher was able to measure the distance at which the patient could detect the odor. The other nostril was tested after a 90-second delay. The scientists found that patients in the early stages of AD had a dramatic difference in detecting odor between the left and right nostril. The left nostril was impaired and did not detect the smell until it was an average of 10 cm closer to the nose than the right nostril. This was not the case in patients with other kinds of dementia; these patients had either no differences in odor detection between nostrils or the right nostril was worse at detecting odor than the left.

There are currently four medications approved by FDA to treat AD.

Of the 24 patients tested who had mild cognitive impairment, which sometimes signals AD and sometimes turns out to be something else, about 10 patients showed a left nostril impairment and 14 patients did not. The clinicians running the test did not know the patients' diagnosis, which was con-

firmed weeks after the initial clinical testing. It's possible that this test could be used by clinics that do not have access to the personnel or equipment to run other, more elaborate tests required for a diagnosis.[17]

Treating AD

There are currently four medications approved by FDA to treat AD. The first was a result of a collaboration between the National Institute on Aging (NIA), the Alzheimer's Association and the Warner-Lambert Pharmaceutical Company (now known as Pfizer) in 1987. Together, they started the first clinical trial of a drug, tacrine (Cognex), designed to treat the symptoms of AD, which was approved by FDA in 1993. Four more Alzheimer's drugs were approved during the next decade.[1]

The only way to make a definite diagnosis of AD is to determine whether there are plaques and tangles in the individual's brain tissue, which can only be done in an autopsy.

Tacrine (now discontinued in the U.S. because of its serious side effects) is in a class of drugs called cholinesterase inhibitors, which are used to treat mild to moderate AD. Currently, the three FDA-approved drugs in this class are rivastigmine (Exelon), donepezil (Aricept) and galantamine (Razadyne, formerly Reminyl). Donepezil is the only cholinesterase inhibitor approved to treat all stages of AD, including moderate to severe. Cholinesterase inhibitors inhibit (block) the action of acetylcholinesterase, the enzyme responsible for the destruction of acetylcholine. Acetylcholine is one of several neurotransmitters in the brain, chemicals that nerve cells use to communicate with one another. Reduced levels of acetylcholine in the brain are believed to be responsible for some of the symptoms of AD. By blocking the enzyme that destroys acetylcholine, the drugs increase the concentration of acetylcholine in the brain, and this increase is believed to be responsible for the improvement in thinking, memory and speaking skills, and may help with certain behavioral problems.[18,19]

Memantine (Namenda) is another drug approved by FDA to treat moderate to severe AD. Memantine is prescribed to improve memory, attention, reason, language and the ability to perform simple tasks. The drug regulates the activity of glutamate, a different messenger chemical involved in learning and memory; delays worsening of symptoms for some people temporarily; and can cause side effects, including headache, constipation, confusion and dizziness. And, it can be used alone or with other AD treatments. Individuals who are taking a cholinesterase inhibitor might also benefit by taking memantine.[20]

It should be noted that none of the FDA-approved drugs has been directly compared with another, and while patients may respond better to one drug than to another, they work in a similar way, and it is not expected that switching from one to another will produce significantly different results. In addition, these drugs don't change the underlying disease process. And, while they are effective for some but not all people, they may help only for a limited time.[19]

As with most diseases, there also are many alternative treatments. These include caprylic acid (Ketasyn), coenzyme Q10 (ubiquinone), coral calcium, ginkgo biloba, huperzine A, omega-3 fatty acids, phosphatidylserine and tramiprosate (ViviMind). However, claims about the safety and effectiveness of these products are based largely on testimonials, tradition and a small body of scientific research.[20]

The Future of AD

Today, AD is at the forefront of biomedical research, and the future of the disease will depend on furthering our understanding of it, diagnosing it early and discovering ways to prevent, treat and even cure it.

Diagnosing it early and preventing it could be a matter of genetics. In a recent study, a research team divided 52 participants between the ages of 32 and 72 who were free of dementia into four groups: those who had either a mother with AD, a father with AD, both parents with AD or no family with AD. After participants underwent a series of brain scans, including an MRI and PET, researchers found that those whose mother and father both had AD showed 5 percent to 10 percent more brain plaques in specific brain regions and more severe brain abnormalities in brain volume and metabolism compared with people who had one parent or no family members with AD. They also found that those who have mothers with AD are more likely to develop the condition compared with people who have fathers with the disease.[21] The hope is that the study will be helpful to future genetic investigations, one of which is currently ongoing. In 2003, the Alzheimer's Association and the NIA started accepting people in the National Alzheimer's Disease Genetic Study. Funded by the federal government, researchers take and store blood samples from people in

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PROFILNINE is a mixture of vitamin K-dependent clotting factors IX, II, X, and low levels of VII and is stable for 3 years at room temperature (provided that the storage temperature does not exceed 25 °C [77 °F]).

Potency	Diluent Size	NDC Numbers
500 IU FIX Range	5 mL	68516-3201-1
1000 IU FIX Range	10 mL	68516-3202-2
1500 IU FIX Range	10 mL	68516-3203-2

Important Safety Information

PROFILNINE® (factor IX complex) is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B). PROFILNINE contains non-therapeutic levels of factor VII and is not indicated for use in the treatment of factor VII deficiency.

Because PROFILNINE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The use of factor IX concentrates has historically been associated with development of thromboembolic complications, and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis, or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. PROFILNINE should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

After repeated treatment with PROFILNINE, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. As with intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, or manifestation of allergic reactions.

During post-approval use of PROFILNINE, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis of disseminated intravascular coagulation (DIC) have been reported.

Do not administer PROFILNINE at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Please see brief summary of PROFILNINE Package Insert on adjacent page.

Mix2Vial® is a registered trademark of Medimop Medical Projects, Ltd., a subsidiary of West Pharmaceutical Services, Inc.

For more information: **Grifols Biologicals Inc.**
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GRIFOLS

Profilnine®

Factor IX Complex

Solvent Detergent Treated/Nanofiltered

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

DESCRIPTION

Factor IX Complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine does not contain heparin and contains no preservatives. Profilnine contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.

Profilnine is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment have been incorporated into the Profilnine manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step. The ability of the manufacturing process to eliminate virus from Profilnine was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvovirus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloped viruses.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo[a]	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Non-Env	Hepatitis B	NT	NT	≥ 5.3

[a] Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

INDICATIONS AND USAGE

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).

Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such products can potentially transmit disease: therefore the risk of infectious agents cannot be totally eliminated. The physician must weigh the risks and benefits of using this product and discuss these issues with the patient. Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX complex concentrates is recommended.

The use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. Profilnine should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Exercise caution when handling Profilnine due to the limited risk of exposure to viral infection. Discard any unused Profilnine vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse components.

Information for Patients

After repeated treatment with Profilnine, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. Patients must be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients must be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care if these symptoms occur.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine. It is also not known whether Profilnine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 have not been established. However, across a well controlled half-life and recovery clinical trial in patients previously treated with factor IX concentrates for Hemophilia B, the two pediatric patients receiving Profilnine responded similarly when compared with the adult patients.

ADVERSE REACTIONS

As with other intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling lethargy, hives, or manifestation of allergic reactions.

In addition, during post-approval use of Profilnine, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) have been reported. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

* Unit refers to International Unit in the labeling of Profilnine.

Rx only

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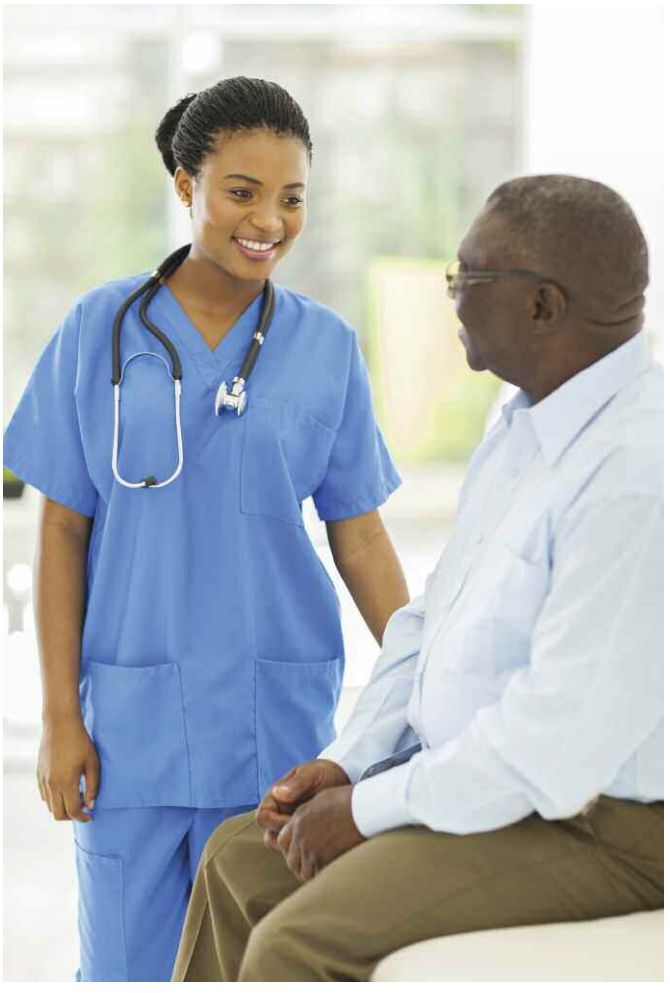
families with more than one member with AD. The goal of the ongoing study is to find genes that may make someone more likely to get AD.[1]

There are many studies that are focusing on development therapies for AD, many of which fall under the Alzheimer's Disease Cooperative Study (ADCS), a large clinical trials consortium supported by the NIA with sites throughout the U.S. that is investigating both the cognitive and behavioral symptoms of AD. Some of the recent therapies being investigated are intravenous immune globulin (IVIG), resveratrol and nerve growth factor. IVIG contains naturally occurring antibodies against beta-amyloid. Preliminary studies have shown that it may improve cognition, increase levels of anti-beta-amyloid antibodies in plasma, and promote clearance of beta-amyloid from cerebrospinal fluid. Baxter conducted one NIA-supported IVIG study, known as the GAP study, which was a Phase III double-blind, placebo-controlled study to examine the safety, effectiveness and tolerability of IVIG in people with mild to moderate AD.[22] Unfortunately, the study did not meet its co-primary endpoints of reducing cognitive decline and preserving functional abilities in patients with mild to moderate AD. Therefore, the company is reconsidering the current approach for the AD program, and will determine next steps after full data analyses.[23]

Grifols also is currently undergoing its own study, the AMBAR (Alzheimer Management by Albumin Replacement) study, to determine whether plasmapheresis with infusion of human albumin combined with IVIG is able to modify cognitive, functional, behavioral and global domains in patients with mild to moderate Alzheimer's disease. Begun in July 2012, the

Some of the recent therapies being investigated are intravenous immune globulin, resveratrol and nerve growth factor.

study is being conducted in hospitals in Spain and the United States and includes 350 Alzheimer's patients at the mild to moderate stage of the disease, randomly grouped into three treatment groups and a fourth control group. The treatment groups consist of plasmapheresis with 20% albumin and IVIG high dose, plasmapheresis with infusion of 20% albumin and



IVIG low dose and plasmapheresis with infusion of 20% albumin low dose. Patients will be treated with a propotype of a plasmapheresis machine developed by Fenwal that was specially adapted to make the treatment experience more pleasant for the patient and easier for the medical staff to administer, which the study also seeks to validate. The estimated duration of the study is two years.

In September 2009, Grifols published partial results (29 patients out of 42) of a preliminary trial conducted in two hospitals in Spain and two in the U.S., which showed a tendency for the treatment to stabilize the disease. "This study is the fruit of over five years of research that have produced encouraging results, with patients receiving prior treated maintaining cognitive stability through the study period and achieving positive ADAS-cog scores," said Dr. Merce Boada, medical director of Fundacio ACE and clinical head of the Neurology Service of the Vail d'Hebron Hospital in Barcelona. "The AMBAR study opens up new prospects and hopes in dealing with an illness where success involves maintaining the quality of life of these patients."[24]

Resveratrol is an antioxidant compound found in grapes and red wine. Observational studies have shown that moderate consumption of red wine is associated with a lower incidence

of AD, and animal studies have demonstrated resveratrol's neuroprotective properties. The resveratrol in AD study is a Phase II double-blind, randomized, placebo-controlled trial that began recruiting 120 volunteers at 26 sites affiliated with the ADCS across the U.S. in early 2012. It is evaluating the impact of resveratrol treatment on biomarkers and clinical outcomes in people with AD.[22]

Also currently underway is a Phase II clinical study of Ceregene's CERE-110, a gene therapy product designed to deliver nerve growth factor (NGF) to the brain for the treatment of AD. The rationale behind the study is that NGF is known to promote survival of certain neurons, called cholinergic neurons, that degenerate in AD, and therefore may provide sustained functioning of these neurons. Direct delivery of CERE-110 into the brain aims to selectively target the Nucleus Basalis of Meynert (NBM), where cholinergic neuronal degeneration occurs in AD. The study will examine the safety and effectiveness of NGF on AD in 50 patients at 11 research sites affiliated with the ADCS across the U.S.[25]

Today, AD is at the forefront of biomedical research, and the future of the disease will depend on furthering our understanding of it, diagnosing it early and discovering ways to prevent, treat and even cure it.

In 2011, President Obama signed into law the National Alzheimer's Project Act (NAPA). NAPA is the first law to outline a national strategy for research and care of people with AD. The act also addresses support for people caring for AD patients. A year later, the National Alzheimer's Plan was released, which set a goal of creating AD prevention methods by 2025.[1]

It may be too late to find a treatment for my uncle. But, with so much research in progress and the dedication of so many groups to make progress in preventing this disease, it is certainly possible there may be hope for future generations. ❖

RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

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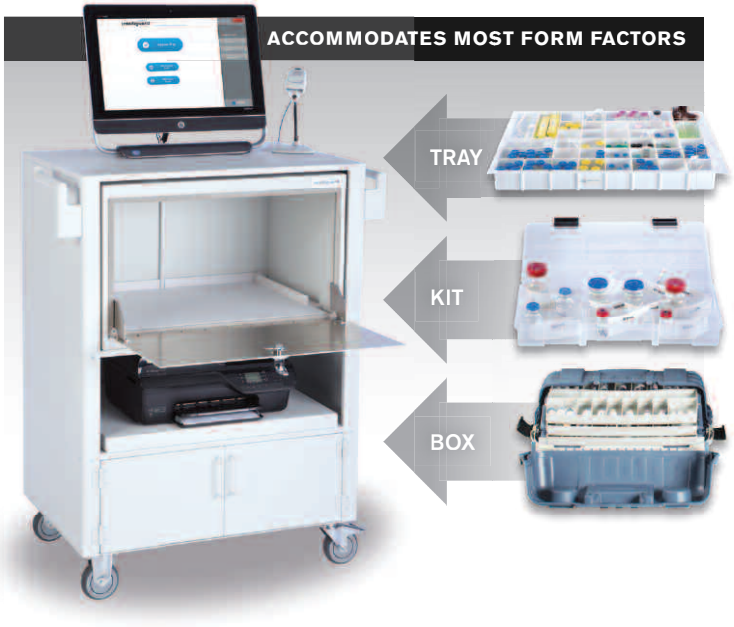

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Myths and Facts:

von Willebrand Disease

With increased knowledge and understanding about VWD, the disease can be more quickly diagnosed and treated, helping patients to lead normal and healthy lives.

By Ronale Tucker Rhodes, MS

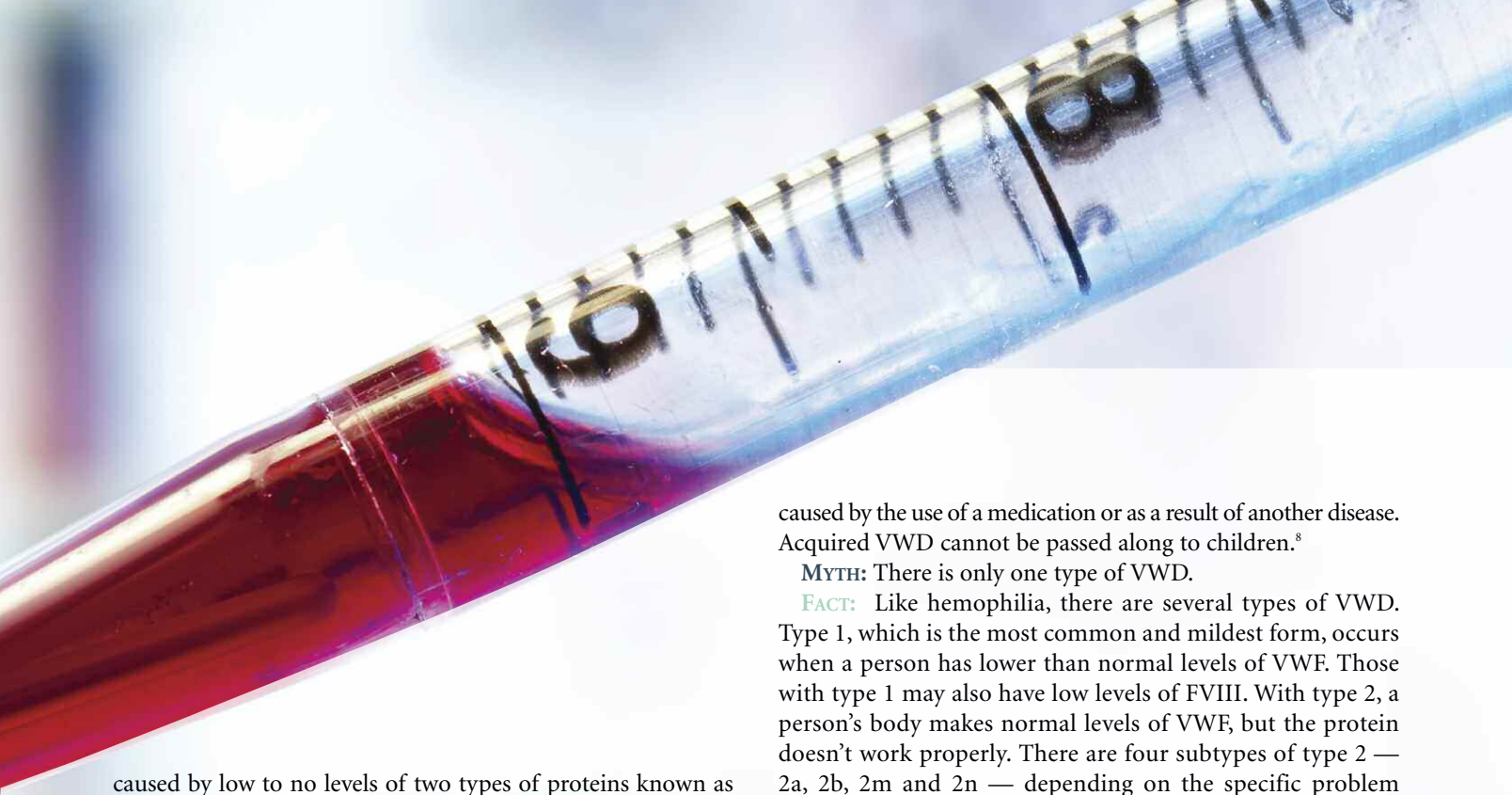
In 1926, Erik Adolf von Willebrand, a physician who spent his professional career studying the properties of blood and its coagulation, was the first to describe a blood coagulation disorder that was later named after him: von Willebrand disease (VWD). His discovery occurred while treating a 5-year-old girl with an extensive history of bleeding in her family. After mapping the girl's 66 family members, he found that 23 of them were also affected.[1] Von Willebrand described patients with the syndrome as having mucocutaneous bleeding, normal clotting time, autosomal inheritance and prolonged bleeding times by the Duke method (ear lobe bleeding time).[2]

VWD is a bleeding disorder that affects the blood's ability to clot due to low to no levels of a certain protein that acts like glue to help platelets stick together to plug the hole in the blood vessel and stop the bleeding.[3] Today, it is estimated that one in 100 people (or 1 percent of the population) suffers from VWD, yet most are unaware they have it. In fact, research has shown that nine out of 10 people suffering from VWD have yet to be diagnosed. And, of those who have been diagnosed, a Centers for Disease Control and Prevention (CDC) study reports an average of 16 years between the onset of bleeding symptoms and diagnosis.[4] Quicker diagnosis of VWD so that it can be properly treated can occur only if more is known and understood about VWD, a less severe bleeding disorder that is similar to hemophilia and that, in most cases, causes little or no disruption to the lives of those affected except when there is a serious injury or need for surgery.[5]

Separating Myth from Fact

Myth: Like other forms of hemophilia, VWD is a male disease.

Fact: While VWD is a bleeding disorder similar to hemophilia, its cause differs and, therefore, it equally affects both males and females. Hemophilia types A and B are typically



caused by low to no levels of two types of proteins known as clotting factor VIII (FVIII) and IX. They are typically inherited diseases passed on to children from a gene located on the X chromosome. Females have two X chromosomes and males have an X and Y chromosome. A female carrier of hemophilia has the hemophilia gene on one of her X chromosomes, so there is a 50/50 chance of passing that gene on to her children. If passed on to a son, he will have the disease. If passed on to a daughter, she will be a carrier. If a father has hemophilia but the mother doesn't carry the hemophilia gene, then none of the sons will acquire hemophilia, but all of the daughters will be carriers.

With VWD, on the other hand, the missing protein is called von Willebrand factor (VWF), which is not located on the X chromosome. Instead, it is on a chromosome that is not gender determined, which is why the disease affects both males and females equally. VWD is autosomal dominant, meaning a parent with the gene has a 50/50 chance of passing it on. If passed on, the child will likely develop symptoms.[6]

Myth: VWD is not a common bleeding disorder.

Fact: While most people have heard of hemophilia, that's not true of VWD. However, VWD is more common than either of the most common types of hemophilia, occurring in approximately one in 100 people vs. one in 5,000 for hemophilia A and one in 25,000 for hemophilia B.[7]

Myth: VWD is an inherited disease.

Fact: Most people with VWD inherited it from a parent. Yet, it is possible for "spontaneous mutation" to occur due to a change in a person's gene. Normally, though, this mutation occurs prior to birth, and children are born with the affected gene. Only rarely does a person who is not born with VWD acquire it or have it first occur later in life. VWD is acquired when a person's immune system destroys his or her VWF caused by the use of a medication or as a result of another disease. Acquired VWD cannot be passed along to children.[8]

Myth: There is only one type of VWD.

Fact: Like hemophilia, there are several types of VWD. Type 1, which is the most common and mildest form, occurs when a person has lower than normal levels of VWF. Those with type 1 may also have low levels of FVIII. With type 2, a person's body makes normal levels of VWF, but the protein doesn't work properly. There are four subtypes of type 2 — 2a, 2b, 2m and 2n — depending on the specific problem with the VWF protein, which is important to know because treatment is different for each. The most severe form of VWD is type 3 in which there is very little or no VWF and low levels of FVIII.[8]

Today, it is estimated that one in 100 people (or 1 percent of the population) suffers from VWD, yet most are unaware they have it.

Myth: Symptoms of VWD are the same for men and women.

Fact: While the symptoms of VWD are similar for men and women, the severity of symptoms differs for all VWD patients, and women experience additional symptoms. Bleeding usually involves the mucous membranes of the body.[9] Symptoms can present as frequent, large bruises from minor bumps and injuries, frequent or hard-to-stop nosebleeds, prolonged bleeding from the gums after a dental procedure, bleeding in the stools from bleeding in the intestines or stomach, blood in the urine from bleeding in the kidneys or bladder, and heavy bleeding after a cut or other accident. Women also suffer from menorrhagia (heavy menstrual bleeding) and bleeding problems during delivery and heavy bleeding for an extended time after childbirth.[3]

Myth: VWD is easy to diagnose.

Fact: Because VWD types 1 and 2, the more common types, don't present with major bleeding problems, they are sometimes hard to diagnose. In some instances, these types may not be diagnosed unless the person has heavy bleeding after surgery or some other trauma. VWD type 3, on the other hand, is almost always diagnosed during the first year of life because it can cause major bleeding problems during infancy and childhood.[3]

To diagnose VWD, a physician will conduct a medical history and physical exam, checking for bruises or other signs of recent bleeding, and will ask about past bleeding episodes and whether parents or siblings have had bleeding problems. Blood tests will also be conducted. Specific blood tests include a VWF antigen that measures the VWF protein to determine the level of VWF in the blood; a ristocetin cofactor activity to analyze how well the VWF works in the clotting process; a FVIII clotting activity test to show whether there are abnormally low levels and activity of FVIII; a von Willebrand factor multimers test to evaluate the specific structure of VWF in the blood, its protein complexes (multimers) and how its molecules break down to help identify the type of VWD that is present; and a platelet function test (PFA-100) to measure how efficiently platelets are functioning in the blood.[10]

Unfortunately, VWD is on the rise.

Myth: All people with VWD need treatment.

Fact: Most people have very mild VWD, so they don't need treatment unless they have a surgical or dental procedure. For those with more severe VWD, the two main treatment options are desmopressin (DDAVP) and transfusion therapy with blood products.[11] DDAVP, a synthetic analogue of vasopressin, is the treatment of choice for type 1 VWD. It is a naturally occurring hormone in the body that works by stimulating release of both VWF and FVIII found in storage sites lining the blood vessels to correct the prolonged bleeding time. It also is used prior to procedures involving mucous membranes such as dental work, for home treatment of minor injuries and for minor or moderate surgeries. DDAVP comes in a nasal spray, but it can also be injected intravenously or subcutaneously.[12,13]

Because DDAVP is not effective in the majority of type 2 and 3 VWD patients, transfusion with plasma concentrates containing VWF and FVIII is prescribed.[13] When major surgery or treatment for serious bleeding episodes is required, VWF-containing FVIII concentrates are the treatment of choice.[11] Factor concentrates with VWF to treat people with types 2a, 2b and 3 include Alphanate (Grifols), Humate P (CSL Behring), Koate DVI (Kedrion) and Wilate (Octapharma).[14] In April, Baxter announced results of its Phase III clinical trial evaluating the safety, efficacy and pharmacokinetics of BAX III, a recombinant VWF. Baxter intends to file for approval of BAX III before the end of 2014.[15] Although the bleeding time defect is not always corrected by plasma concentrates, they are effective and safe. When there is poor correction of bleeding time associated with continued bleeding, platelet concentrates or DDAVP can be used as adjunctive treatments.[13]

Other treatments include birth control pills to control heavy menstrual periods in women with type 1 VWD and antifibrinolytic agents (Amicar [aminocaproic acid] and Cyklokapron [tranexamic acid]) to treat nosebleeds and to prevent bleeding in the mouth during dental surgery. Antifibrinolytic agents help prevent blood clots from breaking down in the mucous membranes of the mouth, nose, stomach, intestines and urinary tract, and they are sometimes used in combination with DDAVP and plasma replacement therapy.[16] If antibodies to VWF develop, recombinant FVIIIa is prescribed.[17]

Myth: Symptoms of VWD can't be prevented.

Fact: There are steps that can be taken to prevent bleeding and stay healthy. For instance, over-the-counter medicines that can affect blood clotting such as aspirin, ibuprofen and other nonsteroidal anti-inflammatory drugs should be avoided. Before dental work, patients should ask their doctor, dentist or pharmacist whether any medicine is needed to reduce bleeding. For those with serious forms of VWD, a medical ID bracelet or necklace can be worn to let healthcare providers know of the disease in case of a serious accident or injury. And, patients may also want to let other people such as an employee health nurse, gym trainer or sport coach know about their condition in case of an injury.[3]

Myth: Individuals with VWD should avoid sports.

Fact: VWD patients are encouraged to be physically active. According to Ann Kirschman, WHNP, BSN, women's health nurse practitioner at the Mountain States Regional Hemophilia and Thrombosis Center at the University of Colorado, Aurora, "the health benefits of being in shape outweigh, in most cases, the risks of playing sports. Muscles that are not in good shape cannot hold the joints in proper alignment and protect them." Kirschman adds, however, that she doesn't encourage high-contact sports because of the risk of abdominal or intracranial bleeding, but she does promote weight control and muscle training and fitness as a protection against bleeding.[18] Some safe physical activities include swimming, biking and walking.

Myth: Pregnancy is too risky for women with VWD.

Fact: Pregnancy can be a challenge for women with VWD,

Half the volume
Twice the factor*

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is now available in a **2000 IU FVIII vial** with a reconstitution volume of only **10 mL**.

*That's **TWICE** the amount of factor of the largest vial available for other FVIII/VWF products,[1-4] so patients may require:

- **Less volume**
- **Less time**
- **Fewer syringes**

Isn't it time you tried ALPHANATE?

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Alphanate®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

- Control and prevention of bleeding in patients with hemophilia A
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with ALPHANATE should be discontinued, and emergency treatment should be sought.

Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

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

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** CSL Behring. Humate P Package Insert. August 2013; **3.** Octapharma. Wilate Package Insert. January 2012; **4.** Kedrion. Koate-DVI Package Insert. August 2012.

For more information: **Grifols Biologicals Inc.**
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GRIFOLS

ALPHANATE®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Alphanate safely and effectively. See full prescribing information for Alphanate.

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])

Sterile, lyophilized powder for injection.

Initial U.S. Approval: 1978

----------INDICATIONS AND USAGE ----------

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

----------DOSAGE AND ADMINISTRATION ----------

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

Hemophilia A: Control and prevention of bleeding episodes

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

----------DOSAGE FORMS AND STRENGTHS ----------

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, 1500 and 2000 IU FVIII in single dose vials.

----------CONTRAINDICATIONS ----------

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

----------WARNINGS AND PRECAUTIONS ----------

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients has been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

----------ADVERSE REACTIONS----------

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed.
- Pediatric Use: Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.

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but most women can have successful pregnancies. Monitoring during and after pregnancy is required. Limited evidence suggests that DDAVP use is relatively safe during pregnancy. But, with DDAVP, women should limit their fluid intake to reduce the risk of hyponatremia, especially after repeated doses. Women unresponsive to DDAVP or with other contraindications should receive a VWF-FVIII concentrate for prophylaxis or treatment of bleeding.

Women with type 3 VWD require VWF replacement at the time of delivery and postpartum. Prophylaxis is also recommended for those with persistently low FVIII and VWF levels at term.

Although rare, spontaneous miscarriage can occur before childbirth. And, because of the rapid fall in FVIII and VWF levels after birth, women are at substantial risk for postpartum hemorrhage (PPH), although the risk is higher for those with VWD types 2 and 3, and that risk persists for several weeks after delivery.[19] PPH is the leading cause of death among women during childbirth, and women with VWD are more likely to experience PPH and are 10 times more likely to die from childbirth complications than women without VWD.[20]

Dispelling the Myths Now

While there is no cure for VWD, it can be treated, and individuals can live a normal life. Unfortunately, VWD is on the rise. CDC reports that the number of women seeking treatment at hemophilia treatment centers for bleeding disorders such as VWD has increased by 50 percent during the past 10 years to more than 10,000 in 2009.[4] Therefore, much more needs to be known about the disease to better diagnose and treat it.

The National Heart, Lung and Blood Institute has identified a number of areas that would benefit from further research, including a better understanding about the pathophysiology and classification of VWD since the level of functional VWF and many other factors are poorly understood, as is the disease's heterogeneity. Increasing awareness and understanding how to diagnose and evaluate VWD is needed, as well as how to manage it since many of the standard treatments for the disease have limited experimental support. Further, it's possible that severe type 3 VWD can be treated with gene therapy, but its prevalence and clinical symptoms have not yet warranted gene therapy trials. It's clear more needs to be understood about VWD issues related to women.[21] CDC is conducting research that aims to improve the health outcomes of women with bleeding disorders, including determining what percentage of women who had PPH have a bleeding disorder; identifying symptoms, risk factors and other complications; and assessing the adverse pregnancy outcomes.[20]

In addition to research needs, there is a shortage of skilled clinicians and laboratorians with expertise in VWD and other bleeding disorders. The National Heart, Blood and Lung Institute provides grants for clinical opportunities in non-malignant hematology (grants.him.gov/grants/guide/rfa-files/RFA-HL-06-006.html), and the National Hemophilia Foundation has established a clinical fellowship program funded by Baxter Healthcare Corp. for the study of hemophilia (www.hemophilia.org/Researchers-Healthcare-Providers/Research-Grant-Programs/NHF-Baxter-Clinical-Fellowship-Program).[21] ❖

RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

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Long-Acting Factor Concentrates: The Next Leap Forward in Hemophilia Care Arrives

Innovation is the calling card of the future. — Anna Eshoo

BY KEITH BERMAN, MPH, MBA

FEW IN NUMBER are successful collaborations between clinical scientists and industry that eventually transform a generally devastating or seriously debilitating chronic disease into a readily manageable condition compatible with a long and healthy life.

One such disorder is type 1 diabetes, which once committed most young victims to a life diminished by cardiovascular disease, retinopathy, neuropathy and nephropathy — the most serious results of chronic poorly controlled blood glucose. Numerous innovations relating to the form and delivery of insulin — multiple daily insulin injection (MDII), insulin products with varying onsets of action, continuous glucose monitoring and insulin pump therapy — have dramatically improved glucose control and long-term prognosis.

A succession of treatment advances over the last 40 years has similarly transformed the lives of children and adults with hemophilia. The transition in the early 1970s from transfused fresh frozen plasma or cryoprecipitate to self-administered plasma-sourced factor VIII (hemophilia A) and IX (hemophilia B) concentrates immediately translated into less severe bleeds and reduced long-term joint disease. Later development of validated pathogen separation and inactivation processes and recombinant human factor VIII and IX products have virtually eliminated HIV and hepatitis infection risk.

Beginning in the 1990s, prescription of long-term prophylaxis regimens to maintain the circulating factor VIII level above 1 percent to 3 percent of normal (and factor IX typically above 2 percent of normal) has helped patients with more severe disease sharply cut the number of breakthrough bleeding episodes. Under the care of a well-trained hemophilia treatment specialist, an infant male born today with a severe factor VIII deficiency can prophylactically self-administer factor VIII every other day to three times weekly* to minimize or avert serious bleeding events and irreversible joint damage, and live a long, active life.

But not unlike type 1 diabetics who maintain glycemic control with MDII therapy, a price must be paid by persons with hemophilia who commit to routine prophylaxis: the need for frequent self-injections. The diabetes management industry responded to needlestick-related treatment compliance problems and other shortcomings of MDII by developing continuous subcutaneous insulin infusion (CSII) by self-programmable insulin pumps and, very recently, the creation of a new inhalable insulin product used in conjunction with long-acting insulin.[1] But for persons with hemophilia on a prophylaxis regimen, there is no option other than frequent intravenous (IV) self-administration of their factor product.

Today nearly two-thirds of persons with moderate or severe forms of hemophilia A, and one-third with hemophilia B, manage their disease with some form of prophylaxis.[2] But, unfortunately, some fail to reliably adhere to their prescribed schedule of regular infusions of clotting factor. Poor compliance results in periods of sub-protective levels of circulating factor VIII or IX and consequent breakthrough bleeding events. But even for those who have the discipline to do so, self-administration of their drug into a

* Factor IX is generally dosed prophylactically two to three times weekly. The sole conventional recombinant factor IX approved for routine prophylaxis (RIXUBIS; Baxter Healthcare) is dosed twice weekly.

vein several times a week is an unpleasant and burdensome experience.

Of course the optimal solution is to cure hemophilia itself through gene therapy. A number of clinical and preclinical studies are currently in progress to investigate various gene therapy candidates, but prospects for approved treatments remain uncertain. For hemophilia A in particular, which accounts for about 80 percent of all persons with moderate and severe disease, safe and effective gene therapy remains many years away.

Meanwhile, the biopharmaceutical industry has pursued the next best option: Reduce the number of necessary infusions. As with other long-acting versions of approved biotherapeutics, this is achievable by variously modifying factor VIII or IX to persist longer in the circulation while still retaining the protein's key functionality in the blood coagulation pathway. The need, as well as the commercial stakes involved, are well-appreciated: Five leading biopharmaceutical firms have invested heavily in development of eight proprietary long-acting factor VIII and IX product candidates.

First Long-Acting Hemophilia Therapies Have Arrived

In the race to introduce these products are most of the major suppliers of today's conventional recombinant

Table 1. Long-Acting Factor VIII Products in the Development Pipeline

Product	Manufacturer	Half-life extension technology	Development status	Selected findings
BAX 855	Baxter	PEGylation	Completed Phase III trial in 138 severe hemophilia A patients aged 12 years and older; evaluated on-demand treatment and twice-weekly prophylaxis. Application for FDA marketing approval expected before end of 2014.	1.5-fold increase in half-life over conventional recombinant factor VIII. Twice-weekly prophylaxis reduced ABR by 95 percent vs. on-demand treatment.
BAY 94-9027	Bayer	Site-specific PEGylation	Completed Phase II/III trial in 134 severe hemophilia A patients aged 12-65 years; evaluated on-demand treatment and prophylaxis twice weekly and every 5 and 7 days. Phase III study in previously treated children currently in progress.	1.5-fold increase in half-life over conventional recombinant factor VIII. All prophylaxis regimens sharply reduced ABR vs. ABR in subjects receiving on-demand treatment.
N8-GP	Novo Nordisk	GlycoPEGylation	Completed Phase III trial in 186 hemophilia A patients aged 12 years and older; evaluated prophylaxis every 4 days and on-demand regimens. Trials in children, PUPs, surgical procedures and as once-weekly prophylaxis currently in progress.	1.5-fold increase in half-life over conventional recombinant factor VIII. Prophylaxis reduced ABR by >95% vs. ABR in subjects receiving on-demand treatment.
rFVIII-SingleChain (CSL627)	CSL Behring	Covalent binding of heavy and light factor VIII chains	Phase III trial in 200 subjects of any age with severe hemophilia A started in June 2014; testing prophylaxis and on-demand regimens. Phase III study in children with severe hemophilia up to age 11 years in progress.	Roughly 1.5-fold extended half-life vs. conventional recombinant factor VIII in primate pharmacokinetic study.

ABR: annualized bleeding rate PUPs: previously untreated patients VWF: von Willebrand factor

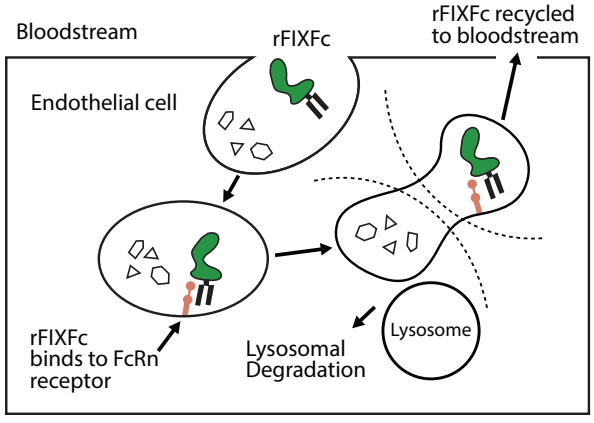
Table 2. Long-Acting Factor IX Products in the Development Pipeline

Product	Manufacturer	Half-life extension technology	Development status	Selected findings
rIX-FP	CSL Behring	Fusion protein with human albumin	Completed Phase II/III trial in 63 previously treated subjects with severe hemophilia B aged 12-65 years; evaluated weekly prophylaxis and on-demand regimens. Extension study and Phase III trial in children currently in progress.	Phase I/II study: mean 95-hour half-life (~4-fold increase over conventional recombinant factor IX)
N9-GP	Novo Nordisk	GlycoPEGylation	Completed Phase III trial in previously treated children up to age 12 years with moderately severe or severe hemophilia B; evaluating weekly prophylaxis. Phase III trial in previously untreated children currently in progress.	Phase III study: mean 110-hour half-life (~5-fold increase over conventional recombinant factor IX)

coagulation factors: Baxter, Bayer, CSL Behring and Novo Nordisk. But the first to secure regulatory approvals for its both long-acting factor VIII and factor IX products — Biogen Idec — turns out to be an entirely new entrant to the hemophilia therapy market. In March, the U.S. Food and Drug Administration (FDA) approved its ALPROLIX (Factor IX [Recombinant], Fc Fusion Protein), followed just three months later by approval of ELOCTATE (Antihemophilic Factor [Recombinant], Fc Fusion Protein).

Fusing the Fc portion of human IgG1 is believed to extend the half-life of these recombinant clotting proteins by exploiting the natural process that enables IgG to persist in the circulation for several weeks. Following endocytosis by vascular endothelial cells, the factor protein-bound constant Fc region of IgG1 binds to cellular neonatal Fc receptors (FcRn), which divert the protein-Fc complex away from lysosomes and facilitate its return to the bloodstream (Figure 1). The half-life of Biogen Idec's ALPROLIX factor IX fusion protein is about 86 hours, compared with about 26 hours for Baxter's RIXUBIS and just under 19 hours for Pfizer's BeneFIX recombinant factor IX products. The half-life of ELOCTATE, a much larger factor VIII fusion protein, is increased about 1.5-fold over the mean half-life of 12 hours for adults treated with Baxter's ADVATE, the market-leading conventional recombinant factor VIII.

Figure 1. Presumptive Mechanism of Factor IX Protein (rFIXFc) Half-Life Prolongation



rFIXFc: Recombinant factor IX Fc fusion protein; same mechanism applies for rFVIIIFc (recombinant factor VIII fusion protein)

This Fc fusion technology is hardly new: The first of seven Fc fusion-based protein therapeutics approved in the U.S. over the last 15 years was the anti-tumor necrosis factor drug Enbrel (etanercept) in 1998, whose worldwide sales for treatment of autoimmune rheumatologic disorders now reportedly top $8 billion. Antibody-based therapeutics that utilize IgG1 Fc fusion to prolong half-life now account for about 20 percent of all licensed antibody-based medicines.[3]

Whether long-acting or not, the therapeutic principle behind factor VIII or IX prophylaxis is the same: Keep the trough level of the missing clotting factor above a low threshold associated with increased bleeding risk. Pharmacokinetic simulations of Biogen Idec's long-acting factor VIII found a clear association between number of days with a factor VIII activity under 1 international unit (IU)/dL and increased bleeding tendency. A mean of 224 out of 365 days under 1 IU/dL was documented in clinical trial subjects

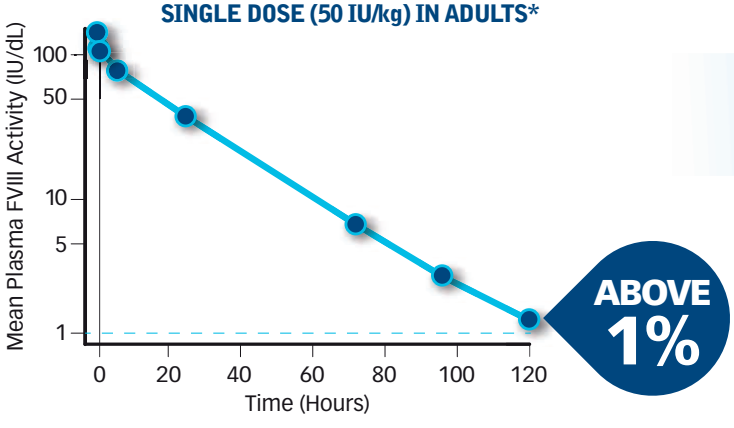
Find out more at ELOCTATEpro.com

ELOCTATE

THE FIRST AND ONLY rFVIII WITH A PROLONGED HALF-LIFE

5 DAYS WITH FACTOR LEVELS ABOVE 1%

MEAN FACTOR ACTIVITY PROFILE AFTER A SINGLE DOSE (50 IU/kg) IN ADULTS*



MEAN TERMINAL HALF-LIFE AFTER A SINGLE 50 IU/kg DOSE IN ADULTS*†

19.7 HOURS (17.4, 22.0)

Mean terminal half-life after a single 50 IU/kg dose in pediatric and adolescent patients*†‡

- 16.4 (14.1, 18.6) hours in subjects 12 to 17 (n=11)
- 14.6 (11.5, 17.7) hours in subjects 6 to 11 (n=27)
- 12.0 (9.55, 14.4) hours in subjects 2 to 5 (n=10)

*The pharmacokinetics of ELOCTATE were evaluated following a single dose of 50 IU/kg in the Phase 3 study of 28 adults and 11 adolescents (ages 12 to 17 years), and in an open-label, multicenter study of 37 pediatric, previously treated patients (ages 2 to 5 years and 6 to 11 years).

†Presented in arithmetic mean (95% confidence interval).

‡Compared to adults and adolescents, clearance was higher in children 2 to 5 years of age, indicating a need for dose adjustments. For patients 6 years and older, an age-based dose adjustment is not required.

Indications

- ELOCTATE [Antihemophilic Factor (Recombinant), Fc Fusion Protein] is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: control and prevention of bleeding episodes, perioperative management (surgical prophylaxis), and routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- ELOCTATE is not indicated for the treatment of von Willebrand disease

Selected Important Safety Information

- ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

ELOCTATE™
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

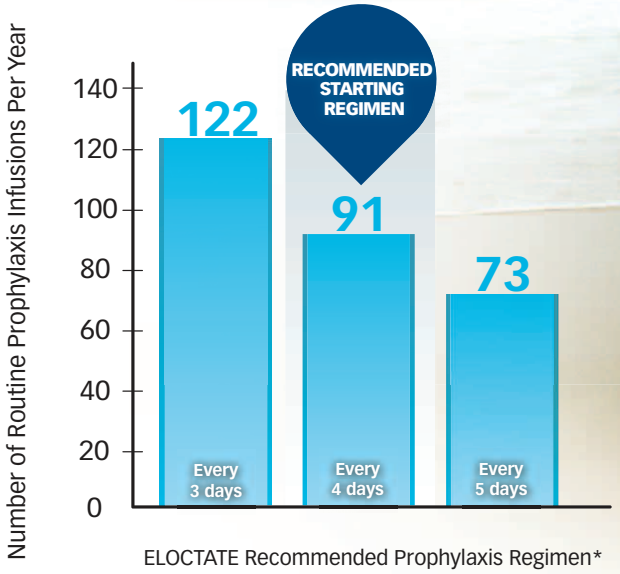
ELOCTATE Prophylaxis Starting With
INFUSIONS EVERY 4 DAYS

Recommended starting regimen
50 IU/kg administered every 4 days

- Regimen may be adjusted based on patient response in the range of 25-65 IU/kg at 3-5 day intervals
- More frequent or higher doses up to 80 IU/kg may be required in children <6 years of age

- After administering ELOCTATE, the one-stage clotting assay or chromogenic assay can be used to monitor plasma Factor VIII levels

Potential For
MORE TIME BETWEEN INFUSIONS



*Number of infusions may vary per individual.

- Among 112 subjects treated for ≥6 months, 29% achieved a dosing interval of ≥5 days during the last 3 months on study

Important Safety Information

CONTRAINDICATIONS: ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

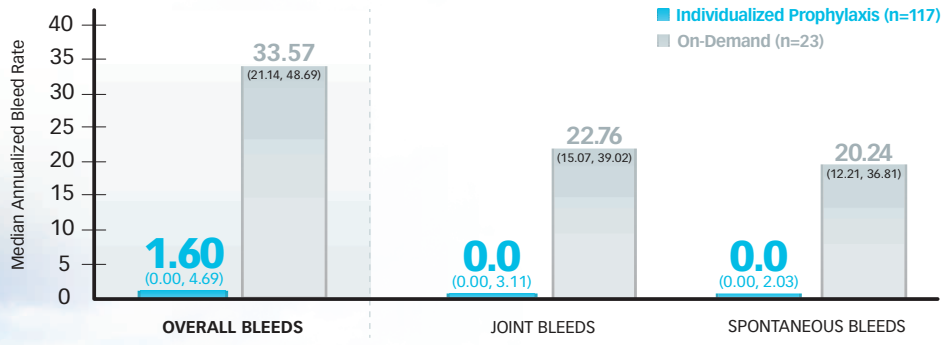
WARNINGS AND PRECAUTIONS: Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Immediately discontinue ELOCTATE and initiate appropriate treatment if hypersensitivity reactions occur. Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Patients using ELOCTATE should be monitored for the development of Factor VIII inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor VIII levels have been achieved and maintained.

ADVERSE REACTIONS: Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

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

With Individualized Prophylaxis
PROVEN PROTECTION* FROM BLEEDS

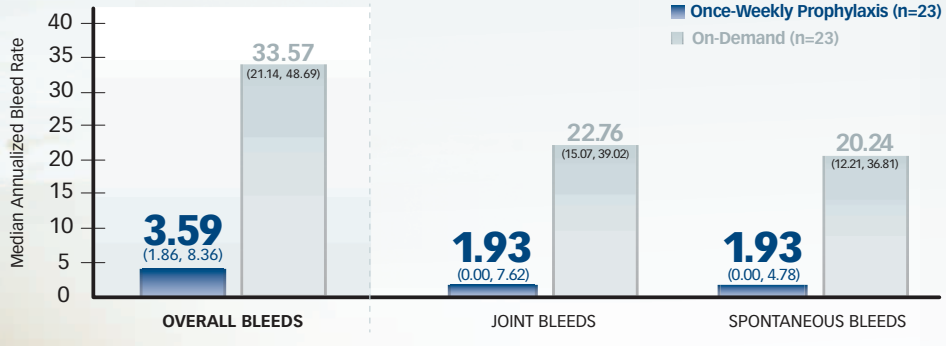
MEDIAN ANNUALIZED BLEED RATE†‡



ADDITIONAL PIVOTAL TRIAL RESULTS

Once-Weekly Prophylaxis—Not a labeled dosing regimen

MEDIAN ANNUALIZED BLEED RATE†‡



*Protection is the prevention of bleeding episodes using a prophylaxis regimen.

† Median (interquartile range 25th and 75th percentiles).

‡ A-LONG, a multicenter, prospective, open-label, Phase 3 study (N=165), evaluating the safety and efficacy of ELOCTATE in previously treated male patients aged 12 to 65 years with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) that compared the efficacy of each of two prophylactic treatment regimens (individualized interval and fixed weekly) to episodic (on-demand) treatment. Hemostatic efficacy was determined in both: treatment of bleeding episodes and during perioperative management in subjects undergoing major surgical procedures. 164 and 163 subjects were evaluable for safety and efficacy, respectively. 146 and 23 subjects were treated for at least 26 weeks and 39 weeks, respectively.

OTHER SAFETY CONSIDERATIONS

Zero Inhibitors in the Clinical Trial, No Anaphylaxis Was Reported, And Low Incidence Of Adverse Reactions (ARs)

- Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests
- One subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter
- Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur
- The most common ARs in the Phase 3 clinical study were arthralgia and malaise (each 1.2%) and: abdominal pain, lower; abdominal pain, upper; angiopathy§; bradycardia; chest pain; cough; dizziness; dysgeusia; feeling cold; feeling hot; headache; hypertension; joint swelling; myalgia; procedural hypotension; and rash (each 0.6%). Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia

§Vascular pain after injection of study drug.

Find out more at ELOCTATEpro.com

ELOCTATE™
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

ELOCTATE™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein]
Lyophilized Powder for Solution For Intravenous Injection.

Brief Summary of Full Prescribing Information.

1 INDICATIONS AND USAGE
ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:

- Control and prevention of bleeding episodes,
- Perioperative management (surgical prophylaxis),
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ELOCTATE is not indicated for the treatment of von Willebrand disease.

4 CONTRAINDICATIONS
ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies
Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, suspect the presence of an inhibitor (neutralizing antibody). [*see Monitoring Laboratory Tests* (5.3)]

5.3 Monitoring Laboratory Tests
- Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained. [*see Dosage and Administration* (2)]
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of ELOCTATE. Use Bethesda Units (BU) to report inhibitor levels.

6 ADVERSE REACTIONS
Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

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

In the multi-center, prospective, open-label, clinical trial of ELOCTATE, 164 adolescent and adult, previously treated patients (PTPs, exposed to a Factor VIII containing product for ≥150 exposure days) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) received at least one dose of ELOCTATE as part of either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. A total of 146 (89%) subjects were treated for at least 26 weeks and 23 (14%) subjects were treated for at least 39 weeks.

Adverse reactions (ARs) (summarized in Table 3) were reported for nine (5.5%) subjects treated with routine prophylaxis or episodic (on-demand) therapy.

Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia. In the study, no inhibitors were detected and no events of anaphylaxis were reported.

Table 3: Adverse Reactions Reported for ELOCTATE (N=164)

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%)
General disorders and administration site conditions	Malaise Chest pain Feeling cold Feeling hot	2 (1.2) 1 (0.6) 1 (0.6) 1 (0.6)
Nervous system disorders	Dizziness Dysgeusia Headache	1 (0.6) 1 (0.6) 1 (0.6)
Musculoskeletal disorders	Arthralgia Joint swelling Myalgia	2 (1.2) 1 (0.6) 1 (0.6)
Gastrointestinal disorders	Abdominal pain, lower Abdominal pain, upper	1 (0.6) 1 (0.6)

(continued)

Table 3: Adverse Reactions Reported for ELOCTATE (N=164)

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%)
Vascular disorders	Angiopathy* Hypertension	1 (0.6) 1 (0.6)
Cardiac disorders	Bradycardia	1 (0.6)
Injury, poisoning, and procedural complications	Procedural hypotension	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	Cough	1 (0.6)
Skin and subcutaneous tissue disorders	Rash	1 (0.6)

*Investigator term: vascular pain after injection of study drug

6.2 Immunogenicity
Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No subjects developed confirmed, neutralizing antibodies to Factor VIII. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter.

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Animal reproductive studies have not been conducted with ELOCTATE. It is not known whether or not ELOCTATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELOCTATE should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether or not ELOCTATE is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when ELOCTATE is administered to a nursing woman.

8.4 Pediatric Use
Pharmacokinetic studies in children have demonstrated a shorter half-life and lower recovery of Factor VIII compared to adults. Because clearance (based on per kg body weight) has been shown to be significantly higher in the younger, pediatric population (2 to 5 years of age), higher and/or more frequent dosing based on body weight may be needed. [*see Clinical Pharmacology* (12.3)]

Safety and efficacy studies have been performed in 56 previously treated, pediatric patients <18 years of age who received at least one dose of ELOCTATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 were enrolled in an ongoing pediatric trial. Twelve subjects (21%) were <6 years of age, 31 (55%) subjects were 6 to <12 years of age, and 13 subjects (23%) were adolescents (12 to <18 years of age). Interim pharmacokinetic data from a pediatric study of the 38 subjects <12 years of age showed that no dose adjustment had been required for patients ≥6 years old. Children age 2 to 5 years had a shorter half-life and higher clearance (adjusted for body weight); therefore, a higher dose or more frequent dosing may be needed in this age group. [*see Clinical Pharmacology* (12.3)]

8.5 Geriatric Use
Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 and over to determine whether or not they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION
Advise the patients to:

- Read the FDA approved patient labeling (Patient Information and Instructions for Use)
- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing.
- Report any adverse reactions or problems following ELOCTATE administration to their healthcare provider.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII therapy because this may be a sign of inhibitor development.

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receiving solely on-demand treatment with ELOCTATE. The annualized period under 1 IU/kg was shortened to about 52 days in subjects managed with a fixed prophylactic dose of 65 IU/kg once weekly, and further shortened to just two days in subjects on individually tailored prophylactic regimens.

Thus, for each patient managed prophylactically with ELOCTATE or any factor concentrate, a balance must be found between increasing the time interval between infusions and maintenance of a protective clotting factor activity level. In the pivotal ELOCTATE clinical study, pharmacokinetic parameters were used to guide the dosing interval (every three to five days) and dose (25 to 65 IU/kg) in a group of subjects on individualized prophylaxis; the mean annualized bleeding rate (ABR) in this group was 95 percent lower than the ABR in the on-demand group. The ABR in a separate group managed with weekly prophylaxis at a fixed 65 IU/kg dose was 90 percent lower than the on-demand group — good, but still a meaningfully higher rate than the group on individualized prophylaxis. Consistent with these findings, the prescribing information for ELOCTATE advises physicians to start with 50 IU/kg every four days, then individualize dose and injection frequency based on patient response.

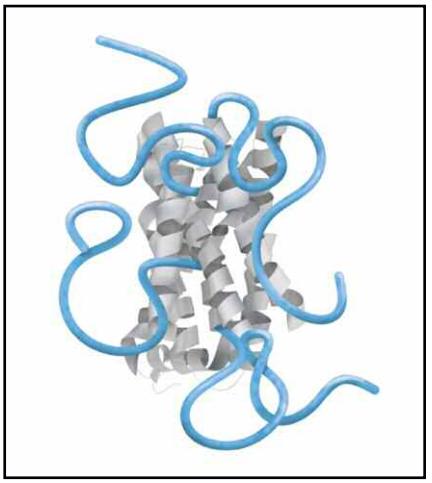
The practical advantage of ELOCTATE for patients is straightforward: A prophylaxis regimen can maintain a protective factor VIII level with fewer self-infusions than conventional recombinant factor VIII products while realizing similar benefits in reduced breakthrough bleeds compared with on-demand treatment. An individual who required conventional factor VIII dosing three times weekly, for example, may need to dose ELOCTATE only twice a week. Similarly, because its elimination half-life is several times longer than that of Pfizer's BeneFIX, Baxter's RIXUBIS or plasma-based factor IX products, including AlphaNine SD and Mononine, the frequency of ALPROLIX prophylaxis can be significantly reduced.

Other Long-Acting Factors Advance Toward Approval

Biogen Idec currently offers the only licensed long-acting factor VIII and IX products, but that advantage is likely to be short-lived. Four investigational recombinant factor VIII and two recombinant factor IX products with extended half-lives are now in advanced clinical development (Tables 1 and 2).

Half-life extension in four of these six products — Novo Nordisk's "N8-GP," Baxter's "BAX 855" and Bayer Pharmaceutical's "BAY94-9027" factor VIII products and Novo Nordisk's "N9-GP" factor IX — is achieved by attaching long polymer chains of polyethylene glycol (PEG) to the therapeutic protein via a process of covalent conjugation known as PEGylation, or a variant method called glycoPEGylation. In addition to other benefits, these long PEG polymer strands shield the protein from exposure to proteolytic enzymes and immune clearance mechanisms, thus protecting its functionality and prolonging its intravascular persistence (Figure 2).

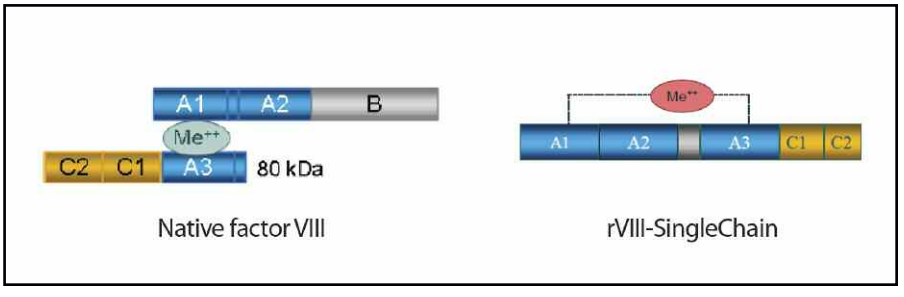
Figure 2. Graphic Representation of a PEGylated Recombinant Protein



CSL Behring has pursued its own innovative approaches. The company has redesigned recombinant human factor VIII to covalently bond its heavy and light chains together (Figure 3). Its resulting "rVIII-SingleChain" molecule is both more intrinsically stable and has a much higher affinity for von Willebrand factor (VWF), further enhancing its stability in the circulation.

CSL Behring's long-acting recombinant factor IX exploits recombinant albumin fusion technology. Fusing albumin to factor IX creates at least two potential advantages: Albumin has a remarkably long intravascular half-life of about 20 days and, like the Fc portion of IgG1, it is unlikely to elicit unwanted immunogenicity. Albumin fusion technology has appeal as well from the production standpoint: A high-quality product can be manufactured with fewer post-expression modifications and purification steps than PEGylation, and it can be produced more efficiently

Figure 3.
Schematic of Native Factor VIII and Covalently Bound rVIII-SingleChain (CSL Behring)



than other fusion protein approaches, including use of the IgG1 Fc fragment.[4] However, while numerous albumin fusion proteins are currently in clinical and preclinical development, to date just one therapeutic applying this technology has been approved for human use.**

Assuming most or all of these investigational products receive FDA marketing approval, we can expect an unusually spirited competition as new entrants strive to win over physicians and their patients. Most safety, pharmacokinetic and efficacy findings reported to date from the four investigational long-acting factor VIII agents are remarkably similar to those for Biogen Idec's Fc fusion-based ELOCTATE. All appear to have about a 1.5-fold extended circulating half-life compared with conventional recombinant factor VIII. Phase III clinical trial data suggest that optimized prophylaxis with several of these could reduce the risk of breakthrough bleeds by around 95 percent in relation to episodic therapy — again quite similar to ELOCTATE.

No safety-related concerns have been described for any of these six investigational long-acting coagulation factor therapies. With the exception of a single isolated instance, inhibitor antibodies in pivotal clinical trials of these investigational agents have not been reported. It is not unreasonable to expect that physicians and patients could soon be in a position to choose from among four or five long-acting factor VIII products and as many as three long-acting factor IX products.

What Comes Next?

For persons with hemophilia either on or contemplating a prophylaxis regimen, the arrival of this new generation of long-acting clotting factors will translate into a reduced self-infusion burden, much-improved likelihood of treatment compliance, fewer bleeding events, and reduced joint disease and related disability. Fewer units of factor will be infused, but offsetting this will be higher cost per unit.

Will extended half-life factor VIII and IX therapies turn out to be the last important wave of innovation we see from industry until gene therapy someday reduces or eliminates the need for replacement therapy altogether?

Don't count on it. Researchers at Chugai Pharmaceuticals have developed a humanized bispecific monoclonal antibody, named ACE910, designed to mimic the physiologic function of factor VIII by acting as a cofactor that promotes the activation of factor X by factor IXa. Importantly, it has been shown to be phospholipid-dependent, implying that its activity will be limited to the hemostatic site when introduced into the circulation. In a primate model, a single bolus was shown to have potent hemostatic activity equivalent to a therapeutic dose of human factor VIII.[5]

ACE910 has been in-licensed by Roche, and renamed RG6013. An 82-subject Phase I clinical trial of RG6013 is now in progress in Japan. Preliminary pharmacokinetic, safety and tolerability findings will be presented this December at the annual meeting of the American Society of Hematology in San Francisco. Should this Chugai/Roche factor VIII mimetic prove to be safe and effective, consider these two features: It is dosed subcutaneously and appears to have a half-life of about three weeks.

As much as the extraordinary collaboration of clinical scientists and industry has done to improve health and the quality of life for persons with hemophilia, all indications suggest that more innovation yet lies ahead. ❖

Five leading biopharmaceutical firms have invested heavily in development of eight proprietary long-acting factor VIII and IX product candidates.

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** TANZEUM (albiglutide) (GlaxoSmithKline). TANZEUM is a GLP-1 receptor agonist indicated for use in adults with type 2 diabetes. Approved April 2014.

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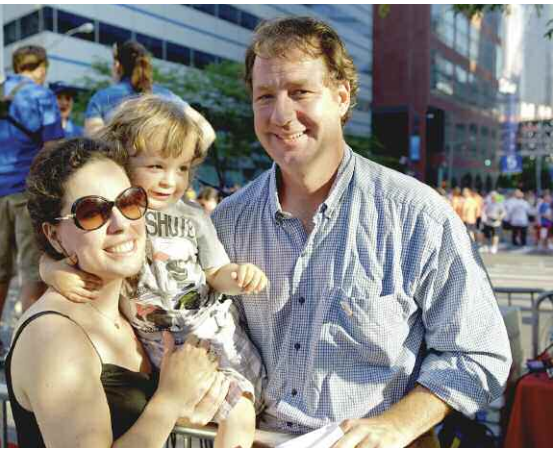
Stroke Prevention: A Patient's Perspective

BY TRUDIE MITSCHANG



At age 41, Eric Jordan suffered a massive ischemic stroke and lost his ability to speak.

THE DAY BEGAN like any other day. Eric Jordan's young son, Gabriel, woke up crying at 5:30 a.m., and as a doting dad, Eric scrambled out of bed to comfort him. But, from the moment his feet hit the floor, it was clear this day would prove to be anything but ordinary. In a matter of minutes, Eric was writhing on the floor, and his wife, Christina, was frantically calling 911. At age 41, Eric was in the throes of a massive ischemic stroke.

Waking Up Speechless

Numb on one side and unable to speak or focus, Eric was rushed by paramedics to Columbia University Medical Center/New York Presbyterian Hospital's primary stroke care center. Although Eric arrived at the hospital within the critical three-hour window required to receive the tissue plasminogen activator (tPA) clot-busting drug, it proved ineffective in dissolving his blood clot. In a race against time, interventional neuroradiologist Dr. Daniel H. Sahlein was called in to perform a life-saving surgical procedure using a Solitaire Flow Restoration Revascularization Device. This mechanical thrombectomy device restores blood flow and retrieves clots in patients experiencing acute ischemic stroke. Although it required two attempts, Dr. Sahlein successfully removed the large blood clot in the left middle cerebral artery of Eric's brain. In many ways, Eric was fortunate; if his young son had not awakened him, he might have died in his sleep. If paramedics had not rushed him to a skilled stroke care center, he might not have been treated in time. Thankful to be alive, Eric was nevertheless devastated when he woke up to a new reality: he'd lost the ability to speak. "How ironic is it to become an opera singer who cannot speak?" asks Eric. "I felt like a cave man unable to pronounce my Italian, German or Russian. I could not even remember my music."

The Road to Recovery

According to the American Stroke Association, ischemic stroke accounts for about 87 percent of all cases and occurs as a result of an obstruction within a blood vessel supplying blood to the brain. The interrupted blood flow deprived Eric's brain of oxygen, which caused cells to die. In Eric's case, the affected part of his brain was the left hemisphere, the part that manages right-sided motor skills, as well as receptive and expressive language. Statistically, one in four stroke survivors experience a language impairment called aphasia, and, unfortunately, Eric was one of them. A mere two years after

As an opera singer at the Metropolitan Opera in New York City who recovered his ability to sing, Eric Jordan's newfound passion is for helping others recovering from a stroke.

embarking on his career dream of singing with the Metropolitan Opera in New York City, it appeared his singing career was over. "I went from singing at the Met to being unable to recall the alphabet song," recalls Eric. "As frightening as it was, I vowed that I would never let fear stop me from becoming a better husband and father. I was determined to recover, no matter what."

Despite the dire prognosis, Eric began therapy within the first few weeks of his stroke, but progress was slow. He felt like he had an "iron tongue" that needed to be untied. Then, in a positive ironic turn, Eric discovered that while he struggled relearning to speak clearly, the ability to sing was returning quickly. He

later learned singing involves different parts of the brain than speaking does, so while his speech remained impaired, his singing gift began to thrive. "This experience has taught me patience," says Eric. "I have moderate-to-serious aphasia, which makes it hard for me to read, write or say what I mean, as well as apraxia, the inability to execute purposeful movements, so it takes patience for me to communicate and make any sense. Basically, my mind needs to slow down enough to let my tongue catch up."

Fighting through the frustration and discouragement, Eric surprised everyone by returning to the opera stage a mere six weeks after his stroke, with his wife, parents and doctor sitting proudly in the audience.

Advocacy for Others

Like many people who survive a life-threatening illness, Eric has taken time to reflect on his life's work and purpose. After reading an inspirational book titled *Wherever You Go, There You Are* by Jon Kabat-Zinn, Eric discovered the art of mindfulness and meditation, a practice he credits with helping him regain his equilibrium. After discussing his newfound passion with his neighbor, a yoga instructor, the pair teamed up and founded a "wellness ensemble," a nonprofit whose goal is to use therapeutic movement and music to help stroke survivors and others with brain injuries. Eric says his goal is to train a team of performers that can attend stroke camps and clinics to teach patients how to use music and movement to facilitate healing. In addition to those recovering from stroke, the program is proving helpful for Alzheimer's patients and children with autism. "We based our program on the findings of UCLA neurology professor Dr. Jeffrey Saver," says Eric. "We discovered that singing, movement and percussion were all vital components when it comes to helping people regain lost motor skills."

Eric's life post-stroke is a busy one, and in many ways, it is a "new normal." While he is still contracted to sing at the Met through the spring of 2015, his passion for giving back and speaking about stroke recovery has made his schedule these days especially hectic. "Strokes impact people of all ages and from all walks of life," explains Eric. "If what I do inspires someone to stretch their brain for the greater good, I am thankful. I'm well-armed with patience, a good sense of humor and a desire to help others. That's what keeps me going." ❖

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

Courtesy of the American Stroke Association

Stroke Prevention: A Physician's Perspective

BY TRUDIE MITSCHANG

Dr. Philip Meyers treats vascular disorders of the brain and spinal cord using minimally invasive, image-guided techniques.

DR. PHILIP MEYERS, MD, FAHA, is professor of radiology and neurological surgery at Columbia University, College of Physicians and Surgeons. He is also clinical director, neuroendovascular service at New York Presbyterian–Columbia Neurological Institute of New York and first past president of the Society of Neurointerventional Surgery.

BSTQ: How common is stroke?

Dr. Meyers: Current American Heart Association statistics document 800,000 strokes in the United States each year, and it's the fourth leading cause of adult death and leading cause of adult disability. When you look at those statistics, it's sobering to realize that while there are lifestyle and hereditary factors, nearly everyone is at risk.

BSTQ: What are the main risk factors?

Dr. Meyers: The risk factors for stroke are the same as heart attack: smoking, obesity and high blood pressure. The big challenge with stroke is that, unlike a heart attack, a stroke can occur with minimal symptoms. If patients do not realize they are having a stroke, they may delay seeking treatment. One of the biggest public health challenges we are trying to address is the need for early recognition. We know that other countries are doing a better job than we are; recent statistics out of the Netherlands and Scandinavia show really rapid response times compared to the U.S. Again, because patients may not recognize symptoms, many choose to get themselves to the hospital instead of calling an ambulance, increasing the risk of permanent disability or death.

BSTQ: What are some of the warning symptoms of stroke?

Dr. Meyers: Stroke symptoms appear suddenly and include numbness or weakness, especially on one side of the body; confusion or trouble speaking; trouble seeing out of one or both eyes; trouble with walking, dizziness, loss of balance or coordination; or severe headache with no known cause.

BSTQ: Tell us about your work in neurointerventional surgery.

Dr. Meyers: Neurointerventional surgery is a minimally invasive procedure to diagnose and treat diseases of the brain, head, neck and spine. With stroke patients, the goal is to reach inside the blood vessels and pull clots out of the artery, much the way a heart surgeon goes in to reopen an artery. This type of procedure is typically performed on patients presenting symptoms of a major stroke, and in situations where tissue plasminogen activator (tPA), a U.S. Food and Drug Administration-approved clot-busting drug, would be ineffective. At Columbia, there may be 1,000 stroke patients a year, but I only use this type of surgery to treat the most severe.

BSTQ: Are there promising new stroke treatments on the horizon?

Dr. Meyers: There is constant effort and research to uncover new treatment options. Millions of dollars are being spent to help prevent or delay artery blocks before irreversible damage occurs, and new clot-busting drugs are on the horizon. One area that's received a lot of attention is hypothermic therapy — cooling the stroke patient for 12 to 24 hours following the stroke. This treatment is now part of the American Heart Association's treatment guidelines after several studies showed that it can improve survival rates and brain function by decreasing the brain's oxygen demand, reducing the production of neurotransmitters like glutamate, as well as reducing free radicals that might damage the brain. The lowering of body temperature may be accomplished by the use of cooling blankets, cooling helmets and cooling catheters.

BSTQ: How is the healthcare industry addressing the needs of stroke patients?

Dr. Meyers: Great advances have been made in the development of a tiered system of stroke care centers that provide stroke patients with the best long-term outcomes. The first level of care is a local "stroke-ready" hospital, where the patient can be rapidly assessed. These facilities have communication systems in place that facilitate collaboration with outside stroke experts who can advise on preferred treatment plans. The second level of care is the primary stroke hospital, where patients can be rapidly evaluated and given the clot-busting drug tPA. However, for many patients, tPA alone may not be sufficient. In these cases, more advanced interventional techniques are required. This is where a comprehensive stroke hospital offering the full range of neurology and neurosurgical services is essential. Comprehensive stroke center designation is established by the Joint Commission and the American Heart Association/American Stroke Association, and recognizes significant effort in everything from training to infrastructure to providing state-of-the-art complex stroke care. ❖

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

BioResearch

Summaries of up-to-date clinical research published internationally.

Protein C Concentrate Added to Standard Therapy May Reduce Mortality Risk in Sepsis-Induced Purpura Fulminans

Despite an extremely poor prognosis, eight consecutive patients with acute-onset purpura fulminans (PF) secondary to systemic bacterial infection survived following treatment with a licensed human plasma-derived protein C concentrate (Ceprotin, Baxter Healthcare) in conjunction with standard sepsis therapy. In a ninth patient with PF caused by heat shock, protein C infusion was halted after two days; he died after 10 days from refractory multi-organ failure. Coagulopathy and severe vasopressor-dependent sepsis were present in all nine patients, who were managed at three Austrian hospitals. Prior to initiation of protein C therapy, the predicted mortality was 100% and 78.3% (range 31% to 88.5%) in four children and five adults, respectively.

Protein C was given as an initial bolus infusion (100 U/kg) followed by continuous infusion at 10 U/kg/hour, adjusted to obtain a plasma protein C activity level of 1.0 U/mL. Platelet, red blood cell, fibrinogen and antithrombin products were administered as needed. Coagulopathy resolved within a few days in all eight patients, and organ function was completely restored without residual dysfunction. At a median follow-up of eight months, all patients were fully active without apparent limitations.

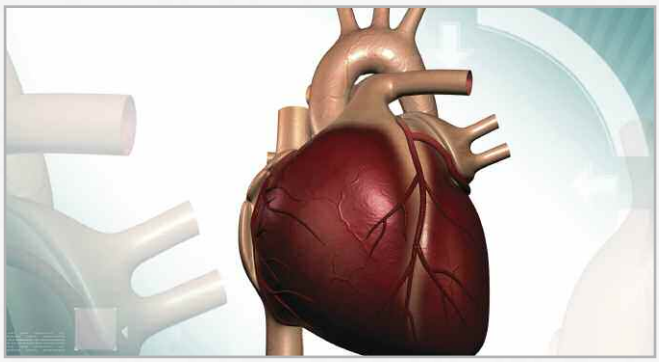
Currently, Ceprotin is approved only for congenital protein C deficiency. Given these very encouraging results and the known association between PF and breakdown of the protein C system, the investigators concluded that "controlled clinical studies are urgently needed to gain more scientific evidence for this potentially lifesaving, but still off-label therapy in patients with PF."

Knoebl P, Schellongowski P, Staudinger T, et al. Treatment of infection-associated purpura fulminans with protein C zymogen is associated with a high survival rate. American Society of Hematology Annual Meeting. Oral and Poster Abstract 3606. Monday, Dec. 9, 2013.

High-Dose IVIG Associated with Improved Recovery of Left Ventricular Function in Acute Myocarditis and/or Early DCM

To evaluate the effect of intravenous immune globulin (IVIG) on cardiac rhythm and function in children younger than 12 years of age presenting with acute myocarditis and/or early dilated cardiomyopathy (DCM), investigators at a tertiary hospital in India conducted a retrospective analysis of case records between January 2010 and December 2012. Of 28 children who met inclusion criteria, 12 had received treatment with IVIG (1 g/kg per day) for two days, while the remaining 16 did not receive IVIG therapy. At baseline, children in the two groups did not differ significantly with regard to echocardiographic measures of left ventricular function, including mean left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD).

At both three months and six months post-treatment, children treated with IVIG had significantly higher LVEF than those not treated with IVIG. From a mean baseline of 35.3%, LVEF in the IVIG group at three and six months increased to 50.8% and 62.2%, respectively, while LVEF in the control group increased from a mean of 33.5% to 43.3% and 50.6%. Differences at both three and six months were highly significant ($P < 0.01$). LVEDD in the IVIG group also significantly improved in relation to the control group: respectively decreasing by 11% and 2% at three months ($P < 0.01$), and by 14.4% and 7.5% at six months ($P < 0.01$).



Episodes of ventricular tachycardia/fibrillation and atrioventricular block were reduced significantly in the IVIG group. There were two deaths in the IVIG therapy group and seven deaths in the non-treated control group ($P = 0.032$). In their brief report, the investigators concluded that these results suggest that IVIG treatment of acute myocarditis and/or early dilated cardiomyopathy is associated with improved recovery of left ventricular function and a reduction in episodes of fulminant arrhythmias.

Prasad AN and Chaudhary S. Intravenous immunoglobulin in children with acute myocarditis and/or early dilated cardiomyopathy. Indian Pediatr *2014 Jul 8;51(7):583-4.*

KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of* International Blood Plasma News, *a blood products industry newsletter.*

BioProducts

New products in the marketplace.

Migraine Headband

The U.S. Food and Drug Administration has approved Cefaly, a battery-powered plastic headband worn across the forehead and atop the ears with a self-adhesive electrode intended to prevent the throbbing pain associated with migraines that can be prescribed in the U.S. for patients 18 and older. The device, which is designed to be worn for 20 minutes or less per day, applies an electric current to the skin and underlying body tissues to stimulate branches of the trigeminal nerve, which has been associated with migraine headaches. The user may feel a tingling or massaging sensation where the electrode is applied. Cefaly was approved based on a clinical study of 67 migraine sufferers conducted in Belgium. Those who used the device experienced "significant fewer" migraines than those who used a placebo, and they used less medication to treat the migraines when they got them. However, the device didn't eliminate migraines altogether, nor did it make them less severe. In another study, 53 percent of participants were satisfied enough with Cefaly that they would purchase it for future use, while others complained they didn't like the feeling while wearing it, felt sleepy or experienced headache after treatment. No serious side effects were reported.
Cefaly Technology, (514) 326-7780, www.cefaly.ca

CDC Vaccine Schedules app

The CDC Vaccine Schedules app for clinicians and other immunization providers visually mimics the printed recommended immunization schedules and footnotes, which are reviewed and published annually. The free tool provides the most current version of the child and adolescent schedules with immunization recommendations from birth through age 18; the catch-up schedule for children 4 months through 18 years; the adult schedule, including recommended vaccines for adults by age group and by medical condition; and a contraindications and precautions table, with all footnotes that apply to schedules. Any changes in the schedules will be released through app updates. Features of the app include color coding coordinates with printed schedules, a hyperlinked vaccine name that opens as a pop-up with dose specifics, a catch-up schedule for children that shows minimum dosing intervals, and related vaccine resources and websites. The app requires iOS 5.0 or later, it is compatible with the iPhone, iPad and iPod touch, and it is optimized for the iPhone 5.
Centers for Disease Control and Prevention, (800) 232-4636,
www.cdc.gov/vaccines/schedules/hcp/schedule-app.html#download

Melanoma Scanner

MelaFind is designed for dermatologists to use in their efforts to detect melanoma at the most curable stage. It is a handheld tool approved by the U.S. Food and Drug Administration for multispectral analysis of tissue morphology. The MelaFind optical scanner is not for definitive diagnosis but rather to provide additional information a doctor can use in determining whether to order a biopsy. The goal is to reduce the number of patients left with unnecessary biopsy scars, with the added benefit of eliminating the cost of unnecessary procedures. The MelaFind technology uses missile navigation technologies originally paid for by the Department of Defense to optically scan the surface of a suspicious lesion at 10 electromagnetic wavelengths. The collected signals are processed using heavy-duty algorithms and matched against a registry of 10,000 digital images of melanoma and skin disease.
Mela Sciences, (855) 635-2345, www.melafind.com

BioResources

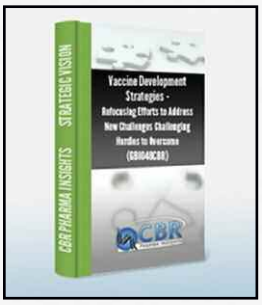
Recently released resources for the biopharmaceuticals marketplace.

Quality System Training DVD for Drugmakers

Author: U.S. Food and Drug Administration

"Quality System Training DVD for Drugmakers" is designed to give companies high-level employee education with the flexibility of in-house training. Staff can be trained at their own pace or at an all-day session watching all 12 modules. In addition to the video presentation, the system contains a second disc with hundreds of pages of valuable resources, including the full text of the regulations; FDA and International Conference on Harmonisation (ICH) guidances on good manufacturing practices and quality systems; the FDA report *Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach*; *FDAnews Management Report — A Process Approach to Pharmaceutical Quality Systems: A Guide to ICH Q10 Compliance*; and copies of the presentation slides in note-taking format.

www.fdanews.com/QualityDrugDVD

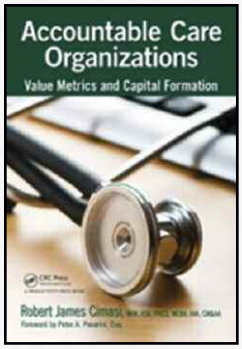


CBR Pharma Insights: Vaccine Development Strategies — Refocusing on Innovation, Targets and Markets to Address Clinical, Regulatory and Access Challenges

Author: GBI Research

This report provides readers with an understanding of the key developing trends in the vaccines market and how these are expected to impact the overall competitive landscape, the major players and forecasted growth. It provides an overview of the preventive vaccines market, including insights into clinical development strategies, recommendations for maximizing potential for development of preventive vaccines and discussion about potential areas of growth in the near term. It also provides in-depth analysis of the developing landscape for therapeutic vaccines, including recent activities of major pharmaceutical companies, insight into the challenges being faced by companies developing therapeutic vaccines and recommendations on clinical development strategies to overcome these potential obstacles and hurdles. Last, it assesses the evolving competitive vaccines landscape, profiling the major pharmaceutical players and providing information into the emerging vaccines companies and assessing how the vaccines market is expected to develop in the short to medium term.

www.gbiresearch.com/Report.aspx?ID=CBR-Pharma-Vaccine-Development-Strategies-Refocusing-on-Innovation-Targets-and-Markets-to-Address-Clinical-Regulatory-and-Access-Challenges&ReportType=Industry_Report&coreindustry=ALL&Title=Pharmaceuticals_and_Healthcare?utm_source=email&utm_medium=pr&utm_campaign=gbihcprq2&utm_nooveride=1



Accountable Care Organizations: Value Metrics and Capital Formation

Author: Robert James Cimasi

This book explores the historical background and evolution of the accountable care organization (ACO) model, which is rapidly expanding since its adoption as part of the Affordable Care Act. It examines the four pillars of value in the healthcare industry — regulatory, reimbursement, competition and technology — in addressing the value metrics of ACOs, including requirements for capital formation, financial feasibility and economic returns. The discussion is focused on non-monetary value on a review of aspects of population health within the context of such objectives as improved quality outcomes and access to care.

www.crcpress.com/search/results/1/?kw=Accountable+Care+Organizations%3A+Value+Metrics+and+Capital+Formation&category=all&x=-775&y=-63

Clinical Trial Magnifier Weekly

Author: U.S. Food and Drug Administration

Clinical Trial Magnifier Weekly monitors and reports on 150,000 trials in 185 countries around the world every week. Subscribers can scan all the changes and drill down using links in the newsletter to focus on the ones that are important. Included are all new, first-time sponsors launching studies in the past week; all new studies launched during the past week; all studies that are newly under planning in the past week; all studies that reported results in the past week; all studies that report a new status in the past week; all studies that are ended or halted during the past week; and all studies opening their first site in a new country in the past week. Subscriptions cost $497 for nonprofit institutions and $997 for companies.

http://www.fdanews.com/subscribe-now/clinical-trial-magnifier-weekly?hittrk=14624&utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=43332578

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective October 1, 2014 through December 31, 2014.

Product	Manufacturer	HCPCS	ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$72.41	$71.25
CARIMUNE NF	CSL Behring	J1566	$53.51	$52.65
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$75.51	$74.30
GAMMAGARD LIQUID	Baxter	J1569	$78.72	$77.46
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$53.51	$52.65
GAMMAKED	Kedrion	J1561	$80.04	$78.76
GAMMAPLEX	Bio Products Laboratory	J1557	$71.67	$70.52
GAMUNEX-C	Grifols	J1561	$80.04	$78.76
OCTAGAM 5% & 10%	Octapharma	J1568	$73.85	$72.66
PRIVIGEN	CSL Behring	J1459	$74.05	$72.86

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

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PIDD	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PIDD, ITP	3 g, 6 g, 12 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			0.5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxter	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxter	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Laboratory	IVIG: PIDD, ITP	2.5 g, 5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PIDD	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Baxter	SCIG: PIDD	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g

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

2014-2015 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
bioCSL	AFLURIA (IIV3)	5.0 mL multi-dose vial	9 years and older*	90658/Q2035
		0.5 mL single-dose syringe		90656
GlaxoSmithKline	FLULAVAL (IIV3)	5.0 mL multi-dose vial	3 years and older	90658/Q2036
	FLULAVAL QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	3 years and older	90688
	FLULAVAL QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
	FLUARIX QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 mL single-use nasal spray	2–49 years	90672
Novartis	FLUVIRIN (IIV3)	5.0 mL multi-dose vial	4 years and older	90658/Q2037
		0.5 mL single-dose syringe		90656
	FLUCELVAX (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661
Protein Sciences	FLUBLOK (RIV3)	0.5 mL single-dose vial	18–49 years	90673
Sanofi Pasteur	FLUZONE (IIV3)	5.0 mL multi-dose vial	3 years and older	90658/Q2038
			6-35 months	90657
		0.5 mL single-dose syringe	3 years and older	90656
	FLUZONE QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	3 years and older	90688
			6–35 months	90687
		0.25 mL single-dose syringe	6–35 months	90685
		0.5 mL single-dose syringe	3 years and older	90686
		0.5 mL single-dose vial	3 years and older	90686
	FLUZONE HIGH-DOSE (IIV3)	0.5 mL single-dose syringe	65 years and older	90662
	FLUZONE INTRADERMAL (IIV3)	0.1 mL single-dose microinjection system	18–64 years	90654

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 Cell culture-based trivalent 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.

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